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OPINION REVIEW

- 11665** Combined use of lactoferrin and vitamin D as a preventive and therapeutic supplement for SARS-CoV-2 infection: Current evidence
Cipriano M, Ruberti E, Tovani-Palone MR

REVIEW

- 11671** Role of adherent invasive *Escherichia coli* in pathogenesis of inflammatory bowel disease
Zheng L, Duan SL, Dai YC, Wu SC
- 11690** Emerging potential of ubiquitin-specific proteases and ubiquitin-specific proteases inhibitors in breast cancer treatment
Huang ML, Shen GT, Li NL

MINIREVIEWS

- 11702** Overlap of diabetic ketoacidosis and hyperosmolar hyperglycemic state
Hassan EM, Mushtaq H, Mahmoud EE, Chhibber S, Saleem S, Issa A, Nitesh J, Jama AB, Khedr A, Boike S, Mir M, Attallah N, Surani S, Khan SA

ORIGINAL ARTICLE**Case Control Study**

- 11712** Comparing the efficacy of different dexamethasone regimens for maintenance treatment of multiple myeloma in standard-risk patients non-eligible for transplantation
Hu SL, Liu M, Zhang JY

Retrospective Cohort Study

- 11726** Development and validation of novel nomograms to predict survival of patients with tongue squamous cell carcinoma
Luo XY, Zhang YM, Zhu RQ, Yang SS, Zhou LF, Zhu HY

Retrospective Study

- 11743** Non-invasive model for predicting esophageal varices based on liver and spleen volume
Yang LB, Zhao G, Tantai XX, Xiao CL, Qin SW, Dong L, Chang DY, Jia Y, Li H

Clinical Trials Study

- 11753** Clinical efficacy of electromagnetic field therapy combined with traditional Chinese pain-reducing paste in myofascial pain syndrome
Xiao J, Cao BY, Xie Z, Ji YX, Zhao XL, Yang HJ, Zhuang W, Sun HH, Liang WM

- 11766** Endothelial injury and inflammation in patients with hyperuricemic nephropathy at chronic kidney disease stages 1-2 and 3-4

Xu L, Lu LL, Wang YT, Zhou JB, Wang CX, Xin JD, Gao JD

Observational Study

- 11775** Quality of life and symptom distress after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

Wang YF, Wang TY, Liao TT, Lin MH, Huang TH, Hsieh MC, Chen VCH, Lee LW, Huang WS, Chen CY

- 11789** Development and validation of a risk assessment model for prediabetes in China national diabetes survey

Yu LP, Dong F, Li YZ, Yang WY, Wu SN, Shan ZY, Teng WP, Zhang B

Case Control Study

- 11804** T-cell immunoglobulin mucin molecule-3, transformation growth factor β , and chemokine-12 and the prognostic status of diffuse large B-cell lymphoma

Wu H, Sun HC, Ouyang GF

META-ANALYSIS

- 11812** Prostate artery embolization on lower urinary tract symptoms related to benign prostatic hyperplasia: A systematic review and meta-analysis

Wang XY, Chai YM, Huang WH, Zhang Y

CASE REPORT

- 11827** Paraneoplastic neurological syndrome caused by cystitis glandularis: A case report and literature review

Zhao DH, Li QJ

- 11835** Neck pain and absence of cranial nerve symptom are clues of cervical myelopathy mimicking stroke: Two case reports

Zhou LL, Zhu SG, Fang Y, Huang SS, Huang JF, Hu ZD, Chen JY, Zhang X, Wang JY

- 11845** Nine-year survival of a 60-year-old woman with locally advanced pancreatic cancer under repeated open approach radiofrequency ablation: A case report

Zhang JY, Ding JM, Zhou Y, Jing X

- 11853** Laparoscopic treatment of inflammatory myofibroblastic tumor in liver: A case report

Li YY, Zang JF, Zhang C

- 11861** Survival of a patient who received extracorporeal membrane oxygenation due to postoperative myocardial infarction: A case report

Wang QQ, Jiang Y, Zhu JG, Zhang LW, Tong HJ, Shen P

- 11869** Triple hit to the kidney-dual pathological crescentic glomerulonephritis and diffuse proliferative immune complex-mediated glomerulonephritis: A case report

Ibrahim D, Brodsky SV, Satoskar AA, Biederman L, Maroz N

- 11877** Successful transcatheter arterial embolization treatment for chest wall haematoma following permanent pacemaker implantation: A case report
Zheng J, Tu XM, Gao ZY
- 11882** Brachiocephalic to left brachial vein thrombotic vasculitis accompanying mediastinal pancreatic fistula: A case report
Kokubo R, Yunaiyama D, Tajima Y, Kugai N, Okubo M, Saito K, Tsuchiya T, Itoi T
- 11889** Long survival after immunotherapy plus paclitaxel in advanced intrahepatic cholangiocarcinoma: A case report and review of literature
He MY, Yan FF, Cen KL, Shen P
- 11898** Successful treatment of pulmonary hypertension in a neonate with bronchopulmonary dysplasia: A case report and literature review
Li J, Zhao J, Yang XY, Shi J, Liu HT
- 11908** Idiopathic tenosynovitis of the wrist with multiple rice bodies: A case report and review of literature
Tian Y, Zhou HB, Yi K, Wang KJ
- 11921** Endoscopic resection of bronchial mucoepidermoid carcinoma in a young adult man: A case report and review of literature
Ding YM, Wang Q
- 11929** Blue rubber bleb nevus syndrome complicated with disseminated intravascular coagulation and intestinal obstruction: A case report
Zhai JH, Li SX, Jin G, Zhang YY, Zhong WL, Chai YF, Wang BM
- 11936** Management of symptomatic cervical facet cyst with cervical interlaminar epidural block: A case report
Hwang SM, Lee MK, Kim S
- 11942** Primary squamous cell carcinoma with sarcomatoid differentiation of the kidney associated with ureteral stone obstruction: A case report
Liu XH, Zou QM, Cao JD, Wang ZC
- 11949** Successful live birth following hysteroscopic adhesiolysis under laparoscopic observation for Asherman's syndrome: A case report
Kakinuma T, Kakinuma K, Matsuda Y, Ohwada M, Yanagida K
- 11955** What is responsible for acute myocardial infarction in combination with aplastic anemia? A case report and literature review
Zhao YN, Chen WW, Yan XY, Liu K, Liu GH, Yang P
- 11967** Repeated ventricular bigeminy by trigeminocardiac reflex despite atropine administration during superficial upper lip surgery: A case report
Cho SY, Jang BH, Jeon HJ, Kim DJ
- 11974** Testis and epididymis-unusual sites of metastatic gastric cancer: A case report and review of the literature
Ji JJ, Guan FJ, Yao Y, Sun LJ, Zhang GM

- 11980** t(4;11) translocation in hyperdiploid *de novo* adult acute myeloid leukemia: A case report
Zhang MY, Zhao Y, Zhang JH
- 11987** Sun-burn induced upper limb lymphedema 11 years following breast cancer surgery: A case report
Li M, Guo J, Zhao R, Gao JN, Li M, Wang LY
- 11993** Minimal change disease caused by polycythemia vera: A case report
Xu L, Lu LL, Gao JD
- 12000** Vitreous amyloidosis caused by a Lys55Asn variant in transthyretin: A case report
Tan Y, Tao Y, Sheng YJ, Zhang CM
- 12007** Endoscopic nasal surgery for mucocele and pyogenic mucocele of turbinate: Three case reports
Sun SJ, Chen AP, Wan YZ, Ji HZ
- 12015** Transcatheter arterial embolization for traumatic injury to the pharyngeal branch of the ascending pharyngeal artery: Two case reports
Yunaiyama D, Takara Y, Kobayashi T, Muraki M, Tanaka T, Okubo M, Saguchi T, Nakai M, Saito K, Tsukahara K, Ishii Y, Homma H
- 12022** Retroperitoneal leiomyoma located in the broad ligament: A case report
Zhang XS, Lin SZ, Liu YJ, Zhou L, Chen QD, Wang WQ, Li JY
- 12028** Primary testicular neuroendocrine tumor with liver lymph node metastasis: A case report and review of the literature
Xiao T, Luo LH, Guo LF, Wang LQ, Feng L
- 12036** Endodontic treatment of the maxillary first molar with palatal canal variations: A case report and review of literature
Chen K, Ran X, Wang Y
- 12045** Langerhans cell histiocytosis involving only the thymus in an adult: A case report
Li YF, Han SH, Qie P, Yin QF, Wang HE

LETTER TO THE EDITOR

- 12052** Heart failure with preserved ejection fraction: A distinct heart failure phenotype?
Triposkiadis F, Giamouzis G, Skoularigis J, Xanthopoulos A
- 12056** Insight into appropriate medication prescribing for elderly in the COVID-19 era
Omar AS, Kaddoura R
- 12059** Commentary on "Gallstone associated celiac trunk thromboembolisms complicated with splenic infarction: A case report"
Tokur O, Aydın S, Kantarci M
- 12062** Omicron targets upper airways in pediatrics, elderly and unvaccinated population
Nori W, Ghani Zghair MA

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Editorial Board Member of *World Journal of Clinical Cases*, Camelia Cristina Diaconu, FACC, FACP, FESC, MHSc, PhD, Associate Professor, Department of Internal Medicine, "Carol Davila" University of Medicine and Pharmacy, Clinical Emergency Hospital of Bucharest, Bucharest 014461, Romania. drcameliadiaconu@gmail.com

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Combined use of lactoferrin and vitamin D as a preventive and therapeutic supplement for SARS-CoV-2 infection: Current evidence

Massimiliano Cipriano, Enzo Ruberti, Marcos Roberto Tovani-Palone

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Massimiliano Cipriano, Department of Laparoscopic Surgery, Umberto I General Hospital, Medical School Sapienza University, Rome 161, Italy

Enzo Ruberti, Department of Human Neuroscience, Sapienza University of Rome, Rome 00185, Italy

Marcos Roberto Tovani-Palone, Department of Research Analytics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Chennai 600 077, India

Corresponding author: Marcos Roberto Tovani-Palone, PhD, Academic Research, Department of Research Analytics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Chennai 600 077, India. marcos_palone@hotmail.com

Abstract

Lactoferrin is a multifunctional protein that exhibits anti-inflammatory, immune regulating and anti-infective properties. One of its receptor sites is located on severe acute respiratory syndrome coronavirus 2. The binding of lactoferrin with heparin sulfate proteoglycans may prevent the first contact between the virus and host cells, thus preventing subsequent infection. Given that lactoferrin may act as a natural mucosal barrier, an intranasal treatment together with its oral intake can be hypothesized to prevent the spread, infection and inflammation caused by coronavirus disease 2019 (COVID-19). Moreover, the literature reports that vitamin D plays an essential role in promoting immune response. With its anti-inflammatory and immunoregulatory properties, vitamin D is critical for activating the immune system's defenses, improving immune cell function. Different studies also demonstrate that lactoferrin is a potential activator of the vitamin D receptor. In this sense, the combined use of lactoferrin (through an association of oral intake and a nasal spray formulation) and vitamin D could represent a valuable therapy for COVID-19 treatment and prevention. However, further randomized clinical trials are needed before recommending/prescribing them.

Key Words: Lactoferrin; Vitamin D; SARS-CoV-2; COVID-19; Pandemics

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Core Tip: The combined use of lactoferrin, using a nasal spray formulation in association with its oral intake, and vitamin D could represent, through a synergistic action, a valuable therapy for coronavirus disease 2019 treatment and prevention.

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INTRODUCTION

Lactoferrin (LF), which belongs to the genus of glycoproteins and is contained in human secretions, is part of a non-specific defense system with a significant role in fighting both bacterial and viral infections, in addition to producing significant anti-inflammatory effects on various mucosal surfaces and acting in the regulation of iron metabolism[1]. However, it is worth noting that the biological activities of LF have been attributed only in part to the iron-sequestering activity[2], given that its mechanism of action also involves binding to other specific receptors, cell signaling and protein folding [3,4]. An important study reported that LF can directly interact with virus capsid proteins[5], which may hinder viral entry into target cells by blocking the virus from binding to host cell components that are used as receptors or co-receptors.

Direct binding of LF to viral particles has been recognized in the literature for many viruses[6-9]. In this sense, a protective role of LF could also occur in relation to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection[10,11]. In this review, we discuss evidence on the potential clinical and molecular effects of LF (alone or in combination with another supplement) related to coronavirus disease 2019 (COVID-19) prevention or treatment.

SCIENTIFIC FINDINGS SUPPORTING THE ROLE OF LACTOFERRIN IN SARS-COV-2 INFECTION

In the current scientific landscape, special attention has been paid to the potential role of LF as a supplemental adjuvant, whether in terms of preventing SARS-CoV-2 infection or treating COVID-19, due to its ability to interact with different receptors. Results of recent research show that the cellular entry of the virus occurs *via* high-affinity interactions between the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein and the human host angiotensin-converting enzyme 2 (ACE2) receptor[12]. However, for cellular entry of the virus, there must also be the interaction of SARS-CoV-2 with other molecules, including heparan sulfate and cell proteases (such as lysosome-localized Cathepsin B/L and serine proteases of the TMPRSS family). This is essential to virus adhesion to the cell membrane, which may facilitate the interaction of the viral spike protein with the ACE-2 receptor, as well as the internalization process of SARS-CoV-2[13-15].

In particular the binding of LF with heparin sulfate proteoglycans (HSPG) may prevent the first contact between the virus and host cells, thus preventing subsequent infection. Indeed, in SARS-CoV-2 infections, HSPGs play a considerable role in the cell entry process, as the anchoring sites provided by HSPGs allow the initial interaction between SARS-CoV-2 and host cells and the concentration of viral particles on the cell surface. In other words, the virus, by binding to HSPGs, rolls across the cell membrane and scans specific entry receptors, thus enhancing the ability of the virus to infect the host cell[16].

Computational studies[17] have sought explanations for a direct interaction between LF and the ACE2 receptor or between LF and the viral spike protein, identifying possible reciprocal interactions that may provide a molecular explanation for the preventive effect of LF against SARS-CoV-2 infection. The results found show that LF has the ability to bind to the ectodomain of ACE2 with a significantly high affinity. On the other hand, the researchers did not observe any binding to RBD up to the maximum "physiological" concentration range of LF. This suggests that the inhibitory effect of LF on the formation of the ACE2/RBD complex may be related to its binding to the ACE2 receptor, thus weakening the evidence of binding to the RBD domain of the spike protein[18].

Based on data from the animal and human studies, Zimecki *et al*[19] postulated that LF may have a clinical benefit in preventing and ameliorating the COVID-19 induced cytokine storm and its devastating consequences on lungs and other vital organs. Kell *et al*[20] suggest a similar process. More precisely, LF is capable of performing two functions in cases of SARS-CoV-2 infection: On the one hand,

it sequesters iron and inflammatory molecules that significantly increase during the cytokine storm; on the other hand, it helps to occupy receptors (ACE2/RBD) and HSPGs, preventing the virus from binding to host cells. Receptor blockade is, in fact, an important peculiarity of LF, when used as a supplement. Moreover, LF may help prevent thrombocytopenia and hypercoagulation, which are major complications of COVID-19.

Studies with swabs for SARS-CoV-2 detection demonstrated that viral ribonucleic acid (RNA) in the upper airways has higher viral loads than in the throat, in both symptomatic and asymptomatic patients. This suggests that the nasal epithelium may be an important site for initial infection, acting as a "key reservoir" for viral spread through the respiratory mucosa [12]. In light of this, it could be hypothesized that local treatment of the nasal mucosa with LF in a nasal spray formulation or through its oral intake may counteract SARS-CoV-2 infection and inflammation. LF, in fact, has the ability to serve as a natural barrier of the respiratory and intestinal mucosa, and, moreover, its inclusion in preservative structures (liposomes) may reduce gastric and intestinal denaturation, which is critical to maintaining its integrity and biological functionality. Such findings suggest that LF could be a supplement to be used in both asymptomatic and mildly symptomatic patients to prevent the exacerbation of COVID-19[21].

MYELOID-DERIVED SUPPRESSOR CELLS VERSUS COVID-19: ACTION OF LACTOFERRIN

Recent research has verified the presence of a dysregulated myeloid cell compartment containing an increased number of myeloid-derived suppressor cells (MDSCs) in severe COVID-19 patients, which may be correlated with disease severity. In this sense, the mechanism of action of MDSCs involves promoting the survival of SARS-CoV-2 through the suppression of T-cell responses, leading to a highly pro-inflammatory state in response to the secretion of various mediators of immune activation[22]. MDSCs are defined as bone marrow-derived innate immune cells with ability to suppress effector T-cell responses. This heterogeneous population of cells is composed mainly of two distinct subtypes that include polymorphonuclear or granulocytic-MDSCs (PMN-/G-MDSCs) and monocytic MDSCs (M-MDSCs). Among their roles is the ability to regulate a wide variety of adaptive (T and B cells) and innate (including natural killer cells, macrophages, and dendritic cells) immune cells[23].

Results of an important study that evaluated the effect of LF on MDSCs show that MDSCs from mice and human infants are sensitive to LF, whereas the same is not true of adult MDSCs. To explain the rationale for this reduced sensitivity, the authors also assessed the expression of different receptors capable of binding to LF, such as lipoprotein receptor-related protein (LRP)-1, LRP2, intelectin (ITLN)-1 and ITLN2. MDSCs from newborn mice were found to have a much stronger expression of LRP2 compared to ITLN1, ITLNb or LRP1. Another finding of interest was that the expression of LRP2 decreased with age, resulting in a substantial reduction in LRP2 expression on the cell surface[24]. This may, in addition to explaining differences in the sensitivity of MDSCs to LF between infants and adults, serve as evidence to understand more about the molecular peculiarities of COVID-19 in different age groups in order to propose more appropriate preventive and/or therapeutic protocols.

EVIDENCE FOR COMBINED USE OF LACTOFERRIN AND VITAMIN D

In light of the benefits that seem to be associated with the use of LF in COVID-19 patients, it may be useful to conduct further studies on the potential benefits of a combination of LF with others nutraceuticals in order to verify the possible synergistic effects in the fight against SARS-CoV-2 infection. In particular, in recent years, research on vitamin D has been extensive and evolving, evidencing that there is an important interaction between vitamin D and cells of the innate and adaptive immune system. Regarding the role in supporting innate immunity, it is known that serum 25-hydroxyvitamin D [25-(OH)D] bound to vitamin D-binding protein allows intracellular entry of free [25-(OH)D] into antigen-presenting cells (APCs). This results in both endogenous production and the action of 1-alpha, 25-dihydroxyvitamin D [1,25(OH)2D] through the vitamin D receptor (VDR), leading to the induction of antimicrobial proteins like cathelicidin, nuclear factor kappa β , and β -defensins that may contribute to the elimination of SARS-CoV-2[26].

In this context, the innate immune system is expected to fight the viral infection first until the adaptive immune system (T and B cells) is sufficiently activated, which usually occurs within 7 to 10 d after the primary infection. Moreover, SARS-CoV-2 infection causes the activation of APCs that can induce SARS-CoV-2 phagocytosis, through communication with naïve T cells (Th-0). An optimal serum vitamin D level may lead to differentiation of naïve T cells into T helper (Th) 2 cells instead of Th1 cells, promoting the production of anti-inflammatory cytokines such as interleukin (IL)-10, IL-5, and IL-4. Anti-inflammatory cytokines have the ability to decrease the secretion of pro-inflammatory cytokines, including interferon- γ , IL-6, IL-2 and tumor necrosis factor- α , by down-regulation of Th1 cells. All this may result in an important anti-inflammatory reaction with potential to control the overreaction of the

immune system against COVID-19[25].

On the other hand, in the presence of vitamin D deficiency, the adaptive immune response shifts towards differentiation of naïve T cells into Th1 cells, which may cause hyper-inflammation/cytokine storm[25]. According to Prietl *et al*[26], numerous cells (including immune cells) possess enzymes that metabolize vitamin D. This process appears to be critical for normal immune function; indeed, altered or insufficient levels of vitamin D may cause dysregulation of immune responses. In an important review article, four potential mechanisms by which vitamin D may affect T-cell function were proposed: direct endocrine effects on T lymphocytes mediated by systemic calcitriol; direct intracrine conversion of 25(OH)D to calcitriol by T lymphocytes; direct paracrine effects of calcitriol on T cells following conversion of 25(OH)D to calcitriol by monocytes or dendritic cells; or indirect effects on antigen presentation to T lymphocytes mediated by localized APCs affected by calcitriol[27].

Two recent studies have evaluated the effects of LF on vitamin D. The first demonstrated that LF is a potential activator of the VDR through the expression of VDR messenger ribonucleic acid (mRNA), postulating that LF directly targets the cell nucleus to regulate VDR transcription activity in vitamin D-deficient mice. LF appears to show an affinity for three specific deoxyribonucleic acid (DNA) sequences that interestingly appear similar in the VDR- promoter. Thus, the authors of this study hypothesize that LF regulates VDR expression by binding directly to these DNA elements and that therefore it may act as a transcription factor or coactivator to stimulate VDR expression[28]. In the other study, Wang *et al*[29] demonstrated that LF, in addition to having a protective role in the intestine in mice deficient in vitamin D and reducing elevated serum pro-inflammatory cytokines, it also has the ability to stimulate, increasing the expression of the vitamin D receptor.

CONCLUSION

The combined use of LF and vitamin D could represent, through a synergistic action, a valuable therapeutic support and also for the prevention of SARS-CoV-2 infection. In addition, the association of oral intake of LF and a nasal spray formulation would be an additional tool to prevent the spread and worsening of the infection. Although the combined use of LF and vitamin D seems to be a promising approach as an adjuvant for the COVID-19 management, there are still no *in vivo* studies with robust evidence to prove the benefits of using this combination of supplements against SARS-CoV-2 infection. Further randomized clinical trials are needed to evidence any related beneficial action before recommending/prescribing them for the population[30]. With the exception of the use of approved drugs, what is known so far is that the practice of physical exercises may be an ally for COVID-19 prevention and treatment, as well as to enhance SARS-CoV-2 vaccine immunogenicity[31].

FOOTNOTES

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ORCID number: Enzo Ruberti 0000-0002-1609-5492; Marcos Roberto Tovani-Palone 0000-0003-1149-2437.

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REFERENCES

- 1 Rosa L, Cutone A, Lepanto MS, Paesano R, Valenti P. Lactoferrin: A Natural Glycoprotein Involved in Iron and Inflammatory Homeostasis. *Int J Mol Sci* 2017; **18** [PMID: 28914813 DOI: 10.3390/ijms18091985]
- 2 Varki A. Biological roles of glycans. *Glycobiology* 2017; **27**: 3-49 [PMID: 27558841 DOI: 10.1093/glycob/cww086]

- 3 **Bishop JR**, Gagneux P. Evolution of carbohydrate antigens--microbial forces shaping host glycomes? *Glycobiology* 2007; **17**: 23R-34R [PMID: 17237137 DOI: 10.1093/glycob/cwm005]
- 4 **Miotto M**, Di Rienzo L, Gosti G, Milanetti E, Ruocco G. Does blood type affect the COVID-19 infection pattern? *PLoS One* 2021; **16**: e0251535 [PMID: 33984040 DOI: 10.1371/journal.pone.0251535]
- 5 **Yi M**, Kaneko S, Yu DY, Murakami S. Hepatitis C virus envelope proteins bind lactoferrin. *J Virol* 1997; **71**: 5997-6002 [PMID: 9223490 DOI: 10.1128/JVI.71.8.5997-6002.1997]
- 6 **Harmsen MC**, Swart PJ, de Béthune MP, Pauwels R, De Clercq E, The TH, Meijer DK. Antiviral effects of plasma and milk proteins: lactoferrin shows potent activity against both human immunodeficiency virus and human cytomegalovirus replication in vitro. *J Infect Dis* 1995; **172**: 380-388 [PMID: 7622881 DOI: 10.1093/infdis/172.2.380]
- 7 **Superti F**, Siciliano R, Rega B, Giansanti F, Valenti P, Antonini G. Involvement of bovine lactoferrin metal saturation, sialic acid and protein fragments in the inhibition of rotavirus infection. *Biochim Biophys Acta* 2001; **1528**: 107-115 [PMID: 11687297 DOI: 10.1016/s0304-4165(01)00178-7]
- 8 **Puddu P**, Borghi P, Gessani S, Valenti P, Belardelli F, Seganti L. Antiviral effect of bovine lactoferrin saturated with metal ions on early steps of human immunodeficiency virus type 1 infection. *Int J Biochem Cell Biol* 1998; **30**: 1055-1062 [PMID: 9785469 DOI: 10.1016/s1357-2725(98)00066-1]
- 9 **Berlutti F**, Pantanella F, Natalizi T, Frioni A, Paesano R, Polimeni A, Valenti P. Antiviral properties of lactoferrin--a natural immunity molecule. *Molecules* 2011; **16**: 6992-7018 [PMID: 21847071 DOI: 10.3390/molecules16086992]
- 10 **Campione E**, Cosio T, Rosa L, Lanna C, Di Girolamo S, Gaziano R, Valenti P, Bianchi L. Lactoferrin as Protective Natural Barrier of Respiratory and Intestinal Mucosa against Coronavirus Infection and Inflammation. *Int J Mol Sci* 2020; **21** [PMID: 32664543 DOI: 10.3390/ijms21144903]
- 11 **Odolczyk N**, Marzec E, Winiewska-Szajewska M, Poznański J, Zielenkiewicz P. Native Structure-Based Peptides as Potential Protein-Protein Interaction Inhibitors of SARS-CoV-2 Spike Protein and Human ACE2 Receptor. *Molecules* 2021; **26** [PMID: 33918595 DOI: 10.3390/molecules26082157]
- 12 **Zhou P**, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020; **579**: 270-273 [PMID: 32015507 DOI: 10.1038/s41586-020-2012-7]
- 13 **Zang R**, Gomez Castro MF, McCune BT, Zeng Q, Rothlauf PW, Sonnek NM, Liu Z, Brulois KF, Wang X, Greenberg HB, Diamond MS, Ciorba MA, Whelan SPJ, Ding S. Tmprss2 and Tmprss4 promote SARS-CoV-2 infection of human small intestinal enterocytes. *Sci Immunol* 2020; **5** [PMID: 32404436 DOI: 10.1126/sciimmunol.abc3582]
- 14 **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. *bioRxiv* 2020 [PMID: 32699847 DOI: 10.1101/2020.07.14.202549]
- 15 **Shang J**, Wan Y, Luo C, Ye G, Geng Q, Auerbach A, Li F. Cell entry mechanisms of SARS-CoV-2. *Proc Natl Acad Sci U S A* 2020; **117**: 11727-11734 [PMID: 32376634 DOI: 10.1073/pnas.2003138117]
- 16 **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**: e23710 [PMID: 21887302 DOI: 10.1371/journal.pone.0023710]
- 17 **Miotto M**, Di Rienzo L, Bò L, Boffi A, Ruocco G, Milanetti E. Molecular Mechanisms Behind Anti SARS-CoV-2 Action of Lactoferrin. *Front Mol Biosci* 2021; **8**: 607443 [PMID: 33659275 DOI: 10.3389/fmolb.2021.607443]
- 18 **Piacentini R**, Centi L, Miotto M, Milanetti E, Di Rienzo L, Pitea M, Piazza P, Ruocco G, Boffi A, Parisi G. Lactoferrin Inhibition of the Complex Formation between ACE2 Receptor and SARS CoV-2 Recognition Binding Domain. *Int J Mol Sci* 2022; **23** [PMID: 35628247 DOI: 10.3390/ijms23105436]
- 19 **Zimecki M**, Actor JK, Kruzel ML. The potential for Lactoferrin to reduce SARS-CoV-2 induced cytokine storm. *Int Immunopharmacol* 2021; **95**: 107571 [PMID: 33765614 DOI: 10.1016/j.intimp.2021.107571]
- 20 **Kell DB**, Heyden EL, Pretorius E. The Biology of Lactoferrin, an Iron-Binding Protein That Can Help Defend Against Viruses and Bacteria. *Front Immunol* 2020; **11**: 1221 [PMID: 32574271 DOI: 10.3389/fimmu.2020.01221]
- 21 **Liu W**, Ye A, Liu W, Liu C, Singh H. Stability during in vitro digestion of lactoferrin-loaded liposomes prepared from milk fat globule membrane-derived phospholipids. *J Dairy Sci* 2013; **96**: 2061-2070 [PMID: 23375971 DOI: 10.3168/jds.2012-6072]
- 22 **Rowlands M**, Segal F, Hartl D. Myeloid-Derived Suppressor Cells as a Potential Biomarker and Therapeutic Target in COVID-19. *Front Immunol* 2021; **12**: 697405 [PMID: 34220859 DOI: 10.3389/fimmu.2021.697405]
- 23 **Gabrilovich DI**, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. *Nat Rev Immunol* 2009; **9**: 162-174 [PMID: 19197294 DOI: 10.1038/nri2506]
- 24 **Liu Y**, Perego M, Xiao Q, He Y, Fu S, He J, Liu W, Li X, Tang Y, Yuan W, Zhou W, Wu F, Jia C, Cui Q, Worthen GS, Jensen EA, Gabrilovich DI, Zhou J. Lactoferrin-induced myeloid-derived suppressor cell therapy attenuates pathologic inflammatory conditions in newborn mice. *J Clin Invest* 2019; **129**: 4261-4275 [PMID: 31483289 DOI: 10.1172/JCI128164]
- 25 **Shah Alam M**, Czajkowsky DM, Aminul Islam M, Ataur Rahman M. The role of vitamin D in reducing SARS-CoV-2 infection: An update. *Int Immunopharmacol* 2021; **97**: 107686 [PMID: 33930705 DOI: 10.1016/j.intimp.2021.107686]
- 26 **Prieti B**, Treiber G, Pieber TR, Amrein K. Vitamin D and immune function. *Nutrients* 2013; **5**: 2502-2521 [PMID: 23857223 DOI: 10.3390/nu5072502]
- 27 **Hewison M**. An update on vitamin D and human immunity. *Clin Endocrinol (Oxf)* 2012; **76**: 315-325 [PMID: 21995874 DOI: 10.1111/j.1365-2265.2011.04261.x]
- 28 **Li Y**, Huang J, Wang J, Ma M, Lu Y, Wang R, Guo H. Lactoferrin Is a Potential Activator of the Vitamin D Receptor in Its Regulation of Osteogenic Activities in C57BL/6J Mice and MC3T3-E1 Cells. *J Nutr* 2021; **151**: 2105-2113 [PMID: 33982113 DOI: 10.1093/jn/nxab105]
- 29 **Wang J**, Li Y, Zhao L, Ren F, Guo H. Lactoferrin stimulates the expression of vitamin D receptor in vitamin D deficient

- mice. *J Funct Foods* 2019; **55**: 48-56 [DOI: [10.1016/j.jff.2019.02.012](https://doi.org/10.1016/j.jff.2019.02.012)]
- 30 **Giacalone A**, Marin L, Febbi M, Tovani-Palone MR. Current evidence on vitamin C, D, and zinc supplementation for COVID-19 prevention and/or treatment. *Electron J Gen Med* 2021; **18**: em311 [DOI: [10.29333/ejgm/11099](https://doi.org/10.29333/ejgm/11099)]
- 31 **Tovani-Palone MR**, Comini N, Giacalone A, Franchi T. Importance of Healthy Habits During the COVID-19 Pandemic: Perspective and Suggestions. *Electron J Gen Med* 2022; **19**: em369 [DOI: [10.29333/ejgm/11874](https://doi.org/10.29333/ejgm/11874)]



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