



Milk Lactoferrin: A Probable Immunological Agent Against SARS-CoV-2 : A Review

Jahanzaib Azhar¹, Tahereh Mohammadabadi², Masroor Ellahi Babar³ & Tanveer Hussain^{4*}

¹Department of Biotechnology, Virtual University of Pakistan, Lahore, Pakistan.

²Department of Animal Science, Faculty of Animal Science and Food Technology, Agricultural Sciences and Natural Resources University of Khuzestan, Ahvaz, Iran

³The University of Agriculture, Dera Ismail Khan, Khyber Pakhtunkhwa, Pakistan

⁴Department of Molecular Biology, Virtual University of Pakistan, Lahore, Pakistan

*Corresponding author: tanveer.hussain@vu.edu.pk

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Abstract: In current COVID-19 pandemic, when there is no specific antiviral treatment and vaccine is available yet, many nutritional supplements have caught the attention to manage the disease. Lactoferrin is one of a natural nutritional supplement found in the milk of livestock mammals and has immunomodulation property due to its iron withholding ability and capacity to bind to multiple cellular receptors. The antiviral ability of lactoferrin has been evaluated against many viruses including SARS-CoV which is closely related to SARS-CoV-2 (causative agent of COVID-19). Furthermore, lactoferrin also possesses anti-inflammatory efficacy and can inhibit the circulating inflammatory cytokines (e.g. Interferon γ , interleukin (IL-) 1B, IL-6, IL-12) and chemokines (CCL2 and CXCL10) which are reported to be present in higher levels in COVID-19 patients. A particular research about exploring the potential of lactoferrin against SARS-CoV-2 is highly demandable because lactoferrin might prevent the SARS-CoV-2 from infecting the host cells due to its biological activities regarding antiviral immunity. We are hopeful that further research on evaluating the pharmacological effect of lactoferrin against SARS-CoV-2 will signify its role to combat COVID-19.

Key words: Lactoferrin, SARS-CoV-2, COVID-19, Immunomodulation, Antiviral.

Introduction

The novel coronavirus disease (COVID-19), caused by SARS-CoV-2, has been rapidly spread to all over the world and created the global health crisis. The spike protein has been reported as a determinant of virus entry into the host cells via ACE2 receptor; Infected individ-

uals represent mild to severe clinical manifestations of dry cough, fever, shortness of breath, bilateral pneumonia and some a typical symptoms including sore throat, diarrhoea and vomiting (Zhu *et al.*, 2020). The infection can be spread through close contact with infected

persons and respiratory droplets (Shereen *et al.*, 2020). Many antiviral treatments are proposed but yet there is no properly established therapeutics to contain virus and vaccine development against the disease is in the human trial phase which may take some months or a year to make a breakthrough (Kuchler *et al.*, 2020). The current methodology to control pandemic is to be confined in isolation, personal hygiene measures and taking immunity booster nutritional supplements.

In current situation, one should must be aware of immunity boosting specific food because nutrition is closely associated with immune system function and host resistance to infection. The existing evidences indicate that the supplementation of several nutrients can reduce the risk of viral infections and are correlated with positive impact on enhancing immunity (Jayawardena *et al.*, 2020). These nutrients include vitamins, proteins, metabolites and probiotics which are vital for body's immune system working and strengthening. For immunity development, these components are shown to involve in B and T cells activation and their subsequent proliferation (Wu *et al.*, 2019). Moreover, they are also involved in inducing and modulating the both innate and adaptive immune response (Gombart *et al.*, 2020). Hence the strong immunity through optimal nutrition is the only sustainable way to withstand COVID-19.

Dairy products from livestock animals especially milk and its proteins are considered to be beneficial for human health and the immune system (Al-Hatim *et al.*, 2020). The existing epidemiological studies showed that consumption of cow and camel's milk is correlated with the lower prevalence of bacterial and viral infections (Claeys *et al.*,

2013). This clearly suggests that components (vitamins, globulins, glycoproteins and oligosaccharides) present in the milk of livestock animals may provide the immunity against microbial infections if taken in adequate amount (Loss *et al.*, 2015). One of the important components is milk lactoferrin which is a multifunctional protein of the transferrin family.

Lactoferrin is a non-toxic globular glycoprotein that has been evident to provide protection against respiratory viruses including SARS-CoV (Lang *et al.*, 2011) which is closely related to SARS-CoV-2 that is the etiological agent of COVID-19 (Chen *et al.*, 2020). Recently, the immunoprotective and anti-inflammatory property of lactoferrin has captured the immense interest in the scientific community to assess its potential against COVID-19 because of its dual capability to provoke the immune system to fight pathogen attack (Legrand & Mazurier, 2010) and simultaneously preventing the inflammatory responses (Lepanto *et al.*, 2019). To examine the potential of lactoferrin in immunoprotection against COVID-19, knowledge of its biology including structure, membrane receptors, immunomodulatory and antiviral mechanisms as well as sources is necessary. Thus, in the current review, we have explored the immunoprotective and antiviral mechanism of lactoferrin within the scope of its preventive and therapeutic applications against viruses and discussed the possible role of lactoferrin as an adjunct treatment for COVID-19.

Sources and structural chemistry of Lactoferrin

In 1939, Lactoferrin molecule was first identified and isolated from Bovine milk

(Sorensen & Sorensen, 1939) containing 689 amino acids (Moore *et al.*, 1997). It is present in rich amount in milk and also regarded as a nutraceutical or act as a functional food. After its discovery and isolation from bovine milk, lactoferrin was also found and isolated in the milk of other livestock mammals including camel, sheep and goat (Conesa *et al.*, 2008). Moreover, lactoferrin is also produced in the body by secondary granules of neutrophils and as a secretion by exocrine glands (Okubo *et al.*, 2016). Our specific focus is on its source from animal milk because the lactoferrin present in animal milk and colostrum has more influence in immunomodulation and provide resistance to viral and bacterial infections (Iglesias-Figueroa *et al.*, 2019).

A wide range of lactoferrin concentrations has been estimated in animal milk depending on milk yield, somatic cell count and stage of lactation. In bovine milk, the concentration of lactoferrin varies from 31.78 $\mu\text{g.mL}^{-1}$ to 485.63 $\mu\text{g.mL}^{-1}$ depending on stage of lactation, parity of cow and somatic cell count (Cheng *et al.*, 2008) but its concentration was found to be high in colostrum ranging between 1-5 mg/mL (Stelwagen *et al.*, 2009). Furthermore, the concentration of lactoferrin in camel's milk was estimated to be 20-2100 $\mu\text{g.mL}^{-1}$ (Al-Majali *et al.*, 2007) and has the highest antimicrobial activity (Conesa *et al.*, 2008). Studies showed that camel milk lactoferrin varies widely in normal milk from 0.02 to 7.28 mg.mL⁻¹ but the maximum amount of lactoferrin (2.3 g.L⁻¹) was seen about 48 hours after parturition (El-Hatmi *et al.*, 2007). Lactoferrin from bovine and human possess sequence homology and showed similar bioactivities which suggested the animal milk as a cheap lactoferrin supplement.

Three different isoforms of lactoferrin exist which include lactoferrin alpha (LF- α), beta (LF- β) and gamma (LF- γ). LF- α binds iron but the other two isoforms LF- β and LF- γ are non-iron binding isoforms (Furmanski *et al.*, 1989). In addition to iron, lactoferrin also binds many other metals including Mn^{2+} , Cu^{2+} and Zn^{2+} (Berlutti *et al.*, 2011). The polypeptide chain of lactoferrin contains 600-700 amino acid residues which vary according to the origin of the molecule. Protein structure is composed of α -helix and β -sheets and further divided into two lobes including N⁻ and C⁻ lobe connected by 3-turn helix structure which gives extra flexibility to the protein (Anghel, 2014). The iron withholding capacity of lactoferrin is associated with its anti-microbial activity as well as in immunomodulation (Valenti & Antonini, 2005).

Biology of Lactoferrin membrane receptors

Knowledge of the membrane receptors of lactoferrin is important to understand the mechanism of its biological activities as lactoferrin binds to multiple receptors which include Lactoferrin receptor, TLR2, TLR4 (Gao *et al.*, 2018), CD14 (Rawat *et al.*, 2012), Cytokine receptor (Takayama *et al.*, 2017) and Intelectin-1 (Shin *et al.*, 2008). All of these receptors are reported to be expressed on multiple types of cells and tissues including lymphocytes and intestinal epithelial cells (Suzuki *et al.*, 2005). The capability of lactoferrin to bind to multiple receptors make it an important substance for antiviral immunity and host defence mechanism. Lactoferrin exerts its immunomodulatory activities by competing with infectious molecules or microbial particles for receptor occupancy thus inhibit the attachment of the particles (Kell *et al.*, 2020). Interestingly, lactoferrin also binds to heparan

sulfate proteoglycans (HSPGs) which is utilized by SARS-CoV and human coronavirus NL63 as a receptor for attachment and entry into the cell (Lang *et al.*, 2011; Milewska *et al.*, 2014). SARS-CoV-2 use ACE2 as its functional receptor but may bind to heparan sulfate proteoglycans (HSPGs) as SARS-CoV has been reported to utilize both receptors, yet no study has confirmed about the utilization of HSPGs by SARS-CoV-2 for its early attachment.

Epithelial cells are considered to be the first physical barrier to restrict the entry of harmful particles and have a role in innate immunity. Various milk components including lactoferrin have been shown to regulate the barrier functioning in which after cellular internalization, lactoferrin can induce differentiation and proliferation of epithelial cells (Liao *et al.*, 2012). Another major component in cow's milk is transforming growth factor-beta (TGF β) which is also involved in the regulation of barrier functioning. Lactoferrin is involved in the intracellular cascade that leads to the production of endogenous TGF β 1 which further promotes the barrier functioning and strengthens it by regulating the expression of tight junctions (Perdijk *et al.*, 2018). Thus the lactoferrin has diverse biological functions when it interacts with its membrane receptors.

The immunomodulatory effects of Lactoferrin

Lactoferrin (LF) has an important role in the immune system and host defence against infection and inflammation (Puddu *et al.*, 2009). Some of its immunomodulatory effects are based on complexes with lipopolysaccharide (LPS). The lactoferrin binds to the same lipoproteins that the virus is bound

to, and thus able to prevent the virus from attaching to the cell, but if the virus penetrates the cell, it prevents its replication by stimulating the killer immune cells like natural killer cells, granulocytes and macrophages (Valenti & Antonini, 2005).

Lactoferrin can regulate the production of cytokines/chemokines, production of ROS and peroxides (Britigan *et al.*, 2001), the recruitment, activation, differentiation, and proliferation of immune cells (Legrand & Mazurier, 2010), particularly macrophages, neutrophils, basophils, eosinophils, mastocytes, and dendritic cells (Legrand, 2012). LF modulates the phagocyte capacity of cells and lytic activity through the recognition of specific binding sites (Legrand *et al.*, 2006).

LF transported into the nucleus, binds to DNA (Gonzalez-Chavez *et al.*, 2009; Queiroz *et al.*, 2013) and activates different signaling pathways (Gonzalez-Chavez *et al.*, 2009). The researchers concluded that LF shows anti-inflammatory activity through the inhibition of pro-inflammatory cytokines such as interferon-gamma, tumor necrosis factor-alpha and interleukin (IL)-1, IL-2 and IL-6. Also at the cellular level, LF strengthens the recruitment of blood polymorph nuclear cells and stimulates the myelopoietic process (Gonzalez-Chavez *et al.*, 2009). Also in chronic viraemia, lactoferrin promote a Th1 cytokine profile in peripheral blood (Ishii *et al.*, 2003).

Lactoferricin derived from lactoferrin degradation limits initiation of the inflammatory cascade; enhances IL-10 production; thereby encouraging Th2 (anti-inflammatory)-like activity. Lactoferrin interference appears mediated through fibroblast gene expression, modulating protein

production and altering the extracellular matrix, thus modulating the motility of immune cells (Embleton *et al.*, 2013).

Antiviral effects of Lactoferrin

Lactoferrin is primary defence factor against mucosal infections and cell surfaces, thus inhibiting microbial and viral adhesion and their entry into host cells by blocking of binding to heparan sulfate proteoglycan cell receptors and or by direct binding to host cells and or virus particles (Van der Strate *et al.*, 2001; Berlutti *et al.*, 2011). The cationic nature of lactoferrin and its capability for keeping iron at acidic condition of stomach and may be responsible for the binding ability to viral negative surface structures (Berlutti *et al.*, 2011).

Lactoferrin prevents viral invasion of the host cells and avoiding the infection (Queiroz *et al.*, 2013). The apo form of lactoferrin is shown to be more potent than the holo form, but the reasons for this have not been elucidated yet (Berlutti *et al.*, 2011). The antiviral activity of lactoferrin is against both DNA and RNA viruses (Van der Strate *et al.*, 2001), including rotavirus, respiratory syncytial virus, herpes viruses and HIV (Berlutti *et al.*, 2011). The inhibiting activity of lactoferrin on viruses takes place in the early cycles of viral infection, rather than inhibiting virus replication after the cell infection (Orsi, 2004). Another group of researchers also reported that the property of lactoferrin to inhibit viral entry into the host cell is more significant than its ability of immunomodulation (Jenssen & Hancock, 2009).

Lactoferrin showed importance as defence molecule of host and its physiological activities includes antibacterial, antiviral, antioxidant,

anti-inflammatory, immunomodulatory, anticarcinogenic, antiprotozoan and antifungal (Gonzalez-Chavez *et al.*, 2009). According to studies, iron withholding capability of lactoferrin is also effective in the modulation of motility of immune cells, and inhibition of biofilm formation of pathogenic microorganisms (Berlutti *et al.*, 2011).

The antiviral activity of human Lf and bovine Lf against enveloped and naked viruses has been shown since 1994. In many research studies, when both types of lactoferrin and their isoforms (apo- and holo forms) were examined, no significant differences were observed in the antiviral effects of different forms (Berlutti *et al.*, 2011). Both lactoferrins and their isoforms are effective in the early phase of the viral infection thus prevent virus entry into the host cell by blocking cellular receptors or binding to virus particles (Valenti & Antonini, 2005). But Superti *et al.* (2008) indicated that bovine Lf has higher antiviral activity than human Lf.

COVID-19 and Lactoferrin

Control methods of COVID-19 pandemic are only containment and hygiene measures, while there are no antiviral treatments and vaccines yet. Its proposed nutritional supplements are useful against SARS-CoV-2 which causes COVID-19. Lactoferrin (Lf), as an anti-viral nutritional supplement has been studied against the broad range of viruses including SARS-CoV, and interestingly which is close to SARS-CoV-2 (Chen *et al.*, 2020). Furthermore, it has immunomodulatory and anti-inflammatory characteristics which can boost host immune responses to infections and prevent microbial infections (Bruni *et al.*, 2016). Moreover, Lf inhibited the virus entry via binding to heparan sulfate proteoglycans (HSPGs) in the cell

surface in murine coronavirus, and human coronaviruses hCOV-NL63 (Milewska *et al.*, 2014) and pseudotyped SARS-CoV (Lang *et al.*, 2011). Most (79%) of sequences of the SARS-CoV and SARS-CoV-2 are identical, and their receptor-binding domain structure is also very similar (Peroni & Fanos, 2020). But there are no published researches on Lf effects on SARS-CoV-2 entry into host cells.

In some patients, mortality from COVID-19 is not only due to viral infection but cytokine storm syndrome associated with hyper-inflammation leads to acute respiratory distress and subsequently mortality (Mehta *et al.*, 2020). In severe COVID-19 cases, increases in cytokines and acute phase reactants such as interleukin IL-6, tumor necrosis factor- α (TNF α) and ferritin happens. Lf can modulate an immune and inflammatory response to viral infection, so Lf could be a candidate for adjunct treatment for more severe cases of COVID-19.

Conclusion

Milk lactoferrin as an important nutritional supplement is effective against viral attacks by binding specifically to many virus particles or viral receptors, boosting the immune system. Furthermore, Lf with unique properties of immunomodulatory, anti-inflammatory and antiviral may have precious potential as a preventative and adjunct treatment for COVID-19 as it involves both viral infection and immune responses of host. But it needs further researches and development on Lf nutritional supplementation on SAR-CoV-2.

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Conflict of interest

The authors declare that there is no conflict of interest.

ORCID

J. Azhar : 0000-0002-2210-1422

T. Mohammadabadi: 0000-0002-8250-6704

M.E. Babar: 0000-0001-6417-6222

T. Hussain:0000-0002-2522-2406

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مقالة مرجعية: لاکتوفیرین الحليب: الفعالية المناعية المحتملة ضد فيروس سارس Cov-2

جاهانزيب ازهر¹، طاهره محمدابادي²، الهام مسرور بابار³ و تانفير حسين⁴

¹ قسم التقنيات الحياتية، الجامعة التطبيقية الباكستانية، لاهور، باكستان

² قسم علوم الحيوان، كلية علوم الحياة والتقنيات الغذائية جامعة خوزستان للعلوم الزراعية والثروات الطبيعية، اهواز، ايران

³ الجامعة الزراعية، دير اسلام خان، خيبر باختونخوا، باكستان

⁴ قسم الاحياء الجزيئي، الجامعة التطبيقية الباكستانية، لاهور، باكستان

الملخص: خلال جائحة كورونا الحالية، ومع عدم وجود علاج أو لقاح للتعامل مع الفيروس المسبب للمرض، نالت المكملات الغذائية اهتماماً كبيراً في إدارة هذا المرض. ويعد اللاكتوفيرين من المكملات الغذائية الطبيعية التي تتواجد في حليب اللبائن، ومن بينها حيوانات المزرعة ويتميز بخواصه المناعية نتيجة لامتلاكه خاصية مسك الحديد والارتباط مع العديد من المستقبلات الخلوية. أن المقدرة التثبيطية للاكتوفيرين تجاه الفيروسات تم تقييمها تجاه عديد من الفيروسات ومن بينها SARS-CoV والذي يعد قريباً من الفيروس الممرض SARS-Cov2 فضلاً عن دور اللاكتوفيرين كعامل مضاد للالتهابات مما يشكل عاملاً مهماً في تثبيط السابتوكينات الالتهابية مثل IL-6, IL-12, Interleukin (IL-) 1B, Interferon γ و Chemokines بنوعيه CCL2 و CXCL10 التي سجلت بمعدلات عالية جداً في مرضى كوفيد-19. أن أهمية دراسة اللاكتوفيرين تجاه SARS-CoV تعد أساسية خلال هذه الفترة، ولك لاحتماالية مقدرة اللاكتوفيرين على منع الفيروس من احدث الإصابة بسبب الفعالية البايولوجية العالية له وتحفيز المناعة. ونأمل قريباً أن تتم تغطية الفعالية العلاجية والمناعية للاكتوفيرين تجاه SARS-CoV للتغلب على مرض كوفيد-19.

الكلمات المفتاحية: لاکتوفیرین، فيروس سارس كوفيد 2، تحفيز مناعي، مضاد فايروسي.