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Critical evaluation of the antibacterial potential of commercial bovine lactoferrin against clinical isolates of nosocomial pathogens

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ABSTRACT

Background: Lactoferrin, a protein from the transferrin family found in human and bovine milk, has been extensively documented in the literature for its significant properties, including antibacterial activity. Numerous studies have explored the potential of lactoferrin as an adjunctive treatment for bacterial infections in children, both within and outside pediatric hospitals.

Objective: The evaluation of the antibacterial potential of commercial lactoferrin against clinical isolates of nosocomial pathogens.

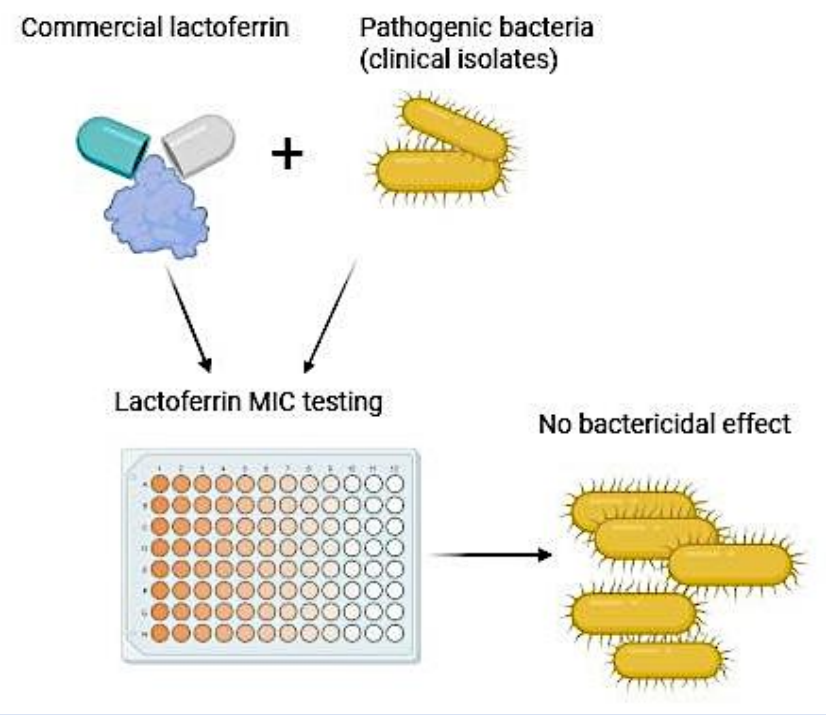
Methods: The antimicrobial activity of lactoferrin samples was assessed using the minimum inhibitory concentration (MIC). MIC was evaluated as recommended by the European Committee for Antimicrobial Susceptibility Testing. Additional experimental cell concentration was also used in the study.

Results: The commercial lactoferrin samples had no antibacterial effect within the concentration ranges used in the study on tested nosocomial pathogens isolates from a pediatric hospital. No differences were observed in the activity of commercially available lactoferrin samples over the range of the investigated concentrations.

Conclusion: Multi-drug resistant clinical isolates of *Pseudomonas aeruginosa, Klebsiella pneumoniae*, the causative agents of hospital-acquired infections, were used in the study. Antibacterial potential of the lactoferrin against the bacterial strain depends on the strain-lactoferrin pair used in the study. In addition, the verification of in vitro experimental results in clinical trials is essential for accurately assessing and understanding both the antibacterial potential of lactoferrin against multidrug-resistant (MDR) clinical isolates and its possible applications in clinical practice as a bioactive compound with potential for functional food development.

Keywords: lactoferrin, bioactive compound, nosocomial infections, antibacterial activity

Graphical Abstract: Critical evaluation of the antibacterial potential of commercial bovine lactoferrin against clinical isolates of nosocomial pathogens.



INTRODUCTION

Lactoferrin is a multifunctional glycoprotein present in human and bovine milk, known for its antioxidant, anti-inflammatory, and antimicrobial properties [1-3]. Interest in the clinical application of lactoferrin as an additional therapeutic agent with antibacterial activity remains high, with several studies demonstrating the antibacterial effects of human and bovine lactoferrin both in vitro and in volunteer-based studies [4-6]. The promising potential of lactoferrin is particularly relevant in cases with limited antibiotic options, such as in infants, and in situations where pathogens exhibit antibiotic resistance. The issue of drug resistance is particularly acute in pediatric hospitals, prompting the medical community to seek additional control measures [7-8].

Functional foods are natural or processed foods containing biologically active compounds that, at certain effective levels, provide proven and documented health benefits and could be a promising strategy for the treatment of some human infections [9-12]. The

effectiveness of functional foods in the prevention of various diseases has been demonstrated in several studies [13-16].

Determining the suitable dosage regime for consuming bioactive compounds is a crucial stage in developing functional food products [11].

Consequently, lactoferrinis is a bioactive compound with potential for functional food development and has thus become the focus of research and clinical trials. In this context, the objective of this study was to investigate the antibacterial potential of bovine lactoferrin in the form of commercial supplements against nosocomial pathogens in pediatric hospitals, and to evaluate its potential as an additional antibacterial agent and functional food candidate.

Novelty of the Study: This study explores the under-investigated antibacterial potential of lactoferrin derived specifically from commercial functional food supplements against MDR nosocomial pathogens isolated from a pediatric hospital setting. While lactoferrin's antimicrobial activity is well documented, its effectiveness against real-world clinical isolates from children remains unclear. By focusing on strain-specific interactions and clinically relevant MDR bacteria, this research adds new insights into the variable efficacy of supplement-grade lactoferrin.

MATERIALS AND METHODS

Materials: The study utilized two commercial lactoferrin preparations: "Jarrow Formula" (USA), which contains pure bovine lactoferrin as per the manufacturer's specifications, and "Biakon" (Russia), which contains bovine lactoferrin and lyophilized bovine milk. Sensitivity studies were conducted using Mueller-Hinton medium (Himedia, India). Multi-drug-resistant clinical isolates of *P. aeruginosa*, *K. pneumoniae,* the causative agents of hospital-acquired infections, were provided by the N.F. Filatov Children's City Hospital of the Moscow Healthcare Ministry.

Methods: Commercial lactoferrin samples were dissolved in Hanks' reagent with phenol red (PanEco, Russia) at the maximum concentration that allowed for the collection of a clear supernatant after precipitation (82.5 mg/mL for "Jarrow Formula" and 32.5 mg/mL for "Biakon"). To obtain a clear supernatant, samples were subjected to three consecutive rounds of precipitation at 15,000 g for 15 minutes, with the supernatant collected sequentially. The samples were sterilized using a 0.22-micron low protein binding PVDF filter (Millex, Ireland). The sterility of the lactoferrin samples was confirmed by culturing on solid nutrient Mueller-Hinton agar (Himedia, India). The presence and concentration of lactoferrin in the commercial samples in SDS-PAGE was determined densitometrically relative to BSA samples of known concentration.

The electrophoretic profiles were analyzed using the ChemiDoc MP Imaging System (BioRad). The antimicrobial activity of lactoferrin samples was assessed using the minimum inhibitory concentration (MIC) according to European Committee for Antimicrobial Susceptibility Testing (EUCAST) recommendations. MIC values were determined through serial dilutions in Mueller-Hinton broth (MHB) enriched with Ca^{2+} and Mg^{2+} ions, containing 24-hour cultures of different strains at concentrations of 5×10^5 and 1×10^3 CFU/mL for each strain. Pure microorganism cultures for each strain, sterile medium, and sterile lactoferrin samples served as controls. Experiments were conducted in triplicate.

RESULTS

Microbiological Purity Determination of lactoferrin: Culturing commercial lactoferrin samples on solid nutrient medium after filtration showed no presence of microorganisms in both "Jarrow Formula" and "Biakon" lactoferrin samples, confirming their suitability for further study.

Lactoferrin Concentration in Commercial Samples Post-Filtration: Lactoferrin was detected in the filtrates of commercial supplements at concentrations of 65 mg per 100 mg dry matter for "Jarrow Formula" and 26 mg per 100 mg dry matter for "Biakon." The maximum working solution concentrations were 82.5 mg/mL for "Jarrow Formula" and 32.5 mg/mL for "Biakon."

Antibacterial Activity Assessment: MIC Determination for Clinical Isolates of *P. aeruginosa* and *K. pneumoniae*: The antibacterial activity of lactoferrin was evaluated on clinical isolates of *P.aeruginosa* and *K.pneumoniae* at different concentrations—standard (5×10^5 CFU/mL) as recommended by the EUCAST, and experimental (1×10^3 CFU/mL)—and assessed visually. The MIC results for standard and experimental concentrations are presented in Figs. 1 and 2, respectively.

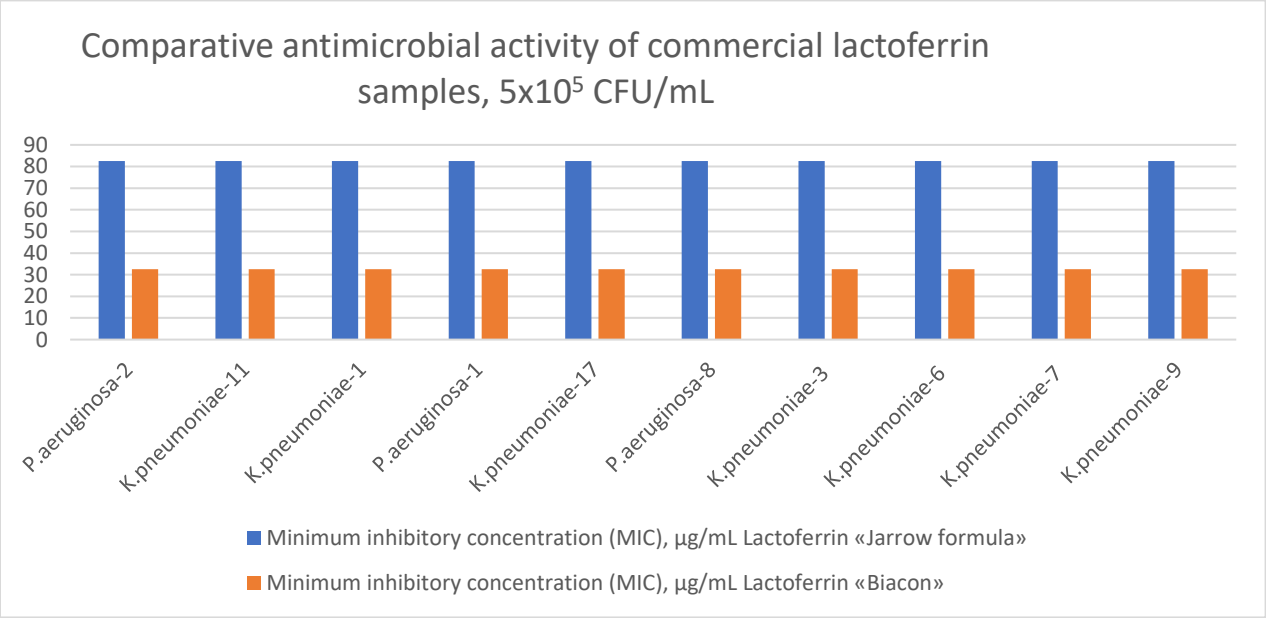


Figure 1. Comparative Antimicrobial Activity of Commercial Lactoferrin Samples, 5×10^5 CFU/mL.

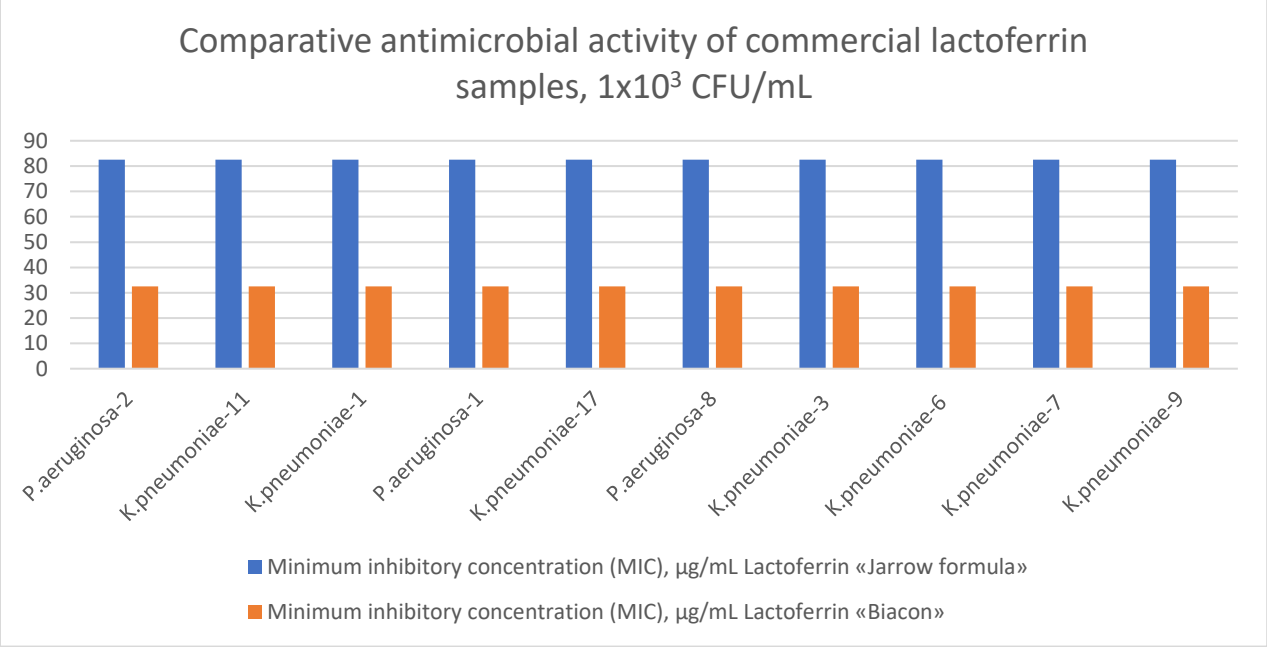


Figure 2. Comparative Antimicrobial Activity of Commercial Lactoferrin Samples, 1×10^3 CFU/mL.

Note: The maximum concentrations of Jarrow Formula lactoferrin and Biakon lactoferrin in the study were 82.5 mg/mL and 32.5 mg/mL, respectively, based on the maximum solubility of each sample.

The data presented indicates that the commercial lactoferrin substances tested did not exhibit antibacterial activity within the concentration ranges used: 0.16-82.5 mg/mL for Jarrow Formula lactoferrin and 0.03-32.5 mg/mL for Biakon lactoferrin, against clinical isolates of *P.aeruginosa* and *K.pneumoniae* at any of the selected cell concentrations. No differences were observed in the activity of commercially available lactoferrin samples over the range of the investigated concentrations.

DISCUSSION

All tested clinical isolates from the N.F. Filatov Children's City Hospital were not susceptible to the commercial lactoferrin supplements Jarrow and Biakon. The use of lactoferrin as an adjuvant that potentially reduces the MIC of an antibiotic that a microorganism is resistant to must take into account the fact that for such an antibiotic to be used in clinical practice, its MIC must be reduced to 16 μg /mL or lower for different antibiotics in order for the microorganism to be considered sensitive. Moreover, a reliable reduction in MIC should be stable throughout the course of antibiotic therapy. When working with MDR strains whose MIC often exceeds 100 μg/ml, it is important to realize that even when using adjuvants and reducing the MIC value by 2-3 times, we will still be in the "resistant zone" and such results will not have prospects for use in clinical practice. Such a task could be the goal of a new separate study.

The lack of lactoferrin activity is attributed to the high virulence and aggressiveness of the clinical strains compared to collection strains, as well as the specific characteristics of the commercial preparations and the lactoferrin-pathogen interaction. In this study, we were limited to the lactoferrin concentration of 32.5 and 82.5 μg/mL due to the solubility constraints of commercial bovine lactoferrin in the medium. The next stage of the work will include additional future experiments to explore adjunctive effects with antibiotics and use lactoferrin-sensitive strains to validate the assay.

The objective of this study was not only to review the results obtained but also to discuss the potential role of lactoferrin as an antibacterial agent in pediatric practice. The authors analyzed clinical trials of lactoferrin against bacterial infections over the past 10 years and found some studies suggest the efficacy and promise of lactoferrin as an antibacterial agent [17-18]. It is important to note that in one of the few studies found, the antibacterial effect of lactoferrin was evaluated in calves [17]. The authors found no more large clinical studies confirming the antibacterial effect of lactoferrin not only in children but also in adults.

The large-scale clinical trials involving infants have not yielded optimistic results [19-22]. These studies aimed to determine whether enteral administration of bovine lactoferrin (The Tatua Cooperative Dairy Company Ltd, Morrinsville, New Zealand) at a dosage of 150 mg/kg/day, with a maximum of 300 mg/day, reduces the risk of late-onset septic infections (acquired 72 hours after birth) and other morbidity and mortality in severely premature infants (less than 32 weeks gestation). The administration of lactoferrin did not affect the incidence of sepsis, mortality, or the severity of infections [22-23]. Although previous studies have demonstrated that supplemental administration of bovine lactoferrin to preterm infants (less than 32 weeks gestation) reduces late-onset sepsis (LOS), the Enteral Lactoferrin in Neonates (ELFIN) study in the UK sought to further investigate this through a double-blind, placebo-controlled trial involving over 2200 preterm infants. The results of the ELFIN study indicated no decrease in life expectancy and no significant changes in other clinically important parameters. 29% of patients in the experimental group developed late sepsis compared to 31% in the control group [24]. The authors attribute the differences in the results of the ELFIN trial and other

studies to population differences, the routine use of antifungal prophylaxis in the UK, the timing of lactoferrin administration relative to disease onset, or the specific properties of the lactoferrin used in the different trials.

In another randomized controlled trial, the administration of 200 mg/kg/day of bovine lactoferrin for 8 weeks did not reduce the incidence of sepsis in infants with a birth weight of less than 2000 grams in a sample of 414 subjects [25]. However, a subsequent clinical trial involving 335 infants weighing less than 1500 grams found that the same dose of bovine lactoferrin (200 mg/kg/day) reduced the number of late sepsis episodes by 10% compared to a control group receiving a placebo [26]. Conversely, in another multicenter, double-blind, randomized controlled trial involving 5000 infants weighing less than 1500 grams, which evaluated whether supplementation of enteral nutrition for very low birth weight infants with lactoferrin reduced all-cause mortality, lactoferrin supplementation did not reduce mortality and morbidity [27]. For future clinical trials, it is essential to use drugs with proven biological activity. Studies should be sufficiently large to reliably detect moderate and clinically significant effects, and higher doses of lactoferrin should be evaluated in infants not exclusively breastfed or those with extremely low birth weight.

Additionally, the results of in vitro evaluations of lactoferrin's antibacterial potential may be influenced by irrational study designs and non-standard methods of determining antimicrobial activity [28]. In some studies, the MIC of bovine lactoferrin was determined using standard methods, but the numerical value was estimated as an interval of more than 5 mg/mL, leaving its true activity in question. Furthermore, testing was conducted on collection strains, making it impossible to assess the true antibacterial potential against clinical isolates, which are the primary source of hospital-acquired pneumonia and other complications in pediatric hospitals [29-30]. Another factor that may significantly distort the current understanding of lactoferrin's antibacterial potential is the lack of studies with negative results or those critically evaluating its antimicrobial activity [31].

It is hypothesized that lactoferrin's antibacterial effect could be realized as an adjuvant to antibacterial agents. Evidence suggests that the combined use of lactoferrin or its derivatives with antibiotics can, in some cases, reduce the MIC of the antibiotic compared to its use without an adjuvant [32-33]. However, this issue requires further investigation, as in some cases, the use of lactoferrin at low doses (<0.39 μM) in combination with antibiotics may have the opposite effect and stimulate bacterial growth [4]. It is important to notice that further work in this direction (using lactoferrin as an adjuvant) will be possible after obtaining positive results in the first stage (*in vitro* testing) of the investigation. Furthermore, it should be noted that lactoferrin functional food potential requires an extensive pre-market approval [34].

Scientific Innovations: The study introduces a strain-lactoferrin pairing approach to assess antibacterial potential, moving beyond generic assessments of antimicrobial activity. Utilizing MIC analysis on clinically isolated strains of *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, the research highlights the importance of strain specificity when evaluating lactoferrin efficacy. The results suggest that the antibacterial properties of lactoferrin are not universally applicable and may depend on both the bacterial strain and the source/formulation of the lactoferrin supplement.

Practical Implications: These findings underscore the critical need for rigorous in vitro and clinical trial validation before recommending lactoferrin supplements as adjunctive antibacterial agents in pediatric healthcare. The absence of activity in tested concentrations against MDR isolates suggests limited

standalone use in clinical settings. Future development of functional food products containing lactoferrin should prioritize targeted efficacy testing and standardized protocols to ensure relevance and safety in real-world clinical applications.

CONCLUSIONS

Multi-drug-resistant clinical isolates of P. aeruginosa, K. pneumoniae, the causative agents of hospital-acquired infections, were used in the study. Antibacterial potential of the lactoferrin against certain bacterial strains depend on the strain-lactoferrin pair used in the study. Furthermore, it is crucial to emphasize that standard methodologies, appropriate test strains for research, and the verification of in vitro experimental results in clinical trials are essential for accurately assessing and understanding both the antibacterial potential of lactoferrin against multidrug-resistant (MDR) clinical isolates and its possible applications in clinical practice as the bioactive compound with potential for functional food development.

List of Abbreviations: MIC, minimum inhibitory concentration; MHB, Muller-Hinton bullion; MDR, multidrug-resistant; LOS, late onset sepsis; ELFIN, enteral lactoferrin in neonates.

Competing interests: Authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author contributions: D.S. and M.Y. performed experiments and created the research data. V.D. provided clinical isolates of *P.aeruginosa* and *K.pneumoniae.* N.B., S.M. and A.F. wrote the first version of the manuscript. All authors read, made significant edits, and approved the final manuscript.

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