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Potential Role of Lactoferrin and Heparin in COVID-19: A Review

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Abstract

Aim: The aim of the research is to evidence the potential role of lactoferrin (LF) and heparin in coronavirus disease 2019 (COVID-19). Moreover, we discuss and underline the mechanisms involved in this possible association. *Methods*: PubMed and Scopus databases were used to conduct the literature search. *Findings and Conclusion*: Studies have widely proven the principal activity of LF, in the inflammatory process, as an anti-inflammatory and immunomodulatory glycoprotein. Evidence shows that LF has important antibacterial and antiviral effects against human and animal pathogens. Heparin and LF could reduce viral entry by preventing the attachment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as a result of competitive binding to heparan sulfate proteoglycans (HSPGs). Clinical studies are necessary to specify LF and heparin mechanisms of action and the therapeutical dose in patient affected with COVID-19.

Keywords: Lactoferrin, heparin, coronaviruses, heparan sulfate proteoglycans

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in December 19, while a cluster of patients with acute respiratory illness of unknown origin was reported in Wuhan, China (Huang et al., 2020). The Coronavirus disease 2019 (COVID-19) outbreak, originated by the novel betacoronavirus with a high capacity of rapidly human to human transmission, has caused so far more than 2,000,000 deaths worldwide (Chan et al., 2020; WHO, 2020). While the number of COVID-19 cases are rising and the tabloid of the clinical signs is starting to be clearer, we still don't have a specific therapy nether a standardized analytic procedure for blood specific disease biomarkers.

The infection common clinical manifestations consist in high fever, chills, cough, shortness of breath, myalgia and rarely diarrhea (Guan et al., 2020). In the elderly a major risk of developing acute respiratory distress syndrome (ARDS), followed by a hyperactive immune reaction, is related to a higher mortality as a result of a severe manifestation of the infection (Chen et al., 2020). Studies demonstrated that the host cell entry of SARS-CoV-2 depends on the SARS-CoV receptor angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) suggesting potential antiviral targets for therapy (Hoffmann et al., 2020). The prevalent expression of ACE2 protein in the lung epithelia may help to understand the pathogenesis of the virus infecting primary the pneumocytes and quickly progressing to ARDS in certain cases (Hamming et al., 2004) but doesn't explain the multiorgan failure or the "cytokine storm". Activated neutrophil accumulation, especially in pneumocyte, may be associated with an aggravation of lungs damage as a result of fibrin deposition thought releases of procoagulant species (Kapoor et al., 2018). A subsequent alveolar fibrosis may explain the development and progression of respiratory complication and further cardiovascular failure. Moreover, lower limbs and deep vein thrombosis were observed mediate compression ultrasonography in COVID-19 patients suggesting also the presence of pulmonary embolies as a result of an impaired endothelial function (Panigada et al., 2020). Studies showed also that patients presenting cardiopathies were more susceptible to this coagulation dysregulations (Shi et al., 2020).

Carefully observing the further laboratory blood analysis in different studies (Chen et al., 2020; Wu et al., 2020; Chen et al., 2020; Wang et al., 2020), we can detect the main anomalies such as a decreased lymphocyte count, higher neutrophil count, elevated C-reactive protein (CRP) and elevated lactate dehydrogenase in COVID-19 patients. Especially a pronounced elevated D-dimer serum level (≥ 0.5 mg/L) was more noticeable among severe cases (Guan et al., 2020). Indeed, the most important predictor of the severity

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of the disease are the increased expression of interleukin 2 (IL-2) and interleukin 6 (IL-6) in these patients serum (Chen et al., 2020).

This pro-inflammation biomarkers pool, through time, lead to a systemic inflammation compromising multiple cell types in several organs. Hepatocyte damage, sensitively indicated by alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevated serum levels (Pelsers et al., 2002), presents important abnormalities in the biochemical liver profile in COVID-19 severe cases (Wu et al., 2020). Pronounced increased levels of CRP, principally synthesized in these cells, promote excess thrombin response and fibrin formation (Idell et al., 1991). Further, an excessive release of essential pro-coagulation proteins such as factor VIII (FVIII) and von Willebrand factor was observed (Panigada et al., 2020). Coagulation factor FVIII levels increase with age (Luxembourg et al., 2009) and result as the strongest risk factor for chronic thromboembolic and pulmonary arterial hypertension inflammation (Shovlin et al., 2007; Kyrle et al., 2000). Additionally, IL-6 in the liver contributes to an up-regulation of the hepcidin synthesis as a principal iron homeostasis regulator (Ganz, 2011). Hight CRP level is also a marker related to increased serum hepcidin concentrations (Iqbal et al., 2015). Consequently, iron export from macrophage, duodenal enterocyte and hepatocytes decreases because of ferroportin internalization, reducing therefore serum iron, resulting in a diminished free iron level available and in an intracellular iron overload which can promote viral replication and spread (Ganz, 2011). Low blood iron level has been linked to a high FVIII concentration (Begbie et al., 2000). Moreover, we cannot exclude the possibility that an iron deficiency might elevate the risk of thrombosis as a result of a further serum elevation of factor FVIII. Clearly these biochemical alterations indicate a deep impact in the hemostasis of hematopoietic system, iron and cell life span.

The dysfunction of these complex fundamental mechanisms, persisting in time, can profoundly damage the balance of the coagulation pathway in the microvascular bed of the organs leading to increased blood viscosity and prothrombotic endothelial events. These could influence the COVID-19 condition resulting in an additional multi-organ oxygen deprivation as a result of an impaired homeostatic mechanisms of the organism to solve it, especially in elderly patients with multiple underlying pathologies. Therefore, this impairment could explain the increased mortality and morbidity as a result of respiratory, heart, and liver failure among patients with comorbidities.

Lactoferrin (LF) is a versatile glycoprotein, with an important role on iron homeostasis (Levay and Viljoen, 1995), which secretion occurs in various mucosal fluids presented in higher concentration in breast milk (Trend et al., 2016). LF has a significant activity in the innate immune system and enhance

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human and animal immunity against bacterial and viral infections (Teraguchi et al., 2004; Redwan et al., 2014). The ability to inhibit the entry and replication into the host cell involve multi-mechanisms. LF improve host's antiinflammatory response in particular by directly binding to the pathogen particles, blocking their cellular receptors or stabilizing immune factors (Elass-Rochard et al., 1998; Baveye et al., 1999). LF prevents the entry of both DNA and RNA viruses (Ng et al., 2015; Wakabayashi et al., 2014) which commonly utilize heparan sulfate proteoglycans (HSPGs) on cell membrane host to accelerate their internalization (Andersen et al., 2004; Belting, 2003). Recently, was suggested that SARS-CoV-2 could require a second interaction through binding to HSPGs to facilitate cell entry (Clausen et al., 2020; Zhang et al., 2020). Therefore, LF could achieve an important role against COVID-19 infection blocking SARS-CoV-2 internalization by competitively binding to HSPGs (Lang et al., 2011) (Figure 1). Also, the antiinflammation potential of LF restrict tissue damage by directly restoring iron homeostasis and immunomodulating pro-inflammation molecules during the cytokine "storm" (Legrand, 2016). LF implement an immunomodulation activity controlling the release of proinflammatory cytokines like IL-6 and TNFα. (Valenti et al., 2017). Also, this glycoprotein can increase phagocytosis and directly bind iron to prevent oxidative stress induced by reactive oxygen species (ROS) that forms during excess inflammatory response (Frioni et al., 2014; Kell and Pretorius, 2018). Hence, LF could also implement a preventive role in hypercoagulation events and low thrombocyte levels in COVID-19 infection. Actually, in order to limit the related coagulation dysregulation, a prophylactic antithrombotic therapy with low molecular weight heparins or unfractionated heparin has been utilized as shown in some studies (Tang et al., 2020; Hunt et al., 2020). Due to probable drug interactions, heparin has been proposed over direct oral anticoagulants (Thachil et al., 2020). Additionally, it was observed that glycosaminoglycans such as heparin could explicate an important antiviral role in COVID-19 infection potentially based on the ability to interfere with some receptors used by coronaviruses such as HSPGs (Clausen et al., 2020). Data support that heparin can reduce viral entry as a result of a competitive inhibition of spike-mediated SARS-CoV and CoV-2 entry reducing therefore the virus load (Zhang et al., 2020). Further studies are needed to better characterize the new potential therapeutic mechanism of action, the type and dose of heparin for creating a standardize protocol of prevention.

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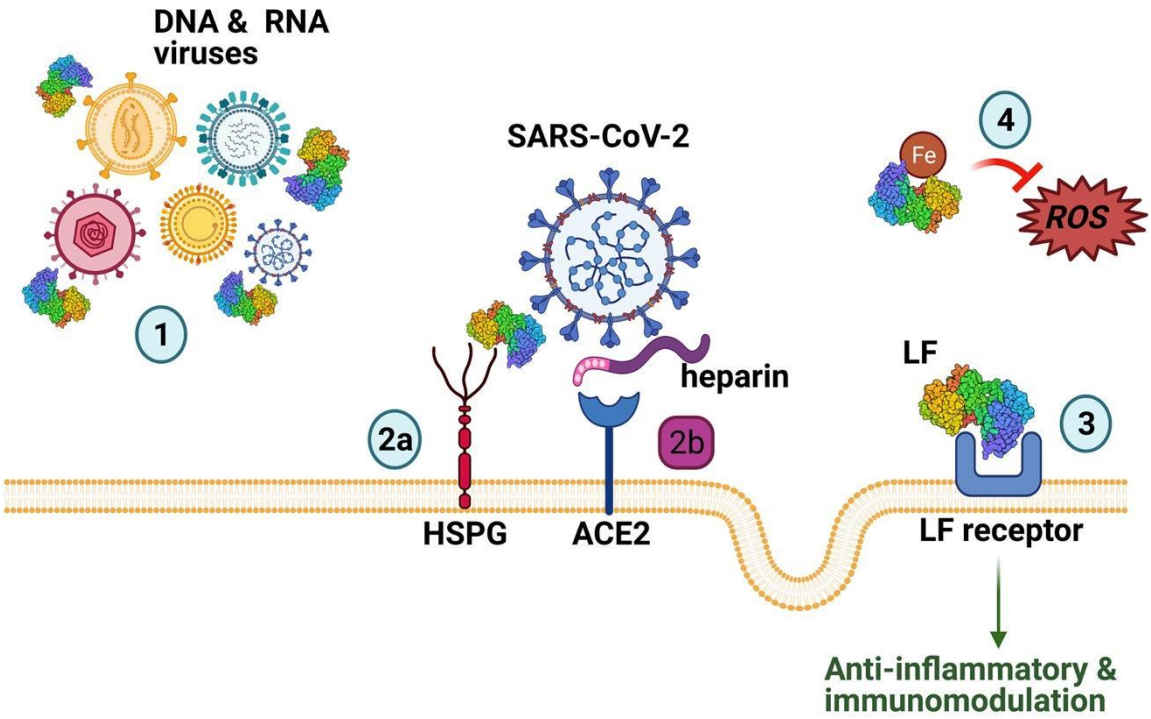

Figure 1. Overview of LF and heparin possible mechanisms involved in COVID-19: 1) LF directly binding to the pathogen, 2a) LF could block SARS-CoV-2 internalization by competitively binding to HSPGs, 2b) probable heparin competitive inhibition of spike-mediated SARS-CoV-2 entry, 3) LF antiinflammation potential and immunomodulation activity to restrict tissue damage, 4) LF directly bind iron to prevent oxidative stress. (Figure created with Biorender)

Consequently, a possible iron homeostasis surveillance with an accurate clinical diagnosis for a probable iron serum deficiency or cells overload condition may be necessary especially in anemic cases, hereditary hemochromatosis, thalassemic patients and viral hepatitis patients (Drakesmith and Prentice, 2008). Regarding the biomarker predictors to quickly diagnose a potential iron deficiency might be the examination of serum hepcidin levels (Theurl et al., 2009; Motta et al., 2020). Instead, elevated presence of serum ferritin in COVID-19 patients might potentially reflect inflammation rather than iron stores, not excluding an iron deficiency (Witte, 1991).

Conclusion

In summary, a new approach for an accurate clinical evaluation of specific biomarkers on time and an adequate therapeutical intervention could represent an important factor to limit the complications and improve the pathogenesis of COVID-19 especially in patients with comorbidities. LF could

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represent a safe approach that may be applied to prevent or treat COVID-19. Nevertheless, large clinical trials are needed to ensure the supposed mechanisms of action and to evaluate the safe and effective treatment dose for COVID-19 patients.

References:

1. Andersen JH, Jenssen H, Sandvik K, Gutteberg TJ. Anti-HSV activity of lactoferrin and lactoferricin is dependent on the presence of heparan sulphate at the cell surface. J Med Virol. 2004 Oct;74(2):262-71.
2. Baveye S, Elass E, Mazurier J, Spik G, Legrand D. Lactoferrin: a multifunctional glycoprotein involved in the modulation of the inflammatory process. Clin Chem Lab Med. 1999 Mar;37(3):281-6.
3. Begbie M, Notley C, Tinlin S, Sawyer L, Lillicrap D. The Factor VIII acute phase response requires the participation of NFkappaB and C/EBP. Thromb Haemost. 2000 Aug;84(2):216-22.
4. Belting M. Heparan sulfate proteoglycan as a plasma membrane carrier. Trends Biochem Sci. 2003 Mar;28(3):145-51.
5. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, Xing F, Liu J, Yip CC, Poon RW, Tsoi HW, Lo SK, Chan KH, Poon VK, Chan WM, Ip JD, Cai JP, Cheng VC, Chen H, Hui CK, Yuen KY. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 2020 Feb 15;395(10223):514-523.
6. Chen L, Liu HG, Liu W, Liu J, Liu K, Shang J, Deng Y, Wei S. [Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia]. Zhonghua Jie He He Hu Xi Za Zhi. 2020 Mar 12;43(3):203-208. Chinese.
7. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, Ma K, Xu D, Yu H, Wang H, Wang T, Guo W, Chen J, Ding C, Zhang X, Huang J, Han M, Li S, Luo X, Zhao J, Ning Q. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020 Mar 26;368:m1091.
8. Clausen TM, Sandoval DR, Spliid CB, Pihl J, Perrett HR, Painter CD, Narayanan A, Majowicz SA, Kwong EM, McVicar RN, Thacker BE, Glass CA, Yang Z, Torres JL, Golden GJ, Bartels PL, Porell RN, Garretson AF, Laubach L, Feldman J, Yin X, Pu Y, Hauser BM, Caradonna TM, Kellman BP, Martino C, Gordts PLSM, Chanda SK, Schmidt AG, Godula K, Leibel SL, Jose J, Corbett KD, Ward AB, Carlin AF, Esko JD. SARS-CoV-2 Infection Depends on Cellular Heparan Sulfate and ACE2. Cell. 2020 Nov 12;183(4):1043-1057.e15.
9. Drakesmith H, Prentice A. Viral infection and iron metabolism. Nat Rev Microbiol. 2008 Jul;6(7):541-52.

 ISSN: 1857-7881 (Print) e - ISSN 1857-7431

10. Elass-Rochard E, Legrand D, Salmon V, Roseanu A, Trif M, Tobias PS, Mazurier J, Spik G. Lactoferrin inhibits the endotoxin interaction with CD14 by competition with the lipopolysaccharide-binding protein. Infect Immun. 1998 Feb;66(2):486-91.
11. Frioni A, Conte MP, Cutone A, Longhi C, Musci G, di Patti MC, Natalizi T, Marazzato M, Lepanto MS, Puddu P, Paesano R, Valenti P, Berlutti F. Lactoferrin differently modulates the inflammatory response in epithelial models mimicking human inflammatory and infectious diseases. Biometals. 2014 Oct;27(5):843-56.
12. Ganz T. Hepcidin and iron regulation, 10 years later. Blood. 2011 Apr 28;117(17):4425-33.
13. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020 Apr 30;382(18):1708-1720.
14. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004 Jun;203(2):631-7.
15. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020 Apr 16;181(2):271-280.e8.
16. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497-506.
17. Hunt B, Retter, A., McClintock, C. Practical guidance for the prevention of thrombosis and management of coagulopathy and disseminated intravascular coagulation of patients infected with COVID-19. British Society for Haematology. 2020.
18. Idell S, Koenig KB, Fair DS, Martin TR, McLarty J, Maunder RJ. Serial abnormalities of fibrin turnover in evolving adult respiratory distress syndrome. Am J Physiol. 1991;261:L240-8.

 ISSN: 1857-7881 (Print) e - ISSN 1857-7431

19. Iqbal T, Stein J, Sharma N, Kulnigg-Dabsch S, Vel S, Gasche C. Clinical significance of C-reactive protein levels in predicting responsiveness to iron therapy in patients with inflammatory bowel disease and iron deficiency anemia. Dig Dis Sci. 2015 May;60(5):1375-81.
20. Kapoor S, Opneja A, Nayak L. The role of neutrophils in thrombosis. Thromb Res. 2018;170:87-96.
21. Kell DB, Pretorius E. No effects without causes: the Iron Dysregulation and Dormant Microbes hypothesis for chronic, inflammatory diseases. Biol Rev Camb Philos Soc. 2018 Aug;93(3):1518-1557.
22. Kyrle PA, Minar E, Hirschl M, Bialonczyk C, Stain M, Schneider B, Weltermann A, Speiser W, Lechner K, Eichinger S. High plasma levels of factor VIII and the risk of recurrent venous thromboembolism. N Engl J Med. 2000 Aug 17;343(7):457-62.
23. Lang J, Yang N, Deng J, Liu K, Yang P, Zhang G, Jiang C. Inhibition of SARS pseudovirus cell entry by lactoferrin binding to heparan sulfate proteoglycans. PLoS One. 2011;6(8):e23710.
24. Legrand D. Overview of Lactoferrin as a Natural Immune Modulator. J Pediatr. 2016 Jun;173 Suppl:S10-5.
25. Levay PF, Viljoen M. Lactoferrin: a general review. Haematologica. 1995 May-Jun;80(3):252-67.
26. Luxembourg B, Schmitt J, Humpich M, Glowatzki M, Seifried E, Lindhoff-Last E. Intrinsic clotting factors in dependency of age, sex, body mass index, and oral contraceptives: definition and risk of elevated clotting factor levels. Blood Coagul Fibrinolysis. 2009 Oct;20(7):524-34.
27. Motta I, Migone De Amicis M, Pinto VM, Balocco M, Longo F, Bonetti F, Gianesin B, Graziadei G, Cappellini MD, De Franceschi L, Piga A, Forni GL. SARS-CoV-2 infection in beta thalassemia: Preliminary data from the Italian experience. Am J Hematol. 2020 Aug;95(8):E198-E199.
28. Ng TB, Cheung RC, Wong JH, Wang Y, Ip DT, Wan DC, Xia J. Antiviral activities of whey proteins. Appl Microbiol Biotechnol. 2015 Sep;99(17):6997-7008.
29. Panigada M, Bottino N, Tagliabue P, Grasselli G, Novembrino C, Chantarangkul V, Pesenti A, Peyvandi F, Tripodi A. Hypercoagulability of COVID-19 patients in intensive care unit: A report of thromboelastography findings and other parameters of hemostasis. J Thromb Haemost. 2020 Jul;18(7):1738-1742.
30. Pelsers MM, Moravat A, Alexander GJM, Hermens WT, Trull AK, Glatz JFC. Liver fatty acid-binding protein as a sensitive serum marker

 ISSN: 1857-7881 (Print) e - ISSN 1857-7431

of acute hepato- cellular damage in liver transplant recipients. Clin Chem. 2002; 48:2055–7.

31. Redwan EM, Uversky VN, El-Fakharany EM, Al-Mehdar H. Potential lactoferrin activity against pathogenic viruses. C R Biol. 2014 Oct;337(10):581-95.
32. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, Huang H, Yang B, Huang C. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiol. 2020 Jul 1;5(7):802-810.
33. Shovlin CL, Sulaiman NL, Govani FS, Jackson JE, Begbie ME. Elevated factor VIII in hereditary haemorrhagic telangiectasia (HHT): association with venous thromboembolism. Thromb Haemost. 2007 Nov;98(5):1031-9.
34. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020 May;18(5):1094-1099.
35. Teraguchi S, Wakabayashi H, Kuwata H, Yamauchi K, Tamura Y. Protection against infections by oral lactoferrin: evaluation in animal models. Biometals. 2004 Jun;17(3):231-4.
36. Thachil J, Tang N, Gando S, Falanga A, Levi M, Clark C, Iba T, Cattaneo M. Type and dose of heparin in Covid-19: Reply. J Thromb Haemost. 2020 Aug;18(8):2063-2064.
37. Theurl I, Aigner E, Theurl M, Nairz M, Seifert M, Schroll A, Sonnweber T, Eberwein L, Witcher DR, Murphy AT, Wroblewski VJ, Wurz E, Datz C, Weiss G. Regulation of iron homeostasis in anemia of chronic disease and iron deficiency anemia: diagnostic and therapeutic implications. Blood. 2009 May 21;113(21):5277-86.
38. Trend S, Strunk T, Lloyd ML, Kok CH, Metcalfe J, Geddes DT, Lai CT, Richmond P, Doherty DA, Simmer K, Currie A. Levels of innate immune factors in preterm and term mothers' breast milk during the 1st month postpartum. Br J Nutr. 2016 Apr 14;115(7):1178-93.
39. Valenti P, Frioni A, Rossi A, Ranucci S, De Fino I, Cutone A, Rosa L, Bragonzi A, Berlutti F. Aerosolized bovine lactoferrin reduces neutrophils and pro-inflammatory cytokines in mouse models of Pseudomonas aeruginosa lung infections. Biochem Cell Biol. 2017 Feb;95(1):41-47.
40. Wakabayashi H, Oda H, Yamauchi K, Abe F. Lactoferrin for prevention of common viral infections. J Infect Chemother. 2014 Nov;20(11):666-71.
41. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics

 ISSN: 1857-7881 (Print) e - ISSN 1857-7431

of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020 Mar 17;323(11):1061-1069.

42. Witte DL. Can serum ferritin be effectively interpreted in the presence of the acute-phase response? Clin Chem. 1991 Apr;37(4):484-5.
43. World Health Organization [Available from: https://covid19.who.int/]
44. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Zhou X, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J, Song Y. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020 Jul 1;180(7):934-943.
45. Zhang Q, Chen CZ, Swaroop M, Xu M, Wang L, Lee J, Wang AQ, Pradhan M, Hagen N, Chen L, Shen M, Luo Z, Xu X, Xu Y, Huang W, Zheng W, Ye Y. Heparan sulfate assists SARS-CoV-2 in cell entry and can be targeted by approved drugs in vitro. Cell Discov. 2020 Nov 4;6(1):80.
46. Zhang Q, Chen CZ, Swaroop M, Xu M, Wang L, Lee J, Wang AQ, Pradhan M, Hagen N, Chen L, Shen M, Luo Z, Xu X, Xu Y, Huang W, Zheng W, Ye Y. Targeting heparan sulfate proteoglycan-assisted endocytosis as a COVID-19 therapeutic option. bioRxiv [Preprint]. 2020 Jul 14:2020.07.14.202549.