GOAT'S MILK PROTEINS – HYPOALLERGENIC AND THERAPEUTIC SIGNIFICANCE

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Abstract

Goat milk is recognized for its hypoallergenic and therapeutic properties in human nutrition and health, suggesting that goat's milk may have certain bioactive and metabolically active components that may be unique to the milk of this species. Goat milk is regarded as a high-quality milk protein source. The protein fractions of goat and bovine milk are qualitatively very similar, and the major difference among these milks is related to the proportions and classes of caseins. The hypoallergenicity of goat milk compared to bovine milk relates to the low levels of αs1-casein in goat milk. Also, the unique composition of goat milk, combined with its nutritional value, is related to the release of peptides, fragments resulting from protein digestion or technological processing, which are able to perform specific biological activities. Thirty-eight individual peptides were identified from goat milk with ACE-inhibitory, antimicrobial, antioxidant, immunomodulatory, opioid, or dipeptidyl peptidase-IV inhibitory bioactivity. The purpose of this review is to evaluate the scientific literature concerning the therapeutic value of goat milk protein.

Key words: *goat milk, protein, biopeptide*

INTRODUCTION

Milk is not only the main source of energy for the newborn of each species, but its components also have the potential to influence many aspects of physiology from the central nervous system to the immune system, while also exerting both antibacterial as well as antiviral effects. That is why milk is considered a functional food.

As technology and science advance, the fields of health and nutrition have focused on several emerging fields, namely nutrigenomics, or "personalized nutrition." The human genome study may lead to specific dietary recommendations to prevent or aid in the treatment of certain diseases.

The reputation of functional foods is growing worldwide and they are becoming part of the daily diet of health-conscious consumers. However, the efficacy of nutraceutical products in disease prevention depends on the preservation of stability, bioactivity and bioavailability of the active ingredients. Functional foods are found in virtually all categories of food products; however, some products are not widely available on the market (Boyazoglu, 2001; Park and Haenlein, 2006).

Milk protein derived hydrolysates are also consumed as a rapidly digestible protein source for humans, which results in higher milk protein utilization rate. It is also a potential source of BAPs (Davoodi et al., 2016) and can be generated by enzyme-based hydrolysis of milk protein.

THE HYPOALLERGENIC PROPERTIES OF GOAT'S MILK

Protein macromolecules such as milk caseins and cow's whey proteins can cause allergic responses in some people. Cow's milk allergy is a common disease in infants. Caseins, as well as beta-lactoglobulin (MW 36,000), the major whey protein in cow's milk, are not found in human breast milk and are responsible for cow's milk allergy (Heyman et al., 1990; Park, 1994).

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Goat's milk has been recommended as a substitute for cow's milk for infants and allergic patients suffering from allergies to cow's milk or other food sources (Haenlein, 2004; Prosser, 2021).

Given the bioactive components in milk, the hypoallergenic properties of goat's milk are very important for human health and medicine. This premise is of constant interest to producers and consumers of goat's milk, especially in recent years in developed countries (Park and Haenlein, 2006).

Various studies have shown that goat's milk has been used for hypoallergenic infant food or milk substitute in infants allergic to cow's milk and in those patients suffering from various allergies such as eczema, asthma, chronic catarrh, migraine, colitis, hay fever, gastric ulcer, epigastric distress, and abdominal pain due to the allergenicity of cow's milk proteins (Taitz and Armitage, 1984; Park, 1994; Haenlein, 2004).

Park (1994) reported that those children who were reactive or allergic to cow's milk but not to goat's milk also reacted to cow's milk cheese but not to goat's milk cheese. Many scientists have recommended goat milk powder for infant formula (McLaughlan, et al. 1981; Taitz and Armitage 1984; Coveney and Darnton-Hill 1985), because the heat applied in the processes of manufacturing reduces allergic reactions (Park and Haenlein, 2006). Thermal denaturation alters the basic structure of proteins and causes them to decrease in allergenicity (McLaughlan et al. 1981). Since goat's milk has a relatively low α s1 casein content, it is logical that children with increased sensitivity to cow's milk α s1 casein should tolerate goat milk quite well (Juàrez and Ramos, 1986).

In French clinical studies conducted over a period of over 20 years on patients allergic to cow's milk, Sabbah et al. (1997) concluded that substitution with goat's milk resulted in "undeniable" improvements. In other extensive French clinical studies with child patients with cow's milk allergy, treatment with goat's milk produced positive results in 93% of children and was recommended as a valuable aid in children's nutrition because goat's milk had less allergenic capacity and better digestibility compared to cow's milk (Fabre 1997; Grzesiak 1997; Reinert and Fabre 1997).

THE THERAPEUTIC PROPERTIES OF GOAT'S MILK PROTEINS

Proteins from animal or vegetable foods can be rich sources of biologically active peptides. Milk protein derived hydrolysates are also consumed as a rapidly digestible protein source for humans, which results in higher milk protein utilization rate (Davoodi et al., 2016). Once bioactive peptides are released through digestion or proteolysis, they can exert various physiological effects in the body on the gastrointestinal tract, cardiovascular, endocrine, immune and nervous systems (Korhonen and Pihlanto, 2007).

The main bioactive peptides of goat's milk and its derivatives are described below:

1. Peptides with antihypertensive role

Several epidemiological studies have linked dietary intake of milk and dairy products to a reduced risk of hypertension. The antihypertensive effect of these products has been attributed to a high content of minerals (calcium, potassium and magnesium) and certain proteins present in these products (as well as in their hydrolysates) (Engberink et al, 2009). Several studies have been conducted to investigate the bioactivity of goat's milk protein hydrolysates and the release of angiotensin converting enzyme (ACE) inhibitory peptides and antioxidant peptides by the action of individual proteases such as thermolysin, trypsin, subtilisin, papain and pepsin. or their combinations (Ahmed et al., 2015).

Among the bioactive peptides known to date, those with ACE (angiotensin converting enzyme) inhibitory properties have received particular attention due to their potential beneficial effects in the treatment of hypertension.

Four ACE inhibitory peptides were identified and purified from thermolysin-digested goat β-lactoglobulin hydrolysates (Gobbetti et al., 2007). De Gobba et al. (2014) identified several casein-derived peptides that were enzymatically released by hydrolyzing goat's milk proteins with a combination of subtilisin and trypsin. Among them, many peptides contain tyrosine in their sequence and have shown antioxidant and ACE-inhibitory activities.

The studies of Ibrahim et al. (2017) demonstrated that ACE inhibitory peptides can be released from goat milk caseins and whey proteins after gastric digestion with pepsin. In their study they found a peptide derived from whey β-lactglobulin and two peptides derived from caseins, but also fragment 96-106 of κ **-casein** and fragment 56-66 of β-casein. These peptides have an ACE inhibitory activity comparable to that of antihypertensive drugs with ACE inhibitory action.

Silva et al. (2006) obtained active ACE-inhibiting peptides and antioxidant activity in water-soluble extracts from various types of raw or pasteurized sheep and goat cheeses coagulated with Cynara cardunculus plant enzymes. They found that the peptides Tyr-Gln-Glu-Pro, Val-Pro-Lys-Val-Lys, and Tyr-Gln-Glu-Pro-Val-Leu-Gly-Pro derived from β - casein, as well as Arg-Pro-Lys and Arg-Pro-Lys-His-Pro-Ile-Lys-His derived from α s1-casein showed angiotensin-I-converting enzyme inhibitory activity.

During fermentation to make kefir, many peptides can be released by the proteolytic enzymes of lactic acid bacteria. Sixteen peptides were identified in a commercial goat kefir using HPLC coupled with tandem mass spectrometry (FitzGerald and Meisel, 2000). Similarly, the study of Moreno-Montoro and col. (2017) showed that small and non-basic bioactive peptides could be responsible of most of angiotensin-I-converting enzyme inhibitory and antioxidant activities. These findings reinforce the potential benefits of the consumption of fermented goat milk in the prevention of cardiovascular diseases associated to oxidative stress and hypertension.

The presence of low molecular weight ACE inhibitory peptides has also been found in several aged cheeses. They also observed that inhibitory activity increased as proteolysis proceeded, while the inhibitory effect of ACE decreased when cheese ripening exceeded a certain level during proteolysis (FitzGerald and Meisel, 2000). These peptides as well as other hydrophobic peptides also exert antioxidant and anti-inflammatory activities. Therefore, bioactive peptides from goat milk and whey show antihypertensive activity by inhibiting ACE, but considering all the mechanisms involved in the pathophysiology of hypertension, the existence of multifunctional peptides must be considered.

2. Antimicrobial peptides

The antimicrobial activity of milk is mostly attributed to the presence of immunoglobulins and other proteins, such as lactoferrin, lactoperoxidase and lysozyme. Recently, the study of Muñoz-Salinas et al. (2022) demonstrates that goat milk proteins, specifically β-lactalbumin, β-lactoglobulin, α-s1-casein and α-s2-casein, κ-casein and β-casein, can be used as a potential source of antimicrobial peptide. It is now unanimously accepted that the total antibacterial effect of milk is greater than the sum of the individual contributions of the proteins involved in the defense (immunoglobulins and nonimmunoglobulins). This may be due to the fact that naturally occurring proteins and peptides act synergistically with peptides that result from the metabolism of inactive protein precursors (Atanasova and Ivanova, 2010).

After the beneficial effects of human and bovine lactoferrin were demonstrated, goat lactoferrin was also studied. The levels of this protein in goat's milk are slightly higher compared to cow's milk, with values of approximately 0.107 ± 19 mg/ml. The concentration of lactoferrin in goat's milk, during different stages of lactation, varies in direct proportion to the number of somatic cells present in the milk samples. These parameters are influenced by a range of physiological processes (Hiss et al., 2008). Another study, which compared the glycosylation of goat's milk lactoferrin with the glycosylation of other glycoproteins present in human and bovine milk, demonstrated similarities between the glycans present in both human and goat's milk samples.

Given its high digestibility, immunological properties, and high mineral concentration, as well as the similarities between human and goat lactoferrin, goat's milk can be considered an attractive candidate for use in infant supplement formula.

Lactenin was probably the first milk-derived antibacterial factor to be treated with rennet. Casecidins are a group of basic, glycosylated, high molecular weight (about 5 kDa) polypeptides that have bactericidal properties against lactobacilli and various pathogenic bacteria such as Staphylococcus aureus.

Isracidine is another antibacterial peptide derived from chymosin-treated α s1 - casein. It has been shown that isracidin has an inhibitory effect on the in vitro growth of lactobacilli and other Gram-positive bacteria, only at relatively high concentrations (0.1 - 1 mg / ml).

Triprisila et al. (2016) reported an effect of the antimicrobial activity of alpfa-s2 casein protein from Ethawah goat milk and yogurt against pathogenic Gram-positive bacteria (Listeria monocytogenes, Staphylococcus aureus and Bacillus cereus) and Gram-negative bacteria (Escherichia coli, Salmonella typhi and Shigella flexneri). The results of their studies showed a higher inhibitory effect on Gram-positive bacteria than on Gram-negative bacteria. They also demonstrated that milk has greater antimicrobial activity than yogurt.

Recent studies have shown that the different proteins identified in goat whey can inhibit the growth of microorganisms with different characteristics, although there are differences in the inhibition percentage (Campos et al., 2022).

The ability of goat whey proteins to inhibit the growth of the microorganism is linked to electrostatic interactions between the lipopoly-saccharide membrane of bacteria and whey proteins.

Another property of proteins is the amphipathic character of proteins, which causes the lysis of the bacterial cell wall by introducing its hydrophobic region into the apolar domain of the bacterial membrane, (Brandelli et al., 2015).

3. Cytomodulatory and anticancer peptides

Lactoferrin from goat's milk not only has antimicrobial activity, but has been shown to induce apoptosis in a human cervical cancer cell line. Considering the similarity with other lactoferrins, goat lactoferrin could show protective activity against other types of cancer. However, research in this area is only at an early stage. These properties of lactoferrin constitute an interesting alternative to chemoprevention and anticancer drugs currently used. Additionally, its stability in the gastrointestinal tract is beneficial when oral administration is considered (Abbas et al., 2015).

Intact or hydrolyzed goat whey protein concentrates inhibited lymphocyte proliferation in a dose-dependent manner. *In vitro* studies indicate that lactoferricin has potent activity on cell lines of various types of cancer, including colon, leukemia, breast, fibrosarcoma, and ovarian cancer cells. It has also been shown that the action limits cancer cells proliferation without affect normal lymphocytes, endothelial or epithelial cells or fibroblasts (Chalamaiah et al., 2018).

Su et al. (2014) reported that an anticancer bioactive peptide (ACBP), extracted from goat spleen, significantly inhibited the in vitro growth of the human gastric cancer line BGC-823 in a dose-dependent manner. In vivo, ACBP inhibited human gastric tumor growth in a xenograft model without apparent host cytotoxicity. The study suggested that the ACBP bioactive peptide could be a potent anticancer biological product by inducing cell apoptosis and cell cycle arrest. Moreover, Yu et al. (2014) found that, using in vitro and in vivo assays, bioactive peptide-3 (ACBP-3), a peptide isolated from goat liver, exhibited antitumor properties on gastric cancer stem cells.

4. Antioxidant peptides

Milk proteins have shown antioxidant activity for the scavenging of reactive oxygen species. Studies have shown that casein inhibited the lipoxygenase-catalyzed lipid autoxidation. Free amino acids cannot quench the free radicals and for the scavenging of free radicals, primary structure of casein mole- cules acts as scavenger (Khan et al., 2019).

Peptides with antioxidant properties are especially important because they can prevent or delay oxidative stress, but also chronic diseases associated with a low degree of systemic inflammation. Antioxidant peptides can be released from caseins, soy and gelatin by hydrolysis with proteolytic enzymes. Milk proteins, as well as proteins from milk derivatives, are considered potential carriers for antioxidant peptides to the gastrointestinal tract, where they can exert direct protective effects, by eliminating reactive oxygen species and reducing oxidative stress. To date, relatively few studies have been performed on the antioxidant properties of goat's milk protein-derived peptides.

Nandhini et al. (2012) found that goat milk fermented with Lactobacillus plantarum had strong reactive oxygen species scavenging and lipid peroxidation inhibition activity, although they did not identify the active peptides. Li et al. (2013) identified antioxidant peptides in goat milk casein hydrolyzate obtained by using two enzymes (alcalase and pronase), although some of them did not match the goat casein sequences available in protein databases.

The results of Gammoh et al. (2020) and Campos et al. (2022) studies have shown that the goat whey protein in its raw form can perform an antioxidant activity similar to those that have undergone some processing for release of peptides bioactives. This result may be due to the presence of cysteine and methionine amino acids. It is well known that the thiol group reacts with many antioxidants. The main proteins that have these amino acids are: b-La which contains 5 cysteine residues; a-La with 8 residues; serum albumin with 35 residues; and lactoferrin which contains 34 residues.

5. Immunomodulatory and anti-inflammatory peptides

Imbalances in both the oxidative and inflammatory states are implicated in the etiology of several human chronic diseases affecting the digestive tract, such as ulcerative colitis and Crohn's disease. This has encouraged the search for natural preventative treatments against these imbalances and, consequently, against disease.

The minor constituents of goat's milk, namely lysozyme and transforming growth factor β (TGF-β), appear to offer additional protection against intestinal cell damage/inflammation. Several authors have shown that oral administration of TGF-β has anti-inflammatory effects at the intestinal level in animal colitis types. TGF-β supplementation also increased mucin-2 production in the cecum and normalized muscle proteolytic activity. Goat milk has a much higher level of growth factor activity than cow's milk, thus making goat's milk a possible nutraceutical product for gastrointestinal disorders (Carvalho et al., 2012; Lima et al., 2017).

Protein hydrolysates and peptides derived from milk caseins and major whey proteins have immunomodulatory effects (exercising immune cell functions), such as lymphocyte proliferation, antibody synthesis and cytokine regulation. These peptides have been shown to modulate human lymphocyte proliferation, downregulate the production of certain cytokines, and stimulate the phagocytic activities of macrophages (Korhonen and Pihlanto, 2007). Because of their immune cell functions, these peptides have been of particular interest to food researchers and the food processing industry.

Immunomodulatory peptides derived from milk include αs1-immunocassokinin and peptides derived from β - casein f 193 - 202, f 63 - 68 and f 191 - 193 (immunopeptides), which are obtained by pepsin-chymosin hydrolysis. Other studies have shown that the immunopeptide β-casomorphin-7 suppressed the proliferation of lymphocytes in human peripheral blood at low concentrations (<10 - 7 mol / L), but stimulated it at higher concentrations. Several peptides derived from β-casein enhanced IgG production in mouse spleen cell cultures (Gobbetti et al., 2007).

6. Hypocholesterolemic peptides

The serum cholesterol-lowering activity is dependent on the degree of excretion of the steroid in the faeces. Cholesterol becomes soluble in the presence of bile salts and is then absorbed. This fact led to a hypothesis that a peptide with high bile acid binding capacity could inhibit bile acid reabsorption in the ileum and lower blood cholesterol levels.

A hypocholesterolemic peptide (Ile-Ile-Ala-Glu-Lys) was identified from β-lactoglobulin hydrolyzate (Nagaoka et al. 2001). This peptide has been shown to suppress cholesterol absorption in vitro and to induce hypocholesterolemic activity in vivo in rats after oral administration of the peptide solution (Park, 2009).

7. Mineral binding peptides

Phosphopeptides or caseinphosphopeptides function as transporters of various minerals, especially Ca 2+, by forming soluble organophosphate salts (FitzGerald and Meisel, 2000). Cow's milk αs1 -, αs2 - and β - caseins contain phosphorylated regions, which can be released by digestive enzymes. In this situation, specific casein phosphopeptides can form soluble organophosphate salts and lead to increased calcium absorption by limiting calcium precipitation in the distal ileum (Korhonen and Pihlanto, 2007).

Most caseinphosphopeptides contain a common pattern, such as a sequence of three phosphoserine residues followed by two glutamic acid residues. The negatively charged side chains, especially the phosphate groups of these amino acids, represent the binding sites for minerals (Gobbetti et al., 2007). Berrocal et al. (1989) reported that dephosphorylated peptides did not bind minerals, whereas chemical phosphorylation of αs1- and β -caseins increased the binding capacity and stability of these proteins in the presence of Ca 2+ .

Enzymatic digestion (in the presence of pancreatic endoproteinases, in particular trypsin) of casein can generate casein phosphopeptides. Other enzyme combinations, such as chymotrypsin, pancreatin, papain, pepsin, thermolysin, and pronase, have been used for the in vitro production of casein phosphopeptides. They increase the absorption of Ca 2+ and Zn 2+ from rice-based porridge for infants by about 30%, but have no effect when casein phosphopeptides were ingested from high- or low-phytate whole-grain meals (Hansen, 1995).

CONCLUSION

Goat products (mainly meat and dairy products) have particularities in terms of their odor, taste, flavors and fat levels, as well as the specific composition of fats, proteins, amino acids and fatty acids, and have been traditionally consumed in certain regions of the globe. In addition, the nutritional properties of goat's milk and its lower allergenicity compared to cow's milk have sparked interest in goat's milk as a functional food, and it is currently one of the current trends in healthy eating in developed countries. Studies that focus on the discovery of new molecules from natural sources, such as goat whey proteins, can provide tools for prevention and treatment of malignant cells.

Moreover, the use of milk with special nutritional properties, alone or in combination with bacterial strains with probiotic properties and able to produce physiologically active metabolites, could become one of the options for the manufacture of new functional dairy beverages.

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