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Review Article

Bioactive Peptides from Milk and Dairy Products: Applications and Activities

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Abstract: Milk and dairy products serve as natural sources of bioactive peptides, which are protein fragments with significant health-promoting properties. These peptides exhibit a range of biological activities, including antimicrobial, antioxidant, antihypertensive, immunomodulatory, and antithrombotic effects. Bioactive peptides are primarily released through enzymatic hydrolysis, microbial fermentation, or gastrointestinal digestion. Among them, antimicrobial peptides (AMPs) have gained particular attention due to their ability to inhibit pathogenic microorganisms by disrupting cell membranes, interfering with bacterial metabolism, or modulating immune responses. Additionally, bioactive peptides contribute to cardiovascular health by inhibiting angiotensin-converting enzyme (ACE) and preventing blood clot formation. Their antioxidant effects protect against oxidative stress, while opioid-like peptides influence neurological functions. This review provides an overview of bioactive peptides derived from milk and dairy products, focusing on their production, mechanisms of action, health benefits, and potential applications in the food and pharmaceutical industries. Further research is needed to optimize their bioavailability, stability, and large-scale production to enhance their functional applications in human health.

Keywords: Milk; Dairy products; Bioactive peptides; Antimicrobial activity, Functional foods, Health benefits.

1. Introduction

Milk is defined as a white or cream colored liquid secreted from the mammary glands of cows, sheep, goats and buffalos, with a unique taste and consistency, without any added substances or any substances removed (Horne, 2017). The basic components of milk are divided into protein and non-protein nitrogenous components. The protein nitrogenous components of milk consist of casein and serum proteins. Serum proteins have a globular structure and include β-lactoglobulin, α-lactalbumin, serum albumin, proteose-peptones and immunoglobulins and other minor protein fractions (Smithers, 2008). Milk and dairy products have long been recognized as essential sources of high-quality proteins, vitamins, and minerals, making significant contributions to human nutrition. Fermented dairy products such as yogurt, sour milk, and cheese contain a variety of bioactive peptides naturally produced during fermentation. In recent years, the discovery of bioactive peptides derived from dairy proteins has garnered substantial attention due to their potential health benefits. These peptides are encrypted within the protein structures of milk and are released during processes such as enzymatic hydrolysis, fermentation, or gastrointestinal digestion. Upon release, they exhibit a broad range of biological activities, including antihypertensive, antimicrobial, antioxidant, immunomodulatory, and opioid-like effects (Korhonen and Pihlanto, 2006; Nongonierma and FitzGerald, 2015; Park and Nam, 2015; Guha et al., 2021). While many peptides can be obtained under proteolytic conditions, only a few have been identified and characterized for their antimicrobial activity (Tomita et al., 2002; Pellegrini, 2003). Furthermore, several milk protein-derived peptides exhibit multifunctional activities, which are referred to as multifunctional peptides (Tomita et al., 2002; Lopez-Exposito et al., 2007).

The growing interest in bioactive peptides can be attributed to their potential applications in functional foods, nutraceuticals, and pharmaceuticals. With increasing consumer demand for natural and health-promoting food components, bioactive peptides from milk and dairy products are being extensively researched for their role in preventing and managing chronic diseases, such as cardiovascular disorders, diabetes, and inflammation-related conditions (Hernandez-Ledesma et al., 2011). These peptides, which are generated through enzymatic hydrolysis or microbial fermentation, also exhibit inhibitory effects against various pathogenic bacteria, fungi, and viruses (Korhonen and Pihlanto, 2006; Agyei and Danquah, 2011; Nongonierma and FitzGerald, 2015). Among these bioactive peptides, lactoferricin, derived from lactoferrin, has demonstrated potent activity against Gram-negative bacteria and *Candida albicans* (Gifford et al., 2005). Peptides derived from casein, such as those from αs1-casein and αs2-casein, have shown antibacterial effects against foodborne pathogens including *Escherichia coli*, *Helicobacter pylori*, *Listeria monocytogenes*, *Salmonella sp.*, and *Staphylococcus aureus* (Moller et al., 2008). Similarly, peptides derived from β-casein have been reported to inhibit the growth of *Klebsiella pneumoniae* (Hayes et al., 2006). These antimicrobial activities are attributed to various mechanisms, including the disruption of microbial cell membranes, inhibition of bacterial adhesion, and interference with bacterial metabolism (McCann et al., 2006). Specifically, milk-derived antimicrobial peptides (AMPs) are vital components of the innate immune defense, especially on mucosal surfaces such as the lungs and small intestine, which are continuously exposed to a wide range of pathogens (Mohanty et al., 2016). Lactoferrin, among other milk proteins, exhibits bacteriostatic and bactericidal activity against various bacteria by binding to iron (Niaz et al., 2019). Additionally, lactalbumin from infant milk has been shown to have antagonistic effects against *E. coli* and reduce the incidence of diarrhea (Bruck et al., 2003). Several clinical trials have demonstrated antibacterial activity of lactalbumin against antibiotic-resistant *S. aureus* (Nibbering et al., 2001). Furthermore, CAMP211-225, a milk-derived peptide, has been found to exhibit antibacterial activity against *E. coli* and *Yersinia enterocolitica* (Wang et al., 2020). The growing interest in milk-derived antimicrobial peptides is largely driven by their potential applications in food preservation and medical treatments. These peptides offer a natural alternative to synthetic preservatives and antibiotics, thereby contributing to enhanced food safety and human health (Mora et al., 2021).

This review aims to provide an overview of the latest developments in bioactive peptides derived from milk and dairy products, focusing on their production methods, structural characteristics, and functional properties. Furthermore, recent findings on their potential health benefits and applications in the food and pharmaceutical industries will be discussed. By highlighting these advancements, this study seeks to contribute to the growing body of knowledge on bioactive peptides and their promising role in human health and nutrition.

2. Production Methods of Bioactive Peptides Derived from Milk and Dairy Products

2.1. Conventional methods

2.1.1. Enzymatic hydrolysis

This method employs specific enzymes to cleave milk proteins into bioactive peptides under controlled conditions of pH, temperature, and substrate concentration. Enzymes such as pepsin, trypsin, chymotrypsin, alcalase, and thermolysin are commonly used (Figure 1). The choice of enzyme affects the properties and outcomes of the hydrolysis process (Korhonen and Pihlanto, 2006). For instance, trypsin targets lysine and arginine residues, while chymotrypsin acts on aromatic amino acids like tryptophan, phenylalanine, and tyrosine. Pretreatments like heating milk to denature proteins, adjusting pH, ultrafiltration to concentrate proteins, and pre-incubation of enzymes can enhance hydrolysis efficiency (Daliri et al., 2017).

2.1.2. Microbial fermentation

In this approach, microorganisms such as lactic acid bacteria (*Lactococcus lactis*, *Lactobacillus helveticus*) produce proteases that hydrolyze milk proteins during fermentation (Figure 1). These microbial proteases efficiently break down proteins into peptides and amino acids.

Factors influencing protein hydrolysis in microbial fermentation include the selection of microbial strains, optimal pH, temperature, substrate concentration, and control of microbial growth conditions (Daliri et al., 2017). Fermentation with specific strains has been shown to release bioactive peptides with antihypertensive, antioxidative, antimicrobial, and immunomodulatory properties (Bhandari et al., 2020).

2.1.3. Simulated gastrointestinal digestion

This method simulates the human digestive process by exposing milk proteins to gastrointestinal enzymes (pepsin, trypsin, chymotrypsin) under conditions mimicking the stomach and small intestine (Figure 1). This process releases bioactive peptides with various functionalities, including antihypertensive, antibacterial, opioid, and immunomodulatory activities. Simulated digestion provides insights into how food proteins are broken down and how bioactive peptides are released and function within the human body (Choi et al., 2012).

2.2. Advanced techniques

2.2.1. Ultrasound assisted processing

Ultrasound waves induce cavitation, producing shear forces that disrupt electrostatic and hydrophobic interactions in milk proteins, leading to conformational changes. This pre-treatment enhances enzymatic hydrolysis efficiency, resulting in higher yields of bioactive peptides. Ultrasound-assisted processing is considered an innovative, environmentally friendly technique that improves extraction rates and yields (Anusha and Bindhu, 2016).

2.2.2. Microwave assisted processing

Microwave heating offers benefits such as ease of operation, reduced processing time, and high energy efficiency. When combined with enzymatic hydrolysis, microwave-assisted processing accelerates protein denaturation and hydrolysis, facilitating the release of bioactive peptides. This method is suitable for continuous food processing and has been applied to enhance the extraction of bioactive compounds (Gobbetti et al., 2004).

2.2.3. High-pressure processing (HPP)

HPP is a non-thermal technique that applies high pressure to food products, causing conformational changes in proteins. These changes increase protein digestibility and enhance the release of bioactive peptides during subsequent enzymatic hydrolysis. HPP has been applied to milk and dairy products to improve functional properties and peptide yields (Mohanty et al., 2016).

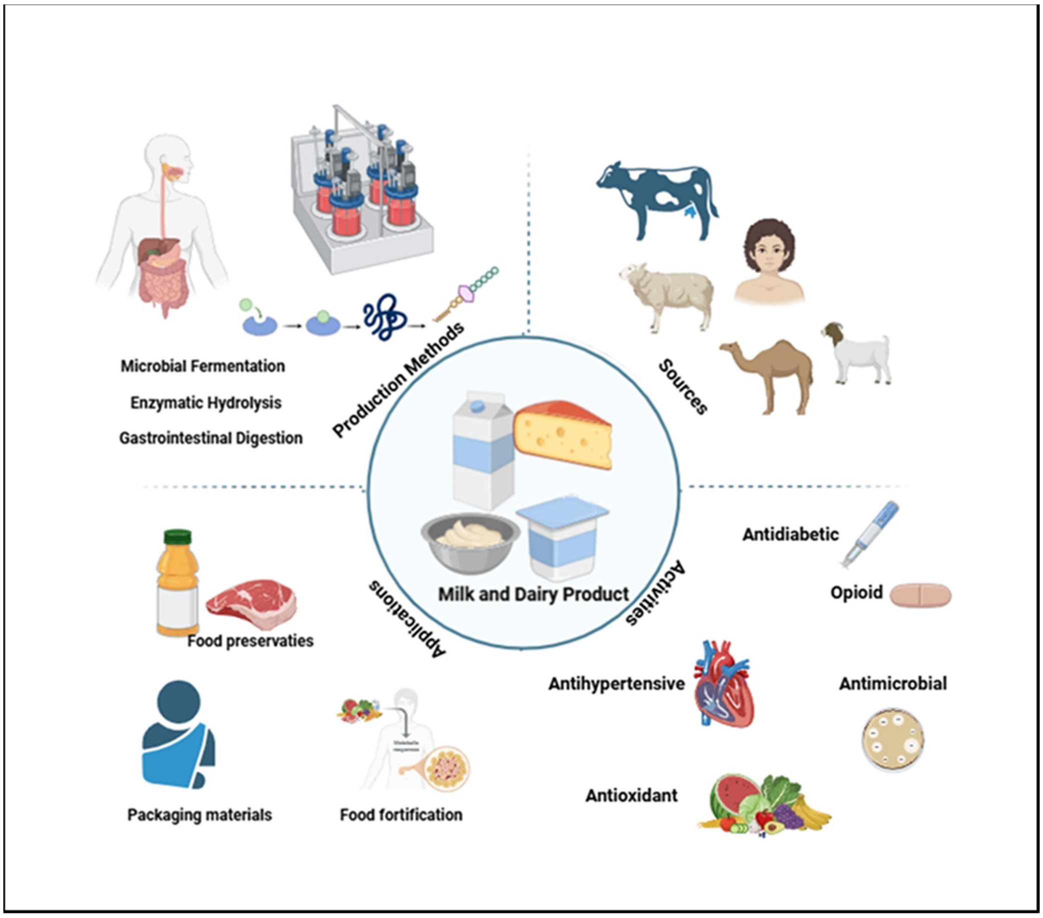

Figure 1. Bioactive peptides derived from milk and milk products of minor dairy species.

3. Structural Characteristics

Milk-derived peptides are bioactive molecules originating from milk proteins, exhibiting significant antimicrobial properties. These peptides are typically cationic, amphipathic, and predominantly adopt α-helical structures. The cationic nature facilitates interaction with negatively charged microbial membranes, leading to membrane disruption and microbial cell death (FitzGerald and Meisel, 2003; Korhonen and Pihlanto, 2006).

αs2-Casein f(183–207): This peptide, consisting of 25 amino acids, demonstrates notable antibacterial activity against pathogens such as *Listeria monocytogenes* and *Cronobacter sakazakii* (Hayes et al., 2006). Specific amino acids, particularly arginine at position 23, play a crucial role in its antimicrobial efficacy. Modifications, such as substituting proline residues at positions 14 and 20, have been shown to enhance its antibacterial potency (Lopez-Garcia et al., 2022).

Lactoferricin: Derived from lactoferrin, lactoferricin exhibits a cationic and amphipathic α-helical structure, which allows it to interact effectively with microbial membranes. This interaction results in pore formation and subsequent cell lysis (Tomita et al., 2009).

β-Lactoglobulin and α-Lactalbumin Derivatives: Peptides derived from β-lactoglobulin and α-lactalbumin demonstrate antimicrobial activity against Gram-positive bacteria. Their structural features contribute to their ability to disrupt bacterial cell membranes (Lopez-Exposito et al., 2007).

4. Mechanisms of Action of Peptides Derived from Milk and Dairy Products

Bioactive peptides can be obtained from various dairy products, including cheese, kefir, milk, and yogurt. These peptides remain inactive within the protein molecules and are released as a result of the breakdown of milk proteins such as α-casein, β-casein, κ-casein, α-lactoalbumin (LA), and β-lactoglobulin (LG) by digestive enzymes like pepsin, trypsin, and chymotrypsin, or through fermentation by starter cultures and microbial-plant-derived enzymes (Akbal and Öner, 2021). Milk- and dairy-derived peptides play a vital role in inhibiting microbial growth through various mechanisms. The main mechanism of action of antimicrobial peptides (AMPs) is membrane permeability and structural disruption. Studies indicate that cell death results from membrane lysis caused by increased peptide permeability. Peptides may also interfere with the biological effects of essential cytoplasmic components in microorganisms, such as proteins, enzymes, DNA, or RNA (Hancock and Sahl, 2006). Some of these peptide effects are similar to the actions of many antibiotics on microbial cells.

4.1. Membrane targeting mechanisms

4.1.1 Barrel stave model

In this model, peptides integrate into the microbial membrane, forming transmembrane pores. The hydrophobic regions of the peptides interact with the lipid bilayer, while the hydrophilic portions create a pore, resulting in ion leakage and cell death (Hayes et al., 2021).

4.1.2. Toroidal pore model

Unlike the barrel-stave model, peptides induce the bending of lipid monolayers, forming pores that are lined with both peptides and lipid molecules. This disrupts the stability of the membrane, causing cell lysis (Xuan et al., 2023).

4.1.3. Carpet model

In this model, AMPs cover the microbial membrane in a "carpet-like" manner. Once a critical concentration is reached, the membrane disintegrates through micellization, similar to the action of detergents (Malmsten, 2016).

4.2. Non membrane targeting mechanisms

4.2.1 Inhibition of nucleic Acid and Protein Synthesis

Some AMPs penetrate microbial cells and interfere with DNA, RNA, or protein synthesis, thereby preventing cellular function and growth (Zhang et al., 2021).

4.2.2. Disruption of biofilm formation

Certain AMPs inhibit biofilm development or degrade existing biofilms by targeting the extracellular polymeric substances (EPS) that stabilize bacterial communities (Park et al., 2011).

4.2.3. Immunomodulatory functions

Apart from their direct antimicrobial effects, dairy-derived AMPs can enhance the host immune response by modulating cytokine production and attracting immune cells to infection sites (Huan et al., 2020).

5. Effects of Bioactive Peptides on Human Health

5.1. Antimicrobial effect

Milk proteins are a natural source for bioactive peptides. An important feature of bioactive peptides formed as a result of protein degradation in milk is their antimicrobial effect. The overall antimicrobial effectiveness of milk resulting from the synergistic activity of milk peptides and proteins other than immunoglobulins, such as lactoferrin, lactoperoxidase and lysozyme, is much higher than that of individual molecules (Park and Nam, 2015). Antimicrobial milk components may demonstrate antibiotic-like activity, and they could pose a natural alternative to antibiotics (Mils et al., 2011). In a study, it was reported that bioactive peptides obtained from milk inhibited Gram-positive and Gram-negative microorganisms such as *E. coli* (MTCC82), *Aeromonas hydrophila* (ATTC7966), *Salmonella typhi* (MTCC3216), *Bacillus cereus* (ATTC10702), *Salmonella typhimurium* (SB300), *Salmonella enteridis* (125109), *S. aureus* (MTCC96) (Mohanty et al., 2016).Casein is broken down by the enzyme chymosin, resulting in the release of caseicidin peptides. These peptides have been reported to have antimicrobial effects against *Staphyloccoccus* spp., *Bacillus subtilis* and *Streptococcus pyogenes*. In addition, isracidin, obtained from α-casein, has been reported to be a peptide with strong protective effects against *S. aureus*, *S. pyogenes* and *L. monocytogenes* (Lahov and Regelson, 1996).

Lactoferrin and its derivatives show antibacterial activity in vitro against various pathogens such as *Clostridium perfringens*, *C. albicans*, *Haemophlus influenzae*, *H. pylori*, *L. monocytogenes*, *S. enteridis*, *S. aureus*, *Vibrio choleara* (Farnaud and Evans, 2003). Lactoferrampin (a fraction of lactoferrin) has inhibitory activity against *S. mutans, E. coli, B. subtilis* and *Pseudomonas aeruginosa* (Van der Kraan et al., 2004). It has been clearly established that lactoferrin obtained from whey proteins has a bacteriostatic effect against *Bacillus stearothermophilus*, *B. subtilis, Clostridium* spp., *H. influenza, S. mutans*, *V. cholerae* and *E. coli* both in vivo and in vitro. The antimicrobial activity of hydrolysates obtained from whey with pepsin, trypsin and chymotrypsin was tested on *Listeria ivanovii* and *E. coli.* Hydrolysates obtained from trypsin and chymotrypsin did not show any significant antimicrobial activity. However, whey protein hydrolysates obtained as a result of digestion with pepsin enzyme (45-90 min) showed antimicrobial activity against *L. ivanovii*. Again, hydrolysates obtained with pepsin enzyme did not have any effect on *E. coli* (Theolier et al., 2013). In another study, the antimicrobial activities of hydrolysates obtained by hydrolyzing fat-free colostrum and whey proteins with alcalase and neutrase were investigated. In the study where the antimicrobial effect was measured by impedimetric method, it was reported that the hydrolysate obtained by digesting colostrum with neutrase showed 82% and 19% inhibition on *E. coli* (ATCC 8739) and *S. aureus* (ATCC 6538), respectively. It was also determined that this hydrolate showed higher antimicrobial activity compared to other hydrolysates obtained with alcalase (Halavach et al., 2020). In a study in which hydrolyzation of goat milk was performed with trypsin, ficin and a combination of these two enzymes, it was reported that the obtained hydrolysates showed antimicrobial activity against *E. coli* and *B. cereus*. In addition, in this study, hydrolysates were separated into fractions according to their molecular weights by ultrafiltration. Fractions with a molecular weight of less than 3 kDa obtained from hydrolysates obtained with ficin were the fractions that showed the highest antimicrobial activity against *E. coli* and *B. cereus* (Esmaeilpour et al., 2016).

In another study, whey hydrolysates obtained from goat milk were obtained using alcalase enzyme produced from *Bacillus licheniformis*. Goat whey hydrolysate with the highest degree of hydrolysis showed higher antibacterial activity than unhydrolyzed goat whey. In addition, one of the four peptide fractions obtained showed antibacterial activity against *E. coli* and *B. cereus* with minimum inhibitory concentration (MIC) values of 0.09 and 0.03 mg/mL, respectively. Two of the peptides obtained also showed antimicrobial activity against *S. aureus* (Osman et al., 2016). In another study, it was reported that sodium caseinate hydrolysates obtained from Bacillus sp. P7 with extracellular protease enzyme showed antimicrobial activity against *L. monocytogenes* (ATCC 15131), *Corynebacterium fimi* (NCTC 7547), *S. enteritidis* (ATCC 13076) and *E. coli* (ATCC 8739) (Hidalgo et al., 2015). In a study investigating the antibacterial effects of 8 peptides (βC1, βC3, βC5, βC6, βC8, βC11, βC12, βC14) on *E. coli, S. aureus*, *Lactobacillus casei* and *Lactobacillus acidophilus*, when the MIC values of the peptides were examined, it was determined that Gram-positive bacteria showed more sensitivity than Gram-negative bacteria. When the results were examined, it was seen that the MIC values of the antibacterial peptides against Gram-positive bacteria varied between 10-30 μg/mL and against Gram-negative bacteria between 30-60 μg/mL. Due to the hydrophobic structure of the peptides, they are thought to have high antibacterial properties (Sedaghati et al., 2016).

In a study examining the properties of bioactive peptides of three different commercial Cheddar cheeses sold in Austria, the antimicrobial activities of the peptides were tested on *E. coli* (ATCC 87399, *S. aureus* (ATCC 6538) and *B. cereus* (ATCC 11778). It was determined that the peptides obtained from the cheeses had no significant effect on *S. aureus*, but showed inhibitory effects on *B. cereus* and *E. coli* (Pritchard et al., 2010). In another study similar to this study, it was reported that water-soluble peptides (0.6-1 mg/mL peptide concentration) obtained from various Italian cheeses exhibited antimicrobial activity against bacteria including *E. coli*, *Bacillus megaterium*, *Listeria innocua* and *S. aureus* (Rizzello et al., 2005). A total of 6 different fractions of antimicrobial peptides, 4 from αs1 casein and 2 from β casein, were obtained from water-soluble peptide fractions of Canastra Artisanal Minas cheeses sold in the market in Brazil on days 9, 23 and 30. It was reported that these peptides exhibited bacteriocidal activity against *E. coli* (Fialho et al., 2018). In a study conducted with reconstituted Cheddar cheese, the inhibition of an extract (APEE) enriched with anionic peptides produced by nanofiltration of hydrolysates obtained from whey proteins with trypsin enzyme on *L. innocua* and *L. monocytogenes* was investigated. In reconstituted cheese, the antimicrobial activity of APEE was higher against L. monocytogenes than *L. innocua*. Also, the antimicrobial activity was determined to be higher at 30 °C storage than at 4 °C

(Demers-Mathieu et al., 2013). Antimicrobial activity of water-soluble extracts obtained from different Koopeh cheese (a traditional Iranian cheese produced from raw sheep or cow milk with a distinctive taste and consumed after ripening) samples was evaluated against Gram-positive (*B. cereus*, *L. monocytogenes* and *S. aureus*) and Gram-negative *(E. coli*, *P. aeruginosa* and *S. enterica*) microorganisms. Water-soluble extracts showed significant antimicrobial activity against *P. aeruginosa, B. cereus* and S. *enterica* (Banihashemi et al., 2020).

Proteases with different purity rates (40%, 60% and 80%) were produced from *Aspergillus flavipes* and *Aspergillus oryzae* molds by solid-state fermentation. Cow and goat milks were hydrolyzed by these proteases. The obtained hydrolysates showed antimicrobial activity against many bacteria (Gram positive and Gram negative) such as *P. auruginosa*, *S. enteritidis*, *E. coli*, *S. aureus, L. monocytogenes* and fungi such as *C. albicans*, *Penicillium expansum*, *Fusarium oxysporum* (Zanutto-Elgui et al., 2019). In another study, it was reported that plectasin obtained from a type of fungus inhibited 5x10^5 cfu/mL *S. aureus* inoculated into milk by 100% at a concentration of 100 µg/mL (Li et al., 2017). Antimicrobial peptide F1 containing 18 amino acids was produced from Tibetan kefir by *Lactobacillus paracasei* subsp. F1 showed antimicrobial activity against many microorganisms such as *E. coli, S. aureus*, *S. enterica, Shigella dysenteriae, Aspergillus flavus*, *Aspergillus niger, Rhizopus nigricans* and *Penicillium glaucum* at concentrations ranging from 62.5 to 250 µg/mL (Miao et al., 2016).

Water-soluble extracts were obtained from kefir produced with sheep milk in Brazil and the antimicrobial activities of these extracts were investigated. Water-soluble peptide extracts (25 mg/mL) obtained on the 7th and 28th days of storage at 4 °C showed 100% inhibition on *E. coli* (ATCC 25922), *K. pneumoniae* (ATCC 29665), *P. aeruginosa* (ATCC 27853), *B. cereus* (ATCC 33019), *B. subtilis* (ATCC 6633) and *S. aureus* (ATCC 6538) (de Lima et al., 2018).

Camel milk casein hydrolysates obtained using alcalase, chymotrypsin and papain enzymes were ultrafiltered and then the antimicrobial activities of the different fractions obtained were investigated. Antibacterial activity was evaluated on Gram positive (*L. monocytogenes, B. cereus* and *S. aureus*) and Gram negative (*E. coli*) bacteria by applying agar diffusion test. All the fractions obtained showed antimicrobial activity against the tested bacteria. In this study, all the hydrolysates showed higher activity compared to their fractions (Kumar et al., 2016). The antibacterial activity of camel milk β casein and its peptic hydrolysate was investigated. The hydrolysate was separated into 1 kDa and 10 kDa fractions by ultrafiltration. The antibacterial activities of β casein and its peptic hydrolysates against *S. aureus* (CNRZ 3), *L. innocua* (ATCC 330909 and *E. coli* (ATCC 25922) were investigated. It was determined that the growth of *S. aureus* and *L. innocua* was not inhibited by β casein, while *E. coli* strain was inhibited to a low extent. However, it was observed that all hydrolysate fractions exhibited some antibacterial activity. It was determined that fractions lower than 1 kDa showed a stronger antimicrobial activity against both different Gram positive bacteria (Almi-Sebbane et al., 2018).

It has been reported that peptides obtained from the fermentation of camel milk with *Lactobacillus plantarum* inhibited the growth of *Enterococcus faecalis, S. dysenteriae*, *S. aureus* and *E. coli* by 20%, 20-25%, 20-25% and 15%, respectively (Muhialdin et al., 2018). The antibacterial activity of whey protein hydrolysates obtained through pepsin and pancreatin activity produced in the digestive system of camel milk colostrum was evaluated. Both hydrolyzed and non-hydrolyzed whey proteins inhibited the growth of *E. coli* (XL1) and *L. innocua* (LRGIA01). In particular, non-hydrolyzed protein (40 g/L) inhibited the growth of *E. coli* and *L. innocua* by 22% and 16%, respectively, while hydrolysates (10 g/L) provided 9% and 11% inhibition, respectively (Jrad et al., 2014). In another study with camel milk, it was found that camel milk whey protein at a concentration of 0.5 g/L had a higher antimicrobial effect on *E. coli* Dh1α compared to bovine milk. When the proteins were hydrolyzed with proteinase K enzyme, the antimicrobial activity of all hydrolysates obtained from whey proteins obtained from camel and cow, respectively, was increased by 2.9 and 4 times (Salami et al., 2010). *Trichosporon asahii* ICVY021 strain isolated from camel milk was found to produce antimicrobial peptide called oranicin P16 against *Kocuria rhizophila* CIP 53.45 belonging to the Micrococcaceae family, which is responsible for enzymatic spoilage in dairy products and is known as an indicator of contamination in camel milk (Ider et al., 2020).

Human milk naturally contains hundreds of antimicrobial peptides. These peptides have been known to prevent various diseases for years. A peptide called PCD213, which is the f(213-226) fraction of human milk β-casein, has been tested as an antimicrobial to inhibit the growth of *S. aureus*, *Y. enterocolitica*, *L. monocytogenes, K. pneumoniae*, *E. coli* and *B. subtilis* using the microdilution method. *S. aureus* and *Y. enterocolitica* were shown to be more sensitive to PDC213 than the other four pathogens. It was observed that PDC213 (15 mg/mL) inhibited at least 80% of the growth of *S. aureus* and *Y. enterocolitica*. On the other hand, PDC213 did not show any antimicrobial activity against other pathogens at a concentration of 50 mg/mL (Sun et al., 2017). Human milk contains specific antimicrobial peptide groups such as beta defensin 2 (hBD_2). hB 2 can support the immune system by inhibiting the growth of pathogenic microorganisms including *Salmonella* spp. and *E. coli* as well as microorganisms such as *S. marcescens*, *P. aerugiunosa* and *Acinetobacter baumoni* (Mohanty et al., 2016).

5.2. Antioxidative effect

Milk peptides have been demonstrated to play a regulatory role in the process of oxidative metabolism, which is a vital component of cellular activity. The overproduction of oxidative free radicals within cells has been associated with the development of various diseases, including cancer, rheumatoid arthritis and diabetes (Abuja and Albertini, 2001). Peptides derived from αs1-casein have been shown to possess antioxidant properties, capable of scavenging free radicals. Consequently, they inhibit both enzymatic and non-enzymatic lipid peroxidation (Rival et al., 2001). Whey proteins subjected to low-temperature processing have been found to contain high levels of specific dipeptides. These dipeptides have been shown to promote the synthesis of glutathione, an important antioxidant that plays a role in the protection and repair of cells. Furthermore, Barac et al. (2016) determined in their study that low molecular weight degradation products of α and β-casein-derived bioactive peptides with antioxidant effects were formed during the ripening process of cheeses.

5.3. Immunomodulatory effect

It is well established that the immune system plays a pivotal role in protecting the individual against bacterial, viral, parasitic, and fungal infections, as well as cancer. Furthermore, bioactive peptides have been shown to have a positive stimulatory effect on the immune system (Beermann and Hartung, 2013). Peptides and protein hydrolysates derived from milk caseins and large whey proteins have been observed to exhibit various immunomodulatory effects, including lymphocyte proliferation, antibody synthesis, and cytokine regulation. Notable examples of immunomodulatory peptides derived from milk include αs1-casein and immunopeptides synthesised by pepsin-chymosin hydrolysis. Cytomodulatory peptides derived from casein have been shown to stimulate immune system cells and impede the growth of cancerous cells (Meisel and Fitzgerald, 2003). These peptides have potential applications in the treatment of larynx and lung cancer (Knyazeva et al., 2008). The β-casein form has been observed to exert an effect on phagocytes in humans (Migliore-Samour and Jolles, 1998), while κ-casein and α-lactalbumin have been shown to offer protection to individuals against viral infections caused by immune system insufficiency in humans.

5.4. Effects on the cardiovascular system

5.4.1. Antithrombotic effect

It is known that bioactive peptides with antithrombotic effect have the ability to reduce or prevent blood clot formation. Caseinomacropeptides (CMP) are obtained from the κ-casein form by coagulation of milk proteins via the rennin enzyme. In other words, these CMPs inhibit the binding of fibrinogen, which has an important role in blood clotting, to glycoprotein receptors localized on the surface of platelets, preventing platelets from clumping (Fiat et al., 1993).

5.4.2. Antihypertensive effect

Hypertension is a risk factor for cardiovascular diseases such as coronary heart disease and peripheral artery disease. The renin-angiotensin system is considered an important regulator of blood pressure. Therefore, drugs that either inhibit the renin-angiotensin system, Angiotensin I Converting Enzyme (ACE), or block angiotensin receptors are widely used in the treatment of hypertension (Seppo et al., 2003). Multifunctional ACE regulates blood pressure through the catalytic conversion of angiotensin I to angiotensin II. Through fermentation, peptides that inhibit this system (ACE) and thus have a blood pressure-lowering effect can be obtained from milk proteins. Casein is a natural inhibitor of ACE. At the same time, milk-derived antihypertensive peptides are known as ACE inhibitor cascokinins and lactokinins, which have a hypertensive effect. It is an exopeptidase that breaks down various peptide substrates from the terminal carbon atom to release dipeptides and has important effects in regulating body blood pressure and water balance. In other words, bioactive peptides obtained from milk have a very important position in preventing some heart diseases such as arteriosclerosis and vascular occlusion (Solieri et al., 2015).

5.5. Effect on the nervous system

As Teschemacher et al. (1997) have demonstrated, bioactive peptides that play an active role in the nervous system are known as opioid peptides. Opioid peptides also have pharmacological similarities with opium (morphine). These peptides are opioid receptor ligands with agonistic and antagonistic activities (Park, 2015). For instance, αs1casein, β-casomorphins and lactorphins have been identified as opioid agonists, while casoxins have been shown to function as opioid antagonists (Gobbetti et al., 2007).Furthermore, it has been determined that UHT milk fermented with Lactobacillus GG secretes several opioid peptides from αs1 and α-lactalbumin as a result of hydrolysis by pepsin/trypsin.The bioactive peptides with opioid activity have been found to play an important role in the realization of important functions such as the regulation of social behaviour, reduction of excretion rate, regulation of amino acid transfer, and secretion of insulin and somatostatin hormones (Meisel, 2005).

6. Discussion and Conclusion

This review study has addressed the potential health effects and applications of bioactive peptides derived from milk and dairy products. Current data in the literature indicate that these peptides exhibit antimicrobial, antioxidant, antihypertensive, immunomodulatory and antithrombotic activities (Korhonen and Pihlanto, 2006; Nongonierma and FitzGerald, 2015). However, more clinical studies are needed to fully demonstrate the effectiveness of these bioactive compounds on human health. One of the most striking features of bioactive peptides is their potential use as natural antimicrobial agents. In particular, the global health problem of antibiotic resistance makes milk-derived antimicrobial peptides an important alternative (Mohanty et al., 2016). However, although in vitro studies have shown that these compounds are effective, their in vivo activities have not yet been fully elucidated. Future studies should focus more on the stability properties and bioavailability of these peptides in the gastrointestinal tract. Studies on the antihypertensive properties of peptides derived from milk and dairy products indicate that they can regulate blood pressure, particularly through the inhibition of angiotensin-converting enzyme. However, the long-term health effects of this effect should be confirmed in different populations and large-scale clinical trials. In addition, the effects of different production processes and fermented dairy products on the formation of these bioactive compounds should be investigated in more detail. This review also discussed the effects of milk-derived peptides on immunomodulatory and neurological functions. In particular, it is suggested that some peptides exhibiting opioid-like activities may interact with the nervous system and have potential neuroprotective effects. However, further studies are needed to confirm these effects at the clinical level. Industrial applications of bioactive peptides are also a very important issue. Considering their potential use in functional foods and pharmaceutical products, large-scale production processes need to be optimized. In particular, the efficiency of methods such as enzymatic hydrolysis and microbial fermentation should be increased and the stability and bioavailability of the obtained peptides should be improved. In addition, it is important to meet the safety criteria determined by regulatory bodies and to evaluate the possible risks associated with long-term consumption of these peptides (Mils et al., 2011).

In conclusion, bioactive peptides obtained from milk and dairy products have great potential in the fields of nutrition and health. However, in order to fully evaluate this potential, molecular mechanisms should be better understood, clinical studies should be increased and industrial scaling studies should be prioritized. Future research will more clearly reveal the benefits of these bioactive components for human health.

Conflicts of Interests
Authors declare that there is no conflict of interests

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