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ANTI – INFLAMMATORY PROPERTIES OF BIOACTIVE PEPTIDES FROM MILK AND MILK PRODUCTS – A REVIEW

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ABSTRACT
Current pharmacological treatments frequently have negative side effects, and chronic inflammation is a major factor to many non-communicable diseases. Promising anti-inflammatory drugs with the potential to be incorporated into the diet and have fewer adverse effects include food-derived bioactive peptides, especially those generated from the proteins of milk and milk products. Additionally, several of these peptides have antioxidant properties that strengthen antioxidant defense systems and neutralize reactive oxygen species. Peptides from milk and milk products proteins are being studied more and more for their potential use in preventive healthcare and adjuvant therapy as consumer demand for functional foods and nutraceuticals rises. The purpose of this review is to shed light on anti-inflammatory peptides that are obtained from milk and milk products, with an emphasis on their origins, modes of action, potential for therapeutic use, and new developments in the treatment of illness.

KEYWORDS: Inflammation**,** Anti-inflammatory peptides**,** Immunomodulatory and Bioactive peptides.

INTRODUCTION

Inflammation is a complex biological response that serves to protect the host from infection and injury. Inflammation is an essential component of the innate immune response, triggered in response to infection, injury, or harmful stimuli. It serves to eliminate pathogens, repair tissue damage, and restore homeostasis. However, chronic or dysregulated inflammation is now recognized as a hallmark of numerous non-communicable diseases (NCDs), including atherosclerosis, type 2 diabetes, rheumatoid arthritis, Alzheimer's disease, inflammatory bowel disease (IBD), and cancer (Medzhitov, 2008; Furman et al., 2019). Chronic inflammation leads to sustained release of pro-inflammatory cytokines and oxidative stress, which contribute to tissue damage and disease progression.

The current pharmacological management of inflammation relies heavily on non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and biologics targeting inflammatory cytokines. While effective, these agents are often associated with adverse effects such as gastrointestinal ulcers, immunosuppression, and cardiovascular risks when used long-term (Bertolini et al., 2020). Consequently, there has been a surge in the search for safer, natural anti-inflammatory alternatives with fewer side effects and potential for dietary integration.

Among the most promising bioactive molecules are food-derived bioactive peptides. These peptides, typically composed of 2–20 amino acids, are released during enzymatic hydrolysis of food proteins by digestive enzymes, microbial fermentation, or food processing methods (Korhonen &Pihlanto, 2006; Möller et al., 2021). Originally inactive within the native protein structure, these peptides exhibit a range of bioactivities, including antioxidant, antihypertensive, antimicrobial, immunomodulatory, and most notably, anti-inflammatory effects (Udenigwe& Aluko, 2012; Nongonierma & FitzGerald, 2015).These peptides, originally encrypted within the primary structure of dietary proteins, can exert a range of physiological effects, including antihypertensive, antioxidant, antimicrobial, immunomodulatory, and anti-inflammatory activities **(Udenigwe & Aluko, 2012**). Animal-derived proteins, especially from milk, eggs, meat, fish, and other marine organisms, have emerged as rich and potent sources of these health-promoting peptides.

Animal-derived proteins including those obtained from milk, eggs, meat, fish, collagen, and marine invertebrates have gained recognition as rich and effective sources of

anti-inflammatory peptides. These peptides exert their bioactivity through multiple mechanisms: they help reduce inflammation by downregulating key pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β; they inhibit central signaling pathways involved in inflammation, notably NF-κB and MAPK; and they suppress the expression of inflammatory enzymes like COX-2 and iNOS. Additionally, many of these peptides possess antioxidant capabilities, allowing them to neutralize reactive oxygen species (ROS) and bolster the body's antioxidant defense systems (Yang et al., 2019; González-Montoya et al., 2022).

In addition to their anti-inflammatory activity, these peptides often exhibit multifunctionality, such as antioxidant and antimicrobial actions, which collectively contribute to the modulation of immune responses and the maintenance of intestinal homeostasis an essential factor in the gut–immune axis (Chalamaiah et al., 2018; Luo et al., 2022).

With rising consumer demand for functional foods and nutraceuticals, peptides from animal proteins are increasingly being investigated for their role in preventive health care and adjunctive therapy. However, challenges remain regarding peptide stability during digestion, oral bioavailability, effective delivery systems, and regulatory approval for clinical use (Daliri et al., 2017; Qian et al., 2021).

This review aims to provide insights of anti-inflammatory peptides derived from animal proteins, focusing on their sources, mechanisms of action, therapeutic potential, and emerging applications in health and disease management.

Bioactive Peptides from Milk

Milk proteins such as casein and whey have been extensively studied for their bioactive peptides. Lactoferrin-derived peptides (e.g., lactoferricin) and casein phosphopeptides have demonstrated significant anti-inflammatory and immunomodulatory effects (Legrand et al., 2005; López-Expósito et al., 2012).

Caseins and whey proteins in particular are milk proteins that are becoming more and more acknowledged as abundant sources of bioactive peptides with strong anti-inflammatory properties. When these proteins undergo enzymatic hydrolysis, whether in the course of microbial fermentation, gastrointestinal digestion, or in vitro enzymatic treatments, brief peptide fragments with a variety of biological activity are released. Peptides made from casein have shown strong immunomodulatory and anti-inflammatory properties in recent years, according to a number of studies. For example, Fernández-Tomé et al. (2020) found that β-casein-derived peptides improved tight junction integrity while also successfully suppressing the generation of TNF-α and IL-6 in LPS-induced Caco-2 epithelial cells. Additionally, these peptides were demonstrated to reduce the expression of pro-inflammatory genes associated with the NF-κBsignalling pathway, suggesting that they may be useful in reducing intestinal inflammation.

The simultaneous anti-inflammatory and antihypertensive properties of casein-derived peptides, such as valine-proline-proline (VPP) and isoleucine-proline-proline (IPP), have also drawn interest. Their immunoregulatory potential was highlighted by Kawasaki et al. (2021), who showed that oral treatment of these tripeptides in a DSS-induced colitis mouse model led to a considerable attenuation of colonic inflammation, reduction in myeloperoxidase activity, and elevated IL-10 expression. The therapeutic benefits of fermented dairy were further supported by a different casein hydrolysate study by Bruck et al. (2022), which found novel peptide sequences generated during fermentation that not only reduced the production of nitric oxide and iNOS in macrophages but also increased levels of the anti-inflammatory cytokine IL-10.

The peptides generated from whey protein have also showed great potential, in addition to casein. Researchers have looked closely at the anti-inflammatory properties of lactoferrin, a multipurpose whey protein, and its constituent peptide, lactoferricin B. According to Wang et al. (2019), lactoferricin B inhibited the TLR4/NF-κB pathway and reduced the expression of pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6 in both a mouse model of colitis and macrophage cells. These results were confirmed by González-Montoya et al. (2022), who observed that whey protein hydrolysates markedly reduced the levels of TNF-α and IL-1β in models of inflamed intestinal cells.

The production of functional peptides with bioactivity against inflammatory indicators has also been made easier by recent developments in milk fermentation. According to Chaves-López et al. (2020), yoghurt fermented with Lactobacillus delbrueckii and Streptococcus thermophilus produced peptides that inhibited RAW 264.7 macrophages' production of pro-inflammatory mediators such prostaglandin E2 and nitric oxide. This is consistent with research by Peñas et al. (2018), which shown that fermentation with probiotic strains such Lactobacillus plantarum resulted in peptides that maintained the integrity of the gut barrier and markedly decreased the release of IL-8 in inflammatory settings. In a more recent study, Yan et al. (2023) separated tripeptides from kefir that both activated the Nrf2 pathway and decreased COX-2 expression, suggesting that these peptides may have both antioxidant and anti-inflammatory properties.

Human clinical validation is still scarce, despite the abundance of data from in vitro and animal models. In their thorough analysis of clinical findings, López-Expósito and Recio (2021) underlined the significance of moving from bench to bedside. They pointed out that although the available data points to the safety and

possible effectiveness of milk-derived peptides, additional randomised controlled studies are necessary to assess the best dosage, bioavailability, and long-term safety in human populations. Individual variability in response, limited oral bioavailability, and peptide breakdown in the gastrointestinal tract have also been highlighted as significant barriers to clinical translation (Qian et al., 2021; Zhang et al., 2022).

However, new methods like peptide conjugation, nano-delivery systems, and microencapsulation are being investigated to get over these restrictions and improve the medicinal effectiveness of peptides generated from milk. These tactics seek to enhance intestinal barrier absorption, prevent peptides from being broken down by enzymes, and guarantee long-term release at specific locations. The importance of milk-derived peptides as appealing candidates for incorporation into nutraceuticals, functional beverages, and therapeutic supplements aimed at inflammatory illnesses is further supported by the rising interest in functional foods and natural health products.

Bioactive Peptides from Milk Products

In addition to their nutritional value, milk-based products especially those that undergo fermentation or enzymatic processing have gained recognition for their function as functional foods that are high in bioactive peptides. Enzymatic hydrolysis, lactic acid bacterial fermentation, or the natural ageing of dairy products can release these peptides, which are locked inside the main structure of milk proteins including caseins and whey proteins. These peptides generated from milk products have been shown in a growing amount of research to have anti-inflammatory properties in recent years, which makes them attractive options for use in therapeutic dietary interventions and nutraceuticals.

One of the most researched milk products in terms of the release of bioactive peptides is fermented dairy products, such cheese, kefir, and yoghurt. Milk proteins are broken down into smaller peptides with significant biological action by the proteolytic activity of lactic acid bacteria (LAB) during fermentation. Peñas et al. (2018) discovered that probiotic strains like Lactobacillus plantarum and Bifidobacterium animalis produced peptides that dramatically decreased the production of interleukin-8 (IL-8) in inflammatory Caco-2 intestinal epithelial cells when milk was fermented. This suggests that the probiotics have strong anti-inflammatory properties. Interestingly, the same study showed that yoghurt fermented by Streptococcus thermophilus and Lactobacillus delbrueckii subsp. bulgaricus was especially rich in low-molecular-weight peptides that could suppress the immune system.

LAB, yeasts, and acetic acid bacteria are all present in kefir, a fermented milk product that has become a particularly powerful source of anti-inflammatory peptides. Yan et al. (2023) separated tripeptides from kefir in a recent study that showed anti-inflammatory and antioxidant properties by successfully inhibiting the expression of cyclooxygenase-2 (COX-2) and activating the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway in inflammatory intestinal cells. Similarly, Santiago-López et al. (2018) found that kefir's peptide content and microbial metabolites caused intestinal inflammation to decrease and mucosal architecture to improve in a rat model of colitis.

A special matrix for the gradual natural production of bioactive peptides is cheese, especially aged types like grana padano, gouda, and cheddar. The anti-inflammatory peptides found in aged cheese extracts were shown by Coda et al. (2019) to decrease the release of TNF-α and IL-6 from activated macrophages. The study underlined that the bioactivity of released peptides is significantly influenced by the maturation period as well as the microbial consortia employed in cheese ripening.

Protein-rich milk fractions and whey-based drinks have also drawn interest. According to Pan et al. (2020), whey protein hydrolysates produced by gastrointestinal enzyme simulation decreased inflammation and oxidative stress in intestinal epithelial cells treated with lipopolysaccharide (LPS) by modulating the NF-κB and MAPK signalling pathways. This was further demonstrated by González-Montoya et al. (2022), who demonstrated that whey-derived peptides with hydrophobic and positively charged residues were very successful in downregulating TNF-α, IL-1β, and other inflammatory mediators.

Additionally, the immune-modulating properties of commercial milk-based protein hydrolysates which are frequently sold as functional components or dietary supplements have been studied. In a rat model of rheumatoid arthritis, Chen et al. (2020) showed that a commercially available whey peptide supplement decreased inflammatory cytokines and paw oedema, indicating the potential for these ingredients to be translated in clinical settings.

Mechanisms of Anti-inflammatory Action of milk bioactive peptides

Bioactive peptides' anti-inflammatory properties are mediated by a number of interrelated metabolic pathways. One of the main ways that these peptides work is by regulating the production of cytokines. They do this by inhibiting pro-inflammatory mediators like TNF-α, interleukin-6, and interleukin-1β, while also encouraging the release of anti-inflammatory cytokines like interleukin-10, which aids in re-establishing immunological balance (Majumder et al., 2015). Controlling the release of cytokines is one of the main ways that milk peptides reduce inflammation. According to a number of studies, these peptides upregulate anti-inflammatory cytokines like interleukin-10 (IL-10) while suppressing pro-inflammatory cytokines including

tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β). For example, β-casein-derived peptides dramatically decreased TNF-α and IL-6 levels in LPS-stimulated Caco-2 intestinal epithelial cells, according to Fernández-Tomé et al. (2020). Similarly, in inflammatory intestinal models, González-Montoya et al. (2022) discovered that whey protein hydrolysates reduced IL-1β production, indicating their effectiveness in reducing immunological hyperactivation.

The inhibition of pro-inflammatory enzymes, specifically cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), is another significant method. Prostaglandin E2 (PGE2) and nitric oxide (NO), two powerful inflammatory mediators, are produced by these enzymes, respectively as observed by Harnedy & FitzGerald, 2011. Research has demonstrated that both casein and whey peptides lower the expression of these enzymes in epithelial cells and macrophages. Chaves-López et al. (2020)found that peptides from yoghurt fermentation effectively suppressed acute inflammatory responses by drastically lowering the production of COX-2 and iNOS in LPS-stimulated RAW 264.7 macrophages.

The suppression of the nuclear factor-kappa B (NF-κB) signalling pathway, a major regulator of inflammation, is another important mechanism.The expression of several inflammatory genes is regulated by the crucial transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). When NF-κB is activated, adhesion molecules, cytokines, and chemokines are produced, which prolong inflammation. It has been demonstrated that milk-derived peptides, especially those found in whey and fermented milk products, inhibit NF-κB activation, which interrupts the subsequent inflammatory cascade. According to Pan et al. (2020), β-lactoglobulin peptides reduced the expression of NF-κB's target genes in intestinal epithelial cells and prevented NF-κB from nuclear translocating. The crucial significance of this route in milk peptide activity was further supported by Yan et al. (2023), who found that NF-κB suppression was accompanied by a significant decrease in COX-2 expression in a recent investigation employing kefir-derived peptides.

Bioactive peptides lower the expression of several inflammatory genes by blocking NF-κB activation (Yang et al., 2019). Furthermore, these peptides can inhibit the synthesis of inflammatory mediators including prostaglandin E2 (PGE2) and nitric oxide (NO) by downregulating enzymes like cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS). Additionally, by neutralising reactive oxygen species (ROS) and increasing the activity of important antioxidant enzymes like superoxide dismutase and catalase, their antioxidant qualities indirectly aid in the control of inflammation by lowering oxidative stress-induced inflammatory damage (Sarmadi& Ismail, 2010).

Numerous peptides generated from milk have strong antioxidant properties that aid in preventing oxidative damage, which is a significant cause of chronic inflammation. These peptides scavenge reactive oxygen species (ROS) and increase the activity of antioxidant enzymes including catalase and superoxide dismutase (SOD). In a colitis animal model, Wang et al. (2021) showed that lactoferrin-derived peptides from whey protein enhanced Nrf2 activation, a master regulator of antioxidant responses, and encouraged the production of antioxidant enzymes. Additionally, Yan et al. (2023) demonstrated that peptides generated from kefir stimulated the Nrf2/HO-1 signalling pathway, establishing a connection between anti-inflammatory and antioxidant defence.

Milk bioactive peptides may help maintain the function of the intestinal epithelial barrier, which is frequently weakened during inflammation, according to new research. These peptides help stop endotoxins and pro-inflammatory bacteria from moving across the intestinal barrier by modifying tight junction proteins including occludin and claudins. Fernández-Tomé et al. (2020) observed that in Caco-2 cells subjected to inflammatory stimuli, β-casein peptides improved transepithelial resistance and tight junction integrity in addition to reducing cytokine release.

Therapeutic Potential and Applications of Milk and milk products derived Bioactive Peptides

Significant interest in naturally derived medicinal compounds with anti-inflammatory qualities has been sparked by the rising prevalence of chronic inflammatory diseases worldwide, such as rheumatoid arthritis, metabolic syndrome, inflammatory bowel disease (IBD), and neurodegenerative disorders. Bioactive peptides generated from milk that are released during food processing, microbial fermentation, or enzymatic digestion have shown great promise in the creation of functional foods, nutraceuticals, and supplemental treatments for diseases characterised by inflammation. Their therapeutic promise across a range of clinical scenarios is highlighted by their capacity to act on various inflammatory pathways with low toxicity and good biocompatibility.

The effectiveness of milk-derived peptides in animal models of inflammation has been validated by a number of preclinical investigations. For instance, in a DSS-induced colitis model in mice, Kawasaki et al. (2021) showed that casein tripeptides, specifically valine–proline–proline (VPP) and isoleucine–proline–proline (IPP), dramatically reduced symptoms. The peptides enhanced the expression of the anti-inflammatory cytokine IL-10, decreased histopathological damage, and inhibited pro-inflammatory cytokines. In a collagen-induced arthritis rat model, Chen et al. (2020) found that whey protein hydrolysates decreased blood IL-6 levels, joint inflammation, and oedema, indicating its potential

for treating autoimmune diseases like rheumatoid arthritis.

Milk peptides are especially well-suited for treating gastrointestinal inflammatory disorders because they have both systemic effects and local anti-inflammatory activities in the gut. Research on fermented dairy products, such kefir and yoghurt, has shown that they can improve tight junction integrity, protect intestinal epithelial cells, and alter the composition of the gut microbiota (Fernández-Tomé et al., 2020; Yan et al., 2023). This implies that milk peptides have a dual function in promoting mucosal immunity and lowering systemic inflammation originating in the gut.

Only a few human investigations have started to corroborate these observations beyond preclinical data. Saito et al. (2021) assessed the effects of a fermented milk beverage enhanced with VPP/IPP in people with mild hypertension and systemic inflammation in a randomised, double-blind, placebo-controlled study. Significant drops in blood pressure and the inflammatory marker C-reactive protein (CRP) were observed in the data, indicating the potential of milk peptides for use in human health applications.

Additionally, milk peptides are being studied more and more in relation to metabolic health, especially in relation to insulin resistance and obesity. The metabolic syndrome is characterised by persistent low-grade inflammation. Recent research has demonstrated that peptides derived from whey proteins can improve insulin sensitivity and decrease inflammatory signalling in liver cells and adipose tissue (González-Montoya et al., 2022; Pan et al., 2020). This demonstrates their possible use in functional diets intended to slow the development of metabolic diseases.

Significantly, milk peptides' multifunctionality combining anti-inflammatory, antioxidant, antihypertensive, and immunomodulatory effects makes them appealing for wide-ranging use in medical nutrition products, functional beverages, and supplements. Their safety profile, which comes from a widely recognised food matrix (milk), increases the likelihood of regulatory approval and consumer trust.

Various preclinical investigations have shown the therapeutic efficacy of anti-inflammatory peptides, especially in models of skin illnesses, metabolic inflammation, inflammatory bowel disease, and arthritis (Erdmann et al., 2008). These peptides are becoming more popular as functional food ingredients and nutraceuticals in addition to their therapeutic uses because of their multifunctionality, safety profile, and natural origin. However, the oral bioavailability of these peptides continues to be a significant concern because they may be limited in their absorption or degraded by digestive enzymes. Protease inhibitors, peptide conjugation, and nanoencapsulation are examples of new approaches being researched to improve their stability and bioefficacy (Daliri et al., 2017).

Although milk-derived peptides show considerable therapeutic potential, their effective application still faces notable challenges. One of the primary issues is that oral delivery of these peptides can be compromised due to enzymatic degradation in the gastrointestinal tract, poor bioavailability, and variability in individual responses. Nevertheless, emerging encapsulation technologies including nanoemulsions, liposomal formulations, and biopolymer-based delivery systems—are being developed to overcome these barriers. These approaches have demonstrated promise in shielding peptides from digestive enzymes and improving their targeted absorption and stability within the body (Zhang et al., 2022; Qian et al., 2021).

CONCLUSION

Milk-derived bioactive peptides represent a promising frontier in the development of natural anti-inflammatory agents. Sourced primarily from casein and whey proteins, these peptides can be released through enzymatic hydrolysis, microbial fermentation, or gastrointestinal digestion, and have demonstrated multifaceted roles in modulating immune responses. A growing body of evidence indicates that they can attenuate inflammation by downregulating pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-1β), inhibiting key enzymes such as COX-2 and iNOS, suppressing the NF-κB and MAPK signaling pathways, and enhancing endogenous antioxidant defenses via the activation of Nrf2-mediated responses. Furthermore, certain peptides contribute to intestinal health by reinforcing gut barrier function and modulating the composition of gut microbiota, which plays a critical role in systemic inflammation.

Beyond mechanistic insights, numerous in vivo studies have validated the therapeutic efficacy of milk-derived peptides in models of colitis, arthritis, and metabolic inflammation. These peptides are also being increasingly formulated into functional foods, dietary supplements, and nutraceuticals aimed at chronic disease prevention and management. Their natural origin, compatibility with food matrices, and relatively low risk of adverse effects make them especially appealing for long-term dietary interventions in inflammatory disorders.

However, the translation of these peptides from experimental models to clinical use is hindered by several challenges. A significant limitation lies in their susceptibility to enzymatic degradation in the gastrointestinal tract, which can significantly reduce their biological activity after oral administration. Additionally, low intestinal absorption and rapid systemic clearance limit their therapeutic effectiveness. To address these barriers, innovative delivery technologies such as microencapsulation, liposomal carriers, nanofiber scaffolds, and biopolymer-based systems are being

actively explored. These strategies aim to improve peptide stability, protect against digestive breakdown, enhance bioavailability, and enable targeted delivery to inflamed tissues.

Despite promising results, well-structured human clinical trials remain sparse. There is an urgent need for randomized controlled trials to establish optimal dosing regimens, evaluate long-term safety, and confirm therapeutic efficacy in specific patient populations. Moreover, standardization in peptide production, purification, and bioactivity assessment will be crucial for the development of consistent and regulatory-compliant peptide-based products.

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