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Open Access Journal of Veterinary Science and Research
ISSN: 2474-9222

Camel Milk Lactoferrin and Its Potential Medicinal Benefits: A Review

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Review Article
Volume 9 Issue 1
Received Date: February 15, 2024
Published Date: March 01, 2024
DOI: 10.23880/oajvsr-16000254

Abstract

Camel milk is a rich source of a number of bio-active molecules with potential nutraceutical benefits. It has been found that camel milk has the highest source lactoferrin compaired to the milk of other domestic ruminants and that of humans. Lactoferrin is one of the most important bio-active and safe proteins because of its bio-activity against cancers and microbes including: bacteria, viruses, fungi and parasites. Camel lactoferrin has also been reported to be widely distributed in mucosal secretions such as tears, saliva, and bile, and is in highest abundance in milk and colostrum. The lactoferrin found in camel milk and colostrum varies in concentrations from 0.020 mg mL−1 to 7.280 mg mL-1, higher than in cows, goats, sheep, buffaloes and humans and has been frequently reported to to be more resistant to heat and to have a higher antimicrobial activity and other biological values than that of other mammalian species. Its high bioavailability in milk, colostrum and fair cost-effectiveness, make it a promising candidate for industrial production for a wider nutrceutical application in the treatment of infectious, metabolic, and neuro-degenerative diseases, including various cancers in humans. This review examines the medicinal benefits of this important biomolecule.

Keywords: Camel Lactoferrin; Camel Milk; Medicinal Properties

Abbreviations: CAGR: Compound Annual Growth Rate; NO: Nitric Oxide; HIV: Human Immunodeficiency Syndrome; RMSD: Root Mean Square Deviations; RMSF: Root Mean Square Fluctuations; SASA: Solvent Accessible Surface Area.

Introduction

Together with blood serotransferrin (siderophilin), egg white (ovotransferrin), conalbumin (melanotransferrin) of malignant melanomas, the porcine inhibitor of carbonic anhydrase, and other proteins found in mammalian milk, blood and other body fluids, lactoferrin (LF) belongs to the family of bio-molecules called transferrins whose common property is the characteristic of binding to two metal cations, preferably Fe^{+3}, at structurally closely related binding sites (Figure 1) [1]. Structurally, Camel lactoferrin (cLF) is reported to be half lactoferrin, half transferrin and more closely related to that of marine mammals (~80.36% identity) and bats (~79.3% identity) than to the one of terrestrial mammals (~75.5% identity) [2]. While LF normally contains two lobes (C- and N-lobes), the C-lobe of cLF was observed to show a high fluctuation, while the N-lobe appeared to be more stable in the absence of ferric ions. The C-lobe and N-lobe of cLF react differently at physiological pH, revealing distinct molecular interactions between these components. In addition, structurally, cLF has been reported to show higher system flexibility derived from its larger Root Mean Square Deviations (RMSD), Root Mean Square Fluctuations (RMSFs), lower intermolecular hydrogen bonds and higher Solvent Accessible Surface Area (SASA) [2].

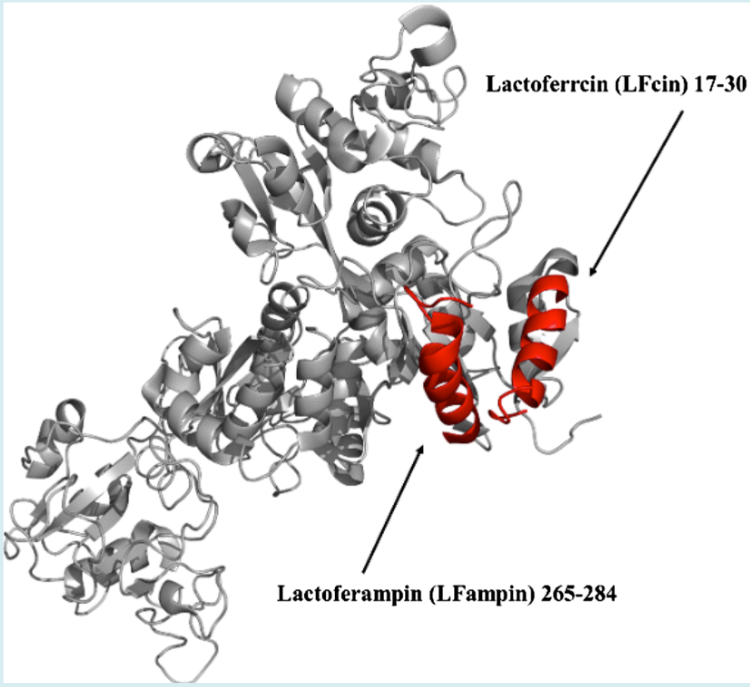

Figure 1: Molecular stracture of Camel Lactoferrin showing the two iron binding sites (Adopted after Pirkhezranian Z, et al. [1].

Camel lactoferrin like the lactoferrin of other species is a highly conserved molecule. It possesses high degree of sequence homology and exerts multiple identical functions with other mammalian species (Figure 2).

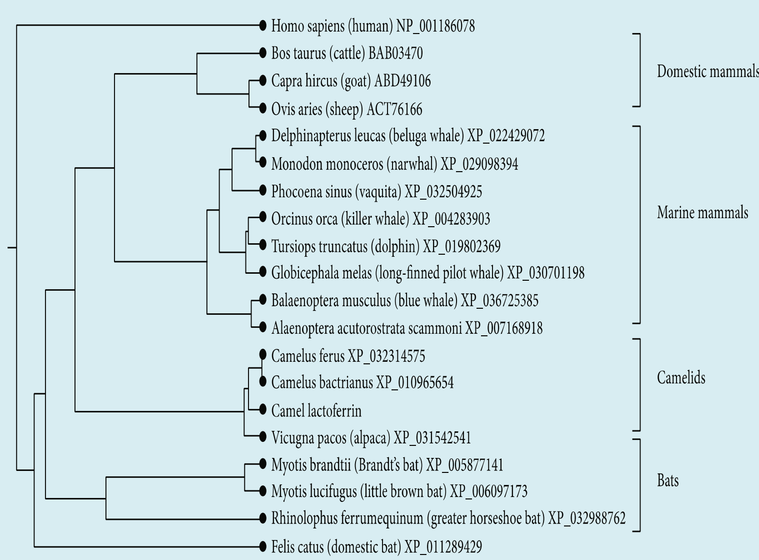

Figure 2: Phylogram showing the relations of camelid LF and the LFs of other domestic animals, Marine mammals and Bats. Adopted after Alhumam MN, et al. [2].

The lactoferrin contents of camel milk and colostrum have been estimated at concentrations of 0.180 to 2.480 mg mL-1 and 0.590 to 5.100 mg mL0.59–5.10 mg mL-1, Table 1 [3-9]. This is significantly higher than that of human, goat, sheep, buffalo and cow [10] and highest level of lactoferrin in camel milk (2.3 g.L-1) has been observed after 2 days of parturition [8]. In the body, most of the proteins of transferrin family contribute to the storage or transport of iron [11]. Lactoferrin is a glycoprotein [12] and is among the most protective bioactive proteins in camel milk with higher concentration and thus prevents microbial overgrowth and that other of invading pathogens [13].

Range of Concentration mg/mL	References
2.000 – 6.000	[3]
0.340 -5.100	[4]
0.020 - 0.080	[5]
0.18 – 2.480	[6]
2.350 - 7.280	[7]
0.140 - 0.420	[8]
0.055 – 0.888	[9]

Table 1: Concentration of Lactoferrin in Camel milk reported by different workers.

In the body, most of lactoferrin is needed for transportation or storage of iron and possess antioxidant and anti-microbial properties [14]. Camel milk lactoferrin is a molecule that not only boosts the immune system but also acts against cancer [13]. The anti-microbial activity of camel lactoferrin against bacteria, some yeast, fungi, viruses, and parasites has been investigated. Moreover, the immunomodulatory effect of lactoferrin on inflammatory response and activation of the immune system have been reported previously [15-20]. Lactoferrin works as an antimicrobial compound through chelating the iron ion, making this essential ion unavailable to the invading pathogens [15]. Lactoferrin is also well recognized as an adjunct to anti-cancer standard therapy by virtue of its immunomodulatory activity. It also exhibits immuno-compatibility, bioavailability, safety, relative abundance, and low-cost effectiveness. Moreover, the oral route of administration makes it very easy to be given to patients and it is usually well-tolerated [21]. Numerous studies on camel lactoferrin have reported that it has anti-bacterial, anti-fungal, anti-viral, and anti-inflammatory, antioxidant, and anti-tumour properties.

Bioavailability, Absorption and Assimilation Qualities of Camel Lactoferrin

Camel LF (cLF) is reported to be more dynamic in nature than Bovine lactoferrin (bLF) and Human lactoferrin (hLF) by showing higher Root Mean Square Deviations (RMSD) values [2]. It has been reported to show a high bioavailability after being administered orally. Moreover it shows a high selectivity toward cancerous cells and a wide range of molecular targets controlling cancer proliferation, survival, migration, invasion, and metastasis. This property may be by enhancing the adaptive immune response mechnisms. However, of more importance to note is that, lactoferrin may either promote or suppress cell proliferation and migration depending on whether its target cell is normal or cancerous. It has been also reported, that its oral administration is well tolerated and does not exhibit any significant side effects. Oral administration of lactoferrin has also led to promising improvement in the immune responses of antiretroviral therapy in naıve children suffering from HIV and tuberculosis [22,23]. Its oral administration has been reported to decrease the occurrence of colon cancer by 83%, while the quantity of adenocarcinoma cells has been shown to reduce in the gut of rats after ingestion and the amelioration of tongue cancer. This may be different from many other therapeutic proteins, which typically require other invasive routes of administration [24]. However, although oral administration of lactoferrin is the most widely adopted method to delivery it into the human body, there are still some challenges that should be addressed before reaping maximum benefit from its intake. Moreover, since the functional domains of lactoferrin are highly dependent on its unique three dimensional structural conformation, the gastro-intestinal environment may cause its breakdown and lead to undesirable loss of some of its functional and beneficial properties. This calls for research into exploring safer ways of its delivery into the human body.

In rats and mice oral addminstration of lactoferrin has been reported to significantly to suppress carcinogenesis and metastasis in the colon, lung and other organs [25] and this might be by increasing expression of relevant cytokines and inducing subsequent activation of immune cells and interaction with a wide range of molecular targets controlling tumor proliferation, metastasis, invasion and survival. Moreover, lactoferrin can promote or inhibit cell proliferation and migration depending on whether it acts upon normal or cancerous cells, respectively. Furthermore, lactoferrin can prevent the development or inhibit cancer growth by boosting adaptive immune response.

Apparently the important receptors of lactoferrin are located in the intestinal mucosa and lymphatic tissue cells in the gut [26-29]. Therefore, the delivery of lactoferrin per os requires that it is protected so that it passes through the harsh stomach acidic environment so that it is delivered to the absorption sites in a functionally active form. Thus, the most important thing to note is that the digestive tract in infants and newborns is not mature enough (e.g., the intragastric pH and the gastric emptying rate are higher than in adults), therefore lactoferrin may not be completely digested under these conditions [30,31]. That notwithstanding, the degradation of lactoferrin during its passage through the gastrointestinal tract could also be beneficial. It has been reported that strong antibacterial peptides such as lactoferrin and lactoferrampin are produced by its pepsin hydrolysis [32,33] in the stomach. This further benefits its utilization in high value food products such as infant formula, nutritional supplements, and other formulations that aim at its delivery through its oral administration.

Camel Milk Lactoferrin as an Antimicrobial, Anticancer, and Immunomodulatory Agent

Based on in vivo studies, oral administration of lactoferrin to rodents significantly decreased the chemically induced carcinogenesis in various organs such as the breast, esophagus tongue, lung, liver, colon, bladder, and hindered angiogenesis [34]. During the past two decades, many animal and human studies have proved that orally administered Lactoferrin exerts many beneficial effects on the health of animals and humans [35]. A commonly accepted method to protect lactoferrin during digestion is to microencapsulate it. In this method, a protective matrix is created around the lactoferrin core. Food grade proteins (e.g., bovine serum albumin, β- lactoglobulin) and polysaccharides (e.g., pectin, carrageenan, sodium alginate, and gum Arabic) are commonly used as the shell materials. This core-shell structure excellently protects lactoferrin from the harsh environment prevailing in the human digestive system. The microencapsulation also helps achieve targeted and controlled release of lactoferrin by simply using shell materials with suitable properties.

Camel lactoferrin is a promising biomolecule for man pharmaceutical and nutraceutical uses. Table 2 and Figure 3 show some of the possible applications and biological activities, respectively.

S/No	Application	Remarks	References
1	Antihypertensive activity	Obtained from Lactoferrin- derived peptides	[36]
2	Protection from anaemia	Serves as an iron-containing protein useful for treatment of anaemia	[37]
3	Bone regeneration	Beneficial effect	[38,39]
4	Prevention of metabolic diseases	For example Obesity and diabetes	[40]
5	Acts as drug nanocarriers	Emphasis on tumour-targeted drug delivery.	[41]
6	Protection from Neurodegenerative diseases	Markedly increased expression upregulation in brain cells	[42]
7	Anti-inflammatory effect	By inhibition of the formation of hydroxyl free radicals.	[43]
8	DNA damage prevention	Prevention of tumour formation in the central nervous syst	[44]
9	Activates the p53 tumour suppressor gene (TSG)	Suppression of tumour formation	[44]
10	Natural substitute for Antibiotics	Antimicrobial activity: Also, a promising candidate to help break the vicious cycle of antibiotic resistance	[43]
11	Natural food preservative	Antimicrobial activity	[43]

Table 2: Potential Application of Camel Lactoferrin.

Its ability to act as an antibacterial, antifungal, antiviral and antiparasitic, anti-inflammatory and immunomodulatory agent is shared amongst most mammalian species and more specifically, it is reported to inhibit the growth of Escherichia coli, Klebsiella pneumonia, Clostridium, Helicobacter pylori, Staphylococcus aureus, Candida albicans and many others [45-47].

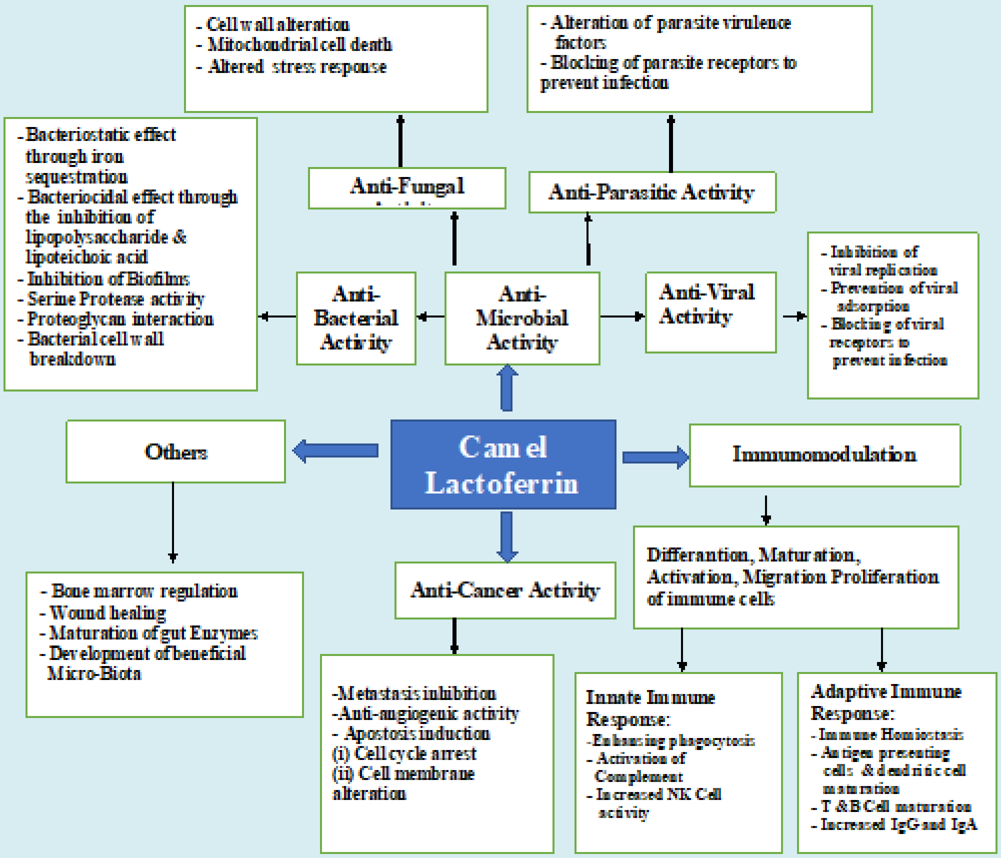

Figure 3: Biological Activities of Camel Lactoferrin.

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