World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Available online at: http://www.wjpsonline.org/
Review Article

Is camel milk lactoferrin effective against COVID-19?

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Received: 25-12-2020 / Revised Accepted: 21-01-2021 / Published: 24-01-2021

ABSTRACT

Lactoferrin is one of the glycoproteins from the transferrin family which binds Fe3+ ion. Lactoferrin is found in mammalian milk but the camel milk has greater quantity of lactoferrinin compared with other livestock species. Lactoferrin strengthens the immune system by protecting the host cells against bacterial and viral infections and inflammations. Activation, proliferation and regulation of the phagocytic action of immune cells are also facilitated by the lactoferrin. The antiviral actions of lactoferrin are against both DNA and RNA viruses and it inhibits viral adhesion and entry into cells and binds viral particles. Generally, camel milk lactoferrin may directly interact with viral molecules or with the viral receptor (heparan sulfate) on the cellular surfaces to prevent the virus attachment and infection. The boosting host immune system by nutritional supplements such as lactoferrin may work against SARS-CoV-2 entry and infection into the host cells. Because of the homology in genetic sequence and receptor binding domain between SARS-CoV and SARS-CoV-2, lactoferrin may inhibit the SARS-CoV-2 invasion in the same way to SARS-CoV, via binding to heparan sulfate and prevent the viral infections and epidemic. Keeping in view this fact that lactoferrin can modulate immune responses to viral infections; it may reduce severe infections. Milk lactoferrin (in particular camel milk with the highest amount of lactoferrin) as powder or tablets may be a novel promising candidate and preventative treatment for more severe cases of COVID-19. However, it needs more studies on the unique medicinal effects of camel milk lactoferrin to verify its efficacy on COVID-19 prevention and treatment.

Keywords: Camel milk, Lactoferrin, COVID-19, Anti-viral

INTRODUCTION

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How to Cite this Article: Tahereh Mohammadabadi and Tanveer Hussain. Is Camel milk lactoferrin effective against COVID-19?. World J Pharm Sci 2021; 9(2): 91-97.

Lactoferrin (LF) is a glycoprotein from bovine milk which binds iron and has the ability to reversibly chelate with two Fe3+ ions. This iron withholding ability of LF is very high, thus it inhibits the microbial growth and reactive oxygen species formation.[1] The LF is found in high quantity in milk and colostrum.[1,2] After isolation from bovine milk, LF was also detected and isolated from milk of camel, sheep and goat.[3] Moreover, lactoferrin is also produced in considerable amounts by neutrophils about $15g/10^6$ neutrophils[1] and mucosal epithelial cells in cows, goats, horses, rodents and humans.[4]Lactoferrin has some physiological activities which include iron absorption and regulation in the intestine, protection against microbial infections, anti-inflammatory, anti-proliferative and immuno-modulator properties.[2] Regarding these important functions, lactoferrin is regarded as a nutraceutical supplement.

Camel milk has many protective proteins and enzymes having anti-microbial and immunological properties against bacterial and viral infections. These include the immunoglobulins, lactoferrin, lysozyme, lactoperoxidase, peptidoglycan recognition protein, vitamins C and oligosaccharides which work against microbial infections.[5] But most of the anti-microbial and anti-viral action of camel milk is because of lactoferrin and immunoglobulins.[6] The studies revealed that the concentration of lactoferrin in bovine milk ranges from 0.02-0.35 mg/mL.[7]Lactoferrin content in camel's milk is shown to be higher when compared with the milk from bovine and ranges from 0.7-2.1 mg/mL.[8]Lactoferrin has immunomodulatory functions by binding to microbial particles or cell receptors and inhibit the infections.[9] Also, it can bind receptors that SARS-CoV and human coronavirus NL63 use for entry into the host cells.[10] Information on the potential of camel milk lactoferrin against the COVID-19 is rarely reported. Therefore, the focus of the current review is exploring the antiviral effects of camel milk lactoferrin against COVID-19.

What is lactoferrin?

Lactoferrin glycoprotein is the part of the transferrin family. The polypeptide chain of lactoferrin contains 600-700 amino acid residues.[2] In addition to Fe2+ or Fe3+, lactoferrin also binds Mn2+, Cu2+ and Zn2+.[1] Protein structure of lactoferrin is composed of α-helix and β-sheets which further divided into N- and C- lobe that are connected by a peptide (334–343 amino acids in human lactoferrin).

Both the lobes of lactoferrin packed together due to hydrophobic connections in this molecule. Also, both lobes of lactoferrin, are highly homologous (about 33–41%)[1] and further divided into two domains (Figure 1). The iron sites of lobes and amino acid sequences are highly conserved and they have a high identity with transferrin. Even ligands for Fe3+ are the same in both lobes.[11] Two types of lactoferrin exist including apo-LF that do not bind iron and holo-LF which binds with iron or Fe3+ and resistance to proteolysis of holo-LF is highest.[12] The iron withholding capacity of lactoferrin cause to anti-microbial activity and immuno-modulation properties. Moreover, without iron binding ability, lactoferrin interact with bacteria and viruses and inhibits their attachment to cell surface receptors. Regarding the most studies, no significant difference was observed in the anti-viral activity of iron-binding and non-iron binding forms of lactoferrin.[13]

Camel milk as important source of lactoferrin

According to studies, human milk showed the highest concentration of lactoferrin (1.7 mg/mL), while the lowest concentration is found in donkey milk (0.07 mg/mL).[7] In human colostrum, the amount of lactoferrin ranges from 5.3±1.9 mg/mL and after the one month of lactation, this amount reaches 1 mg/mL.[14] The concentration of lactoferrin in cow's milk is lower as compared to human milk and ranges from 0.83mg/mL for colostrum and 0.09mg/mL for normal milk.[15]

Higher levels of lactoferrin are observed in camel milk when compared to other mammals. Alhaji et al 2020 reported that the amount of lactoferrin in camel milk is 10 times greater as compared to cow's milk lactoferrin (2.48 mg/mL versus 0.07-0.28 mg/mL, respectively). A high amount of citrate in the milk reduces the inhibitory effects of lactoferrin due to citrate ions and lactoferrin compete for binding Fe. Since camel milk contains less citrate than cows' milk, so the amount of lactoferrin in the milk of camel is greater.[5]

The reason for these variations of lactoferrin in the camel milk is related to milk yield, lactation period, feeds, samples, breeds, and analysis methods[7].

El – Agamy 2006 reported lactoferrin content of camel and bovine colostrum was highest on the first day, but colostrum from a camel in the second day (after parturition) was around 5.1 mg/mL compared to bovine colostrum which was 0.5 mg/mL.

The overview of some lactoferrin actions

The effects of milk lactoferrin on immune responses

Lactoferrin boosts the immune response and protects host cells against bacterial and viral infections.[13] Also, it has a key role in the host defense against inflammation.[16] However, the anti-microbial effects of lactoferrin on the cell surface

area due to preventing the adhesion and proliferation of microbes and destroying the membrane of microorganisms.[13]Immuno-modulatory effects of lactoferrin are based on interfering with infectious particles for adhesion to the receptors on the host cells[9] and complex with lipopolysaccharide (LPS) and neutralizing it connection with to TLR4[16]. Lactoferrin regulates cytokines production, chemokines, ROS (reactive oxygen species) and peroxides.[17]Lactoferrin is involved in activation, differentiation, and proliferation of immune cells and further regulate the modulation of lytic activity and motility of immune cells.[18-19]

It has been proved that the anti-inflammatory activity of lactoferrin is due to the prevention of pro-inflammatory cytokines such as interferon-gamma, tumor necrosis factor-alpha and interleukins 1, 2 and 6. Lactoferrin strengthens the recruitment of neutrophils and leukocytes, induces phagocytosis, stimulates migration and cell activation,[2] affects the expression of immune effectors (cytokines and chemokines) thus control inflammation and immunity.[20]

Milk lactoferrin as anti-viral supplement

The lactoferrin antiviral activity is against many viruses including enveloped and naked viruses, respiratory syncytial virus, herpes simplex viruses, rotavirus and HIVs.[1]Lactoferrin as an innate immunity agent against mucosal infections on the cell surfaces; inhibits the attachment and entry of the virus into host cells, blocks the interaction of viruses with heparan sulfate receptors, binds to virus particles and prevents their localization in the nucleus. The cationic nature of LF may be responsible for binding with viral particles thus inhibits viral invasion to the cells and avoiding the infection.[15]Lactoferrin is shown to inhibit the viruses in the early phase and also prevent viral replication in the host cell.[21] Also the antiviral functions of lactoferrin through avoiding the viruses' entry more than stimulation of the immune cells.[22] According to the studies, bovine and human LF had no significant differences in the antiviral effects[1] and they prevent viral entry inside the host by blocking receptors or connecting to viruses in the early phase.[13] But some studies proved that bovine milk lactoferrin has greater antiviral effects than human milk lactoferrin.[23]Lactoferrin has been considered the most active anti-viral protein in the milk when compared to b-lactoglobulin and a-lactalbumin.[2]

Seganti et al 2004 reported lactoferrin inhibits human respiratory syncytial virus more than human milk lactoferrin.[24] Also, human lactoferrin neutralizes simplex virus-1 and prevents the intracellular spread of viruses.[1] Strong activity of lactoferrin against human immunodeficiency virus (HIV) was due to inhibition of viral replication in the host cells. Both apo and holo-lactoferrin have antiviral action against HIV, but the apo form may show more inhibitory than holo-lactoferrin.[25]

Lactoferrin blocks the internalization of some viruses into the host cell, as poliovirus type 1, herpes simplex virus types I and II and cytomegalovirus. In the case of HCV and rotavirus, lactoferrin showed to inhibit the replication of the virus in the host rather than preventing virus entry. The high lactoferrin of camel milk is a primary drug against HCV infection.[26] Out of many hypotheses the one important is that lactoferrin blocks viral receptor of heparin sulphate and inhibits infection.

Lactoferrin effect on respiratory viruses

Bovine milk lactoferrin inhibited cell apoptosis by interfering in the caspase 3 function; also it blocked the entry of ribonucleoproteins in the H3N2 influenza A virus.[1] According to the studies, lactoferrin inhibited RSV absorption and growth by blocking the internalization of viruses into the host cell but the antiviral activity of lactoferrin will be decreased after processing.[2]

Lactoferrin control IL-8 secretion from cells that induced by RSV and hindered RSV uptake and infectivity.[27] Sano et al 2005 revealed that the lactoferrin directly interacted with F protein for penetration of RSV and occupied sites of protein for attachment of viruses.[27]Lactoferrin has also showed antiviral effects against human para influenza virus type 2 infections by preventing virus adsorption to the cells surface and limiting viral replication and infection.[28] Administration of lactoferrin by 100-1000mg per day in humans reduced the incidences of colds like symptoms.[29]

Anti-viral activity of camel milk lactoferrin

The behavior of lactoferrin from camel milk is different and unique compared to lactoferrin present in the milk of other mammals but the inhibition way of lactoferrin from camel's milk is similar to bovine milk lactoferrin.[26]

Redwan & Tabll, 2007 reported that lactoferrin of camel milk has anti-viral activity and inhibits the virus entry into the cells.[30] The camel milk lactoferrin stops HCV entry and replication in infected HepG2 cells two-times higher than lactoferrin of human, bovine, and sheep milk.[31] Generally, camel milk lactoferrin may directly interact with viral molecules or receptors (heparan sulfate) on the cell surface and prevent the virus attachment to the host cells and hinder infection.[26] The virucidal mechanism of camel milk lactoferrin depends on its alpha-helical structure and cationic

nature. The antiviral effects of lactoferrin from camel milk have been demonstrated against many viruses and the mechanism of action behind this activity is the neutralization of virus particles and inhibition of their replication.[26] According to studies, the most therapeutic effects of camel milk are due to lactoferrin and immunoglobulins.[32]

Connection between camel milk lactoferrin and COVID-19

The spike protein of SARS-CoV-2 causes the virus to gain entry into the host cells, so boosting the immune system will be useful against this virus. Milk of livestock in particular camel milk contains various protective proteins and enzymes such as lactoferrin which have immunological properties against the bacterial and viral infections park. Milk lactoferrin has immuno-modulatory properties that strengthen host immune responses and prevent infections. Nutritional supplements are useful against COVID-19, but there are few clinical trials.[33]Lactoferrin as an anti-viral factor acts against viruses such as SARS-CoV.[34] Since the 79% of sequences of the SARS-CoV and SARS-CoV-2 and also receptor-binding domain are homologous, therefore lactoferrin may inhibit SARS-CoV-2 invasion in the same manner to SARS-CoV.[35] The incidence of COVID-19 in infants was mild without ventilation support and lower respiratory tract infections rarely happened[36]. Lactoferrin inhibited virus entry via binding to heparan sulfate glycosaminoglycan in the cell surface of human coronaviruses hCOV-NL63[10] and pseudotyped SARS-CoV CoV.[35]

Although if there is no published researches on lactoferrin effects on the SARS-CoV-2 entry into host cells but the interaction of lactoferrin with heparan cell receptors, which allow attachment on the cell surface in the primary phase of virus infections particularly in coronaviruses.[37]

Lactoferrin prevents accumulation of viruses on the cell surface and inhibit the contact between the viruses and host cells and prevent the viral infection that is observed in the SARS-CoV epidemic and may be the same for SARSCoV-2. In some severe COVID-19 cases, mortality happens not only due to viral infection but also increases in cytokines and acute phase reactants[37] such as interleukin IL-6, tumor necrosis factor-a (TNFa) and ferritin cause to mortality.[38]Lactoferrin showed 50% inhibitory on human coronavirus of pseudo typed SARS-CoV that is most closely related with SARS-CoV-2 which causes COVID-19. Milk lactoferrin is effective for innate response to infections such as SARS-CoV-2.

Daily administration of 32 mg lactoferrin (liposomal bovine lactoferrin) for 10 days with zinc led to 100 % recovery of 75 SARS-CoV-2 positive patients within 4 – 5 days[39].

Conclusion

Milk lactoferrin of livestock can modulate immune responses to viral infections by binding to virus particles or receptors and may acts against viral attacks and reduce the severe infections, so it could be an adjunct treatment for more severe cases of COVID-19. Immuno-modulatory, anti-bacterial and antiviral properties of lactoferrin make it unique preventative agent against COVID-19. But it needs more studies to verify dosage and efficacy of lactoferrin on prevention and treatment of COVID-19. Therefore, lactoferrin as powder or tablets can be a novel promising method against viral infections and application as a drug carrier. According to this point that camel milk has highest amount of lactoferrin in comparison with the other species milks, so antiviral activity may be high as well; therefore, it will be a precious source of lactoferrin against the viruses. One important point is applying the indirect and mild heating for milks is necessary to save this protein and its anti-viral properties.

Conflict of interest: The authors declared that there is no conflict of interest regarding the publication of this article.

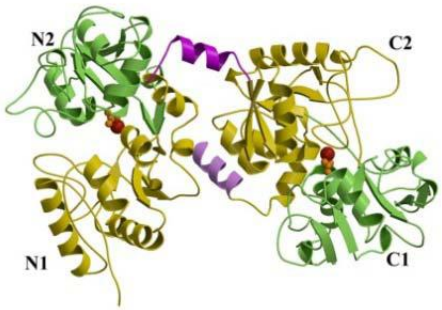

Figure 1: The bovine lactoferrin structure with two lobes and domains. Image is adapted from Baker and Baker, 2005.[30]

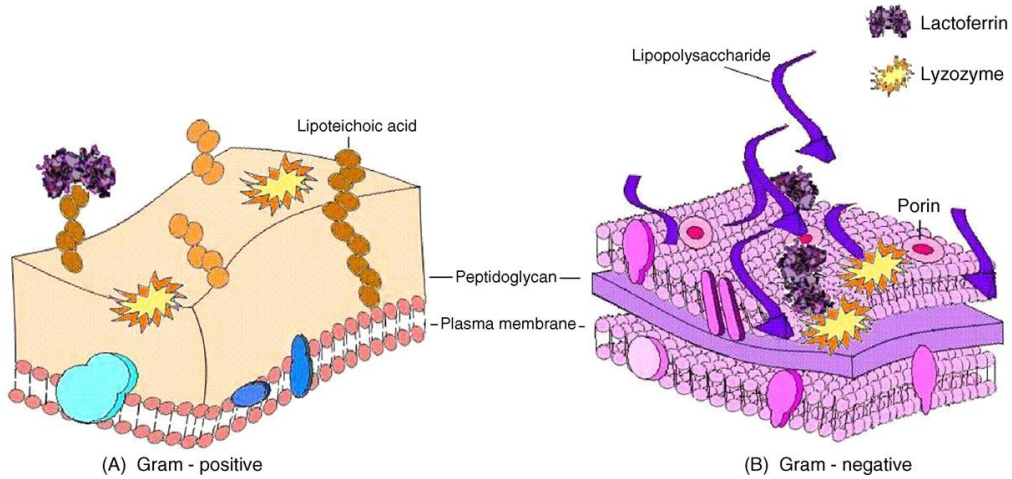

Figure 2: The inhibitory effect of lactoferrin against Gram-positive and Gram-negative bacteria. Image adapted from Gonzalez-Chavez *et al*., 2009.

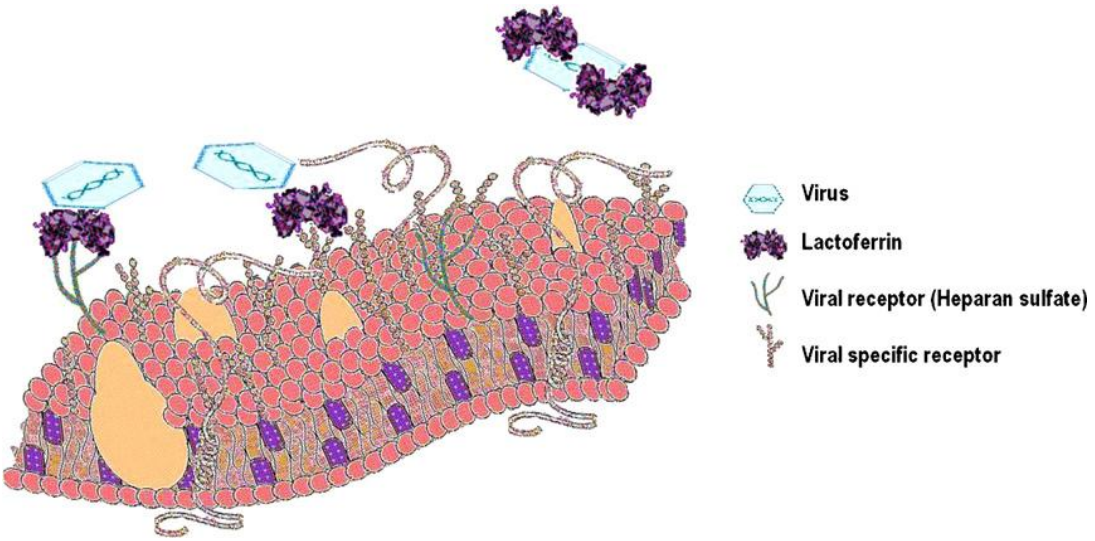

Figure 3: The inhibitory effects of lactoferrin against viruses. Image adapted from Gonzalez-Chavez *et al*., 2009.

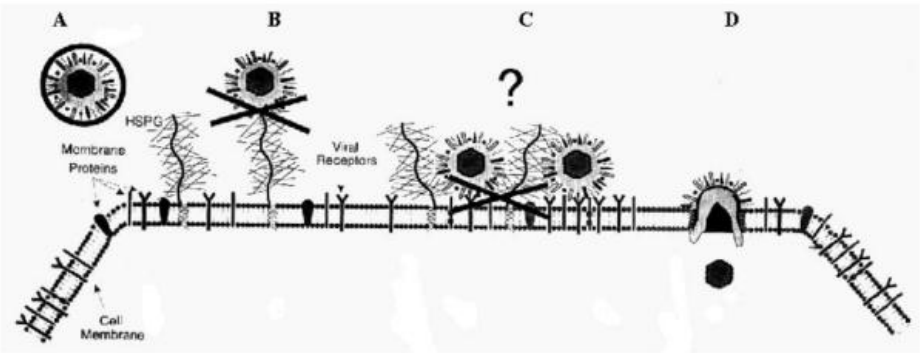

Figure 4: Antiviral action of lactoferrin against several viruses. Image adapted from Vanderstate et al 2001.[25]

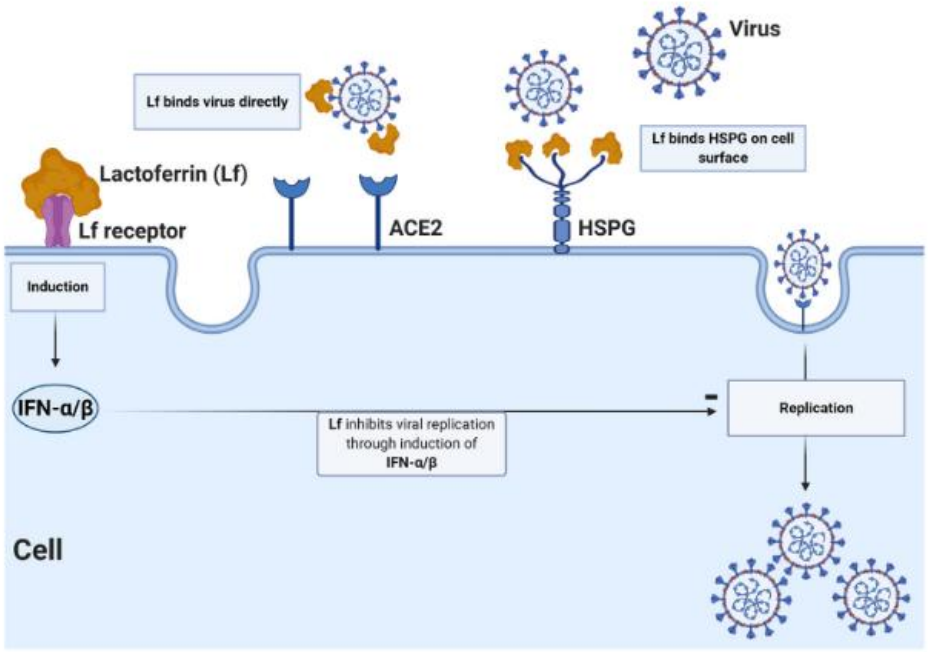

Figure 5: Antiviral mechanisms of lactoferrin. Image adapted from Changet al 2001.[39]

REFERENCES

1. Berlutti F, Pantanella F, Natalizi T, *et al*. Antiviral properties of lactoferrin—a natural immunity molecule. Molecules 2011; 16(8): 6992-7018.
2. González-Chávez SA, Arévalo-Gallegos S, Rascón-Cruz Q. Lactoferrin: structure, function and applications. International journal of antimicrobial agents 2009; 33(4):301. e301-301. e308.
3. Conesa C, Sánchez L, Rota C, et al. Isolation of lactoferrin from milk of different species: calorimetric and antimicrobial studies. Comparative Biochemistry and Physiology Part B: Biochemistry and Molecular Biology 2008; 150(1):131-139.
4. Okubo K, Kamiya M, Urano Y, et al. Lactoferrin suppresses neutrophil extracellular traps release in inflammation. EBioMedicine 2016; 10:204-215.
5. Alhaj O, Faye B, Agrawal R. Handbook of Research on Health and Environmental Benefits of Camel Products. 2020.
6. Mohammadabadi T, Gheibi, M. and Nikzad Z. 2018. Bioactive components in the milk of domestic animals. First ed: Haghshenass Publication.145.
7. El-Agamy E, Nawar M, Shamsia S, Awad S. 2006. The convenience of camel milk proteins for the nutrition of cow milk allergic children.42.
8. Zhang H, Yao J, Zhao D, Liu H, Li J, Guo M. 2005. Changes in chemical composition of Alxa Bactrian camel milk during lactation. Journal of Dairy Science 88(10):3402-3410.
9. Kell DB, Heyden EL, Pretorius E. 2020. The Biology of Lactoferrin, an Iron-Binding Protein That Can Help Defend Against Viruses and Bacteria. Frontiers in Immunology 11:1221.
10. Milewska A, Zarebski M, Nowak P, Stozek K, Potempa J, Pyrc K. 2014. Human coronavirus NL63 utilizes heparan sulfate proteoglycans for attachment to target cells. Journal of virology 88(22):13221-13230.
11. KanyshkovaTyG, Babina SE, Semenov DV, et al. 2003. Multiple enzymic activities of human milk lactoferrin. European journal of biochemistry 270(16):3353-3361.
12. OztasYesim E, Ozgunes N. 2005. Lactoferrin: a multifunctional protein. AdvMol Med.1:149-154.
13. Valenti P, Antonini G. 2005. Lactoferrin. Cellular and Molecular Life Sciences 62(22):2576.
14. Siqueiros-Cendón T, Arévalo-Gallegos S, Iglesias-Figueroa BF, García-Montoya IA, Salazar-Martínez J, Rascón-Cruz Q. 2014. Immunomodulatory effects of lactoferrin. Acta Pharmacologica Sinica 35(5):557-566.
15. de O Queiroz VA, Assis AMO, da Costa R Júnior H. 2013. Protective effect of human lactoferrin in the gastrointestinal tract. Revista Paulista de Pediatria31(1).
16. Puddu P, Valenti P, Gessani S. 2009. Immunomodulatory effects of lactoferrin on antigen presenting cells. Biochimie 91(1):11-18.

17. Britigan BE, Lewis TS, Waldschmidt M, McCormick ML, Krieg AM. 2001. Lactoferrin binds CpG-containing oligonucleotides and inhibits their immunostimulatory effects on human B cells. The Journal of Immunology 167(5):2921-2928.
18. Legrand D, Elass E, Carpentier M, Mazurier J. 2006. Interactions of lactoferrin with cells involved in immune function.Biochemistry and cell biology 84(3):282-290.
19. Legrand D. 2012.Lactoferrin, a key molecule in immune and inflammatory processes.Biochemistry and Cell Biology 90(3):252-268.
20. Embleton ND, Berrington JE, McGuire W, Stewart CJ, Cummings SP. Lactoferrin: antimicrobial activity and therapeutic potential. Paper presented at: Seminars in Fetal and Neonatal Medicine2013.
21. Orsi N. 2004. The antimicrobial activity of lactoferrin: current status and perspectives. Biometals17(3):189-196.
22. Jenssen H, Hancock RE. 2009. Antimicrobial properties of lactoferrin. Biochimie91(1):19-29.
23. Superti F, Berlutti F, Paesano R, Valenti P. 2008. Structure and activity of lactoferrin—A multi functional protective agent for human health.Iron Metabolism and Disease 8:1-32.
24. Seganti L, Di BiaseAM, Marchetti M, Pietrantoni A, Tinari A, Superti F. 2004. Antiviral activity of lactoferrin towards naked viruses.Biometals17(3):295-299.
25. Van der Strate B, Beljaars L, Molema G, Harmsen M, Meijer D. 2001. Antiviral activities of lactoferrin.Antiviral research 52(3):225-239.
26. Badr G, Ramadan NK, Sayed LH, Badr BM, Omar HM, Selamoglu Z. 2017. Why whey? Camel whey protein as a new dietary approach to the management of free radicals and for the treatment of different health disorders. Iranian journal of basic medical sciences 20(4):338.
27. Sano H, Nagai K, Tsutsumi H, Kuroki Y. 2003. Lactoferrin and surfactant protein A exhibit distinct binding specificity to F protein and differently modulate respiratory syncytial virus infection. European journal of immunology 33(10):2894-2902.
28. Yamamoto H, Ura Y, Tanemura M, et al. 2010 .Inhibitory effect of bovine lactoferrin on human parainfluenza virus type 2 infection. Journal of Health Science 56(5):613-617.
29. Vitetta L, Coulson S, Beck SL, Gramotnev H, Du S, Lewis S. 2013. The clinical efficacy of a bovine lactoferrin/whey protein Ig-rich fraction (Lf/IgF) for the common cold: A double blind randomized study. Complementary therapies in medicine 21(3):164-171.
30. Redwan ERM, Tabll A. 2007. Camel lactoferrin markedly inhibits hepatitis C virus genotype 4 infection of human peripheral blood leukocytes. Journal of immunoassay & immunochemistry 28(3):267-277.
31. EL-Fakharany EM, Sánchez L, Al-Mehdar HA, Redwan EM. 2013. Effectiveness of human, camel, bovine and sheep lactoferrin on the hepatitis C virus cellular infectivity: comparison study. Virology journal 10(1):199.
32. Young WP. Bioactive components in milk and dairy products.Wiley Blackwell; 2009.
33. Bruni N, Capucchio MT, Biasibetti E, et al. 2016. Antimicrobial activity of lactoferrin-related peptides and applications in human and veterinary medicine.Molecules 21(6):752.
34. Chen Y, Liu Q, Guo D. 2020. Emerging coronaviruses: genome structure, replication, and pathogenesis. Journal of medical virology 92(4):418-423.
35. Lang J, Yang N, Deng J, et al. 2011.Inhibition of SARS pseudovirus cell entry by lactoferrin binding to heparan sulfate proteoglycans. PloS one 6(8):e23710.
36. Peroni DG, Fanos V. 2020. Lactoferrin is an important factor when breastfeeding and COVID-19 are considered.ActaPaediatrica109:2139–2140.
37. Mehta P, McAuley DF, Brown M, et al. 2020. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet (London, England) 395(10229):1033.
38. Rosa L, Cutone A, Lepanto MS, Paesano R, Valenti P. 2017. Lactoferrin: a natural glycoprotein involved in iron and inflammatory homeostasis. International journal of molecular sciences 18(9):1985
39. Chang R, Zen Sun W, Bun Ng T. Lactoferrin as potential preventative and treatment for COVID-19.International Journal of Antimicrobial Agents 2020; 56 (3): 106118
40. Baker EN, Baker HM, 2005. Molecular structure, binding properties and dynamics of lactoferrin. Cell. Mol. Life Sci.62: 2531-2539.