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# Casein and its Fractions from Goat Milk as Promising Nutraceuticals

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## ABSTRACT

*Goat is one of the major dairy and meat provider. In terms of structure, nutrient content and medicinal properties, goat milk is somewhat different from other milks. The differences in composition are important in determining the technical suitability of goat milk and their products. In recent years there has been increasing attention for the identification and molecular composition of milk proteins and the interest in caprine milk. Casein, which accounts almost 80% of all the proteins is the most significant protein found in 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 αS-casein, β-casein, κ-casein, α-lactalbumin and β-lactoglobulin. The aim of this review is to highlight the importance of goat milk proteins and also focuses on recent findings on their medicinal importance which may be helpful for further research on dairy products with healthy and beneficial properties for humans as a remarkable nutraceutical.*

**Keywords:** Goat Milk, casein, nutraceutical, milk protein

## INTRODUCTION

It is undeniable that goat milk is one of the outstanding sources of food. In all ruminants, the presence of proteins in the goat milk have been recognized for their nutritional and scientific importance. Due to its high amino acid content and greater digestibility, goat's milk proteins are highly nutritious compared to other proteins [1]. Their primary function is to provide amino acids and nitrogen to young children and is an integral component of adult dietary proteins. The physiological importance of milk proteins is to promote the absorption of a number of essential nutrients such as vitamins and trace elements and a group of proteins that play a defensive function [2]. It has positive effects for maintaining health specially in children and senior citizens. According to some authors, it can be taken without causing any harm to people who are allergic to cow milk and this also strengthens goat milk market opportunities [3]. Goat milk consists of a variety of proteins with casein accounting for about 80% of the total, and is arranged as micelles. It contains 4 protein fractions: α1-, α2-, β-, and κ-casein, all of which have different molecular weight. Casein has versatile external structures that are defined as random, unlike most proteins that shows different secondary and tertiary conformational structures [4]. Casein proteins are phosphoproteins which are classified into two classes, one calcium sensitive and the other non-calcium sensitive, which also prevents and inhibits calcium precipitation in mixtures. In milk, Calcium-insensitive is κ-casein, while calcium-sensitive constituents include αS1, αS2, and β [5]. 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 nano-clusters of approximately 2 nanometers in the form of (CCP) colloidal calcium phosphate [6]. Goat milk is considered to have a wide variety of nutritional, physiological and functional activities as a major source of proteins. It is also a valuable source of biologically active peptides. Casein fractions and whey protein-derived peptides, including antihypertensive peptides, lactorphins, casein phosphopeptides, and glycomacropeptides, which show different physiological functions, such as in cardiovascular diseases, hypertension, immunomodulatory activity, antimicrobial and anti-bacterial effects, cancer prevention and several other health benefits [7].

The different types of milk protein present in goat milk and their types are shown in (**Figure 1**).

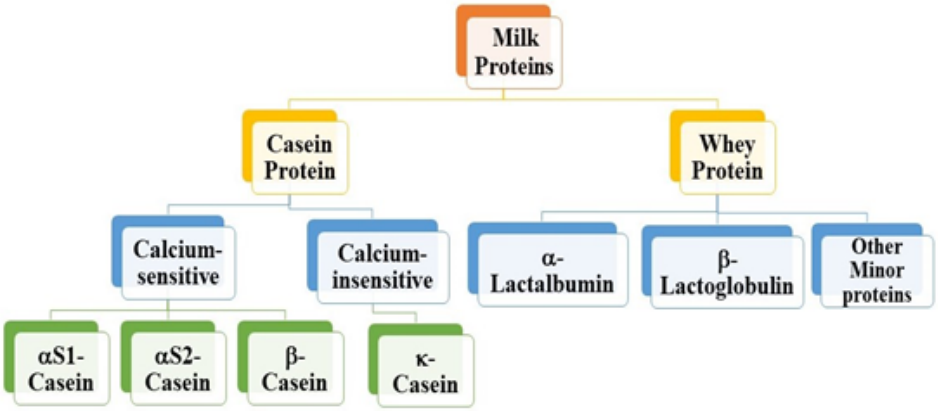


**Figure 1** Types of Milk Protein and their fractions

## MATERIALS AND METHODS

### Casein

Casein is the foundational protein developed into the mammals throughout their lineage. The structure of Casein comprises of amino acids. These amino acids contain chemically reactive groups such as phenolic hydroxy group, ketones, amino group and hydrazine group with peptide bonding [8]. In milk calcium phosphate along with casein forms a large complex which is known as casein micelle. By micelle formation, milk retains high levels of CaP, which support in the creation of mammalian neonates to develop teeth and bones. There are 2 recognized forms of casein Calcium-sensitive casein (α-S, and β) which binds to Ca at high Ca levels, and Calcium-insensitive casein (κ-casein) which normally doesn't really interfere with Ca but help in stabilizing micelle [9]. Casein contains 80% of the total protein in goat milk and in dairy products. It was researched widely because of its commercial benefit and is considered the best food containing protein [10]. Casein form aggregates of several thousand protein molecules along with calcium phosphate with an average diameter of between 150 and 200 nm known as casein micelles. Casein micelles are extremely hydrated with around 3.5 kg of water per kg of protein. So, even though the casein makes up around 2.5% of the overall milk weight, micelles account for about 10% of the amount. Without significant accumulation or disruption of their fundamental structures, the micelles may be mildly heated or cooled. Milk casein micelles are complex macromolecular assembly composite of four distinct forms of casein and phosphates known as Colloidal calcium phosphate. Their key physiological function is to secure transport of insoluble calcium chloride to young mammals [11]. Their composition and consistency is also crucial for milk production. Both structurally and in size, Casein micelles are heterogeneous with much greater polydispersibility than other protein types. The concentration of milk proteins in goat milk is shown in (**Table 1**).

**Table 1** Concentration of goat milk Proteins

| S. No | Protein | Concentration in goat milk (%) |
|---|---|---|
| 1 | Total Casein | 2.33-4.63 |
| 2 | αΣ1 Χαασειν | 0-28.0 |
| 3 | αΣ2 Χαασειν | 10.0-25.0 |
| 4 | β−Χαασειν | 06-64.0 |
| 5 | κ−Χαασειν | 15.0-29.0 |
| 6 | Whey proteins | 0.37-0.70 |
| 7 | α−Λαχταλβυμιν | 17.8-33.3 |
| 8 | β−Λαχτογλοβυλιν | 39.2-72.1 |

### Fractions of casein

**αS1-Casein:** S1- and S2-casein make up the main milk protein, which functions as a molecular chaperone maintaining a variety of stress target proteins against precipitation. αS1-casein accounts for about 40% of the casein fraction and have

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 curds. There are two phosphorylated forms of bovine αS1-casein: 8 and 9 phosphates/mol. CSN1S1 is the gene that codes for αS1-casein. This gene's nucleotide sequence reveals a 15-residue signal sequence that is strongly conserved [12]. The casein αS1 comprises of 214 amino acids in goat milk. αS1-Casein is an amphiphilic molecule with an acidic peptide on one end having the ability to construct hydrophobic bonds on the other end. In alkaline gel which contains urea, five genetic variants named for αS1-casein are A, D, B, C, and E, in order of decreasing electrophoretic mobilities.

**αS2-Casein:** The gene that codes for αS2-casein is CSN1S2 gene. It has a highly conserved signal sequence, while its mature proteins are somewhat different from the αS1-casein. The αS2-casein fraction makes up around 10% of the casein fraction; it is comprised of two major and many minor components with varying amounts of post-translational phosphorylation and variable degrees of intermolecular disulfide bonding. αS2-caseins are phosphorylated peptides with a high level of phosphorylation. The entire amino acid sequence of αS2-casein contains 207 amino acid residues, particularly in the C-terminal segment, with a large number of positively charged side chains. Owing to 3 clusters of anion groups made from phosphoseryl and glutamyl residues, αS2-Casein is the highest hydrophilic of all casein. The C-terminal 47 residues have a net positive charge at the pH of milk, despite being comparatively hydrophobic. The more hydrophilic N-terminal on the other side, contain two anionic clusters and have a net charge of -21 at the predominant pH of milk. The primary structure of αS2-CN can therefore be expressed by 4 fields: a positive hydrophobic domain with a hydrophobic C-terminal, a hydrophilic N-terminal domain with anionic clusters and a central hydrophobic domain with anionic clusters.

**β-Casein:** β-casein is a main component of casein and makes up about 30% of casein. β-casein is likely to play a significant role in caprine micelle stabilisation. They are characterised as "sensitive to calcium" due to their precipitation in the presence of low cation concentrations and play an essential part in determining casein micelle surface properties [13]. The CSN2 gene encodes for β-casein and is considered to be monomorphic. β-casein is especially rich in glutamines. It is well known that there is a single phosphorylation site close to the N-terminus. When compared to αS1 and αS2-casein, these proteins have less phosphorylation sites and a lower degree of phosphorylation. There are approximately 13 genetic variants of β-casein, with the A1 and A2 variants being the most common in dairy cattle. The divergence between the A1 and A2 variants of β-casein is due to the mutation of the A2 allele to the A1 allele at position 67 (Proline A2 and histidine A1), which is significant in the variation of protein content and milk protein composition. BCM-7 is released as a result of the digestion process due to the presence of beta-casein (A1) in milk which causes cleavage of peptide bond, the involvement of A2 allele prevents hydrolysis of peptide bond among residues 66a and 67a, restricting releases of BCM-7.

**κ-Casein:** κ-Casein is the only goat milk casein which determines whole amino acid chain sequence. The chain is 171 instead of 169 amino acids and Val and His are positioned at positions 132 and 133, which are distinct from the bovine equivalents [14]. The gene encoding for κ- Casein is CSN3 gene. The milk protein κ-Casein determines the milk micelle size and their function and allows their development and stabilisation. It has a C-terminal hydrophilic area and varies from other casein in its solubility over a wide range of calcium ion concentrations. In addition to these attributes, the mature κ-Casein does have a labile peptide bond, which when cleaved by chymosin or rennin, yields a soluble hydrophilic glycopeptide which is caseino-macropeptide and an insoluble peptide (para-Casein). The main k-casein component is carbohydrate-free, whereas the minor k-casein component which is a glycoprotein, is believed to be glycosylated versions of the main k-Casein. The Carbohydrate part includes galactose (Gal), N-neuraminic acid (NANA), and N-acetyl galactosamine (NeuNAC), which is either a trisaccharide or a tetra-saccharide. The growing interest in κ-casein stems primarily from its involvement in milk's technical properties, as κ-casein is found on the surface of micelles.

**Whey Protein:** Whey protein is a complex mixture of globular protein representing nearly 20–30% of the total protein. It is made up of α-lactalbumin (α-LA), β-lactoglobulin (β-LG) and other minor proteins. Almost 70 percent of the proteins found in whey contain protein fractions α-LA and β-LG both variants A and B. The word "whey proteins" is being used to characterise the milk protein group that remains soluble in milk serum even after precipitation.

**α-Lactalbumin (α-LA):** It is an acidic, Calcium-binding protein that is essential in a variety of ways. In mammary cell it performs a crucial role, it is among the two lactose synthase components that catalyses the final phase of lactose biosynthesis in the lactating mammary gland. Galactosyltransferase (GT) is another factor in this process that is used to process proteins in numerous secretory cells by transporting galactosyl groups. In order to function α-LA must interact with proteins, low molecular weight substrates, membrane and peptides. Apart from calcium α-LA can bind to a variety of physiologically important cations, including $Mn^{2+}$, $Na^{+}$,$Mg^{2+}$ and $K^{+}$, which compete with $Ca^{2+}$ for the very same binding site, binding of cations to calcium's active site also increases the stability of α-LA.

**Lactoglobulin (β–LG):** These are the main whey protein of the ruminant species. It occurs in the natural pH of bovine milk as a dimer with a molecular weight of 36 kDa. β-Lg was explained and eight gene variants (A, B, C, D, E, F, G and Dr) are

reported to exist. The amino acid sequence and 3-d structure proves that it is a lipocalin, a very diverse family which binds to small hydrophobic ligands, most of which are capable of acting as transporters. It is made up of 162 residues of amino acid. In inside it has a hydrophobic site for binding, and also a weaker one outside of it, which links with different hydrophobic ligand, mostly fatty acid chains and retinol.

## DISCUSSION

### Health Benefits of Goat Milk Proteins

**Hyperglycaemic:** Hyperglycaemia is a metabolic disorder in which there is failure of insulin secretion or increased insulin resistance. Insulin secretion is influenced by both the concentration and composition of plasma AAs therefore, casein and whey consumption can stimulate insulin secretion. Whey and casein have the ability to change tissue glucose absorption and prevent postprandial blood glucose excursions. The casein hydrolysis increases the absorption of AAs and insulin secretion in comparison with the casein micellar. However, Whey protein ingestion allows faster insulin secretion than micellar casein. Insulin stimulates glucose uptake, triglyceride synthesis, protein synthesis, glycogen synthesis, lipid uptake, and inhibits protein breakdown, gluconeogenesis, and lipolysis, along with many other direct and indirect effects on carbohydrate, protein and fat metabolism. As a result, insulin secretion stimulation by milk proteins can have a major impact on metabolic effects in insulin-sensitive tissues, especially skeletal muscle anabolism.

**Antimicrobial activity:** Milk contains many antimicrobial agents. 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 αS1-casein. This cationic peptide has antimicrobial effects on a variety of micro – organisms. Cationic peptides are antimicrobial peptides extracted from milk proteins. A particular method was established for the in situ enzymatic hydrolysis of the ion exchange medium for the isolation of antibacterial peptides from milk proteins.

**Anti-carcinogenic effects:** Many evidences show that milk derived peptides, especially whey protein have anticarcinogenic activity which protects against some cancers. The whey proteins contain a variety of refined proteins binding to iron, B12 vitamin, retinol, riboflavin, folic acid, and vitamin D. Lactoferrin-binding of iron may prevent this possible pro-carcinogenicity for intestinal harm, while vitamin-B binding protein increases the bioavailability of its vitamins and protects against intestinal microorganism usages [50]. Also, whey proteins are capable of enhancing cell glutathione levels as well as improving hormonal and cell-mediated immune responses that can be helpful in cancer prevention.

**Antihypertensive agent and cardiovascular diseases:** Hypertension is considered to be the main risk factor associated with cardiovascular disease (CVD). Angiotensin converting enzyme (ACE) plays a significant role in control of blood pressure. ACE inhibitory peptides can be found in abundance in milk proteins, including casein and whey proteins. Studies demonstrated the antihypertensive effect of casokinins and lactokinins, Casokinins contain high ACE inhibiting function and antihypertensive effects in casein hydrolysate C12 Peptide. Some other ACE inhibitory peptides, which include C7 and C6 peptide, in addition to C12, and may add value to the antihypertensive effect of C12 peptide [15].

**Immunomodulatory agent:** The proper working of the immune system is vital for the maintaining health. Depending on the dose given, experimental conditions, and the peptide's role in the body, they inhibit or stimulate some of the immune system functions. When peptide binds to a specific receptor, the immune responses are promoted downstream and result in either specific or nonspecific immune responses which are suppressed or stimulated. In the case of whey proteins, α-La hydrolysate was found to improve the humoral immune response, which affects the regulation of activity of both the B and T lymphocytes.

**Antithrombic agent:** Casoplatelins are peptide obtained from the caseino-glycomacropeptide C-terminal of κ-casein. Casoplatelins prevent ADP-activated platelets from aggregating and human fibrinogen c-chain binding to a particular target sites on the platelet surface. Antithrombotic peptides of k-casein region 103-116 can both inhibit the process of platelet aggregation and inhibit human fibrinogen ϒ-chain binding to the platelet receptor region. Thus, antithrombic action can occur in these peptides.

**Weight management:** As it is known that increasing protein intake may aid in weight loss and can significantly alter body composition. Milk proteins, which are defined as satiating, can be used as natural food ingredients in order to minimise human food intake [16]. 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. Numerous proteinases and peptidases in the gastrointestinal tract (GIT) cleave milk proteins during digestion, resulting in the generation of free amino acids and peptides. Specific peptide fragments, also referred to as BAP, that have a positive impact on weight management.

## CONCLUSION

As discussed above, casein have certain chemical and physical properties that differentiate them significantly from many

other proteins, they exhibit little or no secondary/tertiary structures. They are phosphorylated and configured in standard micelle mineralized structures. αS1 and αS2 casein are the most phosphorylated of all casein proteins and are responsible for many of its common structural and behavioural properties and also for their insolubility at comparatively low calcium levels. Goat milk proteins are rich in nutrients and also have amazing therapeutic properties. They've been identified as important ingredients in health-promoting functional ingredients, and the milk industry has already commercialised a number of proteins and peptide-based products that can be eaten on a daily basis. They have a wide array of pharmacological and nutraceutical effects, such as for the treatment of hypertension, thrombosis, cardiovascular disorders, mineral malabsorption, immunomodulatory effects, hyperglycaemic agent, in cancer and also in diet and weight management plans.

## DECLARATIONS

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**Conflicts of Interest**

The author declares that there is no conflict of interest.

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