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# The role of lactoferrin in the treatment of upper respiratory tract infections

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**ABSTRACT**

**Introduction**

Lactoferrin is a glycoprotein belonging to the group of transferrins found in most body fluids. It has been shown to possess antimicrobial, anti-inflammatory, immunomodulatory and anticancer properties. The increasing availability and widespread use of dietary supplements containing lactoferrin have been observed as supportive measures in managing various infections.

**Aim of the study**

The objective of this study is to summarize the current knowledge regarding the anti-infective - mostly antiviral - effects of lactoferrin and the justification for its use in the treatment of upper respiratory tract infections.

**Knowledge summary**

Scientific research has consistently confirmed the effectiveness of lactoferrin against pathogenic microorganisms. The antibacterial effect of this protein is based mainly on the management of available iron resources - an ingredient necessary for bacterial growth. On the other hand, the antiviral activity of this protein is based on the induction of interferon production.

**Conclusion**

Dietary supplements containing lactoferrin are approved by the US Food and Drug Administration (FDA) for supportive use in infections. Lactoferrin exhibits antimicrobial activity supported by research in specific infections. It has a good tolerance and safety profile, therefore it seems that it can be used adjunctively in this indication.

**Keywords**

lactoferrin, infections, viral infection, bacterial infection, upper respiratory tract infections, supplements, influenza, COVID-19

## Introduction

Upper respiratory tract infections are the third most common reason for patients' visits to family doctors' offices [1]. They include acute nasopharyngitis (common cold), acute sinusitis and acute pharyngitis/tonsillitis. Most of them are caused by viruses such as RSV, influenza viruses, parainfluenza viruses, adenoviruses, rhinoviruses, enteroviruses and coronaviruses and are treated symptomatically [2].

The antimicrobial properties of lactoferrin are the subject of growing scientific interest. The study conducted by Yunling Xu, Yuji Wang, Jiaolong He, Wanping Zhu shows that the number of publications on the properties of lactoferrin has been increasing significantly since 2019, with a peak during the COVID-19 pandemic. [3]. At the same time, the availability of dietary supplements containing lactoferrin is increasing, with indications for its use as an adjunct during infections. According to IndustryARC forecast the global lactoferrin supplements market was estimated at 200.76 million USD in 2020, growing at a CAGR (compound annual growth rate) of 7.5% during years 2021-2026 [4]. Its value is projected to increase to 411.8 million USD in 2028 [5].

Lactoferrin is a glycoprotein commonly found in body fluids and on mucous membranes. It is also present in the granules of immune cells - neutrophils. It belongs to a group of proteins with the ability to bind iron, which determines its properties. The discovery of lactoferrin in bovine milk in 1939 revealed its role in preventing bacterial growth and biofilm formation, attributed to iron deprivation [6, 7]. Subsequent scientific research demonstrated numerous other properties of lactoferrin. The current state of knowledge indicates its contribution to cell proliferation, differentiation, stimulation of neuron development, development of cognitive functions, bone growth support, protection against oxidative stress, regulation of the hematopoietic system, anti-inflammatory and immunoregulatory properties as well as the potential to inhibit tumor development [8].

## Methodology

Based on articles from the PubMed medical database, the authors compiled a summary of the current knowledge about the antimicrobial action of lactoferrin. Using the search term "lactoferrin" they accessed over 3600 publications dating from 1968 to 2024, with the highest number of articles published during the global COVID-19 pandemic (2021-2022). Using other keywords, the authors selected scientific works to create the following review.

## Current state of knowledge

### *Mechanism of action*

The mechanisms of lactoferrin action are diverse. Initially, its role in combating microorganisms by regulating iron metabolism was recognized. However, it’s the molecular mechanisms activated by lactoferrin that seem to play a more significant role. These include increased expression of proinflammatory cytokines such as interferon- γ, interleukin-1b, interleukin-6 and granulocyte-macrophage colony-stimulating factor (GMCSF) as demonstrated in studies involving exogenous lactoferrin administration [9].

On the other hand, during active inflammatory processes, lactoferrin may promote the production of anti-inflammatory cytokines such as IL-4 and IL-10, while inhibiting the production of proinflammatory factors (TNF- α, IL-1b, IL-6) [10]. In the context of viral infections, which are the most common, lactoferrin's ability to induce the production of interferons α and β (IFN-α and IFN-β) appears crucial. These interferons constitute the body's first line of defense against viruses by inhibiting their replication. Oral supplementation with lactoferrin has been shown to increase interferon levels in the body [11].

### *Oral supplementation*

Gastric gland cells secrete pepsinogen, which, under the influence of hydrochloric acid produced by parietal cells, is converted into its active form – pepsin. Pepsin breaks down proteins during digestion. In the case of lactoferrin, digestion results in the breakdown of the molecule into smaller peptides, known as lactoferricins (Lfcins). While lacking iron-chelating abilities, lactoferricins often exhibit higher bactericidal activity than lactoferrin alone, suggesting justified oral use of lactoferrin as a dietary supplement [12].

***Adenoviruses***

A study on the activity of milk proteins against adenoviruses demonstrated that lactoferrin, among the proteins investigated (mucin, α-lactalbumin and β-lactoglobulin), uniquely exhibited inhibitory effects on adenovirus replication. Importantly, this effect was achieved not only before virus adsorption, but also after virus attachment to the host cell membrane and during replication. Lactoferrin's mechanism of action includes competition for glycosaminoglycans, which serve as the binding sites for virus attachment to the cell membrane [13, 14].

***Respiratory Syncytial Virus (RSV)***

In vitro studies consistently demonstrated that lactoferrin inhibits RSV replication, even at concentrations lower than those normally found in human milk [14, 16, 17, 12]. However, animal studies did not confirm this effect. Lucien Gualdi, Sara Mertz, Ana M Gomez, Octavio Ramilo, Anja Wittke, and Asuncion Mejias found that the concentration of Th1, Th2 and Th17 cytokines and the severity of the disease did not differ significantly between mice infected with RSV and treated with lactoferrin (regardless of dose and route of administration) and animals infected with RSV and untreated with lactoferrin [18].

However, a study on healthy children with recurrent respiratory tract infections showed that lactoferrin and curcumin supplementation helped reduce the frequency of infections by modulating the maturation of CD8+ T lymphocytes and decreasing IL-10 production by CD14+ lymphocytes [19, 12]. Similar conclusions were drawn from studying infants aged 4-6 months fed milk with added lactoferrin, with a lower incidence of RSV infection compared to the control group [20,12].

***Influenza***

According to the World Health Organization, between 300 million and 1.5 billion people worldwide suffer from influenza each year, accounting for 4% to 19% of the global population. A study on mice infected with the influenza virus observed a lower lung consolidation score in the group of animals receiving lactoferrin than in the control group, even though the proinflammatory cytokine IL-6 did not significantly differ between the two groups [21].

Another study identified broad anti-influenza activity among three peptides derived from the lactoferrin molecule. These peptides inhibit virus replication by binding to hemagglutinin on the viral envelope, even at femtomolar concentrations. According to the authors, these are the smallest molecules discovered to be active against the influenza viruses and may be used to develop a new class of drugs against this illness [22].

***Rhinoviruses***

Previous studies did not prove the effective action of lactoferrin against rhinoviruses [23]. However, in their publication, Denani CB et al. demonstrated the inhibition of H1-HeLa cell infection by rhinoviruses by lactoferrin. This effect was most significant when lactoferrin was added simultaneously with the virus and somewhat less when added during the virus absorption stage [24].

***SARS-CoV-2***

The SARS-CoV-2 pandemic erupted in March 2020 in China and rapidly spread worldwide. According to statistics, approximately 7 million people died from COVID-19 by the end of 2023.

Researchers from Brazil conducted an experiment, the results of which are as follows: lactoferrin at a concentration of 1 mg/mL in vitro inhibits the early-stage infection of Vero cells (African green monkey kidney epithelial cells) with the SARS-CoV-2 virus [25].

In vivo studies conducted on hamsters using a model coronavirus GX_P2V (SARS-CoV-2-related coronavirus) demonstrated the antiviral activity of lactoferrin, leading to reduction in viremia in the lungs and trachea of the studied animals and facilitating the healing process [26].

However, human studies did not demonstrate the clinical efficacy of lactoferrin. A study conducted on 209 medical professionals in Peru in 2020 and 2021 involved daily intake of 600 mg of lactoferrin for 90 days. The dose was determined based on previous scientific studies. No significant differences were observed between the treated patients and the control group regarding the frequency, duration or severity of SARS-CoV-2 infection [27].

Similarly, in a randomized, double-blind clinical trial conducted in Italy on 219 patients taking 800 mg of lactoferrin daily, no clinical significance of supplementation for the course of the disease was observed. The experiment did not demonstrate effectiveness in preventing deaths, ICU transfers, the need for oxygen therapy or a decrease in pro-inflammatory biomarkers (CRP, IL-6, ferritin) [28]. It is important to note that none of the above studies reported significant adverse effects, indicating a good safety and tolerance profile for lactoferrin supplementation [27, 28].

### *Enteroviruses*

Enteroviruses are a group of viruses that cause diseases of various specificity and severity - from mild flu-like illnesses, through herpangina, to meningitis. Tsui-Ying Weng et al. in a 2005 study proved that both in vitro and in vivo lactoferrin protects human cells against infection with enterovirus E71. Its mechanism of action involves binding to the VP1 protein of EV71. Additionally, this study showed that lactoferrin enhanced the expression of IFN-α and inhibited the production of IL-6. It follows that lactoferrin protects against infection both by interacting with the virus itself and with host cells. What's more, lactoferrin has been proven to protect mice against lethal EV71 challenge [29, 30].

On the other hand, another in vivo study involving 216 children aged 2 to 6 did not confirm that lactoferrin had an impact on the incidence or severity of enterovirus infections. In this study, IFN-γ and IL-10 (proinflammatory and anti-inflammatory, respectively) were selected as markers. Also in this respect, no significant changes were observed between the levels of cytokines in the group of children examined and in the control group. The authors suspect that the study results could have been influenced by the fact that the observations were made of children in a kindergarten with strict sanitary regime (therefore, the number of infections was naturally lower) [31].

### *Bacteria*

Although the vast majority of upper respiratory tract infections are caused by viruses, some are caused by bacteria. A study conducted by Jialiang Tang et al. in 2019 shows that in the age group 0-5, over 90% of infections had a viral etiology. This percentage decreases with age, reaching the lowest value in the age group 5-45 (approx. 75%). At the same time, the percentage of bacterial infections is increasing - from 6.5% in the 0-5 age group to approximately 15% in the 5-45 age group [32]. The most common bacteria causing upper respiratory tract infections include Group A *streptococci*, *Mycoplasma pneumoniae*, *Streptococcus pneumoniae* and *Staphylococcus aureus* [33].

In 2019 in *Frontiers in Microbiology* a paper examining the effect of lactoferrin on bacteria was published. The study focused on the colonization of the respiratory tract by *pneumococci* and the effect on the existing pneumococcal biofilm. First, the inhibitory effect of lactoferrin on the colonization of the respiratory tract tissues by these bacteria was demonstrated to an extent comparable to the effect of the macrolide antibiotic - erythromycin. Subsequently, the degradation of pneumococcal DNA by lactoferrin was demonstrated and it was proven that bovine lactoferrin is able to eradicate bacterial biofilm, even if the bacteria are resistant to antibiotics (trimethoprim) [34].

In their study, Kosznik-Kwaśnicka K., Kaźmierczak N. and Piechowicz L. also proved the effect of lactoferrin against multidrug-resistant *Staphylococcus aureus* (MDRSA). MDRSA strains classified as strong biofilm producers were selected. Mature MDRSA biofilms were treated with three different concentrations of lactoferrin (chosen based on literature data). After 4, 12 and 24 hours of incubation with lactoferrin it was found that lactoferrin significantly decreased biofilm biomass and viability. What's suprising there were no differences between 1mg/mL and 10mg/mL concentrations. Even though the biomass decreased, the number of cells in the biofilm did not decrease. This may indicate rather bacteriostatic than bactericidal effect of lactoferrin. In the light of this knowledge, the authors propose using lactoferrin as an additive to other antimicrobials to increase their effectiveness rather than a medicine itself [35]. A study by Petitclerc D. et al. also showed that lactorferrin increases the potential of penicillin fourfold against penicillin-susceptible *S. aureus* strains and up to 16-fold in penicillin-resistant strains [36].

## Conclusions

Lactoferrin is sold worldwide in the form of dietary supplements. To date, many experiments both in vitro and in vivo have been carried out in the research on lactoferrin. Most of them focus on the molecular analysis of lactoferrin activity, confirming the induction of pro- or anti-inflammatory action depending on environmental conditions through the influence on cytokine expression. In vivo studies confirm the antibacterial effectiveness of lactoferrin as well as – to varying degrees - the antiviral effectiveness of lactoferrin. Due to the good safety and tolerance profile of this substance, its supportive use in treating upper respiratory tract infections seems to be justified.

## Disclosure

The authors declare that they have no financial or non-financial conflicts of interest that could be perceived as influencing the interpretation of the research findings or the content of this manuscript. This work was conducted independently without any external funding or support.

**Author's contribution**

All authors have read and approved the published version of the manuscript. The data presented in this study are available upon request from the corresponding author.

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As a review paper, our work does not present new data or analyses. Therefore, there are no specific datasets or data availability to report. The information and findings presented in this review are based on previously published studies, which can be accessed through their respective sources as cited in the reference section.

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## Conflict of Interest Statement

The authors declare that there are no significant conflicts of interest associated with this research work.

## References

1. Cooke G, Valenti L, Glasziou P, Britt H. Common general practice presentations and publication frequency. Aust Fam Physician. 2013 Jan-Feb;42(1-2):65-8. PMID: 23529466

2. Lu Y, Tong J, Pei F, Yang Y, Xu D, Ji M, Xing C, Jia P, Xu C, Wang Y, Li G, Chai Z, Liu Y, Han J. Viral aetiology in adults with acute upper respiratory tract infection in Jinan, Northern China. Clin Dev Immunol. 2013;2013:869521. doi: 10.1155/2013/869521. Epub 2013 Apr 15. PMID: 23690828; PMCID: PMC3649347.

3. Xu Y, Wang Y, He J, Zhu W. Antibacterial properties of lactoferrin: A bibliometric analysis from 2000 to early 2022. Front Microbiol. 2022 Aug 17;13:947102. doi: 10.3389/fmicb.2022.947102. PMID: 36060777; PMCID: PMC9428516.

4. https://www.industryarc.com/Report/17805/lactoferrin-supplements-market.html

5. Jańczuk A, Brodziak A, Czernecki T, Król J. Lactoferrin-The Health-Promoting Properties and Contemporary Application with Genetic Aspects. Foods. 2022 Dec 23;12(1):70. doi: 10.3390/foods12010070. PMID: 36613286; PMCID: PMC9818722.

6. Vogel HJ. Lactoferrin, a bird's eye view. Biochem Cell Biol. 2012 Jun;90(3):233-44. doi: 10.1139/o2012-016. Epub 2012 Apr 27. PMID: 22540735.

7. Soerensen M. Soerensen, SPL. The Proteins in Whey. C. R. Trav. Lab. Carlsberg, 23, 55-99, 1939.

8. Avalos-Gómez C, Ramírez-Rico G, Ruiz-Mazón L, Sicairos NL, Serrano-Luna J, de la Garza M. Lactoferrin: An Effective Weapon in the Battle Against Bacterial Infections. Curr Pharm Des. 2022;28(40):3243-3260. doi: 10.2174/1381612829666221025153216. PMID: 36284379.

9. Legrand D, Elass E, Carpentier M, Mazurier J. Lactoferrin: a modulator of immune and inflammatory responses. Cell Mol Life Sci. 2005 Nov;62(22):2549-59. doi: 10.1007/s00018-005-5370-2. PMID: 16261255; PMCID: PMC7079806.

10. Togawa J, Nagase H, Tanaka K, Inamori M, Nakajima A, Ueno N, Saito T, Sekihara H. Oral administration of lactoferrin reduces colitis in rats via modulation of the immune system and correction of cytokine imbalance. J Gastroenterol Hepatol. 2002 Dec;17(12):1291-8. doi: 10.1046/j.1440-1746.2002.02868.x. PMID: 12423274.

11. Wakabayashi H, Takakura N, Yamauchi K, Tamura Y. Modulation of immunity-related gene expression in small intestines of mice by oral administration of lactoferrin. Clin Vaccine Immunol. 2006 Feb;13(2):239-45. doi: 10.1128/CVI.13.2.239-245.2006. PMID: 16467332; PMCID: PMC1391931.

12. Drago-Serrano ME, Campos-Rodríguez R, Carrero JC, de la Garza M. Lactoferrin: Balancing Ups and Downs of Inflammation Due to Microbial Infections. Int J Mol Sci. 2017 Mar 1;18(3):501. doi: 10.3390/ijms18030501. PMID: 28257033; PMCID: PMC5372517.

13. Arnold D, Di Biase AM, Marchetti M, Pietrantoni A, Valenti P, Seganti L, Superti F. Antiadenovirus activity of milk proteins: lactoferrin prevents viral infection. Antiviral Res. 2002 Feb;53(2):153-8. doi: 10.1016/s0166-3542(01)00197-8. PMID: 11750941.

14. Redwan EM, Uversky VN, El-Fakharany EM, Al-Mehdar H. Potential lactoferrin activity against pathogenic viruses. C R Biol. 2014 Oct;337(10):581-95. doi: 10.1016/j.crvi.2014.08.003. Epub 2014 Sep 22. PMID: 25282173.

15. Grover M, Giouzeppos O, Schnagl RD, May JT. Effect of human milk prostaglandins and lactoferrin on respiratory syncytial virus and rotavirus. Acta Paediatr. 1997 Mar;86(3):315-6. doi: 10.1111/j.1651-2227.1997.tb08896.x. PMID: 9099323.

16. Portelli J, Gordon A, May JT. Effect of compounds with antibacterial activities in human milk on respiratory syncytial virus and cytomegalovirus in vitro. J Med Microbiol. 1998 Nov;47(11):1015-8. doi: 10.1099/00222615-47-11-1015. PMID: 9822301.

17.Sano H, Nagai K, Tsutsumi H, Kuroki Y. Lactoferrin and surfactant protein A exhibit distinct binding specificity to F protein and differently modulate respiratory syncytial virus infection. Eur J Immunol. 2003 Oct;33(10):2894-902. doi: 10.1002/eji.200324218. PMID: 14515273.

18. Gualdi L, Mertz S, Gomez AM, Ramilo O, Wittke A, Mejias A. Lack of effect of bovine lactoferrin in respiratory syncytial virus replication and clinical disease severity in the mouse model. Antiviral Res. 2013 Aug;99(2):188-95. doi: 10.1016/j.antiviral.2013.05.013. Epub 2013 Jun 2. PMID: 23735300.

19. Zuccotti GV, Trabattoni D, Morelli M, Borgonovo S, Schneider L, Clerici M. Immune modulation by lactoferrin and curcumin in children with recurrent respiratory infections. J Biol Regul Homeost Agents. 2009 Apr-Jun;23(2):119-23. PMID: 19589293.

20. Chen K, Chai L, Li H, Zhang Y, Xie HM, Shang J, Tian W, Yang P, Jiang AC. Effect of bovine lactoferrin from iron-fortified formulas on diarrhea and respiratory tract infections of weaned infants in a randomized controlled trial. Nutrition. 2016 Feb;32(2):222-7. doi: 10.1016/j.nut.2015.08.010. Epub 2015 Sep 3. PMID: 26602290.

21. Shin K, Wakabayashi H, Yamauchi K, Teraguchi S, Tamura Y, Kurokawa M, Shiraki K. Effects of orally administered bovine lactoferrin and lactoperoxidase on influenza virus infection in mice. J Med Microbiol. 2005 Aug;54(Pt 8):717-723. doi: 10.1099/jmm.0.46018-0. PMID: 16014423.

22. Scala MC, Sala M, Pietrantoni A, Spensiero A, Di Micco S, Agamennone M, Bertamino A, Novellino E, Bifulco G, Gomez-Monterrey IM, Superti F, Campiglia P. Lactoferrin-derived Peptides Active towards Influenza: Identification of Three Potent Tetrapeptide Inhibitors. Sci Rep. 2017 Sep 6;7(1):10593. doi: 10.1038/s41598-017-10492-x. PMID: 28878220; PMCID: PMC5587682.

23. Berlutti F, Pantanella F, Natalizi T, Frioni A, Paesano R, Polimeni A, Valenti P. Antiviral properties of lactoferrin--a natural immunity molecule. Molecules. 2011 Aug 16;16(8):6992-7018. doi: 10.3390/molecules16086992. PMID: 21847071; PMCID: PMC6264778.

24. Denani CB, Real-Hohn A, de Carvalho CAM, Gomes AMO, Gonçalves RB. Lactoferrin affects rhinovirus B-14 entry into H1-HeLa cells. Arch Virol. 2021 Apr;166(4):1203-1211. doi: 10.1007/s00705-021-04993-4. Epub 2021 Feb 19. PMID: 33606112; PMCID: PMC7894240.

25. Alves NS, Azevedo AS, Dias BM, Horbach IS, Setatino BP, Denani CB, Schwarcz WD, Lima SMB, Missailidis S, Ano Bom APD, Silva AMV, Barreto Vieira DF, Silva MAN, Barros CA, Carvalho CAM, Gonçalves RB. Inhibition of SARS-CoV-2 Infection in Vero Cells by Bovine Lactoferrin under Different Iron-Saturation States. Pharmaceuticals (Basel). 2023 Sep 25;16(10):1352. doi: 10.3390/ph16101352. PMID: 37895823; PMCID: PMC10609673.

26. He ST, Qin H, Guan L, Liu K, Hong B, Zhang X, Lou F, Li M, Lin W, Chen Y, He C, Liu F, Lu S, Luo S, Zhu S, An X, Song L, Fan H, Tong Y. Bovine lactoferrin inhibits SARS-CoV-2 and SARS-CoV-1 by targeting the RdRp complex and alleviates viral infection in the hamster model. J Med Virol. 2023 Jan;95(1):e28281. doi: 10.1002/jmv.28281. PMID: 36329614; PMCID: PMC9878033.

27. Navarro R, Paredes JL, Tucto L, Medina C, Angles-Yanqui E, Nario JC, Ruiz-Cabrejos J, Quintana JL, Turpo-Espinoza K, Mejia-Cordero F, Aphang-Lam M, Florez J, Carrasco-Escobar G, Ochoa TJ. Bovine lactoferrin for the prevention of COVID-19 infection in health care personnel: a double-blinded randomized clinical trial (LF-COVID). Biometals. 2023 Jun;36(3):463-472. doi: 10.1007/s10534-022-00477-3. Epub 2022 Dec 7. PMID: 36474100; PMCID: PMC9735051.

28. Matino E, Tavella E, Rizzi M, Avanzi GC, Azzolina D, Battaglia A, Becco P, Bellan M, Bertinieri G, Bertoletti M, Casciaro GF, Castello LM, Colageo U, Colangelo D, Comolli D, Costanzo M, Croce A, D'Onghia D, Della Corte F, De Mitri L, Dodaro V, Givone F, Gravina A, Grillenzoni L, Gusmaroli G, Landi R, Lingua A, Manzoni R, Marinoni V, Masturzo B, Minisini R, Morello M, Nelva A, Ortone E, Paolella R, Patti G, Pedrinelli A, Pirisi M, Ravizzi L, Rizzi E, Sola D, Sola M, Tonello N, Tonello S, Topazzo G, Tua A, Valenti P, Vaschetto R, Vassia V, Zecca E, Zublena N, Manzoni P, Sainaghi PP. Effect of Lactoferrin on Clinical Outcomes of Hospitalized Patients with COVID-19: The LAC Randomized Clinical Trial.

Nutrients. 2023 Mar 4;15(5):1285. doi: 10.3390/nu15051285. PMID: 36904283; PMCID: PMC10005739.

29. Weng TY, Chen LC, Shyu HW, Chen SH, Wang JR, Yu CK, Lei HY, Yeh TM. Lactoferrin inhibits enterovirus 71 infection by binding to VP1 protein and host cells. Antiviral Res. 2005 Jul;67(1):31-7. doi: 10.1016/j.antiviral.2005.03.005. PMID: 15916817.

30. Kaczyńska K, Jampolska M, Wojciechowski P, Sulejczak D, Andrzejewski K, Zając D. Potential of Lactoferrin in the Treatment of Lung Diseases. Pharmaceuticals (Basel). 2023 Jan 28;16(2):192. doi: 10.3390/ph16020192. PMID: 37259341; PMCID: PMC9960651.

31. Yen MH, Chiu CH, Huang YC, Lin TY. Effects of lactoferrin-containing formula in the prevention of enterovirus and rotavirus infection and impact on serum cytokine levels: a randomized trial. Chang Gung Med J. 2011 Jul-Aug;34(4):395-402. PMID: 21880194.

32. Tang J, Chen J, He T, Jiang Z, Zhou J, Hu B, Yang S. Diversity of upper respiratory tract infections and prevalence of Streptococcus pneumoniae colonization among patients with fever and flu-like symptoms. BMC Infect Dis. 2019 Jan 7;19(1):24. doi: 10.1186/s12879-018-3662-z. PMID: 30616564; PMCID: PMC6323860.

33. Dasaraju PV, Liu C. Infections of the Respiratory System. In: Baron S, editor. Medical Microbiology. 4th edition. Galveston (TX): University of Texas Medical Branch at Galveston; 1996. Chapter 93.

34. Angulo-Zamudio UA, Vidal JE, Nazmi K, Bolscher JGM, Leon-Sicairos C, Antezana BS, Canizalez-Roman A, León-Sicairos N. Lactoferrin Disaggregates Pneumococcal Biofilms and Inhibits Acquisition of Resistance Through Its DNase Activity. Front Microbiol. 2019 Oct 18;10:2386. doi: 10.3389/fmicb.2019.02386. PMID: 31681240; PMCID: PMC6813537.

35. Kosznik-Kwaśnicka K, Kaźmierczak N, Piechowicz L. Activity of Phage-Lactoferrin Mixture against Multi Drug Resistant *Staphylococcus aureus* Biofilms. Antibiotics (Basel). 2022 Sep 16;11(9):1256. doi: 10.3390/antibiotics11091256. PMID: 36140035; PMCID: PMC9495459.

36. Petitclerc D, Lauzon K, Cochu A, Ster C, Diarra MS, Lacasse P. Efficacy of a lactoferrin-penicillin combination to treat {beta}-lactam-resistant Staphylococcus aureus mastitis. J Dairy Sci. 2007 Jun;90(6):2778-87. doi: 10.3168/jds.2006-598. PMID: 17517718.