

Review Article

A REVIEW ON LACTOFERRIN PRINCIPLE CONSTITUENT OF BOVINE COLOSTRUM: IN COVID19

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ABSTRACT

The Covid sickness (COVID19) pandemic is quickly expanding across the world. There is no legitimate therapy for this illness except for by supporting our resistance we can battle with this infection so to battle Coronavirus contamination the famous dietary enhancement bovine colostrums having bunches of utilization to battle against viral disease. It go about an immunomodulatory, anti-inflammatory, Antibacterial effect. The most significant part found in colostrum is lactoferrin which is a 80 KDA glycoprotein containing around 703 amino corrosive and having its capacity to tie with iron by restricting with iron, lactoferrin retain iron from the climate and forestalls viral heap of pathogens. The Covid didn't get authoritative therapy because of viral transformation; this review is accommodating for helping the invulnerable framework in coronavirus patient.

Keywords: Bovine colostrum, Lactoferrin, SARS-COVID 19, Antiviral, Antibacterial

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INTRODUCTION

The Covid sickness 19 (COVID-19) is an exceptionally communicable and pathogenic viral contamination brought about by the extreme intense respiratory disorder Covid 2 (SARS-CoV-2), which arose in Wuhan, China and spread all over the planet. Genomic examination uncovered that SARS-CoV-2 is phylogenetically identified with the serious, intense respiratory syndrome. COVID-19 transmission modes are through respiratory drops, actual contact, and airborne particles. There is proof that the infection can be sent from one human to another [1, 2]. The hatching time of COVID-19 is around 2 to 14 d; however, tainted individuals send the infection through close contact and respiratory drops, even before indications show up. There is presently no powerful antibody against COVID-19 [3]. Accordingly, the therapy of this illness is one of the main clinical difficulties in the current age. Research on more powerful therapy is a clinical need; bovine colostrum (BC) is the main emission of the mammary organs during the initial 2–4 d post-pregnancy [4]. It is wealthy in numerous bioactive supplements and immunological substances, which are needed to feed the infant and help in the baby's development and advancement [5]. Except for lactose sum, colostrum has more significant levels of supplements than the developed milk [6]. The immune globulins present in colostrum establish the framework of long-lasting invulnerability in the infant. Colostrum's bioactive fixings help the development of the gastrointestinal lot, forestall diseases, advance separation of bone marrow undifferentiated organisms, increment fit bulk and lessening muscle versus fat in the infant [7]. Because of the great degrees of immunomodulatory supplements present in BC [8], a few specialists have exhibited gainful impacts of BC utilization in working on the respiratory strength of people (fig. 1). The outcomes found up to this point have been promising in controlling hypersensitivities and battling respiratory diseases in grown-ups and kids [9]. BC compounds appear to help competitors, who are more powerless to upper respiratory parcel diseases after serious actual preparing and contests, particularly in perseverance, works out. Albeit the components for this condition are not yet completely comprehended, supplementation with colostrum has shown beneficial outcomes in treating these contaminations since lactoferrin is said to assume a part in smothering viral diseases.

Today, clinical preliminaries are in progress in numerous nations to expand the capability of safe milk items as a preventive treatment against anti-toxin-safe contaminations in people [10]. Lactoferrin

can be refined from milk, particularly colostrum. Lactoferrin is found in many emissions, including milk, tears, and salivation, just as in huge sums in explicit neutrophil granules. It is a glycoprotein with a sub-atomic load of 80 kDa, which has a solid propensity to tie to press [11, 12]. Lactoferrin (Lf), an iron restricting protein, has a place with the vague regular protection, and the main capacity ascribed to it is antimicrobial action, which relies upon its ability to contain iron [6]. Its natural properties remember managing iron assimilation for the digestive tract, mitigating properties, directing the safe framework and antibacterial, viral, and cancer movement [7]. Its protein structure comprises of two sections, amino (N-lope) and carboxylic (C-lope), every one of which can tie to free press [8, 9]. Lactoferrin's capacity to complete the antiviral movement by restricting to have cells as well as viral particles advances that lactoferrin is a significant block in the mucosal divider that is powerful against microbial and viral assaults. By engrossing free iron, lactoferrin denies the climate of this component, consequently denying the microorganisms and microbes that need iron for their development and proliferation to live and can't get by. Likewise, lactoferrin by implication, restrains disease [10].

Can bovine colostrum aid treatment against coronavirus?

The pandemic of Coronavirus Disease 2019 (COVID-19), brought about by the extreme intense respiratory condition Covid 2 (SARS-CoV-2), arose in late 2019 and has since tormented the world, causing great many passings in a few nations [14]. With this occasion, a huge race started worldwide in the quest for successful medicines and antibodies to forestall contamination by the recently known infection. A sufficient, safe framework reaction can smother the contamination now and again. In any case, a useless safe framework reaction in a few cases prompts an overstated arrival of supportive of incendiary cytokines, causing serious, intense respiratory disorder [13]. Accordingly, considering the writing information assembled and examined, it is recommended that the solid antiviral movement of BC given by its bioactive parts, particularly lactoferrin, could assist with easing back the infection movement. The expected use of BC on clinical administration of COVID-19 isn't just founded on the calming, antibacterial and antiviral capacities [15, 16], yet additionally on its ability in fortifying the human inborn and versatile resistant framework [16]. Have detailed that BC has solid antimicrobial action against both Gram-negative and Gram-positive strains. The negligible inhibitory fixation of colostrum was viewed as 100 µg/ml against E. coli, S.

aureus, *P. vulgaris*, *E. aerogenes*, and *S. typhi*. It is conceivable that BC may have viricidal impacts against COVID-19 infection [16]. This theoretical thought might merit seeking after! At present, the antiviral impacts of a few parts of BC are being investigated against SARS-CoV-2. We will, momentarily, feature the utilization of lactoferrin and hyperimmune colostrum with regards to SARS-CoV-2 disease.

Bovine colostrum ensures upper respiratory lot against diseases

Upper respiratory lot diseases (URTIs) are contaminations which influence the mouth, nose, throat, larynx and windpipe, inciting nasorhinitis (normal cold), sinusitis, pharyngitis, laryngitis and laryngotracheitis [17]. The beneficial outcomes of oral BC supplementation against URTIs are clear for the two youngsters and grown-ups. Concentrates on examining this affiliation show that BC had the option to lessen the rate of URTI and decline the term of self-revealed indications. Nonetheless, the components for such impacts are not completely explained. The impacts of colostrum in the eating routine have been tried in research center creatures against Human Syncytial Virus (HRSV), which is quite possibly the most well-known cause of respiratory Disease in kids [18]. Past examinations show that invulnerable framework cells, Called CD8 T, are repressed in HRSV diseases, which impedes the battle against contamination [19]. In a review with mice, [18] showed that colostrum was viable in hindering HRSV, in further developing the contamination indications brought about by the infection and in expanding the reaction of CD8 T cells. Considering these outcomes, studies are expected to examine the impacts of BC in people impacted by HRSV [18] In people, a partner study showed that BC supplementation was powerful in altogether diminishing URTI and looseness of the bowels scenes, just as the quantity of hospitalizations because of URTI and loose bowels in youngsters matured 1–6 y. It is worth focusing on that this study comprised of 160 kids with an intermittent history of URTI and the runs, who gotten from 3.0 g (as long as 2 y of age) to 6.0 g (north of 2 y of age) of supplement for 4 w [21]. A business supplement containing BC (Sinerga™) was assessed in another partner study [21]. The enhancement ended up being effective in decreasing the quantity of respiratory diseases scenes that necessary mediation with anti-toxins in kids. Regardless, as Sinerga™ contains different substances in its creation, the helpful impacts noticed can't be straightforwardly credited to colostrum. These outcomes, notwithstanding, recommend that BC standard utilization could work on the respiratory wellbeing in kids, debilitating the seriousness of aviation route diseases. In a non-relative review, other BC-based enhancement was demonstrated to be compelling in decreasing the quantity of upper respiratory plot contamination, loose bowels and hospitalization scenes for URTI and the runs in youngsters matured 1–8 y. The review included 605 youngsters who got 3.0 g of the enhancement for a very long time. As well as working on broad prosperity, 91.19% and 86.60% of the patients had a decrease in URTI and the runs scenes toward the finish of the treatment, separately [22].

Taking Taking into account that repetitive respiratory plot contaminations might be connected to immunoglobulin A (IgA) insufficiency, Patoroglu and Kondolot examined whether BC supplementation would increment salivary IgA in patients with serum IgA lack [23]. In this clinical preliminary, sixteen youngsters got 42 mg of Igazym® each day, a business supplement of BC and egg white (as the wellspring of the antimicrobial compound lysozyme). Albeit the seriousness score of the URTI viral disease was essentially lower in the experimental group, there was no connection with salivary IgA levels, showing that the immunomodulatory capacity of colostrum in the respiratory framework might be driven by another system [23]. Studies with a bigger example size should be done to affirm these discoveries. A clinical preliminary with sound grown-up men showed that 60 g/day of concentrated BC protein powder supplementation contrasted with 60 g/day of whey protein powder altogether diminished the occurrence of URTIs, despite the fact that there was no factual distinction in the length of self-announced indications between gatherings [31]. A comparative outcome was portrayed by Jones *et al.* [32], in which they noticed that everyday

supplementation with 20 g of BC for a considerable length of time diminished the quantity of URTI scenes, just as the term of indications [31]. noticed a decrease in the length of manifestations as opposed to the concentrate by Brinkworth and Buckley [31] might be because of the kind of supplement utilized in the fake treatment bunch, which in the last option was a cow-like milk subsidiary, while in the previous review it was an isoenergetic/isomacronutrient. Whey protein is known to have a few bioactive peptides, which could be dependable to constructive outcomes on the boundaries considered. Methodical surveys and meta-investigates presumed that supplementation with bovine colostrum can lessen the occurrence rate and the times of upper respiratory side effects in competitors and truly dynamic individuals. In any case, they underscore that many articles are one-sided and there is a hole in logical information concerning what instruments are engaged with this improvement. In this manner, they suggest that new randomized control clinical preliminaries ought to be done to decide the components of activity and an agreement on the best supplementation technique [32]. By and large, the proof summed up thus focuses to the adjuvant capability of BC in alleviating lower respiratory plot diseases in sound kids and grown-up men, just as in rodents contaminated with HRSV. Concentrates on examining the impacts of colostrum on respiratory parcel contaminations, particularly in the more seasoned grown-up populace and in grown-up ladies, are required to assess the helpful capability of BC supplementation in people of the two sexes and of any age.

Bioactive proteins present in bovine

Immunoglobulins (Igs)-Immunoglobulins (Igs) are muddled proteins, known as antibodies, that make up a basic piece of the total protein in bovine colostrum. The immunoglobulins in bovine colostrum mostly come in 3 novel varieties called isotypes, including IgG (IgG1 and IgG2), IgA, IgM. IgG is the common immunoglobulin in bovine colostrum, which makes up 85–90% of the total immunoglobulin content. IgG1 tends to 80–90% of the outright IgG content in bovine colostrum, followed by IgM, IgA, and IgG2 [33–35]. These immunoglobulins are central in the perseverance of the calves and their safe systems and they eliminate gastrointestinal microorganisms like infinitesimal living beings, microorganisms, and contaminations. Using bovine colostrum as a wellspring of checking specialist courses of action to help bovine and human prosperity is a critical investigation subject that has been perused up for quite a while [36]. One of the basic differences between mature milk and colostrum is the high gathering of IgG found in colostrum, which comes to up to 50–100 mg/ml in the essential days after the fact birth [33, 37, 30]. Bovine colostrum IgG1 and IgG2 center decay before parturition; they are moved from the blood into the colostrum. To be sure, for all intents and purposes, all IgG in colostrum is moved from bovine serum into the colostrum and milk [31, 32]. The high centralization of IgG is significant for the perseverance of calves, which is vehemently dependent upon the trading of IgG from cow-like colostrum to calves to give confined invulnerability as cows can't move IgG through the placenta [33]. Undoubtedly, in case of calves don't get colostrum following birth, they are leaned to defilement and will encounter the evil impacts of a higher risk of somberness and mortality [31, 34, 35].

Lactoperoxidase

Lactoperoxidase is a critical antibacterial compound found in cow-like colostrum; it is a central glycoprotein that catalyzes the oxidation of thiocyanate and makes moderate mixtures with antimicrobial activities [36]. The union of lactoperoxidase is 11–45 mg/l in ox-like colostrum and 13–30 mg/l in mature ox-like milk [37]. Its concentration in ox-like colostrum is low from the outset, yet it shows up at the best level inside 3 after 5 d parturition. Lactoperoxidase catalase development is in like manner, higher in ox-like colostrum than in mature milk [38, 39]. Lactoperoxidase is a basic antibacterial compound found in cow-like colostrum, it is a focal glycoprotein that catalyzes the oxidation of thiocyanate and makes moderate combinations with antimicrobial exercises [36]. The association of lactoperoxidase is 11–45 mg/l in bull-like colostrum and 13–30 mg/l in mature bull-like milk [37]. Its fixation

in bull like colostrum is low from the beginning, yet it appears at the best level inside 3 following 5 d parturition. Lactoperoxidase catalase improvement is in like way higher in bovine colostrum than in mature milk [38, 39]. The lactoperoxidase structure moreover inactivates the polio infection, vaccinia disease, and HIV [49, 50]. Oligosaccharides Bovine colostrum is a rich wellspring of complex and significantly explicit oligosaccharides and glycans. The intermingling of oligosaccharides in colostrum is 0.7–1.2 mg/ml and the majority of these developments are acidic oligosaccharides which are lower in mature bovine milk [53, 44]. Forty specific oligosaccharides courses of action have been recognized in ox-like colostrum up until this point [45, 47]. The outright colostrum oligosaccharides fluctuate between cows because of their innate alterability [48]. Overpowering oligosaccharides in cow-like colostrum are 3 sialyl lactose (3SL), 6' sialyllactose (6'SL), 6' sialyllactosamine (6'SLN) and disialyllactose (DSL). 3'SL is 70% of outright oligosaccharide content in cow-like colostrum [44, 46, 49, 50]. Forty explicit oligosaccharides strategies have been perceived in bovine colostrum up until this point [45, 47]. The by and large, colostrum oligosaccharides change between cows in view of their intrinsic alterability [48]. Overwhelming oligosaccharides in cow-like colostrum are 3 sialyllactose (3'SL), 6' sialyllactose (6'SL), 6' sialyllactosamine (6'SLN) and disialyllactose (DSL). 3'SL is 70% of out and out oligosaccharide content in cow-like colostrum [44, 46, 49, 50]. Both free oligosaccharides (cow-like milk oligosaccharides, BMOs) and mind-boggling, framed N-glycans address the majority of the prebiotic parts of cow-like colostrum [52]. Prepartum and early lactation.

Lactoferrin

Lactoferrin (Lf) is a naturally occurring, non-harmful glycoprotein that has been examined against an expansive scope of infections,

including extreme intense respiratory condition Covid (SARS-CoV), which is firmly identified with the clever serious, intense respiratory disorder Covid 2 (SARS-CoV-2) that causes COVID-19 [54]. Besides, Lf has immunomodulatory and calming attributes that can emphatically alter have reactions to contaminations [55]. Lf is accessible as an oral enhancement, and studies recommend that supplemental Lf might treat or forestall a large group of microbial contaminations [56]. Here we look at the antiviral properties and immunomodulatory components of Lf inside the setting of its expected applications against SARS-CoV-2 and propose the chance of supplemental Lf as a likely deterrent and subordinate treatment for COVID-19, a condition whose pathophysiology includes both viral contamination and an unnecessary host reaction.

Mechanism of action lactoferrin

Lf is an exceptionally rationed, pleiotropic, iron-restricting glycoprotein of the transferrin family that is communicated and emitted by glandular cells and is found in most body-liquids [57]. It shows up at particularly high fixations in mammalian milk and was first recognized in cow-like milk [58] and was hence secluded from human milk [59]. It is a 80-kDa glycoprotein containing 703 amino corrosive deposits whose essential construction has been portrayed all around. Since its disclosure, Lf and its connected peptides are fundamentally viewed as significant vague host protection atoms against an assortment of microbes, including the scope of infections [60]. All the more as of late, the mitigating and immunomodulatory jobs of Lf have acquired expanding logical interest since it gives off an impression of being ready to direct the host reaction to diseases and has the double capacity to animate the invulnerable framework to balance pathogenic intrusion while at the same time forestalling hurtful host insusceptible and provocative reactions.

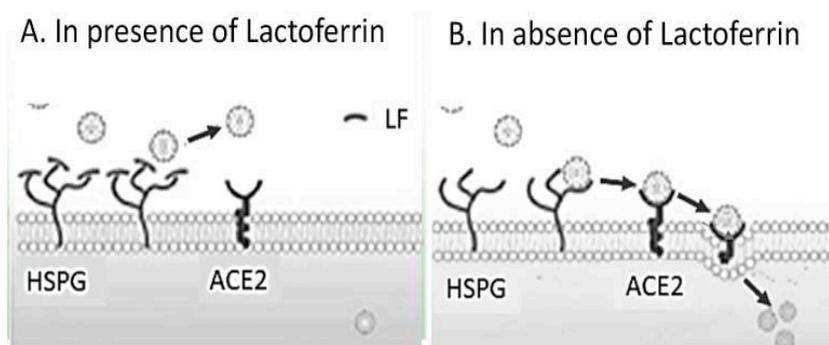


Fig. 1: Mechanism of action of lactoferrin

Lactoferrin as a potential preventative and adjunct treatment for COVID-19

Lf has been found tentatively to repress viral section by restricting to have cell surface HSPGs in murine Covid [70] just as human Covid hCoV-NL63 [62] and pseudotyped SARS-CoV [63]. There are at this point no distributed examinations on the impacts of Lf on SARS-CoV-2 and its entrance into have cells. By the by, given the as of now acknowledged 'viral surfing' model for the job of cell surface HSPGs [64], which the attacking virion particles 'surf' from low-proclivity HSPG mooring destinations to high-liking section receptors in an intrusion, along with the homology of SARS-CoV and SARS-CoV-2 spike protein structures, just as both infections relying upon a similar angiotensin-changing over catalyst 2 (ACE2) receptor for cell passage [65], we have a solid sense of reassurance to hypothesize a comparative component by which HSPGs fill in as SARS-CoV-2 connection locales that assemble the infection on the phone surface and work with explicit passage receptors like ACE2. All things considered, Lf can restrain SARS-CoV-2 intrusion at micromolar fixations and in a portion subordinate way similarly as on account of SARS-CoV [63]. More pertinent to our theory are the new outcomes detailed by Serrano *et al.* that a liposomal ox-like Lf supplement containing 32 mg of Lf directed at four to six dosages each day for 10 d with zinc 10 mg a few times every day brought about 100% recuperation of 75 suggestive SARS-CoV-2-positive patients inside

4–5 d, and a similar treatment at lower portion seemed to forestall the disease in sound contacts [66]. Since one more significant part of Lf bioactivity identifies with its immunomodulatory and calming capacities, on account of viral contaminations specifically, it might frequently be the size of immune reaction and irritation that adds to infection cut off ity, and this is especially important for COVID-19. Current reasoning recommends that mortality from COVID-19 isn't just because of viral contamination however is an aftereffect of a cytokine storm condition in select patients related with hyper inflammation prompting intense respiratory misery and resulting mortality [67]. A cytokine profile in extreme COVID-19 cases is portrayed by in-wrinkles in cytokines and intense stage reactants like interleukin 6 (IL-6), cancer corruption factor-alpha (TNF α) and ferritin. In such manner, Lf is shown to diminish IL-6 and TNF α [68] and to down-regulate ferritin in test settings reproducing sep-sister. On the off chance that the theory that Lf can tweak an overactive resistant and fiery reaction to viral disease is right, then, at that point, Lf could be an up-and-comer subordinate treatment for more extreme instances of COVID-19. 3.

Lactoferrin: an important element in host defense

Lf assumes a significant part in have guard, upon its delivery from the neutrophil [69]. LF additionally upgrades regular executioner cell movement in invulnerable protection [70] and can limit the

passage of the infection into have cells during contamination. As a component of the host's fiery reaction, leucocytes, including neutrophils, discharge LF from their granules, where it is typically put away. Actuated neutrophils additionally discharge chromatin filaments, known as neutrophil extracellular snares (NETs), which trap and dispense with, among others, microbes [71, 72]. These NETs similarly tweak both intense and constant aggravation [73, 74]. NETs are likewise found in different immune system conditions like rheumatoid joint inflammation, and fundamental lupus erythematosus [75, 76]. Strangely, 106 human neutrophils can deliver 15 µg of LF [78]. Notwithstanding DNA and histones, NET strands contain extranuclear proteins and proteins like elastase, myeloperoxidase (MPO), and LF [77]. LF may likewise fill in as a natural inhibitor of NETs discharge into the flow, and may thusly be focal in controlling NETs discharge sBacterial restricting to different receptors, e. g., Toll-like receptors 2 and 4 (TLR2 and 4), just as supplement receptors, prompts protein arginine deiminase 4 (PAD4) initiation, trailed by chromatin decondensation, hypercitrullination of histones 3 and 4 in the core, and atomic layer interruption. Granules likewise discharge lactoferrin. Neutrophil Extracellular Traps (NETs) and their protein constituents (counting lactoferrin) are let out of the neutrophil. Adjusted from Jorch and Kubes [78] and Law and Gray [79]. Microorganisms are removed and caught in the NETs.

Bacteria and lactoferrin

One of the most notable attributes of LF is that it is antibacterial [84], antiviral [85], antifungal [87–89], calming, and against cancer-causing [90]. Its capacity as far as possible iron accessibility to microorganisms is one of its essential amicrobial properties. Microbes have, nonetheless, created different ways of sequestering iron [91]. These siderophore-iron buildings are then perceived by receptors on the bacterium [92]. Have natural resistant capacities are upheld by the flowing protein, siderocalin, otherwise called Neutrophil gelatinase-related lipocalin (NGAL), lipocalin2 or Lcn2 as it restrains siderophore-interceded iron procurement and delivery [92].

Viruses and lactoferrin

LF has solid antiviral movement against an expansive range of both exposed and wrapped DNA and RNA infections [85]. LF restrains the section of viral particles into have cells, either by direct connection to the viral particles or by hindering their phone receptors (talked about in past passages) [85]. A portion of the infections that LF keeps from entering host cells e. g., Herpes simplex infection [93], human papillomavirus [94], human immunodeficiency infection (HIV) [95], and rotavirus [95]. These infections regularly use normal atoms on the cell layer to work with their attack into cells, including HSPGs. HSPGs give the first mooring destinations on the host cell surface and help the infection connect with these phones [93].

COVID-19 and lactoferrin

Coronavirus is caused by extreme intense respiratory condition Covid 2 (SARS-CoV-2). Numerous COVID-19 patients develop acute respiratory problems (ARDS), which prompts pneumonic edema and lung disappointment, and have liver, heart, and kidney harms. These side effects are related with a cytokine storm [97, 98] showing raised serum levels of interleukin (IL) IL-1β, IL-2, IL-7, IL-8, IL-9, IL-10, IL-17, granulocyte province invigorating element (G-CSF), Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF), interferon (IFN)γ, cancer rot factor (TNF)α, Interferon gamma-prompted protein 10 (IP10), Monocyte Chemoattractant Protein-1 (MCP1), macrophage fiery protein 1(MIP1A) and MIP1B [99]. IL-22, as a team with IL-17 and TNFα, prompts antimicrobial peptides in the mucosal organs. IL-22 additionally upregulates mucins, fibrinogen, hostile to apoptotic proteins, serum amyloid A, and LPS restricting protein [100]; consequently, IL-22 might add to the development of hazardous oedema with mucins and fibrin [101], found in SARS-CoV-22 and SARS-CoV patients [99].

The 2003 SARS-CoV strain, which additionally causes extreme intense respiratory disorder, joins to have cells through have receptor ACE2 [102]. This sort I fundamental layer protein receptor is a notable receptor for respiratory infections and is bounteously

communicated in tissues covering the respiratory plot [98]. During COVID-19 disease, SARS-CoV-2 additionally enters have cells by means of the ACE2 receptor [103]. ACE2 is exceptionally communicated on human lung alveolar epithelial cells, enterocytes of the small digestive tract, and the brush line of the proximal rounded cells of the kidney [111]. HSPGs are likewise one of the fundamental docking locales on the host cell surface and assume a significant part during the time spent SARS-CoV cell passage [111]. There is no current affirmed data that SARS-CoV-2 ties to HSPGs, in any case, LF obstructs the contamination of SARS-CoV by restricting to HSPGs [111]. It isn't by and by known whether LF ties to ACE2, yet it ties to HSPGs [111]. Regardless of whether SARS-CoV-2 additionally enters have cells by means of HSPGs similarly, as does (2003) SARS-CoV obviously warrants further examination. Specifically compelling, and with regards to this paper, is the arrangement of collaborations between SARS-CoV-2 and host platelets. This is of significance, as COVID-19 contamination can make hyperinflammation due a cytokine storm [110]. Microbes like the flu infection and Francisella tularensis do trigger perilous cytokine storms [104]. Such a cytokine tempest will essentially influence platelets, as platelets have numerous receptors where these provocative atoms might tie [104] (fig. 3). Flowing cytokines and inflammations will hyperactivate platelets, causing low platelet count (thrombocytopenia), and a huge possibility of hypercoagulation. Thrombocytopenia is related with the expanded danger of serious sickness and mortality in patients with COVID-19, and subsequently fills in as a clinical mark of deteriorating disease during hospitalization [105, 106]. Patients with type 2 diabetes are additionally especially inclined to expanded degrees of circling provocative cytokines and hypercoagulation [112]. Coronavirus patients without other comorbidities yet with diabetes are at higher danger of serious pneumonia, extreme uncontrolled fiery reactions and a hypercoagulable state [107]. Guo and associates in 2020 likewise observed that serum levels of IL-6, C-receptive protein, serum ferritin, and D-dimer were altogether higher in diabetic patients contrasted and those without, proposing that patients with diabetes are more defenseless to a fiery tempest, at last, prompting quick weakening of the patient with COVID-19. Intense aspiratory embolism has likewise been accounted for in COVID-19 disease [108]. Central collection of initiated platelets inside the oedematous region ex vivo related well with the size of the aspiratory embolism [109]. Strangely, anticoagulant treatment, for the most part with (intravenous) heparin (and primarily with low sub-atomic weight heparin, LMWH), has all the earmarks of being related with better anticipation in serious COVID-19 patients [110].

Lactoferrin as a nutraceutical

There is little uncertainty that oral LF can be of medical advantage to the host, and keeping in mind that it isn't viewed as totally essential for mammalian life (so it's anything but a nutrient), it is sensible to class it as a nutraceutical alongside an assortment of different atoms like those referenced in different papers [113, 114]. As a nutraceutical, the bioavailability of LF would obviously be a significant thought in its utilization for the anticipation or treatment of COVID-19. Intestinal covering of LF containers has been proposed as an action to boost the take-up of LF by the receptors situated in the brush-line of the small digestive tract [115]. Intestinal covering permits LF discharge some separation from LF-corrupting pepsin exercises in the stomach, permitting it to stay unblemished in the structure equipped for restricting little digestive LF receptors for take-up and inevitable exchange into the foundational dissemination [115]. In a rat study, the "ingestion" of intestinal defined LF was around 10-crease higher than that of customary LF brought into the stomach of exploratory creatures [116]. Considering these examinations, the creators of this paper view intestinal-covered LF as better than customary LF supplements regarding bioavailability and likely application for the avoidance or treatment for Corvids, for example, the SARS-Cov-2 engaged with COVID-19.

DISCUSSION

LF can be recombinant or gotten normally from bovine colostum and mammalian sources and is considered by the US Food and Drug Administration (FDA) as 'by and large perceived as protected'

(GRAS) without any contraindications. It is generally utilized as a healthful added substance in baby equation, and clinical examinations utilized Lf portions going from 100 mg to 4.5 g daily for different signs without evident poison levels. More up-to-date plans of Lf, including embodiment and li-posomalisation have been investigated, and Lf subsidiaries and related peptides, for example, lactoferricin and lactoferrampin, with more intense antiviral properties are being investigated and created. One perception with respect to the clinical study of disease transmission of the mongrel lease COVID-19 pandemic that might be applicable to Lf is the somewhat low frequency of contamination in youngsters. For sure, it has been accounted for that the frequency of COVID-19 in youngsters matured 0–10 y was just 0.9% in the Chinese cases detailed. Coronavirus cases were more uncommon still in youngsters and babies, with a sum of just nine tainted and hospitalized cases in China between 8 December 2019 and 6 February 2020 out of an all-out 31 211 announced cases across the country.

CONCLUSION

Much advancement has been accomplished to clarify the diverse capacity of Lf in the beyond 30 y as an antiviral just as an extraordinary calming and immunomodulatory atom. We have introduced the exploratory just as clinical reasoning for its utilization in COVID-19; however, further tests to check its hindrance of SARS-CoV-2 just as clinical preliminaries to explain measurement and viability are important to affirm the capability of Lf for SAR-CoV-2 anticipation and COVID-19 treatment. Moreover, it is known to assume a part in iron take-up in the digestive tract and initiation of phagocytes and insusceptible reactions. Receptors for lactoferrin are communicated on digestive tissue, monocytes, macrophages, neutrophils, lymphocytes, platelets, and on certain microbes. bovine lactoferrin supplements are thought to help the invulnerable framework and impact insusceptible cell action, possibly by means of antibacterial and antiviral properties. The best convergence of this protein is found in colostrum, which not really settled to be multiple times more noteworthy than mature milk.

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All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

REFERENCES

- Wang MW, Zhou MY, Ji GH, Ye L, Cheng YR, Feng ZH, Chen J. Mask crisis during the COVID-19 outbreak. *Eur Rev Med Pharmacol Sci.* 2020 Mar 1;24(6):3397-9. doi: 10.26355/eurrev_202003_20707, PMID 32271457.
- Saigal S, Gupta S, Sudhindran S, Goyal N, Rastogi A, Jacob M, Raja K, Ramamurthy A, Asthana S, Dhiman RK, Singh B, Perumalla R, Malik A, Shanmugham N, Soin AS. Liver transplantation and COVID-19 (coronavirus) infection: guidelines of the liver transplant Society of India (LTSI). *Hepatol Int.* 2020 Apr 8;14(4):429-31. doi: 10.1007/s12072-020-10041-1, PMID 32270388.
- Rasmussen SA, Smulian JC, Lednický JA, Wen TS, Jamieson DJ. Coronavirus Disease 2019 (COVID-19) and pregnancy: what obstetricians need to know. *Am J Obstet Gynecol.* 2020 Feb 24;222(5):415-26. doi: 10.1016/j.ajog.2020.02.017, PMID 32105680.
- Godhia ML, Patel N. Colostrum-its composition, benefits as a nutraceutical: a review. *Curr Res Nutr Food Sci.* 2013;1(1):37-47. doi: 10.12944/CRNFSJ.1.1.04.
- Marnila P, Korhonen H. Milk: colostrum. *Encyclopedia of Dairy Sciences.* 2011;2:591-7.
- Abd El-Fattah AM, Abd Rabo FHR, EL-Dieb SM, El-Kashef HAS. Changes in the composition of colostrum of Egyptian buffaloes and Holstein cows. *BMC Vet Res.* 2012;8:19. doi: 10.1186/1746-6148-8-19, PMID 22390895.
- Bagwe S, Tharappel LJP, Kaur G, Buttar HS. Bovine colostrum: an emerging nutraceutical. *J Complement Integr Med.* 2015;12(3):175-85. doi: 10.1515/jcim-2014-0039, PMID 25781716.
- Buttar HS, Bagwe SM, Bhullar SK, Kaur G. Health benefits of bovine colostrum in children and adults. *Res Rev, (Watson), Dairy in Human Health and Disease Across the Lifespan.* 2017. p. 3–20.
- Ramesh Menon P, Lodha R, Kabra SK. Bovine colostrum in pediatric respiratory diseases: A systematic review. *Indian J Pediatr.* 2010;77(1):108-9. doi: 10.1007/s12098-009-0257-0, PMID 19936658.
- Ramezanalizadeh F, Aliasghari A, Khorasgani MR, Khoroushi M, Tahmourethpour A, Jabbari AR. Evaluation of hyperimmune colostrum production in bovine against cariogenic streptococci and its impact on growth and bacterial biofilm formation. *J Dent Med.* 2017 Mar 1;29(4):237-46.
- Legrand D, Mazurier J. A critical review of the roles of host lactoferrin in immunity. *Biomaterials.* 2010 Jun 1;23(3):365-76. doi: 10.1007/s10534-010-9297-1, PMID 20143251.
- Gifford JL, Hunter HN, Vogel HJ. Lactoferricin: a lactoferrin-derived peptide with antimicrobial, antiviral, antitumor and immunological properties. *Cell Mol Life Sci.* 2005 Nov 1;62(22):2588-98. doi: 10.1007/s00018-005-5373-z, PMID 16261252.
- Tay MZ, Poh CM, Renia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol.* 2020;20(6):363-74. doi: 10.1038/s41577-020-03111-8, PMID 32346093.
- Ge H, Wang X, Yuan X, Xiao G, Wang C, Deng T, Yuan Q, Xiao X. The epidemiology and clinical information about COVID-19. *Eur J Clin Microbiol Infect Dis.* 2020;39(6):1011-9. doi: 10.1007/s10096-020-03874-z, PMID 32291542.
- Carvalho CAM, Casseb SMM, Gonçalves RB, Silva EVP, Gomes AMO, Vasconcelos PFC. Bovine lactoferrin activity against chikungunya and zika viruses. *J Gen Virol.* 2017;98(7):1749-54. doi: 10.1099/jgv.0.000849, PMID 28699858.
- Yadav R, Angolkar T, Kaur G, Buttar HS. Antibacterial and anti-inflammatory properties of bovine colostrum. *Recent Pat Inflamm Allergy Drug Discov.* 2016;10(1):49-53. doi: 10.2174/1872214810666160219163118, PMID 26899853.
- Grief SN. Upper respiratory infections. *Prim Care.* 2013;40(3):757-70. doi: 10.1016/j.pop.2013.06.004, PMID 23958368.
- Xu ML, Kim HJ, Wi GR, Kim HJ. The effect of dietary bovine colostrum on respiratory syncytial virus infection and immune responses following the infection in the mouse. *J Microbiol.* 2015;53(9):661-6. doi: 10.1007/s12275-015-5353-4, PMID 26310306.
- Rossey I, Sedeyn K, De Baets S, Schepens B, Saelens X. CD8+T cell immunity against human respiratory syncytial virus. *Vaccine.* 2014;32(46):6130-7. doi: 10.1016/j.vaccine.2014.08.063, PMID 25223272.
- Saad K, Abo-Elela MGM, El-Baseer KAA, Ahmed AE, Ahmad FA, Tawfeek MSK, El-Houfey A, About Khair MD, Abdel-Salam AM, Abo-elgheit A, Qubaisy H, Ali A M, Abdel-Mawgoud E. Effects of bovine colostrum on recurrent respiratory tract infections and diarrhea in children. *Medicine.* 2016;95:1-5.
- Nigro A, Nicastro A, Trodella R. Retrospective observational study to investigate sinerga, a multifactorial nutritional product, and bacterial extracts in the prevention of recurrent respiratory infections in children. *Int J Immunopathol Pharmacol.* 2014;27(3):455-60. doi: 10.1177/039463201402700318, PMID 25280039.
- Patel K, Rana R. Pedimune in recurrent respiratory infection and diarrhea-the Indian experience-the pride study. *Indian J Pediatr.* 2006;73(7):585-91. doi: 10.1007/BF02759923, PMID 16877852.
- Fung SY, Yuen KS, Ye ZW, Chan CP, Jin DY. A tug-of-war between severe acute respiratory syndrome coronavirus 2 and host antiviral defense: lessons from other pathogenic viruses. *Emerg Microbes Infect.* 2020;9(1):558-70. doi: 10.1080/22221751.2020.1736644, PMID 32172672.
- Brinkworth GD, Buckley JD. Concentrated bovine colostrum protein supplementation reduces the incidence of self-reported symptoms of upper respiratory tract infection in adult males. *Eur J Nutr.* 2003;42(4):228-32. doi: 10.1007/s00394-003-0410-x, PMID 12923655.

25. Jones AW, Thatcher R, Mur LAJ, Cameron SJS, Beecroft M, Davison G. Exploring the mechanisms behind the effects of chronic bovine colostrum supplementation on risk of upper respiratory tract infection. *Int J Exer Sci.* 2013;10(1), ISSN 1939-795X.
26. Ahmad S, Anjum FM, Huma N, Sameen A, Zahoor T. Composition and Physico-chemical characteristics of buffalo milk with particular emphasis on lipids, proteins, minerals, enzymes and vitamins. *J Anim Plant Sci.* 2013;23:62-74.
27. Barrington GM, Besser TE, Davis WC, Gay CC, Reeves JJ, McFadden TB. Expression of immunoglobulin G1 receptors by bovine mammary epithelial cells and mammary leukocytes. *J Dairy Sci.* 1997;80(1):86-93. doi: 10.3168/jds.S0022-0302(97)75915-0. PMID 9120099.
28. Korhonen H, Pihlanto A. Technological options for the production of health-promoting proteins and peptides derived from milk and colostrum. *Curr Pharm Des.* 2007;13(8):829-43. doi: 10.2174/138161207780363112, PMID 17430184.
29. Kramski M, Lichtfuss GF, Navis M, Isitman G, Wren L, Rawlin G, Center RJ, Jaworowski A, Kent SJ, Purcell DF. Anti-HIV-1 antibody-dependent cellular cytotoxicity mediated by hyperimmune bovine colostrum IgG. *Eur J Immunol.* 2012;42(10):2771-81. doi: 10.1002/eji.201242469, PMID 22730083.
30. Korhonen H, Marnila P, Gill HS. Milk immunoglobulins and complement factors. *Br J Nutr.* 2000;84Suppl 1:S75-80. doi: 10.1017/S0007114500002282, PMID 11242450.
31. Baumrucker CR, Bruckmaier RM. Colostrogenesis: IgG1 transcytosis mechanisms. *J Mammary Gland Biol Neoplasia.* 2014;19(1):103-17. doi: 10.1007/s10911-013-9313-5, PMID 24474529.
32. Sasaki M, Davis CL, Larson BL. Production and turnover of IgG1 and IgG2 immunoglobulins in the bovine around parturition. *J Dairy Sci.* 1976;59(12):2046-55. doi: 10.3168/jds.S0022-0302(76)84486-4. PMID 1010882.
33. Virtala A-MK, Grohn YT, Mechor GD, Erb HN. The effect of maternally derived immunoglobulin G on the risk of respiratory disease in heifers during the first 3 months of life. *Prev Vet Med.* 1999;39(1):25-37. doi: 10.1016/S0167-5877(98)00140-8.
34. Beam AL, Lombard JE, Koprak CA, Garber LP, Winter AL, Hicks JA, Schlatter JL. Prevalence of failure of passive transfer of immunity in newborn heifer calves and associated management practices on US dairy operations. *J Dairy Sci.* 2009;92(8):3973-80. doi: 10.3168/jds.2009-2225, PMID 19620681.
35. McGuirk SM, Collins M. Managing the production, storage, and delivery of colostrum. *Vet Clin North Am Food Anim Pract.* 2004;20(3):593-603. doi: 10.1016/j.cvfa.2004.06.005. PMID 15471626.
36. Fox PF, Kelly AL. Indigenous enzymes in milk: overview and historical aspects-Part 1. *Int Dairy J.* 2006;16(6):500-16. doi: 10.1016/j.idairyj.2005.09.013. idairyj.2005.09.013.
37. Hahn R, Schulz PM, Schaupp C, Jungbauer A. Bovine whey fractionation based on cation-exchange chromatography. *J Chromatogr A.* 1998;795(2):277-87. doi: 10.1016/S0021-9673(97)01030-3, PMID 9528103.
38. Farkye NY, Bansal N. Enzymes indigenous to milk other enzymes. In: Fuquay JW, Fox PJ, McSweeney PLH. editors. *Encyclopedia of dairy sciences.* Amsterdam: Elsevier; 2011. p. 327-34.
39. Shakeel-ur-Rehman, Farkye FNY. Enzy-mes indigenous to milk lactoperoxidase. In: Roginski H. editor. *Encyclopedia of dairy Scien.* Elsevier; 2002. p. 938-41.
40. Wolfson LM, Sumner SS. Antibacterial activity of the lactoperoxidase system: a review. *J Food Prot.* 1993;56(10):887-92. doi: 10.4315/0362-028X-56.10.887, PMID 31113161.
41. Belding ME, Klebanoff SJ, Ray CG. Peroxidase-mediated virucidal systems. *Science.* 1970;167(3915):195-6. doi: 10.1126/science.167.3915.195, PMID 4311694.
42. Tanaka T, Xuan X, Fujisaki K, Shimazaki K. Expression and characterization of bovine milk antimicrobial proteins lactoperoxidase and lactoferrin by vaccinia virus. In: Roy PK. editors. *Insight and control of infectious disease in global scenario.* IntechOpen; 2012. p. 127-33.
43. Yamauchi K, Tomita M, Giehl TJ, Ellison RT. Antibacterial activity of lactoferrin and a pepsin-derived lactoferrin peptide fragment. *Infect Immun.* 1993;61(2):719-28. doi: 10.1128/IAI.61.2.719-728.1993, PMID 8423097.
44. Nakamura T, Kawase H, Kimura K, Watanabe Y, Ohtani M, Arai I, Urashima T. Concentrations of sialyloligosaccharides in bovine colostrum and milk during the prepartum and early lactation. *J Dairy Sci.* 2003;86(4):1315-20. doi: 10.3168/jds.S0022-0302(03)73715-1. PMID 12741556.
45. Tao N, DePeters EJ, Freeman S, German JB, Grimm R, Lebrilla CB. Bovine milk glycome. *J Dairy Sci.* 2008;91(10):3768-78. doi: 10.3168/jds.2008-1305, PMID 18832198.
46. Tao N, DePeters EJ, German JB, Grimm R, Lebrilla CB. Variations in bovine milk oligosaccharides during early and middle lactation stages analyzed by high-performance liquid chromatography-chip/mass spectrometry. *J Dairy Sci.* 2009;92(7):2991-3001. doi: 10.3168/jds.2008-1642, PMID 19528576.
47. Barile D, Marotta M, Chu C, Mehra R, Grimm R, Lebrilla CB, German JB. Neutral and acidic oligosaccharides in Holstein-Friesian colostrum during the first 3 days of lactation measured by high-performance liquid chromatography on a microfluidic chip and time-of-flight mass spectrometry. *J Dairy Sci.* 2010;93(9):3940-9. doi: 10.3168/jds.2010-3156, PMID 20723667.
48. Ninonuevo MR, Park Y, Yin H, Zhang J, Ward RE, Clowers BH, German JB, Freeman SL, Killeen K, Grimm R, Lebrilla CB. A strategy for annotating the human milk glycome. *J Agric Food Chem.* 2006;54(20):7471-80. doi: 10.1021/jf0615810, PMID 17002410.
49. Martin-Sosa S, Martin MJ, Garcia Pardo LA, Hueso P. Sialyloligosaccharides in human and bovine milk and in infant formulas: variations with the progression of lactation. *J Dairy Sci.* 2003;86(1):52-9. doi: 10.3168/jds.S0022-0302(03)73583-8. S0022-0302(03)73583-8. PMID 12613848.
50. Urashima T, Kitaoka M, Asakuma S, Messer M. Milk oligosaccharides. In: McSweeney P, Fox PF, Esitors. *Advanced dairy chemistry.* New York: Springer New York; 2009. p. 295-349.
51. McJarow P, van Amelsfort-Schoonbeek J. Bovine sialyl oligosaccharides: seasonal variations in their concentrations in milk, and a comparison of the colostrums of jersey and friesland cows. *Int Dairy J.* 2004;14(7):571-9. doi: 10.1016/j.idairyj.2003.11.006.
52. Karav S, Bell JM, Le Parc A Le, Liu Y, Mills DA, Block DE, Barile D. Characterizing the release of bioactive N-glycans from dairy products by a novel endo- β -N-acetylglucosaminidase. *Biotechnol Prog.* 2015;31(5):1331-9. doi: 10.1002/btpr.2135, PMID 26097235.
53. Ten Bruggencate SJ, Bovee Oudenhoven IM, Feitsma AL, van Hoffen E, Schoterman MH. Functional role and mechanisms of sialyl lactose and other sialylated milk oligosaccharides. *Nutr Rev.* 2014;72(6):377-89. doi: 10.1111/nure.12106, PMID 24828428.
54. Chen Y, Liu Q, Guo D. Emerging coronaviruses: genome structure, replication, and pathogenesis. *J Med Virol.* 2020;92(4):418-23. doi: 10.1002/jmv.25681, PMID 31967327.
55. Legrand D, Ellass E, Carpentier M, Mazurier J. Interactions of lactoferrin with cells involved in immune function. *Biochem Cell Biol.* 2006;84(3):282-90. doi: 10.1139/o06-045, PMID 16936798.
56. Bruni N, Capucchio MT, Biasibetti E, Pessione E, Cirrincione S, Giraud L, Corona A, Dosio F. Antimicrobial activity of lactoferrin-related peptides and applications in human and veterinary medicine. *Molecules.* 2016;21(6):752. doi: 10.3390/molecules21060752, PMID 27294909.
57. Levay PF, Viljoen M. Lactoferrin: a general review. *Haematologica.* 1995;80(3):252-67. PMID 7672721.
58. Sorensen M, Sorensen SPL. The proteins in whey. *C R Trav Lab Carlsb Ser Chim.* 1940;23:55-99.
59. Johanson B, Virtanen AI, Tveit RC, Dodson RM. Isolation of an iron-containing red protein from human milk. *Acta Chem*

- Scand. 1960;14:510-2. doi: 10.3891/acta.chem.scand.14-0510.chem.scand.14-0510.
60. Velusamy SK, Poojary R, Ardeshta R, Alabdulmohsen W, Fine DH, Velliyaounder K. Protective effects of human lactoferrin during *aggregatibacter actinomycetemcomitans*-induced bacteremia in lactoferrin-deficient mice. *Antimicrobial Agents and Chemotherapy*. 2014 Jan 1;58(1):397-404. doi: 10.1128/AAC.00020-13, PMID 24189260.
 61. Vitetta L, Coulson S, Beck SL, Gramotnev H, Du S, Lewis S. The clinical efficacy of a bovine lactoferrin/whey protein Ig-rich fraction (Lf/IgF) for the common cold: a double-blind randomized study. *Complement Ther Med*. 2013;21(3):164-71. doi: 10.1016/j.ctim.2012.12.006. PMID 23642947.
 62. Milewska A, Zarebski M, Nowak P, Stozek K, Potempa J, Pyrc K. Human coronavirus NL63 utilizes heparan sulfate proteoglycans for attachment to target cells. *J Virol* 201488. 2014;88(22):13221-30. doi: 10.1128/jvi.02078-14, PMID 25187545.
 63. Burckhardt CJ, Greber UF. Virus movements on the plasma membrane support infection and transmission between cells. *PLOS Pathog*. 2009;5:e1000621. doi: 10.1371/journal.ppat.1000621.
 64. Hoffmann M, Kleine Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Muller MA, Drosten C, Pohlmann S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 2020;181(2):271-80271-280.e8. doi: 10.1016/j.cell.2020.02.052.cell.2020.02.052, PMID 32142651.
 65. Serrano G, Kochergina I, Albors A, Diaz E, Oroval M, Hueso G, Serrano JM. Liposomal lactoferrin as potential preventative and cure for COVID-19. *IJRHS*. 2020;8(1):8-15. doi: 10.5530/ijrhs.8.1.3.
 66. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJHLH. Across speciality collaboration. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395:1033-4:30628-0. doi: 10.1016/S0140-6736(20).
 67. Zimecki M, Wlaszczyk A, Zagulski T, Kubler A. Lactoferrin lowers serum inter-leukin 6 and tumor necrosis factor alpha levels in mice subjected to surgery. *Arch Immunol Ther Exp (Warsz)*. 1998;46(2):97-104. PMID 9613707.
 68. Rosa L, Cutone A, Lepanto MS, Paesano R, Valenti P, Lepanto MS, Paesano R, Valenti P. Lactoferrin: a natural glycoprotein involved in iron and inflammatory homeostasis. *Int J Mol Sci*. 2017;18(9):1985. doi: 10.3390/ijms18091985, PMID 28914813.
 69. Lepanto MS, Rosa L, Paesano R, Valenti P, Cutone A Lepanto MS, Rosa L, Paesano R, Valenti P, Cutone A. Lactoferrin in aseptic and septic inflammation. *Molecules*. 2019;24(7):1323. doi: 10.3390/molecules24071323, PMID 30987256.
 70. Reghunathan R, Jayapal M, Hsu LY, Chng HH, Tai D, Leung BP, Melendez AJ. Expression profile of immune response genes in patients with severe acute respiratory syndrome. *BMC Immunol*. 2005;6:2. doi: 10.1186/1471-2172-6-2, PMID 15655079.
 71. Okubo K, Kamiya M, Urano Y, Nishi H, Herter JM, Mayadas T, Hirohama D, Suzuki K, Kawakami H, Tanaka M, Kurosawa M, Kagaya S, Hishikawa K, Nangaku M, Fujita T, Hayashi M, Hirahashi J. Lactoferrin suppresses neutrophil extracellular traps release in inflammation. *Biomedicine*. 2016;10:204-15. doi: 10.1016/j.ebiom.2016.07.012. PMID 27453322.
 72. Brinkmann V, Reichard U, Goosmann C, Fauler B, Uhlemann Y, Weiss DS, Weinrauch Y, Zychlinsky A. Neutrophil extracellular traps kill bacteria. *Science*. 2004;303(5663):1532-5. doi: 10.1126/science.1092385, PMID 15001782.
 73. F Castanheira FVS, Kubes P VS, Kubes P. Neutrophils and NETs in modulating acute and chronic inflammation. *Blood*. 2019;133(20):2178-85. doi: 10.1182/blood-2018-11-844530, PMID 30898862.
 74. Hahn J, Knopf J, Maueröder C, Kienhöfer D, Leppkes M, Herrmann M. Neutrophils and neutrophil extracellular traps orchestrate initiation and resolution of inflammation. *Clin Exp Rheumatol*. 2016;34(4)Suppl 98:6-8. PMID 27586795.
 75. Lee KH, Kronbichler A, Park DD, Park Y, Moon H, Kim H. Neutrophil extracellular traps (NETs) in autoimmune diseases: a comprehensive review. *Autoimmun Rev*. 2017;16(11):1160-73. doi: 10.1016/j.autrev.2017.09.012, PMID 28899799.
 76. Papayannopoulos V. Neutrophil extracellular traps in immunity and disease. *Nat Rev Immunol*. 2018;18(2):134-47. doi: 10.1038/nri.2017.105, PMID 28990587.
 77. Urban CF, Ermert D, Schmid M, Abu-Abed U, Goosmann C, Nacken W, Brinkmann V, Jungblut PR, Zychlinsky A. Neutrophil extracellular traps contain calprotectin, a cytosolic protein complex involved in host defense against *Candida albicans*. *PLoS Pathog*. 2009;5(10):e1000639. doi: 10.1371/journal.ppat.1000639. PMID 19876394.
 78. Jorch SK, Kubes P. An emerging role for neutrophil extracellular traps in noninfectious disease. *Nat Med*. 2017;23(3):279-87. doi: 10.1038/nm.4294, PMID 28267716.
 79. Law SM, Gray RD. Neutrophil extracellular traps and the dysfunctional innate immune response of cystic fibrosis lung disease: a review. *J Inflamm (Lond)*. 2017;14:29. doi: 10.1186/s12950-017-0176-1. PMID 29299029.
 80. Petrik M, Zhai C, Haas H, Decristoforo C. Siderophores for molecular imaging applications. *Clin Transl Imaging*. 2017;5(1):15-27. doi: 10.1007/s40336-016-0211-x, PMID 28138436.
 81. Beddek AJ, Schryvers AB. The lactoferrin receptor complex in Gram-negative bacteria. *Biometals*. 2010;23(3):377-86. doi: 10.1007/s10534-010-9299-z, PMID 20155302.
 82. Pogoutse AK, Moraes TF. Iron acquisition through the bacterial transferrin receptor. *Crit Rev Biochem Mol Biol*. 2017;52(3):314-26. doi: 10.1080/10409238.2017.1293606, PMID 28276700.
 83. Wandersman C, Stojiljkovic I. Bacterial heme sources: the role of heme, hemoprotein receptors and hemophores. *Curr Opin Microbiol*. 2000;3(2):215-20. doi: 10.1016/Ss1369-5274(00)00078-3, PMID 10744995.
 84. Huang W, Wilks A. Extracellular heme uptake and the challenge of bacterial cell membranes. *Annu Rev Biochem*. 2017;86:799-823. doi: 10.1146/annurev-biochem-060815-014214, PMID 28426241.
 85. Redwan EM, Uversky VN, El-Fakharany EM, Al-Mehdar H. Potential lactoferrin activity against pathogenic viruses. *C R Biol*. 2014;337(10):581-95. doi: 10.1016/j.crv.2014.08.003. PMID 25282173.
 86. Chen JM, Fan YC, Lin JW, Chen YY, Hsu WL, Chiou SS. Bovine lactoferrin inhibits dengue virus infectivity by interacting with heparan sulfate, low-density lipoprotein receptor, and DC-SIGN. *Int J Mol Sci*. 2017;18(9):E1957. doi: 10.3390/ijms18091957, PMID 28895925.
 87. Fernandes KE, Carter DA. The antifungal activity of lactoferrin and its derived peptides: mechanisms of action and synergy with drugs against fungal pathogens. *Front Microbiol*. 2017;8:2. doi: 10.3389/fmicb.2017.00002, PMID 28149293.
 88. Liao H, Liu S, Wang H, Su H, Liu Z. Enhanced antifungal activity of bovine lactoferrin-producing probiotic *Lactobacillus casei* in the murine model of vulvovaginal candidiasis. *BMC Microbiol*. 2019;19(1):7. doi: 10.1186/s12866-018-1370-x, PMID 30621597.
 89. Andres MT, Acosta Zaldivar M, Fierro JF. Antifungal mechanism of action of lactoferrin: identification of H⁺-ATPase (P3A-type) as a new apoptotic-cell membrane receptor. *Antimicrob Agents Chemother*. 2016;60(7):4206-16. doi: 10.1128/AAC.03130-15, PMID 27139463.
 90. Wang B, Timilsena YP, Blanch E, Adhikari B. Lactoferrin: structure, function, denaturation and digestion. *Crit Rev Food Sci Nutr*. 2019;59(4):580-96. doi: 10.1080/10408398.2017.1381583, PMID 28933602.
 91. Nairz M, Schroll A, Sonnweber T, Weiss G. The struggle for iron-a metal at the host-pathogen interface. *Cell Microbiol*. 2010;12(12):1691-702. doi: 10.1111/j.1462-5822.2010.01529.x, PMID 20964797.
 92. Skaar EP. The battle for iron between bacterial pathogens and their vertebrate hosts. *PLoS Pathog*. 2010;6(8):e1000949. doi: 10.1371/journal.ppat.1000949. PMID 20711357.

93. Belting M. Heparan sulfate proteoglycan as a plasma membrane carrier. *Trends Biochem Sci.* 2003;28(3):145-51. doi: 10.1016/S0968-0004(03)00031-8, PMID 12633994.
94. Drobni P, Naslund J, Evander M. Lactoferrin inhibits human papillomavirus binding and uptake *in vitro*. *Antiviral Res.* 2004;64(1):63-8. doi: 10.1016/S0166-3542(04)00123-8j. *antiviral.2004.05.005*, PMID 15451180.
95. 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(9):1055-62. doi: 10.1016/S1357-2725(98)00066-1, PMID 9785469.
96. 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(2-3):107-15. doi: 10.1016/S0304-4165(01)00178-7, PMID 11687297.
97. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet.* 2020;395(10229):1033-4. doi: 10.1016/S0140-6736(20)30628-0, PMID 32192578.
98. Kell DB, Pretorius E. To what extent are the terminal stages of sepsis, septic shock, systemic inflammatory response syndrome, and multiple organ dysfunction syndrome actually driven by a prion/amyloid form of fibrin? *Semin Thromb Hemost.* 2018;44(3):224-38. doi: 10.1055/s-0037-1604108, PMID 28778104.
99. Wu D, Yang XO. TH17 responses in cytokine storm of COVID-19: an emerging target of JAK2 inhibitor Fedratinib. *J Microbiol Immunol Infect.* 2020;53(3):368-70. doi: 10.1016/j.jmii.2020.03.005. PMID 32205092.
100. Zenewicz LA. IL-22: there is a gap in our knowledge. *Immunohorizons.* 2018;2(6):198-207. doi: 10.4049/imunohorizons.1800006, PMID 31022687.
101. Tse GM, To KF, Chan PK, Lo AW, Ng KC, Wu A, Lee N, Wong HC, Mak SM, Chan KF, Hui DS, Sung JJ, Ng HK. Pulmonary pathological features in coronavirus associated severe acute respiratory syndrome (SARS). *J Clin Pathol.* 2004;57(3):260-5. doi: 10.1136/jcp.2003.013276, PMID 14990596.
102. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from wuhan: an analysis based on decade-long structural studies of SARS coronavirus. *J Virol.* 2020;94(7):e00127-20. doi: 10.1128/JVI.00127-20, PMID 31996437.
103. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. *ACS Chem Neurosci.* 2020;11(7):995-8. doi: 10.1021/acscchemneuro.0c00122, PMID 32167747.
104. D'Elia RV, Harrison K, Oyston PC, Lukaszewski RA, Clark GC. Targeting the "cytokine storm" for therapeutic benefit. *Clin Vaccine Immunol.* 2013;20(3):319-27. doi: 10.1128/CVI.00636-12, PMID 23283640.
105. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. *Clin Chim Acta.* 2020;506:145-8. doi: 10.1016/j.cca.2020.03.022, PMID 32178975.
106. Zhang G, Zhang J, Wang B, Zhu X, Wang Q, Qiu S. Analysis of clinical characteristics and laboratory findings of 95 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a retrospective analysis. *Respir Res.* 2020;21(1):74. doi: 10.1186/s12931-020-01338-8, PMID 32216803.
107. Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, Qin R, Wang H, Shen Y, Du K, Zhao L, Fan H, Luo S, Hu D. Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes Metab Res Rev.* 2020:e3319. doi: 10.1002/dmrr.3319. PMID 32233013.
108. Danzi GB, Loffi M, Galeazzi G, Gherbesi E. Acute pulmonary embolism and COVID-19 pneumonia: a random association? *Eur Heart J.* 2020;41(19):1858. doi: 10.1093/eurheartj/ehaa254. PMID 32227120.
109. Heidt T, Ehrismann S, Hovener JB, Neudorfer I, Hilgendorf I, Reiser M, Hagemeyer CE, Zirlirk A, Reinohl J, Bode C, Peter K, von Elverfeldt D, von Zur Muhlen C. Molecular imaging of activated platelets allows the detection of pulmonary embolism with magnetic resonance imaging. *Sci Rep.* 2016;6:25044. doi: 10.1038/srep25044, PMID 27138487.
110. 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;18(5):1094-9. doi: 10.1111/jth.1485117, PMID 32220112.
111. Lang J, Yang N, Deng J, Liu K, Yang P, Zhang G. Inhibition of SARS pseudovirus cell entry by lactoferrin binding to heparan sulfate proteoglycans. *Plos One.* 2011;6(8):e23710. doi: 10.1371/journal.pone.0023710, PMID 21887302.
112. Pretorius E. Platelets as potent signaling entities in type 2 diabetes mellitus. *Trends Endocrinol Metab.* 2019;30(8):532-45. doi: 10.1016/j.tem.2019.05.003. PMID 31196615.
113. Ames BN. Prolonging healthy aging: longevity vitamins and proteins. *Proc Natl Acad Sci USA.* 2018;115(43):10836-44. doi: 10.1073/pnas.1809045115, PMID 30322941.
114. Borodina I, Kenny LC, McCarthy CM, Paramasivan K, Pretorius E, Roberts TJ, van der Hoek SA, Kell DB. The biology of ergothioneine, an antioxidant nutraceutical. *Nutr Res Rev.* 2020;33(2):190-217. doi: 10.1017/S0954422419000301, PMID 32051057.
115. Kawakami H, Park H, Park S, Kuwata H, Shephard RJ, Aoyagi Y. Effects of enteric-coated lactoferrin supplementation on the immune function of elderly individuals: a randomised, double-blind, placebo-controlled trial. *Int Dairy J.* 2015;47:79-85. doi: 10.1016/j.idairyj.2015.02.001.
116. Takeuchi T, Jyonotsuka T, Kamemori N, Kawano G, Shimizu H, Ando K, Harada E. Enteric-formulated lactoferrin was more effectively transported into blood circulation from the gastrointestinal tract in adult rats. *Exp Physiol.* 2006;91(6):1033-40. doi: 10.1113/expphysiol.2006.0348765543, PMID 16959821.