Acta Scientific NUTRITIONAL HEALTH (ISSN:2582-1423)

Volume 5 Issue 10 October 2021

Review Article

A Comprehensive Review on Functional Role and Additive Application of Lactoferrin

Barkha Binyameen[1], Muhammad Abdul Rahim[2], Waseem Khalid[2]*, Naqash Nasir[2], Saleem Ilyas[3], Fareed Afzal[2], Muhammad Rehan[4], Ravi Prakash Jha[5], Anwar Ali[6], Muhammad Zubair Khalid[2], Zahra Maqbool[2], Noman Aslam[2], Muhammad Safwan Siddique[2] and Hamza Israr[2]

[1]Institute of Plant Breeding and Biotechnology, Muhammad Nawaz Shareef University of Agriculture, Multan, Pakistan

[2]Department of Food Science, Government College University, Faisalabad, Pakistan

[3]Department of Food Technology, Government College of Technology, Faisalabad

[4]Institute of Agricultural Sciences, The Punjab University, Lahore, Pakistan

[5]Department of Community Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India

[6]Department of Epidemiology and Health Statistics, Xiangya School of Public Health, Central South University, China

***Corresponding Author:** Waseem Khalid, Department of Food Science, Government College University Faisalabad, Pakistan.

Received: August 16, 2021

Published: September 16, 2021

Abstract

This review discusses the nutritional and biological properties of the LF. Lactoferrin [LF] is a multifunctional protein naturally present higher amount in milk and the lower amount is evaluated in rice and various secretions such as tears, saliva, pancreatic juice and bile. All existing non-animal LF expression systems have been improved from the point of view of their expression efficiency, purification procedure of target protein as well as the sophisticated cultivation, harvesting and biological activity. LF is used to activate humoral and cellular immune reactions. Therefore, it may be effective against COVID-19 and metabolic diseases. LF is an iron-binding glycoprotein that can be used to regulate iron absorption, also used as an antiviral and antibacterial agent in various food products. Furthermore, LF has been used for the formulation of infant feed and also used in pharmaceutical and nutraceutical industries. Moreover, LF is also used as an antioxidant and to protect against bacterial and viral infections. LF is very effective against many diseases caused by iron deficiency. Concluded that LF may inhibit iron absorption and can be used as a functional ingredient in many food products.

Keywords: Lactoferrin; Milk; COVID-19; Antiviral; Antibacterial

Introduction

Lactoferrin (LF)

Lactoferrin is initially discovered from bovine milk [1] and after that, in 1960 it was recognized in human milk [2]. Its concentration is found to be very high in breast milk and to some broaden found more modest amounts in some exocrine fluids, for example, pancreatic juice, intestinal secretions, bile and mucosal secretions [3]. It belongs to a protein family called transferrin [4]. Its significant feature is the production of extreme red shading as incubates within the ions of $Fe3+$, which proves that LF is an analog of serum iron-binding protein.

The expression of LF is shown in most exocrine secretions by epithelial for example, uterine secretions, saliva, tears, pancreatic exocrine secretions, seminal fluid and in milk where the concentration may fluctuate somewhere in the range of 1 to 7g/L [colostrum] in humans [5]. LF lines all epithelia and mucosa where, along with discharged IgA and further defensins and inferable from its inherent antimicrobial activity, it might impact on homeostasis of microbes [6].

Structure of lactoferrin

Around 703 amino acids contained by human LF can be determined through cDNA cloning [7] and chemical techniques [8]. HoloLactoferrin is folded into two globular lobes and it is a polypeptide chain, and an iron-binding site contained by C- and N-terminal [9]. The N-and C- lobes have inner homology at 1-338 and 339-703 which exhibit 37% indistinguishable residues of amino acids in the equivalent partitions [10]. This offer ascent to the hypothesis of gene duplication brings about the arrangement of two domains and offering an increase to a protein family containing the molecular masses 80KDa range [11].

Lf is a bilobal, monomeric, glycoprotein having a molecular mass of around 80 kDa. The structure of three-dimensional human diferric Lf was primarily reported in the year 1987 [12]. Since then the diferric protein structure has been advanced and additional structures reported for apolactoferrin of human and apo and iron-loaded forms of further Lf [13]. The diferric human lactoferrin has protein that involves two homologous lobes comparing to its amino- [1-333 residues] and carboxyl- [345-692 residues] terminal parts, associated by a three-turn - helix at 334-344 residues. Every lobe is additionally partitioned into two domains, with one iron-binding site located between the inner faces of the inter-domain gap. Each atom of Fe^{3+} is co-ordinated to 4 protein ligands, in particular, 1 histidine, 1 aspartate and2 tyrosines and furthermore to a synergistic anion—typically carbonate *in vivo*. Little angle scattering examines have revealed that the two lobes go through a substantial confrontational alteration because of iron-binding, consistent with the closing of inter-domain gap [14].

Sources of lactoferrin

In human milk, during lactation, the LF is a prevailing whey protein and can tie two ions of ferric [16]. LF has been identified in a huge number of mammal's milk and the sequence of its amino acids is recognized in some species namely: mouse, camel, goat, sheep, buffalo, cow, horse, pig and human [13].

LF has been additionally recognized in African elephant milk. The LF of sheep, goats, buffalo and cows share more than 90% identity with one another and structure an amazingly firmly related group [14].

LF comprises a polypeptide chain that structures two globular lobes, each containing two domains. The site of iron-binding is situated in every lobe and the atoms of iron are composed of four amino acid ligands: one aspartate, one histidine and two tyrosines. At the site of binding an HCO_3^- or CO_3^{2-} ions neighboring an arginine side chain additionally partakes have revealed the glycan arrangement differences of LF from various species, for example, goat, bovine, mouse and human [17].

Every LF has 1 to 4 glycans relying upon the species and the carbohydrate moiety characteristics are explicit to every LF. Lactoferrin was available in enormous amounts by a few groups not just in milk discharged by the mammary glands yet additionally in different exocrine secretions like white blood cells, bronchial secretion, seminal fluid, cervical mucus, tears and saliva [18]. Since Lactoferrin is overwhelmingly found in the products of digestive, reproductive and respiratory exocrine glands, it is however that Lactoferrin plays a role in the host nonspecific resistance against invading pathogens [19].

Lactoferrin from genetically modified rice

Rice [*Oryza sativa* L.] is the second-biggest crop cultivated worldwide and feeds almost half of the whole populace. In any case, an enormous number of individuals staying alive on rice experience inadequacy regarding micronutrients, for example, zinc, vitamin A and C, and iron. The World Health Organization [WHO] has perceived that the anemia disastrous effects on human health and personal satisfaction which are brought about by the lack of iron [20].

With the quick advancement of transgenic innovation, the quality of nutrition of conventional rice might be enhanced to balance for expected deficiency. A few cultivars of rice were produced with the point of lessening deficiency of iron [anemia] [21]. Although, the organized assessment of nutrition for these strains is reported infrequently. The novel strain of rice which is genetically modified expresses the human LF gene [hLF rice], produced through the Zhejiang University of China. In hLF rice, the content of iron was expanded to 24.7 mg/kg, which was double as compared to parental rice [PR rice] known as "Xiushui 110" [*Oryza sativa* L. ssp. japonica]. Various endeavors have been made to develop [rhLF] utilizing the expression system of eukaryotes and prokaryotes [22].

Transgenic mice with rhLF were effectively developed by the group of Platenburg, which prepared for collecting rhLF by methods for a mammary bioreactor [23]. As such, a mammary bioreactor of cattle would be an outstanding system for huge rhLF production due to its well-known accurate incorporation of post-translational alterations and effectiveness for heterologous proteins. Until now, in excess of ten recombinant proteins have been developed in the milk of pigs, rabbits, sheep and goats [24].

Health benefits/functions

Immune stimulating effects

Bovine LF [bLF] might invigorate both mucosal and systemic immune reactions *in vivo* when administrated orally [25]. It is demonstrated that lactoferrin complexation with monophosphoryl lipid A might be utilized as a productive adjuvant to activate humoral and cellular immune reactions [26].

The principle system through which this protein can incite immunity is the stimulation of T-lymphocytes differentiation, phagocytes activation and looking after the balance of Th1/Th2 cytokine [27]. If there should arise an occurrence of non-pathogenic circumstances, Lactoferrin can upgrade the T cells differentiation from their equivalent undeveloped precursors through CD4 [antigen] introduction [28] Furthermore, bLF orally administrated can advance host resistance by means of actuation of some fundamental genes of intestine transcription, for example, NOD2, IL-12 and p40 [29].

Besides, lactoferrin originates to stimulate macrophages through the incitement of TLR4 independent and dependent pathways of signals [30], which can additionally actuate CD40 and IL-6 development. Additionally, lactoferrin attachment to macrophages originates to activate the process of phagocytosis of microorganisms [31].

Initiation of T lymphocytes incites the existence of lactoferrin-binding in the cell membrane [32,33] and likewise binds B cells are reported [34]. Lf is essential for the system of innate host defense and has a broad range of capacities, like an antioxidant, immunomodulatory and antimicrobial agent [35].

Lactoferrin can fight with LPS for CD14 binding, part of toll-like receptor 4, subsequently, keeping LPS from initiating a pro-inflammatory cascade, which can prompt the damage of tissues [36]. Extra immune-modulating impacts of Lf might be receptor-mediated, as natural killer [NK] cells and activated lymphocytes express LFRs [36,37].

Antioxidant activity of LF

Remarkably, LF might be found at both sites. The Iron saturated LF contains more resistance against proteolysis as compare to iron unsaturated LF. The LF capability to bind with the cell membrane improves its antioxidative capacity to forestall iron-intervened peroxidation of lipid [38].

The natural compounds of phenol impact on prooxidant and antioxidant LF activity have been considered in oil-in-water emulsions [with iron] and in liposomes [39]. The antioxidants that were tried with LF incorporate phenolic extracts, tyrosol, coumaric acid, ferulic acid and α-tocopherol [39].

Lactoferrin has been distinguished as an antioxidant protein and has the capacity to decrease ROS formation and increase antioxidant capacity [40]. A few reports have shown antihypertensive impacts of this food-derived peptide and its hydrolysate in normal and in spontaneously hypertensive rodents [SHR] [41,42]. The NO-dependent vasodilation, the inhibition of the activity of the endothelin-converting enzyme [ECE] and angiotensin I-converting enzyme [ACE] action have been recommended as the process liable for antihypertensive impacts of lactoferrin [43-45]. Lactoferrin as a food-derived peptide is accepted to be more secure than the medications at present utilized for the treatment of hypertension [46].

Lactoferrin might cross and be internalized through a particularly low density of lipoprotein receptor-related protein in a number of capillary endothelial cells or it goes about as an antioxidant aspect [47]. The antihypertensive impacts of lactoferrin might be credited to the ECE and ACE inhibitor activity and furthermore the activity of LF as an endothelium dependant relaxant [44]. It has been proposed that the activity of LF as a vasodilatory is unequivocally intervened by NO creation in light of complete blockade of this impact by an inhibitor known as NO synthase [48].

Mechanism of iron absorption

Iron is perhaps the main segments of catalase, peroxidase, cytochromes, iron-sulfur protein, myohemoglobin and hemoglobin which assume a fundamental role in oxygen digestion and bio-oxidation. The body iron originates from endogenous degradation and food ingestion and its assimilation in the duodenum and the jejunum proximal part. Inorganic Fe2+ is further readily metabolized and absorbed as compare to Fe3+. Various proteins are associated with iron use invertebrates, together with ferritin, which stores iron in cells, uteroferrin help in the transportation of iron in the uterus, transferrin helps in the transportation of iron in the blood, and lactoferrin, which transports iron in the intestine. Since transferrin cannot help in the transformation of iron under the acidic condition, just lactoferrin has the capability of iron transportation in the gastrointestinal tract. Lactoferrin directs the amount of iron consumed in the digestive system. The iron-binding areas are found at the C- and N-terminals of the molecule, which has an elevated affinity for iron and binds it reversibly to keep up the utilization and absorption of iron in the duodenum at an enormous pH range. Kawakami., *et al*. discovered that the mechanisms of iron absorption varied by whether it was in the form of iron saturated lactoferrin or salts of soluble iron [49].

Antibacterial activity

The LF bactericidal action chiefly happens by direct cooperation with the surface of bacteria. Accordingly, the membrane permeability of Gram-negative bacteria can be harmed by communication of the protein part of lactoferrin [cationic area in its structure] with the A lipid of lipopolysaccharide [LPS] containing anionic nature and its consequent neutralization [50]. Through binding to LPS, lactoferrin can hinder bacterial adhesion, in this way restraining quite possibly the significant virulence variables of these bacteria [51,52].

The lactoferrin communication with the LPS or other proteins of the bacterial membrane is known to upgrade the bactericides effects, for example, lysozymes, secreted alongside with lactoferrin in high concentration in the mucosa. By binding with the lipoteichoic acid [anionic molecules] the lactoferrin acts against Gram-positive bacteria, decreasing the negative burden on the cell wall of bacteria. This offers contact between peptidoglycan and lysozyme, encouraging the impact of enzymes [53]. The lactoferrin can likewise upgrade the impact of certain bactericide drugs, for example, Rifampicin [50,51].

Antiviral activity

The lactoferrin antiviral action to viruses of RNA or DNA without or with envelopes has been identified [55]. Lactoferrin able to provide protection to the host from diseases caused by viruses through restricting the virus attachment to the targeted cell, in this manner, hindered the intracellular replication and enhancing the systematic function of the immune system [56].

Different mechanisms of activity have been planned to underlie lactoferrin antiviral impacts, and perhaps the most broadly acknowledged depends on its capacity to bind and block receptors of the virus, for example, glycosaminoglycans, particularly heparan sulfate [HS]. Accordingly, the lactoferrin binding to HS keeps away from the main contact between the virus and host cell, prevent infections of virus [57].

The modulation of the immune system is an additional proposed system, and lactoferrin able to enhanced the phagocytic action of macrophages in diseases by vesicular stomatitis viruses [36]. Administration of lactoferrin additionally improves Natural Killer [NK] activity of cell and the TH1 lymphocytes response, which secreted cytokines that secure to infections of viruses [58].

Lactoferrin and COVID-19

Coronavirus is frequently described by a surprisingly long asymptomatic period [3 to 14 days], whereas patients of asymptomatic might be similar, if not more, infectious contrasted with patients of symptomatic, which creates anticipation very troublesome, especially during the season of flu [59]. The system following the asymptomatic period might include the reality that SARS-CoV-2 has built up an extra cleavage site of furin protease in the spike protein [in domains of S1 and S2], which empowers the virus to cause infection and multiply in enormous amounts in the throat, salivary glands and nostril, whereas ACE2 and furin protease are together shown expression at a very high level [60].

Throughout some stretch of time, the infection multiplying in the upper respiratory tract is able to move to the lower respiratory tract and pass on a disease to others by means of liquid droplets. In the event that prophylactic processes are set aside in an effort to diminish the load of the virus and additionally avoid infection to further cells, the relational infectivity and severity of afterward symptoms might be noticeably decreased. From the point of view of the SARS-CoV-2 disease measure, keeping viral particles towards the inside of cells and interfere with the pathways of endocytic, give prevention to post-translational preparing of various proteins, and targeted the cell signaling pathway, are a portion of the methodologies that can be utilized to recognize compelling treatments [61].

Moreover, because of the similarity between SARS-CoV and SARS-CoV-2, drugs that have a remedial impact on SARS-CoV can likewise be measured as a potential healing arrangement. The antiviral impact of lactoferrin is intervened by keeping the virus from binding to the cell surface, which would be especially viable during the early increasing period of the virus in the upper respiratory tract, throat and salivary glands [62].

The pandemic of SARS-CoV-2 is spread very rapidly and become a significant worldwide concern of health. It is consequently earnest to produce successful agents of therapeutics for the prevention and treatment of SARS-CoV-2 disease. Lactoferrin has shown broad, wide range of antiviral action, demonstrating its ability for the prevention and treatment of SARS-CoV-2 [62,63]. For instance, the treatment with lactoferrin on ACE2 and HSPGs can keep SARS-CoV from the infection of host cells [64], and it has broad effects of anti-inflammatory and immunoregulatory [65,66], which might demonstrate helpful in the SARS-CoV-2 treatment and the anticipation of its destructive impacts for various targeted organs. Besides, contrasted to other antiviral medications, lactoferrin has a superior security profile. The utilization of lactoferrin might in this manner hold guarantee in the COVID-19 treatment and warrant additional examination.

Applications of lactoferrin in food products

Infant formula

Subsequent to the advancement of freeze-drying and ultrafiltration in dairy industries, profoundly bioactive and pure lactoferrin can be developed, permitting the lactoferrin incorporation in infant formula [67,68]. While in human milk the iron concentration is low and it diminishes over the lactation course [69,70], no babies who are completely breastfeeding demonstrate iron inadequacy during the initial 6 months. This is probably due to the fact that the lactoferrin serves as a promoter in the absorption of iron in the milk of humans [71]. Sherman., *et al*. revealed that lactoferrin is useful for late-onset sepsis and necrotizing enterocolitis in newborns having reduced birth weight [72].

As human and bovine lactoferrin has relative bioactivity, biochemistry and structure bovine lactoferrin have been broadly utilized for its putative advantages of health [73], indicated that intake of lactoferrin fortified milk is related to elevated complete iron of body and more competent iron absorption of the intestine in entirely breastfeeding infants.

Food additives

With the quick improvement of transgenic technologies, lactoferrin would now be able to be produced in rice, cows and goats [74]. Bovine lactoferrin has been utilized as health advancing additives in food items commercially available which are for quite a long time in Japan [75] yet as of late, it has likewise been accepted as a food ingredient in the products by the European Food Safety Authority [76].

In China, lactoferrin has additionally been developed as a food additive, confirmed by the Chinese Food and Drug Administration [CFDA]. As the lactoferrin ingestion increments with the milk consumption, the methods underlying the lactoferrin activity, synthesis and regulation should be better perceived, and this will assist comprehension of the vital Lf roles in the process of metabolism [77].

Conclusion

It is concluded that Lactoferrin is a protein that has nutritional and biological properties. Due to its unique antimicrobial, immunomodulatory, and antioxidant properties, Lactoferrin seems to have great potential in practical medicine. The beneficial effect of LF, it may treat various infectious diseases like Covid-19, bacteria, fungi, protozoa and viruses in animals and humans. However, it can also be used functional ingredient in different food products. Nevertheless, much research and many experiments still need to be carried out in order to obtain a better understanding of its activity and interactions and to enable the full and safe utilization of this glycoprotein.

Bibliography

1. Giansanti Francesco., *et al*. “Lactoferrin from milk: Nutraceutical and pharmacological properties”. *Pharmaceuticals* 9.4 (2016): 61.

2. Shams Homayoun., *et al*. “Characterization of a Mycobacterium tuberculosis peptide that is recognized by human CD4+ and CD8+ T cells in the context of multiple HLA alleles”. *The Journal of Immunology* 173.3 (2004): 1966-1977.

3. Ashida Kinya., *et al*. “Cellular internalization of lactoferrin in intestinal epithelial cells”. *Biometals* 17.3 (2004): 311-315.

4. Wally Jeremy and Susan K Buchanan. “A structural comparison of human serum transferrin and human lactoferrin”. *Biometals* 20.3 (2007): 249-262.

5. El-Loly Mohamed Mansour and Mohamed Bahy Mahfouz. "Lactoferrin in Relation to Biological Functions and Applications: A". *International Journal of Dairy Science* 6.2 (2011): 79-111.

6. Embleton Nicholas D., *et al*. "Lactoferrin: Antimicrobial activity and therapeutic potential". *Seminars in Fetal and Neonatal Medicine* 18.3 (2013).

7. Chen Hong., *et al*. "Molecular cloning and functional expression of a chicken intestinal peptide transporter (cPepT1) in Xenopus oocytes and Chinese hamster ovary cells". *The Journal of Nutrition* 132.3 (2002): 387-393.

8. Zarándi Márta and János Szolomájer. "Amino acids: chemistry, diversity and physical properties" (2017): 1-84.

9. Valenti P and Giovanni Antonini. "Lactoferrin". *Cellular and Molecular Life Sciences* 62.22 (2005): 2576-2587.

10. Mora Lagares Liadys., *et al*. "Homology modeling of the human p-glycoprotein (Abcb1) and insights into ligand binding through molecular docking studies". *International Journal of Molecular Sciences* 21.11 (2020): 4058.

11. Lallemand Tanguy., *et al*. "An overview of duplicated gene detection methods: Why the duplication mechanism has to be accounted for in their choice". *Genes* 11.9 (2020): 1046.

12. Bourne Philip E. "Life is three-dimensional, and it begins with molecules". *PLoS Biology* 15.3 (2017): e2002041.

13. Baker Edward N., *et al*. "Lactoferrin and transferrin: functional variations on a common structural framework". *Biochemistry and Cell Biology* 80.1 (2002): 27-34

14. Baker Heather M and Edward N Baker. "Lactoferrin and iron: structural and dynamic aspects of binding and release". *Biometals* 17.3 (2004): 209-216.

15. Park Young W. "Bioactive components in milk and dairy products". John Wiley and Sons (2009).

16. Rodzik Agnieszka., *et al*. "Interactions of whey proteins with metal ions". *International Journal of Molecular Sciences* 21.6 (2020): 2156.

17. Guo Maolin., *et al*. "TiIV uptake and release by human serum transferrin and recognition of TiIV-transferrin by cancer cells: understanding the mechanism of action of the anticancer drug titanocene dichloride". *Biochemistry* 39.33 (2000): 10023-10033.

18. Steijns Jan M. "Milk ingredients as nutraceuticals". *International Journal of Dairy Technology* 54.3 (2001): 81-88.

19. Cheng J B., *et al*. "Factors affecting the lactoferrin concentration in bovine milk". *Journal of Dairy Science* 91.3 (2008): 970-976.

20. Chen L and X D Zeng. "Iron deficiency anemia-related factors and interventions". *Chinese Journal of Current Traditional and Western Medicine* 5 (2007): 423-424.

21. Suzuki Yasushi A., *et al*. "Expression, characterization, and biologic activity of recombinant human lactoferrin in rice". *Journal of Pediatric Gastroenterology and Nutrition* 36.2 (2003): 190-199.

22. Chong Daniel KX and William HR Langridge. "Expression of full-length bioactive antimicrobial human lactoferrin in potato plants". *Transgenic Research* 9.1 (2000): 71-78.

23. Lipman Neil S., *et al*. "Monoclonal versus polyclonal antibodies: distinguishing characteristics, applications, and information resources". *ILAR Journal* 46.3 (2005): 258-268.

24. Monzani Paulo S., *et al*. "Transgenic bovine as bioreactors: Challenges and perspectives". *Bioengineered* 7.3 (2016): 123-131.

25. Sfeir Rose Mary., *et al*. "The mode of oral bovine lactoferrin administration influences mucosal and systemic immune responses in mice". *The Journal of nutrition* 134.2 (2004): 403-409.

26. Chodaczek Grzegorz., *et al*. "A complex of lactoferrin with monophosphoryl lipid A is an efficient adjuvant of the humoral and cellular immune response in mice". *Medical microbiology and immunology* 195.4 (2006): 207-216.

27. Fischer Romy., *et al*. "Regulation of physiological and pathological Th1 and Th2 responses by lactoferrin". *Biochemistry and Cell Biology* 84.3 (2006): 303-311.

28. Dhennin-Duthille Isabelle., *et al*. "Lactoferrin upregulates the expression of CD4 antigen through the stimulation of the mitogen-activated protein kinase in the human lymphoblastic T Jurkat cell line". *Journal of Cellular Biochemistry* 79.4 (2000): 583-593.

29. Yamauchi Koji., *et al*. "Bovine lactoferrin: benefits and mechanism of action against infections". *Biochemistry and Cell Biology* 84.3 (2006): 291-296.

30. Curran Colleen S., *et al*. "Lactoferrin activates macrophages via TLR4-dependent and-independent signaling pathways". *Cellular Immunology* 242.1 (2006): 23-30.

31. Kai Kenzo., *et al*. "Lactoferrin stimulates a Staphylococcus aureus killing activity of bovine phagocytes in the mammary gland". *Microbiology and Immunology* 46.3 (2002): 187-194.

32. MAZURIER Joël., *et al*. "Expression of human lactotransferrin receptors in phytohemagglutinin-stimulated human peripheral blood lymphocytes: Isolation of the receptors by antiligand-affinity chromatography". *European Journal of Biochemistry* 179.2 (1989): 481-487.

33. Rochard Elisabeth., *et al*. "The N-terminal domain I of human lactotransferrin binds specifically to phytohemagglutinin-stimulated peripheral blood human lymphocyte receptors". *FEBS Letters* 255.1 (1989): 201-204.

34. Butler Thomas W., *et al*. "Immunoreactive lactoferrin in resting, activated, and neoplastic lymphocytes". *Leukemia Research* 14.5 (1990): 441-447.

35. Siqueiros-Cendón Tania., *et al*. "Immunomodulatory effects of lactoferrin". *Acta Pharmacologica Sinica* 35.5 (2014): 557-566.

36. Actor Jeffrey K., *et al*. "Lactoferrin as a natural immune modulator". *Current Pharmaceutical Design* 15.17 (2009): 1956-1973.

37. Liu Kilia Y., *et al*. "Natural killer cell populations and cytotoxic activity in pigs fed mother's milk, formula, or formula supplemented with bovine lactoferrin". *Pediatric Research* 74.4 (2013): 402-407.

38. Mikogami Takashi., *et al*. "Effect of intracellular iron depletion by picolinic acid on expression of the lactoferrin receptor in the human colon carcinoma cell subclone HT29-18-C1". *Biochemical Journal* 308.2 (1995): 391-397.

39. Medina Isabel., *et al*. "Effects of natural phenolic compounds on the antioxidant activity of lactoferrin in liposomes and oil-in-water emulsions". *Journal of Agricultural and Food Chemistry* 50.8 (2002): 2392-2399.

40. Mulder Ann M., *et al*. "Bovine lactoferrin supplementation supports immune and antioxidant status in healthy human males". *Nutrition Research* 28.9 (2008): 583-589.

41. Ruiz-Gimenez Pedro., *et al*. "Antihypertensive properties of lactoferricin B-derived peptides". *Journal of Agricultural and Food Chemistry* 58.11 (2010): 6721-6727.

42. Ruiz-Giménez Pedro., *et al*. "Antihypertensive effect of a bovine lactoferrin pepsin hydrolysate: identification of novel active peptides". *Food Chemistry* 131.1 (2012): 266-273.

43. Hayashida Ken-ichiro., *et al*. "Bovine lactoferrin has a nitric oxide-dependent hypotensive effect in rats". *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* 286.2 (2004): R359-R365.

44. Ruiz-Giménez Pedro., *et al*. "Bovine lactoferrin pepsin hydrolysate exerts inhibitory effect on angiotensin I-converting enzyme-dependent vasoconstriction". *International Dairy Journal* 17.10 (2007): 1212-1215

45. Fernández-Musoles Ricardo., *et al*. "Lactoferricin B-derived peptides with inhibitory effects on ECE-dependent vasoconstriction". *Peptides* 31.10 (2010): 1926-1933.

46. Pihlanto-Leppälä Anne., *et al*. "Angiotensin I-converting enzyme inhibitory properties of whey protein digests: concentration and characterization of active peptides". *Journal of Dairy Research* 67.1 (2000): 53-64.

47. Fillebeen Carine., *et al*. "Receptor-mediated transcytosis of lactoferrin through the blood-brain barrier". *Journal of Biological Chemistry* 274.11 (1999): 7011-7017.

48. Hayashida Ken-ichiro., *et al*. "Oral administration of lactoferrin inhibits inflammation and nociception in rat adjuvant-induced arthritis". *Journal of Veterinary Medical Science* 66.2 (2004): 149-154.

49. Kawakami Hiroshi., *et al*. "Effects of iron-saturated lactoferrin on iron absorption". *Agricultural and Biological Chemistry* 52.4 (1988): 903-908.

50. Jenssen Håvard and Robert EW Hancock. "Antimicrobial properties of lactoferrin". *Biochimie* 91.1 (2009): 19-29.

51. García-Montoya Isui Abril., *et al*. "Lactoferrin a multiple bioactive protein: an overview". *Biochimica et Biophysica Acta (BBA)-General Subjects* 1820.3 (2012): 226-236.

52. Reyes-Cortes Ruth., *et al*. "Antibacterial and cell penetrating effects of LFcin17–30, LFampin265–284, and LF chimera on enteroaggregative Escherichia coli". *Biochemistry and Cell Biology* 95.1 (2017): 76-81.

53. González-Chávez Susana A., *et al*. "Lactoferrin: structure, function and applications". *International journal of Antimicrobial Agents* 33.4 (2009): 301-e1.

54. Jenssen Håvard and Robert EW Hancock. "Antimicrobial properties of lactoferrin". *Biochimie* 91.1 (2009): 19-29.

55. Redwan Elrashdy M., *et al*. "Potential lactoferrin activity against pathogenic viruses". *Comptes Rendus Biologies* 337.10 (2014): 581-595.

56. Wakabayashi Hiroyuki., *et al*. "Lactoferrin for prevention of common viral infections". *Journal of Infection and Chemotherapy* 20.11 (2014): 666-671.

57. Wong Jack Ho., *et al*. "A study of effects of peptide fragments of bovine and human lactoferrins on activities of three key HIV-1 enzymes". *Peptides* 62 (2014): 183-188.

58. Wakabayashi Hiroyuki., *et al*. "Lactoferrin for prevention of common viral infections". *Journal of Infection and Chemotherapy* 20.11 (2014): 666-671.

59. Vellingiri Balachandar., *et al*. "COVID-19: A promising cure for the global panic". *Science of the Total Environment* 725 (2020): 138277.

60. Lan Jun., *et al*. "Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor". *Nature* 581.7807 (2020): 215-220.

61. Nitulescu George Mihai., *et al*. "Comprehensive analysis of drugs to treat SARSCoV2 infection: Mechanistic insights into current COVID19 therapies". *International Journal of Molecular Medicine* 46.2 (2020): 467-488.

62. Van der Strate B W A., *et al*. "Antiviral activities of lactoferrin". *Antiviral Research* 52.3 (2001): 225-239.

63. Redwan Elrashdy M., *et al*. "Potential lactoferrin activity against pathogenic viruses". *Comptes Rendus Biologies* 337.10 (2014): 581-595.

64. Lang Jianshe., *et al*. "Inhibition of SARS pseudovirus cell entry by lactoferrin binding to heparan sulfate proteoglycans". *PloS One* 6.8 (2011): e23710.

65. Berlutti Francesca., *et al*. "Antiviral properties of lactoferrin—a natural immunity molecule". *Molecules* 16.8 (2011): 6992-7018.

66. Legrand Dominique., *et al*. "Lactoferrin". *Cellular and Molecular Life Sciences* 62.22 (2005): 2549-2559.

67. Giansanti Francesco., *et al*. "Lactoferrin from milk: Nutraceutical and pharmacological properties". *Pharmaceuticals* 9.4 (2016): 61.

68. Ke Chen., *et al*. "Iron metabolism in infants: influence of bovine lactoferrin from iron-fortified formula". *Nutrition* 31.2 (2015): 304-309.

69. Ziegler Ekhard E. "Consumption of cow's milk as a cause of iron deficiency in infants and toddlers". *Nutrition Reviews* 69 (2011): S37-S42.

70. Eidelman Arthur I and Richard J Schanler. "Breastfeeding and the use of human milk". *Pediatrics* (2012).

71. Wang Xiaodan., *et al*. "Effects of recombinant human lactoferrin on improving the iron status of IDA rats". *Wei sheng yan jiu= Journal of Hygiene Research* 41.1 (2012): 13-17.

72. Sherman Michael P. "Lactoferrin and necrotizing enterocolitis". *Clinics in Perinatology* 40.1 (2013): 79-91.

73. Ke Chen., *et al*. "Iron metabolism in infants: influence of bovine lactoferrin from iron-fortified formula". *Nutrition* 31.2 (2015): 304-309.

74. Wakabayashi Hiroyuki., *et al*. "Lactoferrin research, technology and applications". *International Dairy Journal* 16.11 (2006): 1241-1251.

75. Tomita Mamoru., *et al*. "Twenty-five years of research on bovine lactoferrin applications". *Biochimie* 91.1 (2009): 52-57.

76. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). "Scientific Opinion on bovine lactoferrin". *EFSA Journal* 10.5 (2012): 2701.

77. Wang Xiao., *et al*. "Research and development on lactoferrin and its derivatives in China from 2011–2015". *Biochemistry and Cell Biology* 95.1 (2017): 162-170.

Volume 4 Issue 10 October 2021