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**Review Article**

# Production, characterization and bio functionalities of bioactive peptides from non-bovine species of milk: A review

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## Abstract

**The exploration of bioactive peptides derived from non-bovine milk has garnered considerable interest due to their potential health-promoting properties and functional applications. This review provides an overview of production, characterization, and biofunctionalities of bioactive peptides obtained from various non-bovine milk sources, including but not limited to goat, sheep, buffalo, and camel milk. The production methods involve enzymatic hydrolysis or fermentation of milk proteins using proteolytic enzymes as trypsin, pepsin, and chymosin, among others or by using different cultures. Subsequently, various separation and purification techniques are employed to isolate the bioactive peptides, including ultrafiltration, chromatography and membrane separation. The structures of the bioactive peptides are identified and clarified through the use of characterization techniques such as nuclear magnetic resonance (NMR) spectroscopy, high-performance liquid chromatography (HPLC) and mass spectrometry. These peptides exhibit diverse biological activities, including antioxidant, antimicrobial, antihypertensive, immunomodulatory and opioid-like properties, among others. Furthermore, the bioactive peptides derived from non-bovine milk have demonstrated potential health benefits, such as reducing blood pressure, enhancing immune function, promoting gut health and exerting anti-inflammatory effects. Additionally, they find applications in functional foods, nutraceuticals and pharmaceutical formulations aimed at improving human health and wellbeing.**

**Keywords:** Bioactive peptides, Biofunctionalities, Fermentation, Lactic acid bacteria, Non-bovine milk

## Highlights

- Bioactive peptides from non-bovine milk produced through enzymatic hydrolysis or fermentation.
- Peptides from non-bovine milk have antibacterial, immunomodulatory, antioxidant, and antihypertensive properties.
- Bioactive peptides from non-bovine milk exhibit improved digestion, immunological response, and cardiovascular health.

## INTRODUCTION

A continuous and sustainable supply of high-quality food products, such as milk, to the populace is essential to maintaining national health and food security in any nation. Improving the production of high-quality livestock products, such as milk and dairy products, is essential to the global growth of animal husbandry. Enhancing the yield of superior livestock products, such as milk and dairy products, is a critical undertaking for the global advancement of animal husbandry. The most significant species for milk production are cattle. The National Dairy Development Board (NDDB), India provided statistics showing that camel milk makes up approximately 0.2% of the world's annual supply, whereas cow milk accounts for 85%, buffalo milk for 11%, goat milk for 3.4% and sheep milk for 1.4% (NDDB, 2021).

Global milk production in 2020 was 886.9 million tonnes, about 2.5 more than that of produced in 1961 (344,184,775 tonnes) and up 11% from the reported figure of 798,476,318 tonnes in 2016. Even with these impressive numbers, the world's total production of goat, sheep and camel milk was just 2.3%, 1.2%, and 0.4%, respectively. Despite making up less than 5% of the world's milk supply, these species are very important to rural economies in places like Southeast Asia and the Mediterranean because they are mostly used to make processed dairy products (Chia *et al*.,

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2017). Even while donkey, deer, and mare milk are not commonly traded or consumed, they have significant cultural value in some communities (Wang *et al*., 2017).

Due to its high protein, fat and key mineral content, milk is regarded as nearly a complete diet (Bhattarai, 2012). In addition to providing essential nutrients, milk from both cow and non-bovine species offers a sufficient source of bioactive components such as immunoglobulins (IgG, IgM, and IgA), lactoferrin (LF), growth factors, enzymes, and hormones (Mehra *et al*., 2021). The investigation of non-dairy milk derived from non-bovine species has attracted interest since these sources can meet different dietary requirements and include unique bioactive elements. Milk from non-bovine animals such as sheep, goats, donkeys, camels, yaks and others, including zebu, horses, mares and reindeer, play essential roles as daily sources of protein, phosphate and calcium in situations when cow milk is unavailable, or meat consumption is restricted. The diversity of non-bovine milk is remarkable, as it contains proteins with distinct structures and amino acid compositions. Goat milk, for example, has different casein proteins than cow's milk, which influences how well it coagulates. Variations in flavor, consistency, and nutritional qualities can be attributed to differences in the types and quantities of fat present in non-bovine milk; goat and sheep milk, for example, have higher concentrations of particular short-chain fatty acids. In addition, non-dairy milk sources have different nutritional profiles. Among these, camel milk is notable for having a higher vitamin C concentration than other types of milk. Moreover, non-bovine milk often has less lactose than cow's milk, which may help those who are lactose intolerant tolerate them better.

The enzymatic breakdown of milk proteins leads to release of active fragments. Scientists are able to produce specific peptides with particular biofunctionalities by carefully examining the intricate mechanisms driving this enzymatic breakdown. This methodical approach not only enhances understanding of the basic biochemical processes but also opens the door to the development of novel functional food ingredients and medicinal treatments (Capriotti *et al*., 2016).

The research of bioactive peptides derived from non-bovine milk has gained much attention in recent years due to its abundance of potential health benefits and real-world applications. Non-bovine animal milk, such as those from sheep, goats, camels, donkeys, and other mammals, have become more significant because they are rich sources of bioactive peptides. These peptides exhibit a variety of functions, including antibacterial, antioxidant, antihypertensive and immunomodulatory qualities. As such, they are interesting candidates for use in a variety of medicinal and nutritional contexts (NAAS, 2021).

Characterization of bioactive peptides is important for comprehending structure-activity relationships, revealing their adaptability to various settings and evaluating their accessibility to biological systems. By using advanced analytical techniques such as nuclear magnetic resonance, mass spectrometry and chromatography, scientists analyzed the complex molecular structure of these peptides. The insights gained from these characterization efforts enable the enhancement of production methods and ensure bioactivity retention in various applications. Mammals ingest milk as their first food, which provides the necessary nutrients for growth and supports the vital physiological processes for neonates. Beyond its well-known nutritional benefits, there is a wide range of biological substances in milk that support bone health, immune system modulation and gut microbiome balance, all essential for general health and wellbeing. Non-bovine milk has been consumed for thousands of years. The Arabian Peninsula, the Mediterranean region, and many European and Asian nations all eat large amounts of goat and sheep milk. Mongolia and the Arabian Peninsula are major consumers of camel milk. In Kazakhstan, Mongolia and Northern China, mare milk is drunk. Russia and northern Europe both drink deer milk. Even though cows are the main source of milk and cow husbandry is still prevalent, the usage of milk from other animals in conventional dairy products has decreased. However, the higher quality of some dairy products made from the milk of non-bovine species and also the possible health benefits have been made clear by cultural understanding and modern communication.

Many factors, including animal-related ones like age, species, lactation stage, parity, breed, health and overall genetic background and, as well as practices of farming like management style, number of offspring and diet, as well as environmental factors like altitude, climate and soil, all have an impact on the composition of milk. Different species' milk compositions and physicochemical characteristics have developed to

meet the dietary requirements of their progeny in terms of nutrients, energy intake, digestibility, and other factors. Milk's physicochemical characteristics, which determine its functional properties, must be taken into account when evaluating it for human consumption. These characteristics also affect later technological factors such as yield, structure, and stability, as well as sensory features and the overall milk value and its derivatives. For example, milk of sheep is widely used in many special cheeses, such as the well-known Spanish Manchego. Non-bovine milk contains large amounts of many different nutrients, such as lipids, oligosaccharides, superior quality protein, vitamins and minerals, all of which have positive effects on health and nutrition. Breed, age of the animal, seasonal fluctuations, feed quality and quantity and environmental conditions are some of the factors that affect the kinds, quantities and compositions of these nutrients (Claeys *et al*., 2014). Small fat globules, for example, high quantities of lactadherin-like protein, phospholipids, saturated fatty acids, essential fatty acids, unsaturated fatty acids and low cholesterol are characteristics of camel milk (Bakry *et al*., 2021). Among non-bovine milk alternatives, camel milk is distinguished by its exceptional nutritional value, great digestion, and health-promoting qualities like antibacterial, anti-inflammatory, and anti-hyperlipidemia effects.

Around the world, non-bovine milk are mostly found in particular geographic areas and ecosystems (Barlowska *et al*., 2011). But in East Asia (China, Japan, and Korea), Southeast Asia, the Indian subcontinent, the Middle East and Sub-Saharan Africa, the production of non-bovine milk, which employs around 150 million milk producers, not only provides vital nutrition and food security but also constitutes a substantial source of household income (Tsakalidou and Papadimitriou, 2016). Even though cow's milk continues to be the main source of milk produced worldwide, between 2000 and 2019, the percentage growth rate of milk produced by minor mammalian species—goats (48.91%), camels (70.87%), and sheep (25.35%)—surpassed the growth rate of cow's milk (46.31%). Additionally, there are numerous nutritional and health advantages linked to non-bovine milk from camels, goats, sheep, and their dairy products. Many medical and therapeutic benefits of camel milk (CM) have been documented, such as its ability to decrease cholesterol, inhibit ACE (Angiotensin-converting enzyme), prevent diabetes, and prevent cancer (Gammoh *et al*., 2020). Due to its lower amounts of $\alpha_{s1}$-casein and β-lactoglobulin, goat milk (GM) has attracted a lot of attention since it has a better nutritional profile, is easier to digest and is less allergic than cow milk (Kiełczewska *et al*., 2020). Furthermore, the fat from goat milk, which has smaller diameter globules (3.2–3.6 μm) and greater concentrations of short- to medium-chain fatty acids (MCFA), is easier to digest and can help manage low mineral bone density, metabolic diseases, anemia and cholesterol imbalances (Kiełczewska *et al*., 2020). A growing number of dairy products, including cheese, yogurt and ice cream are made from sheep milk, which is important economically for areas around the Mediterranean Sea, sub-Saharan Africa, the Middle East and East and Southeast Asia (Balthazar *et al*., 2017). In order to determine these important yet underutilized nutrient sources, suitability for food formulations and potential for export, it is necessary to give them top priority. Due to its alleged health benefits and the desire to include non-bovine milk in baby formulas, because it is less allergenic than cow milk, milk of non-bovine species has become the concentration of a lot of research lately (Nudda *et al*., 2020; Prosser, 2021). The increasing variety of commercialized non-bovine milk products is proof that these non-bovine milk and their derivatives have attracted the attention of processing businesses in recent years.

This review aims to comprehensively explore the current state of knowledge regarding the production, characterization and biofunctionalities of bioactive peptides derived from non-bovine milk. This review discusses a thorough understanding of how these peptides derived from non-bovine milk may be used to improve human health and wellbeing.

## Composition of milk from different mammals

Different species' milk has different vital components as described in Table 1, such as proteins, lipids, carbohydrates and minerals, that are needed to meet the nutritional demands of neonates. Furthermore, milk provides a range of physiologically active substances, including immunoglobulins, antibacterial peptides, antimicrobial proteins, oligosaccharides, growth factors, hormones, and more, that support many physiological processes for the neonate.

The total amount and makeup of milk produced by

**Table 1. Composition of milk from different mammals (approximate concentration and range)**

| Species | Energy (kcal/kg) | Ash (g/kg) | Lactose (g/kg) | Fat (g/kg) | Protein (g/kg) | Total solid on dry matter (g/kg) |
|---|---|---|---|---|---|---|
| Cow | 590-701 | 7 (6-9) | 48 (36-55) | 38 (25-60) | 34 (29-50) | 127 (105-137) |
| Buffalo | 710-1180 | 8 (7-9) | 48 (44-52) | 72 (61-96) | 42 (7-50) | 169 (145-184) |
| Goat | 580-740 | 8 (7-11) | 44 (39-63) | 43 (25-78) | 36 (25-51) | 132 (119-163) |
| Sheep | 930-1080 | 9 (7-10) | 48 (37-55) | 74 (51-90) | 57 (50-65) | 178 (152-193) |
| Camel | 440-790 | 8 (6-10) | 49 (31-58) | 43 (26-67) | 36 (30-50) | 130 (108-145) |
| Yak | 870-910 | 8 (4-10) | 50 (33-62) | 64 (42-108) | 49 (33-64) | 167 (92-282) |
| Donkey | 320-510 | 4 (4-5) | 66 (58-74) | 14 (1-18) | 17 (14-22) | 95 (85-117) |
| Red deer | - | 1.04-1.18 | 2.6-6.2 | 6.6-19.7 | 5.9-10.6 | 20.0-30.5 |
| Horse | - | 0.3-0.5 | 5.6-7.2 | 0.3-4.2 | 1.4-3.2 | 9.3-11.6 |
| Human | 430-1150 | 2 (2-3) | 71 (60-90) | 35 (22-52) | 12 (8-15) | 125 |

(Claeys *et al*., 2014; Alichanidis *et al*., 2016; Crowley *et al*., 2017)

a breed of animal can vary on a daily basis depending on a variety of factors, including individual traits, lactation stage, age, parity, body weight, feeding schedule, seasonal changes, environmental factors (temperature, humidity), milking intervals, gestation and length of dry periods and health status, particularly mastitis cases. The nutritional content of milk is largely determined by its composition, which also affects many of the physicochemical and sensory properties of milk products and its suitability as a main ingredient in dairy and food products. There is a noticeable difference in the milk components of ruminants and non-ruminants. Higher total solids content and high protein, fat and ash content are typical characteristics of ruminant milk. On the other side, donkey milk often contains a larger percentage of lactose.

The protein known as casein separates from milk at approximately 4.6 pH, whereas serum proteins stay soluble in this environment. According to Eigel *et al.* (1984), this casein fraction is varied and includes $\alpha_{s1}$-, $\alpha_{s2}$-, β-, and κ-casein. Genetics determines the various primary structure forms in which each of these variants exists; the main differences are in the residues of amino acids. Furthermore, caseins experience phosphorylation of seryl residues as a result of post-translational modification. Because of this phosphorylation, different forms of casein have variable capacities for binding calcium and calcium phosphate. Milk also contains small quantities of γ-caseins, which result from the partial breakdown of β-casein due to plasmin. κ-casein exhibits a distinct behavior from β-caseins and $\alpha_{s1}$- as well as $\alpha_{s2}$-which typically exhibit strong binding to $Ca^{2+}$ and other polyvalent cations, eventually becoming insoluble when [$Ca^{2+}$] surpasses 6 mmol/L at 20°C. κ-casein's solubility remains unaffected by $Ca^{2+}$. Consequently, by forming spherical aggregates known as casein micelles, κ-casein can stabilize $Ca^{2+}$-sensitive caseins up to ten times their mass. These micelles vary significantly in size across different species.

Several nitrogenous molecules, known as non-protein nitrogen (NPN) are found in milk serum, but in comparatively small amounts. This group includes, among other things, ammonia, urea, creatine, free amino acids, short peptides, creatinine, orotic acid and uric acid. The NPN fraction also contains nucleotides and nucleosides, which have distinct physiological functions, especially in the early stages of life. A number of variables, including the animal's species and dietary habits, herd, breed, lactation stage and season, might affect the amount of NPN in milk. According to DePeters and Ferguson (1992), approximately 5% of the entire nitrogen content in cow's milk is made up of the NPN component, whereas in ruminant milk, it might be anywhere between 3% and 5%. Generally speaking, the NPN concentration of cow milk is lower than that of sheep and goat milk (Tripaldi *et al*., 1998; Park and Haenlein, 2007). Table 2 shows the different protein profiles of different non-bovine species.

Urea is the primary component of milk and accounts for around half of its total nitrogen content. Free amino acids (FAA), which are easier to absorb than amino acids linked to proteins, make up roughly ten to twenty per cent of NPN in bovine milk, 9-10.5% in milk from goats and 16% in sheep milk (Tripaldi *et al*., 1998; Park and Haenlein, 2007). Remarkably, the majority of other amino acids are found in very small amounts in these FAA, which are mainly made up of non-essential amino acids including alanine, glycine and glutamic acid. All forms of milk experience substantial changes in the content of free amino acids (FAA) during lactation, albeit the effects differ for each specific

**Table 2. Comparative profile of protein composition from non-bovine species' milk**

| Protein fraction | Goat | Camel | Yak | Sheep | Donkey | Red deer | Horse | Human |
|---|---|---|---|---|---|---|---|---|
| Lactoferrin (g/kg) | 0.02-0.3 | 0.2-0.9 | 0.2-0.7 | 0.7-0.9 | 0.3 | - | - | - |
| NPN (% total N) | 7-12 | 6-11 | 6 | 6-9 | 11-25 | - | - | - |
| Total casein (g/kg) | 23-38 | 22-48 | 21-40 | 41-66 | 6-10 | ~ 57-84 | 9.4-13.6 | 2.4-4.2 |
| αs 1 - Casein (% total) | 4.5-34 | 21 | 13-32 | 7-40 | - | - | 2.4 | 0.77 |
| αs 2 - Casein (% total) | 9-25 | 9 | 9-18 | 12-23 | - | - | 0.2 | - |
| β - Casein (% total) | 24-64 | 65 | 37-51 | 34-62 | - | - | 10.66 | 3.87 |
| κ - Casein (% total) | 10-19 | 3-5 | 12-21 | 7-23 | - | - | 0.24 | 0.14 |
| γ- Casein (% total) | 5-6 | - | - | - | - | - | - | - |
| Total Whey Protein (g/kg) | 3-12 | 6-10 | 11 | 8-16 | 5-9 | ~ 11-15 | 7.4-9.1 | 6.2-8.3 |
| α - Lactalbumin (% total WP) | 17-50 | 45-53 | 7-20 | 13-45 | 23-33 | - | 2.37 | 1.9-3.4 |
| β - Lactoglobulin (% total WP) | 34-77 | - | 50-86 | 28-72 | 30-57 | - | 2.55 | - |
| Immunoglobulins (g/kg) | 0.15-0.5 | 0.55-0.8 | 0.1-0.4 | 0.5-0.7 | 1.3 | - | - | - |
| Serum albumin (% total WP) | 5-22 | 30-41 | 7-15 | 6 | 6-7 | - | - | - |

(Claeys *et al*., 2014; Alichanidis *et al*., 2016; Crowley *et al*., 2017)

**Table 3. Amino acid content (mg/kg) of the milk of non-bovine species**

| Amino Acid | Goat | Sheep | Camel | Yak | Donkey | Horse | Human |
|---|---|---|---|---|---|---|---|
| Alanine | 1.60-7.73 | 5.25 | 2.19-9.61 | 1.40 | 2.19 | 3.2 | 4.0 |
| Arginine | 1.91-13.49 | 3.65 | 0.34-1.22 | 1.60 | 0.34 | 5.2 | 4.0 |
| Aspartic acid | 1.34-5.19 | 1.86 | 0.93-1.34 | 3.30 | 1.34 | 10.4 | 8.3 |
| Cystine | - | 1.80 | 0.01 | 0.40 | 0.01 | 0.6 | 1.7 |
| Glutamic acid | 25.00-43.51 | 28.37 | 17.15-19.26 | 10.50 | 17.15 | 20.1 | 17.8 |
| Glutamine | 10.07-27.42 | 10.66 | 5.55 | - | - | - | - |
| Glycine | 21.83-32.41 | 11.63 | 0.30-1.38 | 1.20 | 1.38 | 1.9 | 2.6 |
| Histidine | 2.23-2.33 | 1.24 | 0.62-0.88 | 1.20 | 0.88 | 2.4 | 2.3 |
| Isoleucine | 0.26-2.15 | 0.26 | 0.80-1.18 | 2.40 | 0.80 | 3.8 | 5.8 |
| Leucine | 0.26-2.67 | 0.46 | 0.66-3.17 | 4.30 | 3.17 | 9.7 | 10.1 |
| Lysine | 3.21-5.48 | 2.63 | 2.77-3.58 | 3.80 | 3.58 | 8.0 | 6.2 |
| Methionine | 1.43 | 0.30 | 0-0.78 | 1.10 | 0.78 | 1.5 | 1.8 |
| Phenylalanine | 2.00 | 0.25 | 1.93 | 2.20 | 1.93 | 4.7 | 4.4 |
| Phosphoserine | 5.55-8.77 | - | 2.59-11.29 | - | 2.59 | - | - |
| Proline | 1.61-1.79 | 0 | 1.15-2.99 | 4.60 | 1.15 | 8.4 | 8.6 |
| Serine | 0-9.45 | 0.32 | 0-1.32 | 2.30 | 1.32 | 6.2 | 5.1 |
| Tryptophane | 1.77 | - | - | - | - | 1.2 | 1.8 |
| Threonine | 0-3.31 | 5.00 | 1.55-3.60 | 1.90 | 3.60 | 4.3 | 4.6 |
| Tyrosine | 1.45-4.50 | 1.45 | 0-1.13 | 2.20 | 1.13 | 4.3 | 4.7 |
| Valine | 5.79-6.32 | 1.29 | 0.23-2.60 | 2.60 | 2.60 | 4.1 | 6.0 |

(Barlowska *et al*., 2011; Alichanidis *et al*., 2016)

amino acid. When it comes to FAA, glutamic acid is usually the most common kind found in the milk of different mammals (Table 3). Especially interesting is taurine, which is found in greater amounts in colostrum and decreases with the duration of nursing. According to Park and Haenlein (2007), taurine performs a number of tasks, including growth regulation, membrane stabilization, and bile acid production. Taurine is regarded as a "conditionally essential" amino acid in infant feeding due to its important roles (Rassin *et al*.,

1978). Cow milk has comparatively low levels of taurine (around 6 mg/kg), which is why many baby formulae supplement with it. In contrast, goat milk has higher levels of taurine. Compared to cow milk, sheep milk has more taurine.

**Bioactive peptides (BAPs)**

The word "peptide" comes from the Greek word "peptos," which means "digested". Bioactive peptides are defined as specific protein fragments that have positive impacts on physiological processes and medical diseases, possibly influencing general health and wellbeing. It is well known that milk proteins are a substantial source of peptides with a wide range of physiological advantages. There are several ways to produce these bioactive peptides, including: (i) hydrolysis of digestive enzymes, (ii) proteases derived from plants or microorganisms that undergo enzymatic cleavage during food, (iii) processing or industrial processes that involve exposure to heat, acids, or alkalis (Kitts and Weiler, 2003).

The intrinsic sequence and content of amino acids influence the bioactive peptides' functioning. Between two and twenty amino acid residues can make up these active sequences, and many of the peptides have multiple functions. Because lysozyme, lactoferrin, growth factors, and hormones are released by the mammary gland in their active forms, non-bovine milk naturally has a range of bioactivity (Meisel and FitzGerald, 2003). Phosphopeptides were initially the first bioactive peptides to be identified; they were detected in casein hydrolysates (Mellander, 1950). However, the real breakthrough in the study of bioactive peptides began with the discovery and characterization of peptides that resembled opioids and were obtained from casein digest. These peptides are known as casomorphins. Following this, a plethora of bioactive peptides with a variety of biological activities, including immunomodulatory, antihypertensive, antibacterial, antioxidant, antithrombotic, and antiulcerogenic qualities, have been extracted and described from milk proteins. Interestingly, a few of these peptides have several functions.

**Biofunctionalities of non-bovine milk**

When it comes to human milk, non-bovine milk is a good substitute, especially for those who are allergic to cow's milk. This has led to research into substitute mammalian sources. Camels are an essential part of many communities, particularly those in arid areas. They are able to withstand extreme weather conditions and play a major role in transportation, sport and the production of milk and meat, which helps ensure human livelihoods and food security. According to Yassin *et al.* (2015), camel milk is widely recognized for its antibacterial, immunomodulatory, anti-carcinogenic and anti-diabetic qualities. Due to its composition resembling that of human milk and its possible biological benefits, including anti-inflammatory, anti-aging, antibacterial and anti-allergic actions, donkey milk has gained popularity as a natural nutritional and medicinal product (Li *et al*., 2022). Goat milk has become well-liked due to its good digestion property and special qualities like anti-inflammatory, antimicrobial, bifidogenic and antiatherogenic effects (Sonu and Basavaprabhu, 2020). Its growing acceptance is also aided by the fact that its chemical makeup is similar to that of milk the cow.

**Goat milk:** According to Worldostats (2023), there are an estimated 1.2 billion goats in the world. This number has been increasing over time, highlighting the importance of goats for both the environment and the economy in a variety of geographical areas. India's goat milk population was estimated by the National Dairy Development Board (NDDB) to be 148.9 million in 2019 (nddb.coop). According to Ceballos *et al.* (2009), goat milk normally has 30 to 35 g/L of total protein, of which 80% is casein and 20% is whey. It is also acknowledged to contain fewer allergens than cow's milk and to be a possible superior replacement for human milk (Kapila *et al*., 2013). Goat milk's acid-induced coagulate has a more porous structure and thinner protein strands, which may be advantageous since it allows pepsin to diffuse more readily and aids in the digestion of casein proteins (Thevenot *et al*., 2017). Because goat milk has 89% less $\alpha_{s1}$ casein than cow's milk and higher levels of the less allergic $\alpha_{S2}$ casein, it is known to have a lower allergenicity (Leong *et al*., 2019). Additionally, the smaller fat globules in goat's milk inhibit mucus production, which spares humans from mounting a defensive immune response. Goat milk has greater concentrations of polyamines than human or cow milk, which is important for gastrointestinal enzyme maturation, cellular function and preventing allergies in young children (Kumar and Sharma, 2016). Goat milk has been shown to possess antibacterial effects due to the presence of lactoperoxidase (LPO), lactoferrin and medium-chain triglycerides in its composition. According to Koksal *et al.* (2016), compared to cow milk, which has 1.4 units/mL of LPO, goat milk has 3.45 units/mL. LPO is an essential milk enzyme that functions as an oxidoreductase and affects bacteria by oxidizing

sulfhydryl groups. This oxidation obstructs the movement of peptides, amino acids, potassium ions and glucose by the bacterial cytoplasmic membrane. Furthermore, goat milk contains high levels of capric (260 mg/100 g), caprylic (100 mg/100 g) and caproic (90 mg/100 g) fatty acids (Kompan and Komprej, 2012). Because goat milk contains more ACE-inhibitory peptides than other milk, it is well known for having antiatherogenic properties. It is also prized for having anti-infectious and bifidogenic qualities. Goat milk is an important source of oligosaccharides because of its high content, which usually ranges from 250-300 mg/L and is noticeably higher than that of other types of milk (Sousa *et al*., 2019). Additionally, goat milk has 13.3 mg/L of selenium (Se) as opposed to 0.009 mg/L in cow milk (Barrionuevo *et al*., 2003). According to Alferez *et al.* (2003), this selenium is essential for clotting function and serves as an antioxidant.

**Camel milk:** The term "White Gold of the Desert" is frequently used to describe camel milk (Wernery, 2006). There are approximately 39 million camels in the globe (FAO, 2022). According to nddb.coop, there were 0.3 million camels in India in 2019. According to Yasmin *et al.* (2020), camel milk has a protein level that ranges from 2.15% to 4.9%, with caseins making up about 80% of the protein. $\alpha_{S1}$-, $\alpha_{S2}$-, β-, and κ-casein are among them; their respective mean concentrations range from 2.40-10.30 g/L, 0.30-3.90 g/L, 5.50-29.00 g/L, and 0.10-2.40 g/L. Camel milk is similar to human milk because it lacks β-Lg and is notably abundant in α-La (0.30-2.90 g/L; 50%), followed by serum albumin (35%). Camel milk is well known for its hypoglycemic effect and is well acknowledged to have therapeutic benefits. The concentration of insulin-like proteins in camel milk is 52 micro units/mL, about 3 times higher than in bovine's milk (Shori, 2015). It is believed that these proteins imitate how insulin interacts with its receptor. Furthermore, compared to insulin-like proteins from other milk sources, they are more rapidly absorbed into circulation due to their encapsulation within lipid vesicles, which also shows resistance to proteolytic digestion (Shori, 2015). Numerous defensive proteins, including immunoglobulins, lysozyme, lactoferrin and lactoperoxidase, are prevalent in camel milk and have antibacterial and therapeutic qualities. An inherent immune system enzyme called lysozyme targets gram-positive bacteria; It is there in amounts of 288 mg/100 mL (Gul *et al*., 2015). Moreover, camel milk has a high concentration of lactoferrin, which has been shown to have powerful anti-inflammatory and antimicrobial capabilities, including antibacterial inhibition, antifungal activity and antiviral qualities (Gruden and Poklar Ulrih, 2021). Lactoferrin levels in camel milk can reach 220 mg/L. Many methods, including membrane permeabilization, biofilm disaggregation, toxin reduction, adhesion inhibition, and apoptosis induction, are used by lactoferrin to achieve its effects (Xu *et al*., 2010; Zarzosa-Moreno *et al*., 2020).

As camel milk doesn't contain β-lactoglobulin, it also has an anti-allergic effect. Even though camel milk contains β-casein, the protein's structure differs greatly from that of cow's milk (Jilo and Tegegne, 2016). Additionally, camel milk contains tiny molecules that are easily absorbed and processed by the human body due to its low lactose level (Ehlayel *et al*., 2011). Because camel milk contains antioxidants, it has the ability to control genes that either promote or inhibit the formation of cancer cells or decrease the genes that promote them. It has been demonstrated that camel milk lactoferrin inhibits DNA damage and has antioxidant and anticancer effects on colorectal cancer cells (Habib *et al*., 2013). Vitamin C is abundant in camel milk and contributes to the antioxidant qualities that protect skin cells. There are several camel populations in Africa and Asia; Kenya is the world's top producer of camel milk, followed by Somalia and Mali. These populations are made up of two species of camels: the two-humped Bactrian camels (*Camelus bactrianus*), which are usually found in mountainous areas, and the one-humped Arabian camels, also called dromedaries (*Camelus dromedarius*), which live in the plains.

**Sheep milk:** The number of sheep worldwide peaked in 2021 at 1.266 billion, a little bit more than the 1.263 billion recorded in 2020. According to nddb.coop, there were 74.3 million sheep in India in 2019. Global sheep milk production climbed to 10.618.551 tons in 2020 from 10.364.548 tons in 2018 (FAOSTAT, 2024). Out of about 180 different varieties of sheep, about 40 are known for their dairy output, and some breeds even go outside of their native areas. Milk supply and the makeup of milk ingredients are highly influenced by the breed of sheep that is chosen (Skoufos *et al*., 2017; Thomas and Haenlein, 2017; Wendorff and Haenlein, 2017). As per Alichanidis *et al.* (2016), the gross composition of milk from sheep is as follows on average per 100 g: total solids 17.80%, fat 7.40%, protein 5.70%, lactose 4.80%, and ash 0.90%. Although sheep milk is not often drunk, its ideal composition makes it possible to produce a wide range of cheeses with distinct flavors and textures, as well as firm yoghurt with stronger aromas. Compared to cow milk, which

has protein contents of 24-28 g/kg, sheep milk has 4.5-7.2%, or about 4.1-6.6% of caseins and 8.0-16.0% of whey proteins. Compared to cow's milk, sheep milk mostly contains β-casein, which makes up, on average, 42 per cent of the total casein content (ranging from 31.00 to 58.00%). On the other side, in sheep milk, the average amount of $\alpha_{s1}$-casein is about 26%., with a range of 7 to 40%. Less is known about the variations in κ-casein between sheep and cow milk; roughly 10% (ranging from 7 to 23%) and 12% (ranging from 9 to 20%), respectively. Comparably, the percentage of $\alpha_{s2}$-casein in sheep is roughly 14% (varying from 12 to 23 per cent) and in cow milk it is about 11% (varying from 7 to 15%) (Alichanidis *et al*., 2016). Compared to bovine milk, sheep milk, including fermented sheep milk products, has a greater casein concentration, meaning it is greater in nutrients.

**Donkey milk:** Similarities between donkey milk and human milk include low fat content, lower protein levels (particularly in casein and calcium), a higher percentage of lysozyme and lactoferrin than in human milk and a higher lactose concentration. In India, the number of donkeys fell by around 61.23%, from 0.32 million in 2012 to 0.12 million in 2019 (nddb.coop). Whey proteins make up 60% of the milk from donkeys, whereas caseins make up 40%. It is noteworthy that the amount of α-lactalbumin it contains is almost exactly the same as that of human milk and it has a high concentration of β-lactoglobulin, which is not present in human milk (Mati *et al*., 2017). Due to the presence of several bioactive compounds, including Omega 3 fatty acids, vitamin C, lactoperoxidase, lactoferrin, lysozyme, and bioactive peptides, donkey milk is well known for its anti-inflammatory and antioxidant qualities (Martini *et al*., 2021). The protein fraction of donkey's milk, which is low in casein and has a low casein/whey protein ratio (usually average at 1.3 and varying from 0.66 to 1.33 across individual milk samples throughout lactation), is responsible for the milk's low allergenicity (Tidona *et al*., 2011). This ratio is thought to be essential for reducing sensitivity to the cow milk protein fraction and, thus, lowering the likelihood that it may cause allergies. Furthermore, the decreased concentrations of $\alpha_{s2}$-casein and kappa-casein in donkey milk can potentially enhance its decreased hypoallergenic properties. In contrast to other species, donkey milk has a high lactose content, which acts as a substrate for the development of gut microbiota with favorable health traits (Coppola *et al*., 2002). The main reason why donkey milk is antibacterial is because it contains antimicrobial chemicals. The main sources of its antibacterial activity are lactoferrin and lysozyme (Lyz), at a concentration of 4000 mg/L. According to Brumini *et al.* (2016), lysozymes function by cleaving the peptidoglycan's N-acetyl glucosamine and N-acetyl muramic acid link, resulting in fragments with different molecular weights. Amazingly, even after being exposed to the gastrointestinal enzymes of humans, roughly 75% of the lysozyme in donkey's milk is still present. This retention is especially noteworthy because it is thought that intact lysozyme confers antibacterial properties and modifies gut flora in the stool of newborns fed breast milk.

Renowned for its anti-aging qualities, donkey milk is mainly ascribed to its abundant mix of minerals, milk proteins, bioactive enzymes, vital fats and different development elements including vitamin D and riboflavin. These ingredients give the skin organic sustenance, giving the illusion of tone. Furthermore, lysozyme and lactoferrin, two naturally occurring antibacterial substances found in donkey milk, prevent pathogenic bacterial growth on the skin and reduce the risk of infections in the skin (Madhusudan *et al*., 2017). Additionally, donkey milk is essential for the metabolism of glucose. Whey protein level in donkey milk is higher than in conventional milk, which may help prevent and treat diabetes (Herrouin *et al*., 2000). Donkey milk protects against the development of insulin resistance by bolstering antioxidant defense systems (Li *et al*., 2022). Research suggests that donkey milk's lactose, whey protein and bioactive peptides are involved in controlling the insulin response to glucose. Notably, donkey milk contains lysozyme and lactoferrin, which may help prevent and treat diabetes.

**Yak milk:** Yak milk's thick viscosity is attributed to its high protein and lipid content, which is why it's sometimes referred to as natural concentrated milk. Yak is highly valued for making butter and traditional cheese, and it is usually raised at high altitudes with extremely low air pressure (550 hPa) and extremely cold (down to -40°C). According to Zhang *et al.* (2014), the composition of milk normally consists of 16.9–17.7% solids, 4.9-5.3% protein, 5.5-7.2% fat, 4.5-5.0% lactose and 0.8-0.9% minerals. On the other hand, between 2012 and 2019, the yak population decreased by about 24.90%.

**Bio-functionalities of bioactive peptide from non-bovine milk**

**Antidiabetic activity:** A major global health concern, diabetes mellitus (DM) comprises a broad spectrum of

disorders marked by elevated blood glucose levels. The two most prevalent forms of diabetes in people are type I diabetes (insulin-dependent) and type II (insulin-independent) (Lee and Jeon, 2013). Particularly serious is type II diabetes (T2DM), which is prompted by either inadequate production of insulin or opposed to its effects. T2DM is a severe form of metabolic syndrome that affects a large number of people each year all over the world. According to Cho *et al.* (2018), 451,000,000 individuals aged 18 to 99 worldwide were estimated to have diabetes of type II in 2017.

According to projections, this number will rise to 693 million by 2045. Postprandial blood sugar variations are moderated by the release of insulin, which is activated by GLP-1 or glucagon-like peptide in response to glucose levels. The digestion of carbohydrates is initiated by the action of α-amylase and α-glucosidase. After being digested by pancreatic α-amylase, dietary carbohydrates like starch are absorbed in the gut with the aid of intestinal α-glucosidases (Gachons and Breslin, 2016). As α-glucosidase inhibitors can slow down the body's absorption of food carbs, they can be used as a tactical tool to reduce postprandial hyperglycemia in people with type II diabetes (Fig. 1) (Krentz and Bailey, 2005). Peptides such as IPVDM and APLER, which have antidiabetic effects, control blood glucose levels by blocking the actions of the enzymes α-amylase and α-glucosidase, which convert carbohydrates into glucose in the blood (Nong and Hsu, 2021). A study by Shukla *et al.* (2023) showed that camel milk fermented with *L. plantarum* KGL3A showed inhibition activity (%) of α-amylase and α-glucosidase of 55.64 and 31.54 at the 12-hour mark and 80.94% and 64.45%, respectively, at the 48-hour mark. Shukla *et al.* (2023) assessed the inhibitory effects of α-amylase and α-glucosidase on a range of fractions, such as the water-soluble extract (10 kDa retentate) and its corresponding 3 kDa permeate and retentate (3 kDa retentate) and 10 kDa permeate and retentate (10 kDa retentate) fractions. The results showed that all fractions' α-amylase and α-glucosidase activity were significantly inhibited. With an α-amylase inhibitory activity of 82.10%, the 3 kDa permeate showed the greatest level, closely followed by the 10 kDa permeate at 80.19%. In a similar vein, the 10 kDa permeate showed marginally lower but still considerable inhibition at 60.35%, while the 3 kDa permeate showed the highest α-glucosidase inhibitory activity at 64.98%. The retentate fractions exhibited significant inhibitory effects on both enzymes, albeit having significantly less activity than their corresponding permeates. According to Shukla *et al.* (2023), these results underline the fermented camel milk fractions' potential as sources of bioactive chemicals with antidiabetic qualities, calling for more research in this area for possible therapeutic uses. The peptide sequences of EVESAEVPTENK and EDMPSQR that KGL3A releases further demonstrated the anti-diabetic properties of camel milk.

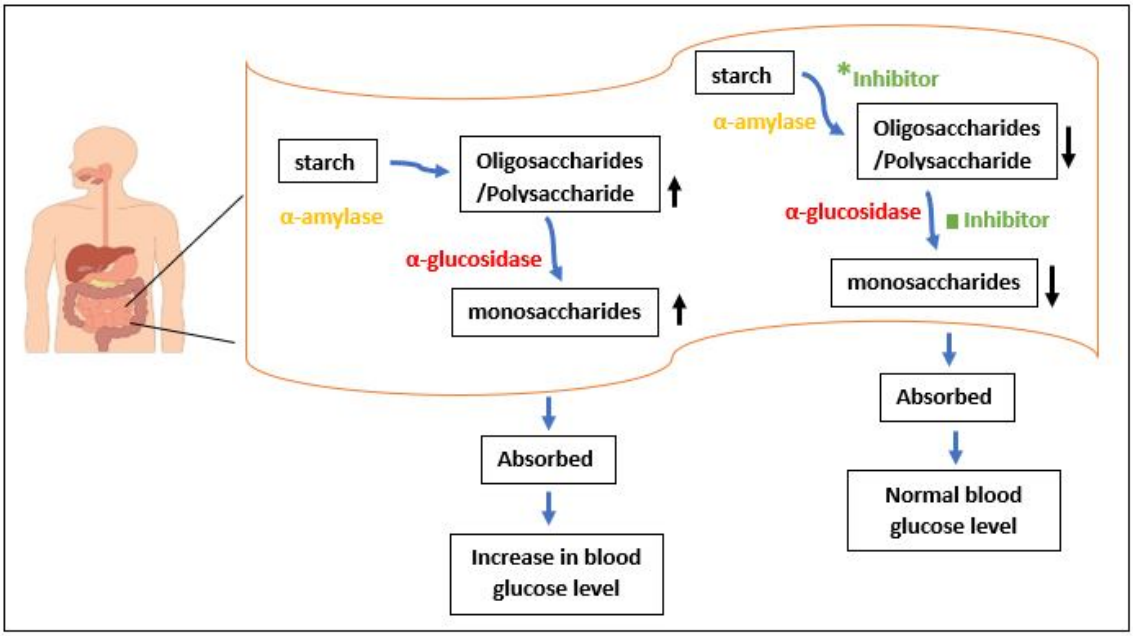


**Fig. 1. Role of α-amylase, α-glucosidase in starch digestion and metabolism (Naveen and Baskaran, 2018)**

Peptides obtained from different fractions of fermented milk protein of camel with *Lactobacillus plantarum* KGL3A were discovered in a study by Shukla *et al.* (2023). The source of these peptides was various milk proteins, such as β-casein, $\alpha_{s1}$-casein and $\alpha_{s2}$-casein. Peptides MMSLVSLLLVGILFPTIQAK, EDMPSQR, ILDLAVVSPIQFR, and YLEELHR were shown to be present in $\alpha_{s1}$-casein. The peptides EVESAEVPTENK, EYGLFQINNK, MKFFIFTCLLA VVLAK, and TDVMPQWW were identified from $\alpha_{s2}$-casein. Furthermore, the β-casein peptides VALALAREK and VMDVPKTKETIIPK were discovered. These results provide information about the peptide profile produced by *L. plantarum* KGL3A-induced fermentation of camel milk, possibly revealing bioactive peptides having beneficial effects on health.

Gliptins, also referred to as dipeptidyl-peptidase-4 (DPP-4) inhibitors, are a class of oral anti-hyperglycemic drugs. Their mechanism of action involves hindering the deactivation of "incretin" hormones, including glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). Through a number of processes, such as increased glucose-dependent insulin secretion, slowed stomach emptying, and decreased postprandial glucagon levels and food intake, this activity affects the management of blood sugar (Fig. 2). Zhang *et al.* (2015) treated goat milk casein with trypsin and chymotrypsin to reveal new inhibitory peptides for DPP-IV: SPTVMFPPQSVL, MHQPPQPL, INNQFL PYPY and VMFPPQSVL.

In a study by Manaer *et al.* (2015), four yeast strains (*Kluyveromyces marxianus*, *Pichia membranifaciens*, *Candida ethanolica*, *Issatchenkia orientalis*) and ten lactic acid bacteria (*Lactobacillus pentosus*, *Lactobacillus paracasei* subsp. *tolerans*, *Lactobacillus par*, *Lactobacillus mucosae*, *Lactobacillus rhamnosus*, *Lactobacillus hilgardii*, *Lactobacillus harbinensis*, *Lactococcus lactis*, *Lactobacillus helveticus*, *Lactobacillus plantarum*) were added to fresh camel milk to produce Shubat. After that, this combination was incubated for 12 hours at 37°C. Next, its hypoglycemic effects were evaluated in rat models of type 2 diabetes (T2D) established by a diet high in glucose and fat together with a low dosage of streptozotocin.

Six groups of varied sizes were randomly selected from among the rats. Group 1 (normal control, NC) was treated with saline. The diabetic rats in Group 2 (diabetic control, DM) received pasteurized camel milk as a treatment. Sitagliptin was given to Group 3 (the positive control) at a dosage of 30 mg/kg. At concentrations of $(6.97\times(10)^6)$ lactic acid bacteria+$(2.20\times(10)^4)$ yeasts CFU/mL, $(6.97\times(10)^7)$ lactic acid bacteria+$(2.20\times(10)^5)$ yeasts CFU/mL, and $(6.97\times(10)^8)$ lactic acid bacteria+$(2.20\times(10)^6)$ yeasts CFU/mL, respectively, shubat was given to Groups 4, 5, and 6 (representing low, medium and high doses). For a period of four weeks, each therapy was given orally once daily at a dosage of 10 mL/kg. Rats were given a high-glucose, high-fat diet for six weeks, and

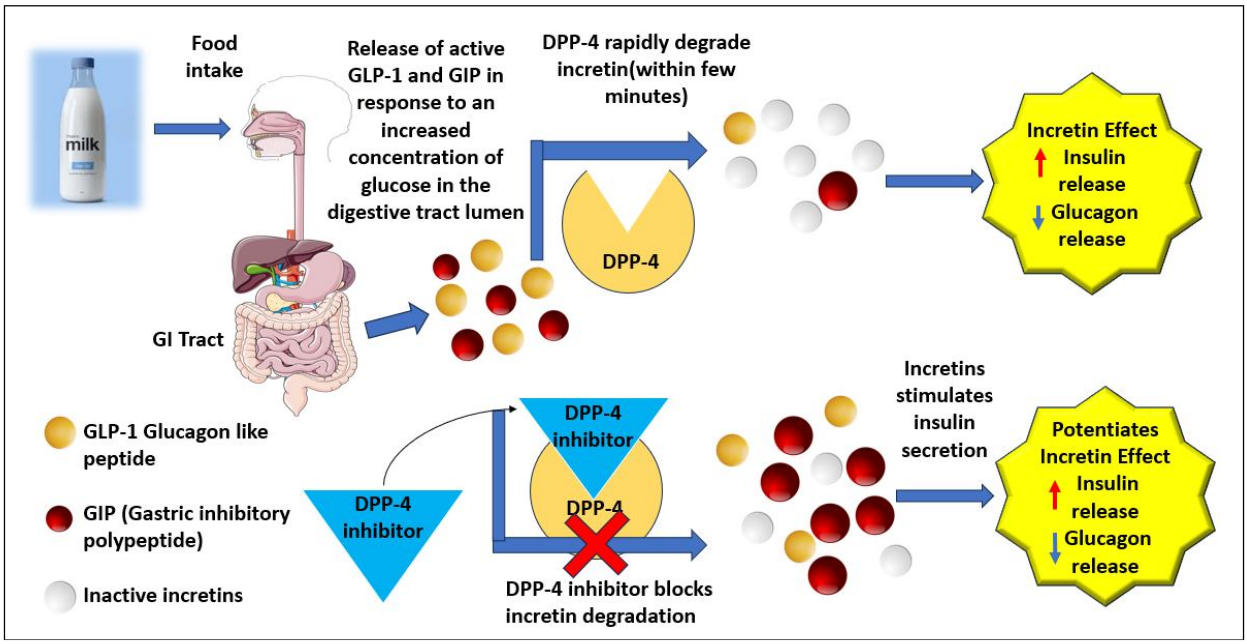


**Fig. 2. Mechanism of DPP-4 inhibitors' action (Makrilakis, 2019)**

**Table 4. Shubat's Effects on FBG (mmol/L) in type 2 diabetes rats**

| Group's | Number | Treatment before | Week 1 | Week 2 | Week 3 | Week 4 | GLP-1 (pmol/L) |
|---|---|---|---|---|---|---|---|
| NC | 10 | 5.1±0.6 | 5.0±0.4 | 4.8±0.5 | 5.0±0.5 | 5.0±0.5 | 28.57±6.92 |
| DM | 11 | 22.6±5.0 | 23.5±5.0 | 24.4±4.8 | 25.3±5.7 | 26.7±6.0 | 16.18±5.61 |
| Sitagliptin | 11 | 22.5±5.5 | 22.0±6.2 | 20.2±6.1 | 18.8±6.5 | 17.8±6.3 | 48.99±6.15 |
| Shubat low | 9 | 22.1±3.5 | 23.8±4.4 | 24.7±5.2 | 25.1±6.0 | 25.9±6.3 | 22.57±5.23 |
| Shubat medium | 11 | 22.2±4.9 | 23.7±6.2 | 22.1±6.5 | 21.4±6.7 | 20.6±7.1 | 25.36±7.07 |
| Shubat high | 11 | 22.2±6.5 | 21.9±5.7 | 20.1±6.4 | 18.9±6.6 | 18.3±7.0 | 32.29±11.77 |

(Manaer *et al*., 2015)

then they received an intraperitoneal injection of streptozotocin (STZ, 30 mg/kg) to cause type 2 diabetes. Rats classified as having type 2 diabetes (T2D) had fasting blood glucose levels higher than 11.1 mmol/L. As shown in Table 4 the results of that study indicate that shubat significantly reduces blood sugar levels in T2D rats.

**Angiotensin converting enzyme (ACE) inhibitory activity:** According to Majumder and Wu (2014), ACE regulates blood pressure by its function in the renin-angiotensin system. It does this by transforming angiotensin I into angiotensin II, a strong vasoconstrictor that increases blood pressure and salt levels by stimulating the production of aldosterone. Pharmacological interventions aimed at ACE have been effective in lowering hypertension. However, food-based ACE inhibitors are seen to be a safer option than prescription medications because they might not cause some of the negative side effects of medicine, like coughing and edema (Beltrami *et al*., 2006). Angiotensin II binds to the AT1 and Ang II type 2 (AT2) receptors, two G-protein coupled receptors, to produce its physiological effects. These receptors serve several biological functions. (i) Growth, fibrosis, inflammation, and vasoconstriction are all associated with the AT1 receptor; (ii) On the other hand, vasodilation and apoptosis are associated with the AT2 receptor. Therefore, ACE inhibition to reduce Ang II synthesis and AT1 receptor blocking with receptor antagonists are standard blood pressure-controlling techniques (Contreras *et al*., 2003).

Six sequences (FFIFTCLLAVVLAK, TDVMP QWW, IDSGLYLG, TAGWNIPM, APGSDPR, FLR) with inhibitory properties against Angiotensin-Converting Enzyme were found in fermented camel milk M11 (*Lacticaseibacillus paracasei)* + WBS2A (*Saccharomyces cerevisiae)*) in a study by Shukla *et al.* (2022). TDVMPQWW was identified as one of these sequences in the investigation including fermented camel milk, camel milk fermented with *Lacticaseibacillus paracasei* (M11), and camel milk fermented with *Lactiplantibacillus plantarum* (KGL3A). Solanki *et al.* (2017) did a study wherein they examined the amino acid sequences of peptides that demonstrate ACE-inhibitory activity in fermented camel milk fractions. Sequences linked to *L. fermentum* (LBF), such as CISSSTPPYDLNRFK, and sequences associated with *Lactobacillus delbrueckii* (09), such as MDTIEPVSVACIS and LQYGPLADILGE, were found within the 3 kDa permeate fraction. Further sequences linked to *L. fermentum* (LBF) including DAMMNQAVRE, QSAPGNEAIPP, and AGFVLKGYTKTSQ, as well as sequences attributed to *L. delbrueckii* (09), including ATVQGGIMYRMP, GFKDLLKGAAKALVKTVLF, and ATVQGGIAY RMP, were also found by analysis of the 10 kDa permeate fraction. The results highlight the wide range of peptide sequences produced throughout the fermentation process, indicating possible uses of fermented camel milk fractions in ACE-inhibitory activity and associated health advantages. Parmar *et al.* (2020) discovered and analyzed the peptides that inhibit ACE that were taken out of goat milk that had fermented. The study looked at peptides that were extracted from different fractions based on molecular weight and culture. For example, the 3 kDa permeate contained peptides from the *Limosilactobacillus fermentum* strain M5, identified as LARPKHPI NHRGLSPE, whereas the 10 kDa fraction contained TEEEKNRLNFLKKISQY. Furthermore, it was found that the 3 kDa and 10 kDa permeate fractions contained peptides from the *Lacticaseibacillus paracasei* strain M16. The sequence was detected as ENSGKTTMPLW in the 3 kDa fraction and PEEIKITVDDKHYQKALNEI in the 10 kDa fraction. The results demonstrate that fermented goat milk may be a source of bioactive peptides with ACE inhibitory characteristics, which may have uses in the promotion of cardiovascular health.

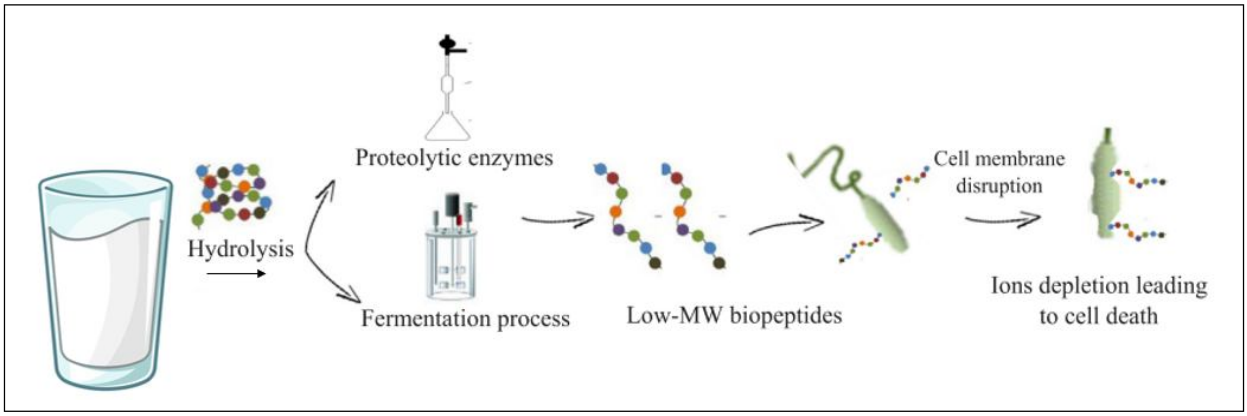


**Fig. 3. The antimicrobial mechanism (Izadi *et al*., 2019)**

**Antimicrobial activity:** Low-molecular-weight proteins with antiviral, antifungal, and antibacterial properties are known as AMPs. In essence, the AMPs are encoded into different food proteins, and when they are released, their main antibacterial action is to break down bacterial cell membranes (Fig. 3) (Singh *et al*., 2023). Hydrolysates with antibacterial action against *Corynebacterium fimi*, *Bacillus cereus, Aspergillus fumigatus*, and *Penicillium expansum* were produced by the protease hydrolysis of sheep caseinate by Bacillus species. Four antimicrobial peptides, V D Q H Q K A M K P W T Q P K T N A I P Y V R Y L, LKKISQYYQKFAWPQYL, PYVRYL, and LKKISQ, were obtained from the hydrolysis of $\alpha_{s2}$-casein in sheep milk (Correa *et al*., 2011).

Yak milk was hydrolyzed by pepsin, and the resultant hydrolysates had antibacterial qualities. Two peptides (KVISMI and RVMFKWA) inside these hydrolysates were found to be in charge of the antibacterial activity. According to Pei *et al.* (2017), these peptides showed efficacy against a range of bacteria, including *Salmonella paratyphi*, *E. Coli, Listeria innocua*, and *Enterobacter cloacae*, in addition to several *fungi*.

Using an *in silico* simulated gastrointestinal digestive enzyme cocktail comprising of pepsin (pH 1.3, EC 3.4.23.1), chymotrypsin A (EC 3.4.21.1) and trypsin (EC 3.4.21.4), the proteins present in goat milk were hydrolyzed. Thirteen peptides that met the requirements of all four antimicrobial algorithms (SVM, DA, RF, and ANN) were identified as possible antimicrobial peptides from a pool of eighty-three projected AMPs. AIPPK, QQR, IAK, TVPAK, β-casein (GPVR, AVPQR, AIAR, GVPK, SQPK, PVPQK, IH, VPK), $\alpha_{s2}$-casein (SIR, AIH, TQPK), and $\alpha_{s1}$-casein (SGK, IQK) are among the milk proteins from which these 13 peptides were generated. All of them were shown to be cationic (Sansi *et al*., 2022).

**Antioxidant activity:** An excessive amount of free radicals can damage cells, which can lead to a number of illnesses like cancer, diabetes, arthritis, and atherosclerosis. It is widely acknowledged that a number of peptides, including Tyr, Met, His, Lys and Trp, are antioxidants. Bioactive peptides exhibit antioxidant activity due to their ability to scavenge radicals, inhibit lipid peroxidation, and chelate metal ions (Singh *et al*., 2014). Recently, Hati *et al.* (2018) also state that the ability of *Lactobacillus* culture to neutralize free radicals is what determines how effective it is in antioxidative activity. According to Ahmad *et al.* (2017), reactive oxygen species (ROS) are very reactive chemicals that can originate from external sources or endogenously as a byproduct of physiological processes. Endogenous ROS are generated as metabolic waste products by oxidation processes that are aided by several intracellular enzymes. According to Dharmaraja (2017), these endogenous ROS are essential for intercellular signaling, cellular defense and reproduction. However, when organisms are unable to balance out an excessive build-up of ROS with antioxidant defenses, oxidative stress can result (Antolovich *et al*., 2002). The use of artificial antioxidants in the food business is closely restricted due to their negative health consequences. This has led to the investigation of natural antioxidative bioactive peptides as potential substitutes for synthetic compounds (Reddy *et al*., 2005). To evaluate the antioxidant capacity of peptides, two approaches are typically used. Using hydrogen atom transfer (HAT), a competitive reaction is used to measure an antioxidant's capacity to scavenge reactive oxygen species (ROS) (Sohaib *et al*., 2017). The second approach, which compares the antioxidant's efficacy against a particular oxidant, is based on electron transfer (Zou *et al*., 2016). Several antioxidant peptide sequences, including

SCQDQPTTLAR, VLPVPQQMVPYPQR, IYTFPQP QSL, LLNEK, and ILELAVVS, were found in camel milk fermented with *Lacticaseibacillus casei* (NK9) (Patel *et al*., 2021).

The antioxidant properties of camel milk fermented with *Lactobacillus plantarum* KGL3A were investigated at different times in a study by Patel *et al.* (2021). Antioxidant activity was tracked during the research at 0, 12, 24 and 48 hours after fermentation. The findings showed that antioxidant efficiency increased gradually over time. When fermentation first started (0 hours in advance), the antioxidant activity was found to be 4.91%. After 12 hours, there was a noteworthy increase to 19.53%, suggesting a noteworthy enhancement in antioxidant capacity. Antioxidant activity continued to rise in accordance with this trend, peaking at 62.19% after 48 hours and rising to 32.57% after 24 hours. These results imply that adding *L. plantarum* KGL3A to camel milk fermentation improves its antioxidant properties, which may improve the milk's overall nutritional profile and health-promoting features. The antioxidant peptides KPVAIR, LAVP, LAVPIN, NEPTE, and VSSTTEQK are obtained from camel milk that has been fermented with *Lactobacillus plantarum* KGL3A.

In a study by Haskito *et al.* (2020), three LAB strains—*Lactophilus, Bacillus bulgaricus,* and *Lactobacillus acidophilus*—were used as a starter culture to produce yogurt. The first step in creating a mother culture was to mix 70 mL of pasteurized goat milk with 0.35 g of Yogourmet® starter powder, which contains *Lactobacillus bulgaricus*, *Streptomyces thermophilus*, and *Lactobacillus acidophilus*. The mixture was then incubated at 45°C for four hours, or until the pH reached 4.4 or 4.5. Five males Rattus norvegicus Wistar strain animals, weighing between 150 and 200 g and aged between 8 and 12 weeks, made up the animal model used. The antioxidant activity evaluation results for goat milk yogurt showed a 4.52 µg/mL concentration. It has been discovered that consuming goat milk yogurt at 900 mg/kg body weight can lessen the effects of oxidative stress on the lungs, especially when responding to 2,3,7,8-tetrachlorodibenzo para dioxin (TCDD) exposure. Therefore, goat milk yogurt's casein may be a useful source of antioxidants to protect against oxidative stress brought on by TCDD.

**Anticancer activity:** Bioactive peptides exhibit a variety of mechanisms of action in cancerous cells, such as pore formation via the barrel-stave and toroidal models, increased calcium ion influx, altered lysosomal membranes, increased proteasome activity, caspase cascade-mediated initiation of the mitochondrial apoptotic pathway, immune pathway modulation, and suppression of DNA replication-related genes while upsetting the cell cycle (Teerasak *et al*., 2016). Three kinds of therapeutic peptides are distinguished by the ways in which they enter cells: 1) Cell-penetrating peptides, which can cross the plasma membrane and transfer small molecules, oligonucleotides, or proteins-a process known as internalization; 2) Pore-forming peptides, which attach to negatively charged molecules on cancer cell surfaces and cause apoptosis or necrosis; and 3) Tumor-targeting peptides, which attach to receptors on cancer cell surfaces to promote cellular internalization.

Antimicrobial peptides have been the source of ACP (anticancer peptides) and have been modified accordingly (Chiangjong *et al*., 2020). ACPs usually have between 12 and 50 residues (Harris *et al*., 2013). Leuprolide, goserelin, and octreotide are the three peptide medications that are specifically used in cancer treatment. That being said, there isn't a unanimous agreement about how ACPs work. These peptides first interact electrostatically with the tumor cells. They can penetrate the membrane and cause its disintegration and micellization if they are concentrated enough on its surface. As a result, pore structures grow and spread across the membrane, which eventually causes cell death. Within 10 ns following the peptide contact, membrane perturbations can be seen (Li *et al*., 2013). Peptide residues and the phosphate groups of bilayer lipids typically establish hydrogen bonds during the first stage of interaction, which is then followed by membrane lysis (Wimley *et al*., 2010; Nguyen *et al*., 2011; Saravanan and Mohammed Al-Kassim, 2015; Loboda *et al*., 2018; Naafs, 2018). A short host defense-like peptide that specifically targets cancer cells was found by Papo *et al*. (2006). This peptide binds to exposed phosphatidylserine (PS) on cell surfaces, causing depolarization of the cytoplasmic membrane and consequent cell death.

In order to be effective anticancer drugs, cytotoxic peptides, like AMPs (Fig. 4.A.), need to selectively target and damage the membranes of cancer cells while leaving healthy cells unharmed. Understanding that cancer cells have unique membrane properties that render them vulnerable to these kinds of cytotoxic peptides is essential to achieving this goal. Cancer cell membranes differ significantly from those of non-cancerous cells in a number of ways. Firstly, they have a more neutral total membrane charge, which can be

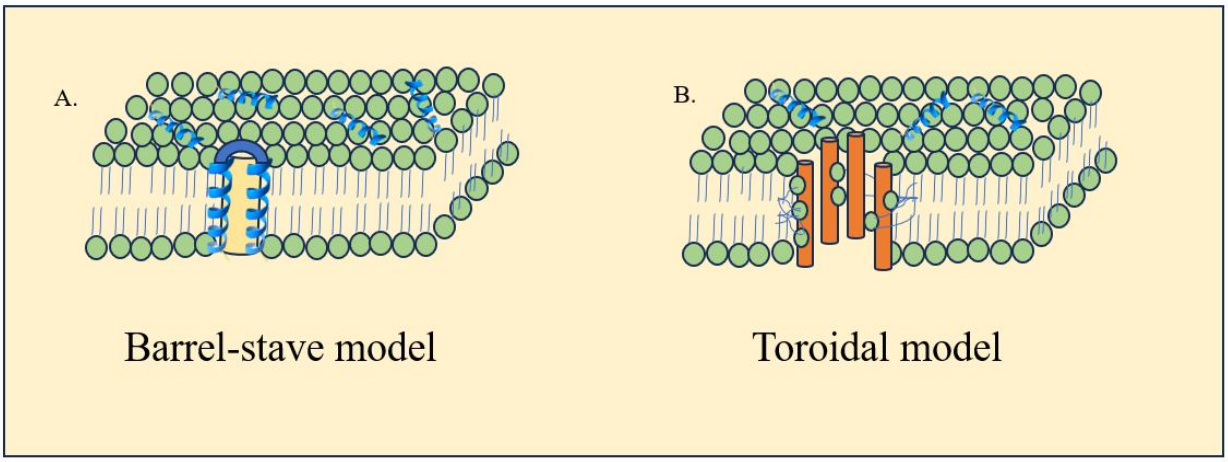


**Fig. 4. Schematic of pore types (Fig. 4.A. Barrel-stave model and Fig. 4.B. Toroidal model) (Loboda *et al*., 2018)**

attributed to the presence of zwitterionic phospholipids such as sphingomyelin and phosphatidylcholine (PC), while phosphatidylserine (PS) and phosphatidylethanolamine (PE) are primarily found in the inner leaflet of the plasma membrane (Saravanan and Mohammed Al-Kassim, 2015). In contrast, a loss of membrane symmetry in cancer cells exposes anionic phosphatidylserine (PS) on the plasma membrane's outer leaflet, increasing the membrane's total negative charge (Utsugi *et al*., 1991). According to Riedl *et al*. (2011), PS exposure is linked to the metastatic phenotype and has been seen in a variety of cancer tissues. The increased negative charges on the membranes of malignant cells can also be attributed to sialic acid residues associated with glycolipids and glycoproteins such as mucins. As an example, Mucin 1 (Muc 1) is significantly overexpressed in many cancer types, such as lung, ovarian, pancreatic, and breast cancers (Bafna *et al*., 2010).

Moreover, proteoglycans with extremely negatively charged side chains, such as chondroitin and heparan sulfate, also have a role in changing the charge on the membranes of cancer cells. It has been well shown that a number of malignancies have altered proteoglycan expression and sulfonation (Aviel-Ronen *et al*., 2008; Fadnes *et al*., 2009). Aside from the increased negative charges on cancer cell membranes, several malignancies have been linked to modifications in membrane fluidity (Sherbet, 1998; Sok *et al*., 2002), which may be connected to increased cholesterol levels (May *et al*., 1998). The larger surface area that results from cancer cells having more microvilli than non-cancer cells is another characteristic that sets them apart (Zwaal and Schroit, 1997). This body of research highlights important differences between cancerous and non-cancerous cell membranes, which may enable peptide therapies to target and kill certain cells. Table 5 shows the bioactive

**Table 5. Bioactive peptides from different non-bovine species milk**

| Species | Function | Peptide sequence | Reference |
|---|---|---|---|
| Camel | Anti-diabetic activity | EDMPSQR, EVESAEVPTENK | Shukla *et al*., 2023 |
| | Anti-diabetic activity | LTFPGSAED | Lammi *et al*., 2016 |
| | Anti-diabetic activity | LAPSLPGKPKPD | Zambrowicz *et al*., 2015 |
| | ACE-Inhibitory activity | LSLSQFKVLPVPQ (β-CN), KVLPVPQQMVPYPQ (β-CN), TDLENLHLPLPL (β-CN) | Alhaj, 2017 |
| | Antimicrobial activity | FRNTATQSEETKE (Lactophorin), IYMESPQPTDTSPAQ (Lactophorin), QMVPYPQR (βCN), QMVPYPQR (βCN), SSFRNTATQSEE ($\alpha_{S1}$-CN), IASEDGGKTDVMPQ ($\alpha_{S1}$-CN) | Muhialdin and Algboory, 2018 |

**Cont. Table 5.**

Table 5., Cont. ...

| Species | Function | Peptide sequence | Reference |
|---|---|---|---|
| | Antioxidant activity | LEEQQQTEDEQQDQL, YLEELHRLNAGY, RGLHPVPQ | Homayouni-Tabrizi *et al*., 2017 |
| Goat | DPP-IV inhibitory activity | MHQPPQPL, SPTVMFPPQSVL | Zhang *et al*., 2015 |
| | Anti-diabetic activity | SDIPNPIGSE, NPWDQVKR, SLSSSEESITH | Gong *et al*., 2020 |
| | ACE-inhibitory activity | TQTPVVVPPFLQPEIMGVPKVKE, VLPVPQKVVPQ, VLPVPQKAVPQ | Aslam *et al*., 2019 |
| | Antimicrobial activity | FHKFICKMMKIYL | Tomazou *et al*., 2019 |
| | Antioxidant activity | PLRVYVEELKP (β-Lg), LHSMKEGNPAHQKQP ($\alpha_{s1}$-CN), SLTLTDVEKLHLPL (β-CN), SDIPNPIGSENSGKTTMPL ($\alpha_{s1}$-CN), PEQSLACQCL (β-Lg) | Ahmed *et al*., 2015 |
| Sheep | DPP-IV inhibitory activity | PSGAW | Iram *et al*., 2022 |
| | ACE-Inhibitory activity | PYVRYL ($\alpha_{s2}$-CN),LKKISQ ($\alpha_{s2}$-CN), VRYL ($\alpha_{s2}$-CN) | Gomez-Ruiz *et al*., 2007 |
| | Antimicrobial activity | VVAPFPEV ($\alpha_{s1}$-CN), VMFPPQSVL (β-CN) | Rizzello *et al*., 2005 |
| | Antimicrobial activity | SPAQTLQWQVLPNAVPAK, GPFPILF, SCQDQPTAMAR, IPAVFK, KFWGKYLYEVAR | Jodhani *et al*., 2022 |
| | Antioxidant activity | HPHPHLSF (κ-CN) | Gomez-Ruiz *et al*., 2008 |
| Donkey milk | ACE-Inhibitory activity | LNVSSETVES (β-CN), GENLRLPVHL (β-CN), IQPFMHQVPQ (β-CN), ENSEKTDIIP ($\alpha_{s1}$-CN) | Srivastava *et al*., 2012 |
| | Antioxidant activity | WFTFLKEAGQGAKDMWR, GQGAKDMW | Zenezini Chiozzi *et al*., 2016 |
| Yak milk | ACE-Inhibitory activity | PLPLL (β-CN), PPEIN (κ-CN) | Jiang *et al*., 2007 |

peptide sequences from different non-bovine milk.

## Conclusion

The lesser animal population and lower economic significance of non-bovine species have resulted in relatively less research focus being paid to milk and its derivatives. On the other hand, the extraction and analysis of bioactive peptides from non-bovine milk offer encouraging prospects for the growth of functional foods and health-related sectors, resulting in novel products. Peptides generated from non-bovine milk are intriguing as a source for functional meals with improved nutritional profiles because of their biofunctionalities and lack of negative effects. While bioactive peptides from goat and sheep milk proteins are now well understood, little is known about peptides from other minor dairy animal species. In-depth, long-term research involving both humans and animals is required to definitively validate these health advantages. Finally, we can say that non-bovine milk-derived bioactive peptides provide an important and long-lasting way to support human health and wellbeing in general.

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