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Mini Review

Milk Proteins and Bioactive Peptides: Functional and Physiological Roles

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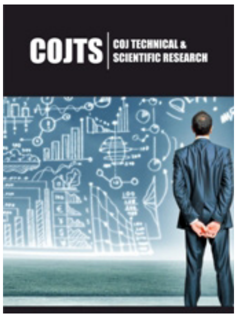

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Milk, a vital source of nutrition, contains two primary protein groups: caseins and whey proteins. Caseins represent approximately 80% of the total protein in bovine milk, existing primarily as casein micelles composed of over 1,000 casein submicelles. These phosphoproteins consist of αs1-, αs2-, β-, and k-casein, each with genetic variations [1]. Caseins are not only essential for nutrition but also serve as precursors to bioactive peptides with significant health implications. Whey proteins, accounting for 20% of milk proteins, are known for their functional and nutritional qualities. β-lactoglobulin and α-lactalbumin make up the majority of whey proteins, with additional components like bovine serum albumin, immunoglobulins, lactoferrin, and various enzymes contributing to its rich bioactivity [2]. Both casein and whey proteins release bioactive peptides during digestion or food processing, which exhibit various physiological benefits.

Bioactive peptides and their role

Bioactive peptides (BPs) are fragments of protein sequences released through enzymatic digestion, either in vitro or in vivo. Although inactive within their native protein structures, these peptides exhibit bioactivity once released, contributing to a range of physiological processes. Many BPs have been identified for their roles in modulating enzyme activities, enhancing mineral absorption, and regulating immune and nervous system functions [3]. In milk, peptides with opioid, hypotensive, antimicrobial, and immunomodulatory properties have been found. For instance, opioid peptides like β-casomorphins influence gastrointestinal function by acting on opioid receptors in the gut, prolonging gastrointestinal transit time, and exhibiting anti-diarrheal effects [4]. Additionally, angiotensin-I-converting enzyme (ACE) inhibitory peptides from milk, such as Val-Pro-Pro and Ile-Pro-Pro, have demonstrated potential for reducing hypertension in both animal models and human studies [5].

Physiological importance of milk proteins and peptides

Milk proteins, primarily caseins and whey proteins, are crucial for providing essential amino acids and nitrogen to young mammals. However, beyond nutrition, they play specific roles in physiological processes. Casein micelles, for example, facilitate the absorption of calcium and other minerals by maintaining their solubility in the digestive system. Casein phosphopeptides (CPPs), which are released during digestion, have shown anticariogenic properties by binding calcium and phosphate in dental plaque, promoting remineralization [6]. In addition, milk-derived bioactive peptides may contribute to cardiovascular health by inhibiting ACE, thereby reducing blood pressure. Studies involving fermented milk products containing ACE-inhibitory peptides have shown promising results in hypertensive individuals. CPPs also enhance calcium absorption in the intestine, suggesting a role in bone health and mineral metabolism. Casein, a major protein found in milk, is an excellent source of bioactive peptides, many of which exhibit significant antimicrobial, antitumor, and mineral-binding properties. These peptides are released during the enzymatic hydrolysis of casein, often through gastrointestinal digestion or fermentation. Among these, casein-derived antimicrobial peptides have gained considerable attention due to their potential applications in food safety, human health, and disease prevention.

Antimicrobial activity of casein-derived peptides

Casein-derived peptides have demonstrated activity against a wide range of pathogenic microorganisms, including both Gram-positive and Gram-negative bacteria. One of the first antimicrobial peptides isolated from casein, isracidin, a fragment of αs1-casein, was found to be effective against Staphylococcus aureus and Candida albicans. Isracidin's potent antibacterial properties make it a promising candidate for treating microbial infections.

Bovine αs1-casein peptides

The hydrolysis of bovine sodium caseinate with pepsin led to the discovery of a peptide fragment corresponding to residues 99-109 of αs1-casein. This cationic peptide exhibits broad-spectrum antimicrobial activity against both Gram-positive and Gram-negative bacteria [7]. The conservation of 10 of the 11 amino acids across species such as sheep, goat, and water buffalo suggest that peptides from these species may also have significant antibacterial potential. Additionally, two antimicrobial peptides, caseicins A and B, were isolated from fermented bovine casein by Lactobacillus acidophilus. These peptides, corresponding to αs1-casein residues 21-29 and 30-38, showed strong activity against Enterobacter sakazakii, a pathogen of concern in infant formula [8]. The use of such peptides in milk-based products could offer an innovative approach to safeguarding neonates against microbial infections.

Bovine αs2-casein peptides

Another important peptide derived from bovine casein is casocidin-I, a fragment of αs2-casein (residues 165-203). This peptide inhibits the growth of Escherichia coli and Staphylococcus carnosus [9]. Another peptide, αs2-casein (183-207), showed significant antibacterial activity against both Gram-positive and Gram-negative bacteria by permeabilizing bacterial membranes [10]. These peptides offer great potential for therapeutic use, especially in combination with other antimicrobial agents like lactoferrin, enhancing their overall effectiveness.

Kappacin: an antimicrobial peptide from k-casein kappacin

A peptide derived from k-casein, is another casein-derived peptide with antimicrobial properties. It corresponds to the nonglycosylated, phosphorylated form of caseinmacropeptide (CMP) and has demonstrated activity against Streptococcus mutans, Escherichia coli, and Porphyromonas gingivalis [11]. Kappacin increases membrane permeability through a membranolytic mechanism, potentially forming an anionic pore in the bacterial membrane (Dashper et al., 2005). Interestingly, the phosphorylated form of kappacin is essential for its antimicrobial activity, emphasizing the importance of post-translational modifications in peptide functionality. Furthermore, CMP, from which kappacin is derived, has been detected in the gastrointestinal tract following milk ingestion, indicating its possible role in protecting infants from gastrointestinal infections [12].

Ovine αs2-casein peptides

The antimicrobial activity of casein peptides is not limited to bovine milk. Peptides from ovine αs2-casein, including fragments 165-181 and 184-208, have demonstrated antibacterial effects, particularly against Gram-positive bacteria. However, these peptides are generally less potent than their bovine counterparts, especially against Gram-negative bacteria.

Antitumor and cytomodulatory properties

Beyond antimicrobial activity, casein-derived peptides may also play a role in cancer prevention. Some peptides, such as β-casomorphin-7 and β-casein (1-25), have been shown to induce apoptosis in human leukemia cells, thereby inhibiting cancer cell proliferation [13]. Other peptides, like kappacin, have demonstrated cytotoxicity against mammalian cells, including human leukemic cell lines. These findings suggest that casein-derived peptides could potentially be developed as anticancer agents, particularly due to their ability to modulate cell growth and apoptosis.

Peptide isolation and analysis techniques

Isolating bioactive peptides is critical for studying their functionality and potential applications. Various separation techniques have been employed, including ultrafiltration, chromatography, and capillary electrophoresis. Ultrafiltration is commonly used for separating peptides based on molecular weight, while chromatographic techniques such as size exclusion and ion exchange chromatography offer more refined separation based on peptide charge and hydrophilicity [14]. Recent advancements in mass spectrometry, such as LC–MS/MS and Nanostructure Laser Desorption/Ionization (NALDI), have improved the identification and characterization of short peptides. These methods allow for the precise analysis of bioactive peptide sequences, facilitating their study for nutraceutical and therapeutic purposes [15].

Conclusion

Milk proteins, particularly caseins and whey proteins, are rich sources of bioactive peptides with significant physiological functions. From enhancing mineral absorption to regulating blood pressure and immune function, these peptides contribute to human health beyond their nutritional value. Casein-derived peptides offer promising antimicrobial, antitumor, and nutraceutical benefits, with a wide range of potential applications in food safety, healthcare, and disease prevention. Their ability to target both Gram-positive and Gram-negative bacteria, along with their cytomodulatory effects, makes them attractive candidates for developing new therapeutic and protective agents. Advances in peptide isolation and analytical techniques are paving the way for the development of functional foods and nutraceuticals that harness the bioactivity of milk-derived peptides for therapeutic applications. As research progresses, the multifaceted roles of milk proteins in health and disease prevention continue to be revealed, emphasizing their importance in human nutrition.

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