

REVIEW

Potential nutraceuticals from the casein fraction of goat's milk

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Abstract

Goat is one of the major dairy and meat providers. In terms of structure, nutrient content, and medicinal properties, goat milk is somewhat different from other milk. The differences in composition are important in determining the technical suitability of goat milk and its products for health benefits. In recent years, there has been increasing attention to the identification and molecular composition of milk proteins and the interest in caprine milk. Casein, which accounts for almost 80% of all the proteins, is the most significant protein found in goat milk. It is a pioneer in the field of nutraceutical formulation and drug production by using the goat mammary gland as a bioreactor. In goat milk, the most prevalent proteins are α S-casein, β -casein, and κ -casein. The aim of this review is to highlight the importance of goat milk casein and also focus on recent findings on their medicinal importance that may be helpful for further research on dairy products with health beneficial properties for humans as a remarkable nutraceutical.

Practical applications

Goat milk casein is considered as a healthy nutrient as well as a therapeutic agent to control abnormal or disease conditions through some of its biologically active peptide residues. Casein fractions of goat milk have been shown to exhibit different biologic activities. Therefore, this study aims to observe the use of goat milk in various disorders and to know about the different products made from goat milk. It will be helpful in the field of medicine to be a new active constituent for the management of various disease conditions.

KEYWORDS

Goat milk, casein, nutraceutical, milk protein

1 | INTRODUCTION

Nutraceuticals provide consumers with numerous health benefits because of the active components present in the food. Many scientific studies elaborated health to be strongly linked to food intake, raising concerns about functional foods (Azhar & Salim, 2017). It is undeniable that goat milk is one of the outstanding sources of nutrients. In all ruminants, the presence of proteins in goat milk has been recognized for their nutritional and scientific importance. Due to the

high amino acid content and greater digestibility, goat milk proteins are highly nutritious compared with other proteins (Almeida et al., 2016). Their primary function is to provide amino acids and nitrogen to young children and is an integral component of adult and senior citizen dietary proteins. When goat milk is given to infants, symptoms such as gastrointestinal disturbances, vomiting, colic, constipation, diarrhea, and respiratory issues are reduced. Because the composition of pasteurized goat milk is comparable with that of human milk, it is easily tolerated by newborns who have gastrointestinal or

respiratory problems. The physiologic importance of milk proteins is to promote the absorption of some essential nutrients such as vitamins and trace elements and a group of proteins that play a defensive function (Alshamiry & Abdelrahman, 2020). According to some research, it can be taken without causing any harm to people who are allergic to cow milk and this also strengthens goat milk market opportunities (Anderson & Moore, 2004).

Goat milk consists of a variety of proteins with casein accounting for about 80% of the total and is arranged as micelles. It contains four protein fractions: α 1-, α 2-, β -, and κ -casein, all of which have different molecular weights. Casein has versatile external structures that are defined as random, unlike most proteins that show different secondary and tertiary conformational structures (Assifaoui et al., 2014). In milk, calcium-insensitive is κ -casein, while calcium-sensitive constituents include α S1, α S2, and β (Boirie et al., 1997). The casein micelle is a complex of protein molecules of α - and β -casein with κ -casein on its surface. Hydrophobic bonding allows casein to interact. Casein micelles contain nanoclusters of approximately 2 nm in the form of colloidal calcium phosphate (CCP; Choi et al., 2011). The presence of a huge amount of three phosphoserine residues and two glutamic acid residues has been identified in casein phosphopeptides (CPP), phosphorylated bioactive peptides produced from casein. This active center was able to bind calcium into soluble and stable complexes, indicating its ability to aid calcium absorption (Gao et al., 2018). Goat milk is considered to have a wide variety of nutritional, physiologic, and functional activities as a major source of proteins and biologically active peptides. The various bioactive peptides, including antihypertensive peptides, lactorphins, casein phosphopeptides, and glycomacropeptides, show different physiologic functions, such as in cardiovascular diseases (CVDs), hypertension, immunomodulatory activity, antimicrobial and antibacterial effects, cancer prevention, and several other health benefits (Bounous et al., 1981). The present study highlights the major health benefit perspective along with the medicinal values of goat milk due to the presence of enlisted major casein fractions.

2 | CASEIN

Casein proteins are phosphoproteins that are classified into two classes, one calcium sensitive and the other noncalcium sensitive, which also prevents and inhibits calcium precipitation in mixtures. Casein is the foundational protein developed into mammals throughout their lineage. The structure of casein comprises amino acids is shown in Figure 1. These amino acids contain chemically reactive groups such as phenolic hydroxy group, ketones, amino group, and hydrazine group with peptide bonding (Cadée et al., 2007).

The bioactive peptides derived from casein have an essential role in biologic functions such as antibacterial, oploid, antioxidant, mineral carrying, and antihypertensive properties. The bioactive peptides released from the casein contain 3–20 amino acids per molecule, according to the researchers during the previous decade (Azhar & Salim, 2017). The deep understanding of this bioactive constituent has increased the demand for this constituent in highly refined form. Casein fractions are physiologically active and a valuable source of several bioactive peptides. However, macromolecular proteins like cow milk and whey protein might trigger allergic reactions in certain people which is less in the case of goat milk (Yangilar, 2013). The types and concentrations of casein fractions are enlisted in Table 1 (de Kruif et al., 2003).

2.1 | Fractions of casein

2.1.1 | α S1-casein

It makes up the main milk protein of goat milk, which functions as a molecular chaperone maintaining a variety of stress target proteins against precipitation (De Wolf, 2003). α S1-casein accounts for about 40% of the casein fraction and has the highest solubility in the presence of calcium among the calcium-sensitive casein. It is a phosphorylated protein that is a structural part of the casein micelle which plays an important function in the production of cheese

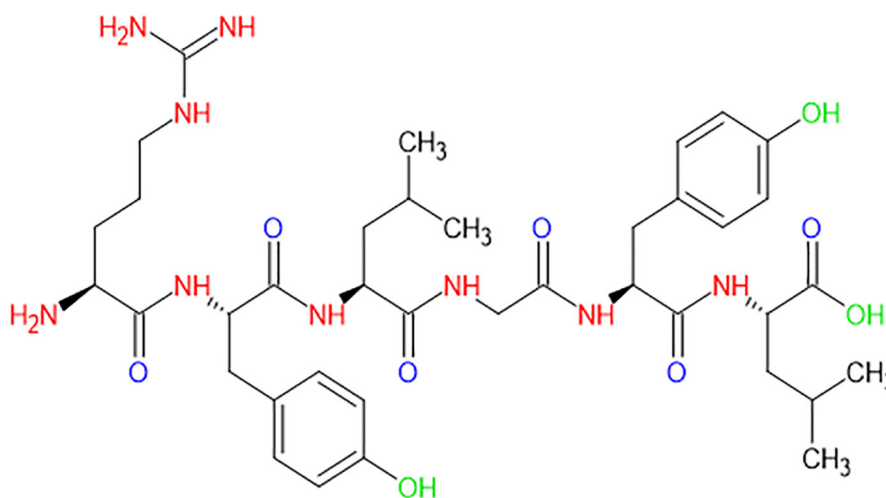


FIGURE 1 The chemical structure of casein protein (Bounous et al., 1981)

TABLE 1 Concentration of goat milk casein and its fractions (de Kruif et al., 2003)

S. no	Fractions of caseins	Concentration of goat milk (%)
1	Total casein	2.33–4.63
2	α -S1 casein	0–28
3	α -S2 casein	10–25
4	β -casein	6–64
5	κ -casein	15–29
6	γ -casein	2–18

curds (Ballabio et al., 2011). CSN1S1 is the gene that codes for α S1-casein. This gene's nucleotide sequence reveals a 15-residue signal sequence that is strongly conserved. The casein α S1 comprises 214 amino acids in goat milk (Eskin & Goff, 2012). α S1-casein is an amphiphilic molecule with an acidic peptide on one end having the ability to construct hydrophobic bonds on the other end (Farrell et al., 2004).

2.1.2 | α S2-casein

α S2-caseins are phosphorylated peptides with a high level of phosphorylation. The entire amino acid sequence of α S2-casein contains 207 amino acid residues, particularly in the C-terminal segment, with a large number of positively charged side chains. Due to three clusters of anion groups made from phosphoryl and glutamyl residues, α S2-casein is the highest hydrophilic of all casein (Fenelon et al., 2019). The gene that codes for α S2-casein is CSN1S2 gene. It has a highly conserved signal sequence, whereas its mature proteins are somewhat different from the α S1-casein. The α S2-casein fraction makes up around 10% of the casein fraction; it is comprised of two major and many minor components with varying amounts of posttranslational phosphorylation and variable degrees of intermolecular disulfide bonding (Huppertz et al., 2018).

2.1.3 | β -casein

β -casein, which comprises about 30% of the total casein protein, is an essential protein component of goat milk. It consists of a single 209 amino acid chain. The molecule has a versatile and flexible, nonintramolecular cross-linked secondary structure and is an amphiphilic phosphoprotein with a hydrophilic region of negative charged N-terminal and a strongly hydrophobic area at the C-terminus (Li et al., 2020). Two primary variants of β -casein A1 and A2, with at least 10 subvariants, can be classified as β -casein families. These variants vary by a specific amino acid at position 67, with the A1-casein type having a histidine amino acid at this position and the A2-casein type having a proline amino acid at this position (Chia et al., 2017).

2.1.4 | κ -casein

κ -casein is a relatively small protein component and contributes around 15%–29% of total casein in goat milk. It is soluble in calcium ions while other casein fractions get precipitated in the presence of calcium ions. κ -casein, which is also known as sialylated glycoprotein, has one phosphate and 14 carboxylic acid groups. It covers mostly the surface of the casein micelle, providing a hydrophilic, charged surface that stabilizes the micelles by intermicellar electrostatic, and steric repulsiveness (Rehan et al., 2019). The main κ -casein component is carbohydrate-free, whereas the minor κ -casein component, which is a glycoprotein, is believed to be glycosylated versions of the main κ -casein (Kawasaki et al., 2011).

3 | GOAT MILK PRODUCTS AND THEIR CHARACTERISTICS

The applications of goat milk have been expanded globally lately. Goat milk has been utilized since ancient times for the production of various kinds of milk products throughout the world. A number of these are produced using goat milk or from blends of goat milk with milk from the dairy animals are produced.

3.1 | Cheese

Cheese is a fermented dairy product that comes in a wide range of flavors. It is likely the most well-known and popular value-added dairy product. A wide variety of cheese products are manufactured globally for imitation and substitution by mixing different flavors, oils/fats, protein, and other components with water to create a smooth, homogenous cheese-like mixture with the help of heat, emulsifying salts, and shearing forces (McSweeney et al., 2017). Some studies suggest that cheese from goat milk has antioxidant and angiotensin-converting enzyme (ACE) inhibitory peptides (Silva et al., 2006). These products are not only good in taste and texture but also provide protein and many health benefits.

3.2 | Yogurt and fermented milk products

Yogurt is a significant fermented dairy item, resulting from symbiotic cultures of *Streptococcus thermophilus* and *Lactobacillus delbrueckii* subsp. *Bulgaricus*. Yogurt has different restorative qualities in human well-being counting treatment of constipation, looseness of the bowels, and infantile gastroenteritis. The yogurt produced using goat milk has further significance in human well-being because goat milk is known for its therapeutic uses and hypoallergenic significance in human nourishment and medication (Gupta et al., 2016). Some studies show the presence of ACE inhibitory peptides in fermented goat milk products (Parmar et al., 2018).

3.3 | Ghee/clarified butterfat

Ghee is a kind of butter refined fat manufactured and used in ancient India. It is utilized as a medicinal substance in Ayurveda and religious rites as well. It is famous in India because of its nutritious characteristics and unique taste and scent. It is prepared from cream, milk, or butter. Ghee can be made by extracting fat from milk, butter, or cream with or without fermentation using direct heat. Ghee is a distinct form of fat distinguished by its distinct flavor, which is a key requirement for its acceptability and is highly impacted by processing methods such as milk, cream, butter, or milk fermentation, as well as heating procedures (Kumar et al., 2018).

3.4 | Ice cream and frozen desserts

Ice cream is an extremely well-known worth-added dairy item made by freezing pasteurized blend with agitation to incorporate air and get a uniform consistency. The innovation for the production of satisfactory quality chocolate enhanced probiotic frozen yogurt was produced using goat's milk utilizing a probiotic bacterial culture including *Lactobacillus acidophilus* LA-5, *Bifidobacterium* (Pal et al., 2017). As ice creams and frozen desserts are the most liked and popular dairy products, it was necessary to develop such items having a less calorific value which will be more beneficial for the consumers and can be consumed by diabetic patients also (Robins et al., 2019).

3.5 | Kefir

Kefir is a fermented drink that is prepared using kefir grains. To prepare traditional kefir, it is generally fermented at ambient temperature overnight. Kefir is a little acidic and foamy product prepared using standardized or decreamed goat milk fat which is first passed through a combination of alcoholic and acidic fermentation of yeast kefir grains and lactic acid bacteria by pasteurizing the milk (Yilmaz-Ersan et al., 2016). It has been identified that kefir from goat milk has antihypertensive and ACE inhibitory activities (Amorim et al., 2019).

3.6 | Cosmetics and tablets

Currently, a large number of personal care products, including creams, cleansers, moisturizers, hair conditioners, and shampoos, aftershave lotions, being marketed in various countries, are being developed from goat milk. Goat milk and its products are beneficial for improving hair care and preventing damage of hair meantime. Goat milk fat contains caprylic acids and capric that improve skin penetrability, fulfilling all criteria to be used in moisturizers and creams as a carrier of other synthetic mixes (Lund & Ahmad, 2021; Sastrawidana et al., 2019). Keeping in view of its medicinal importance research

has already provided the tablet formulation of goat milk using the dry granulation technique (Azfar & Azhar, 2017).

4 | NUTRITIONAL FUNCTIONALITY

Nutrients have now become a significant study subject in food science and nutrition. Goat dairy products are a very intriguing form of diet to investigate with regard to inflammation mainly because of the capacity of milk to encourage the development of the neonatal immune system, prevent bacterial development, and ensure antioxidative and anti-inflammatory defence (Lepage & Van de Perre, 2012). Another aspect that might impact immunologic and inflammatory processes is the capacity of goat milk and products to supply nutrients to the human system that can modify the gut microbiota, a major regulator of immunity (Ceapa et al., 2013; Kau et al., 2011).

5 | HEALTH BENEFITS OF GOAT MILK PROTEINS

5.1 | Antihypertensive agent and CVDs

Hypertension is considered to be the main risk factor associated with CVD and ACE inhibitors plays a significant role in its management. Whereas ACE inhibitory peptides can be found in abundance in milk proteins, Caseins of goat milk, such as two casin peptides, fragment 96–106 of β -casein (ARHPHLSFM) and fragment 56–66 of β -casein (QSLVYPFTGPI), can release AEC-inhibitory peptide (Ibrahim et al., 2017). Studies demonstrated the antihypertensive effect of casokinins and lactokinins, casokinins contain high ACE inhibiting function and antihypertensive effects in casein hydrolysate C12 peptide (Selvaggi et al., 2014). Some other ACE inhibitory peptides found in goat milk, include C7 and C6 peptides, in addition to C12, and may add value to the antihypertensive effect of C12 peptides (Shi & Li, 2021).

5.2 | Antimicrobial activity

Literature shows the presence of antimicrobial agents in goat milk. It has been established that peptides from milk mainly casein have antimicrobial effects. The N-terminal portion is broken quickly when chymosin is applied to an α S1-casein and produces bioactive fragments (2,770 Da, f(1–23) and (residues 194–199)). This cationic peptide has antimicrobial effects on a variety of microorganisms (Recio & Visser, 1999). Cationic peptides are antimicrobial peptides extracted from goat milk proteins. α S2-casein (residues 63–68 and 191–193) that has been degraded by the gastrointestinal enzyme pepsin has been found to have antimicrobial action (El-Sayed & Awad, 2019; Zenebe et al., 2014). A particular method was adopted for the in situ enzymatic hydrolyses of the ion exchange medium for the isolation of antibacterial

peptides from milk proteins and proved their antibacterial property against various strains of microbes (Reyes-Díaz et al., 2018).

5.3 | Immunomodulatory agent

The immunomodulatory effects of goat milk can be linked to components such as peptides and oligosaccharides. It has also been established that goat milk can cause innate and adaptive immunologic responses in the body, which can aid in the defense against inflammation (Zenebe et al., 2014). Some of the peptides which are produced in goat milk are α s1-immunocasein, immunopeptides, and β -CN f193-202 (Park & Nam, 2015). In the innate and adaptive immune response, several types of cells are engaged, Natural Killer cells (NK cells), T-lymphocytes (T cells), and the B-lymphocytes (B cells) act as major stakeholders. A variety of factors impact our immunologic health, with nutrition being the most important factor of the immune response (Madureira et al., 2007).

5.4 | Antioxidant activity

Several milk peptides also regulate oxidative metabolism, which is necessary for cell survival but produces oxidative alterations by releasing free radicals. Antioxidants produced from milk include 5–11 amino acids, including histidine, proline, tyrosine, tryptophan, etc. They may work by scavenging or inhibiting the production of radicals, with free radicals generated by casein peptides having the ability to affect scavenging action as well as inhibit enzymatic and nonenzymatic lipid peroxidation (Khan et al., 2019; Yadav et al., 2016). Casein on treatment with pepsin and trypsin produces peptide fragments α s1-cn f(144–149), β -cn f(98–105), β -cn f(177–183), and β -cn f(169–176), which shows the antioxidant activity (Pihlanto, 2006).

5.5 | Weight management

As it is known that increasing protein intake may aid in weight loss and can significantly alter body composition. Goat milk casein, which is defined as satiating, can be used as natural food ingredients in order to minimize human food intake (Yahyaoui et al., 2003). First, and most significant, evidence to support protein intake and body weight control is the fact that the ingestion of protein eliminates the short-term intake of food (Mittu & Girdhar, 2015). Numerous proteinases and peptidases in the gastrointestinal tract (GIT) cleave goat milk proteins during digestion, resulting in the generation of free amino acids and peptides (Madureira et al., 2007).

5.6 | Anticancer activity

Goat milk has been investigated to be anticarcinogenic in animal models of mammary and colon cancer as well as in vitro human

melanoma, breast cancer, and colorectal cells. The exact method through which conjugated linoleic acid (CLA) suppresses tumor growth is unknown. Furthermore, some lactic acid bacteria isolated from goat milk have been shown to have anticancer properties (Pistrosch et al., 2011). Also, the lactoferrin which is present in goat milk exhibits chemoprotective activity (Zhang et al., 2014).

5.7 | Hypoglycemic activity

Hyperglycemia is mainly caused due to failure of insulin secretion or increased insulin resistance, and insulin secretion is influenced by both the concentration and composition of plasma amino acids. Casein has the ability to change tissue glucose absorption and prevent postprandial blood glucose excursions (Ptiček Siročić et al., 2016). A research study showed that CSN1S2 casein has the ability to regulate the mechanism in the diabetes signaling pathway (Fatchiyah et al., 2020). The casein hydrolysis increases the absorption of amino acids and insulin secretion in comparison with the casein micellar (Pistrosch et al., 2011). As evident insulin stimulates various metabolic processes, such as glucose uptake, triglyceride synthesis, protein synthesis, glycogen synthesis, lipid uptake, and inhibits protein breakdown, gluconeogenesis, and lipolysis, etc., insulin secretion stimulation by goat milk proteins can have a major impact on metabolic effects in insulin-sensitive tissues, especially skeletal muscle anabolism and the management of hypoglycemia (Rangel et al., 2017).

5.8 | Brain development

There have been very few investigations on the effects of goat milk and its by-products on the brain. According to research, goat milk and its products can increase learning and memory performance as well as protect them from memory deterioration, implying that goat milk has the ability to regulate memory processes (Safdar et al., 2020). Sialic acid, which is found in goat milk and colostrum, is also thought to be an important biologic component that aids in cognitive development and immunity in newborns (Kumar et al., 2016).

6 | CONCLUSION

As discussed above, caseins have certain properties that differentiate them significantly from many other proteins. Goat milk caseins are rich in nutrients and also have amazing therapeutic properties. They have been identified as important ingredients in health-promoting functional ingredients, and the milk industry has already commercialized many goat milk proteins and bioactive peptide-based products that can be consumed daily. They are also used for maintaining good health and preventing chronic dietary conditions. Goat milk peptides are typically consumed both as a functional food and as a drug. They have a wide array of pharmacologic and

nutraceutical effects, such as for the treatment of hypertension, thrombosis, cardiovascular disorders, mineral malabsorption, cancer along with immunomodulatory, and hypoglycemia effects. They are also extensively incorporated in diet and weight management plans. This study is expected to be beneficial for the utilization of goat milk and its casein fractions in the development of better medication for the management of aforesaid disorders.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

AUTHORS CONTRIBUTIONS

Shruti Dhasmana: Writing-original draft; Writing-review and editing.

Sanjita Das: Conceptualization. **Shivani Shrivastava:** Writing-review and editing.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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