

Review

Broad-Spectrum Effects of Lactoferrin as a Potential Therapeutic Regimen for the Treatment of Various Human Diseases

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Abstract

Sickness is a universal human problem. A significant proportion of the world's population suffers from one disease or another, while some individuals have two or more chronic diseases simultaneously. The development of one disease, if not properly managed, can often lead to other coexisting health challenges, a condition known as comorbidity. Unfortunately, treating comorbidity is difficult due to overlapping symptoms and the risk of drug interactions. To overcome these challenges, it is necessary to identify active principles with broad-spectrum therapeutic properties. Therefore, this study provides an overview of the multifunctional role of lactoferrin against various human diseases. Information regarding the role of lactoferrin in combating various human diseases was gathered through a systematic literature search. Findings from a retrospective pilot study indicated that lactoferrin has the potential to alleviate symptoms of interstitial cystitis, or painful bladder syndrome. Additionally, lactoferrin has anti-inflammatory, anti-diabetic, anti-cancer, anti-obesity, and antimicrobial properties. It could be beneficial in addressing issues related to microbial drug resistance. The anti-inflammatory effects of lactoferrin are linked to the reduction in cytokines such as tumor necrosis factor-alpha (TNF- α), IL-6, and IL-1 β ; inhibition of Inhibitory kappa B kinase beta (IKK- β) activity; and suppression of Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF- κ B). Furthermore, lactoferrin may provide protection against liver, kidney, and cardiac injuries. Lactoferrin's wide-ranging benefits indicate that it may be used in conjunction with current medications to help treat multiple health issues simultaneously.

Keywords: lactoferrin; diseases; obesity; interstitial cystitis; inflammation; cancer; diabetes; kidney disease

1. Introduction

Diseases are a universal human problem. In the year 2013, a study found that just one in 20 people worldwide (4.3%) had no health problems [1]. This implies that more than



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95 percent of the world's population is sick. While this statement may be overgeneralized, it strongly suggests that a significant proportion of the world population is suffering from one ailment or another. More worrisome is the fact that some sick people are faced with multiple diseases at a time. This is because some diseases can degenerate into others. For instance, diabetes can lead to chronic kidney disease (CKD) and cardiovascular disease (CVD) [2]. Infectious diseases may also increase the risk of certain cancers, CKD, CVD, diabetes, organ impairments, etc. [3]. Unfortunately, the treatment of patients with comorbidity is challenging. This may be due to many reasons, including the issue of fragmented and uncoordinated care.

Most often, healthcare guidelines and drugs are designed for single diseases. Another issue is drug–drug interactions, which can compromise the efficacy of the drugs. To overcome these challenges, it is necessary to identify important active principles with broad-spectrum effects on diseases. Therefore, the aim of this study was to investigate the therapeutic role of lactoferrin against various human diseases.

Lactoferrin is a naturally occurring glycoprotein found in milk and other bodily secretions, playing a key role in the body's innate immune system. In human milk, the concentration of lactoferrin varies. An average content of 350 µg/mL has been reported in mature milk [4]. This concentration can vary depending on factors such as ethnicity, lactation stage, and milk production. For example, individuals from different regions in China have shown lactoferrin levels ranging from 0.99 to 1.91 g/L [5]. Goat milk has been reported to contain levels of 34.61 to 51.94 µg/mL of lactoferrin [6]. Cow milk's lactoferrin concentration can vary between 13.03 and 485.63 µg/mL [7,8]. Transgenic cows have been found to produce higher yields (0.4–3.0 g/L) of recombinant lactoferrin, which exhibits similar biological activity to natural lactoferrin [9].

There are three forms of lactoferrin: apo-lactoferrin (iron-free), monoferric form (one Fe^{3+}), and holo-lactoferrin (two Fe^{3+} bound) [10]. The ferric ion (Fe^{3+}) is bound at the bottom of a deep cleft between two globular lobes of the lactoferrin. The biological function and structural integrity of lactoferrin largely depend on physiological pH. At neutral pH (around 7.4 in body fluids, or slightly lower in certain secretions), the iron is bound extremely tightly to the protein [11]. In an acidic environment, the iron is released.

Lactoferrin is released from certain types of white blood cells (neutrophils) at sites of inflammation, hence it possesses anti-inflammatory activity. This guarantees its application in the management of chronic diseases. It also possesses anti-obesity, anti-cancer, and anti-diabetic properties and offers protection against other chronic diseases [12] as shown in Figure 1.

Chronic diseases are among the leading causes of death and disability worldwide, accounting for 74% of deaths globally [13]. People from low- and middle-income countries are the most affected by chronic diseases. Unfortunately, individuals in these regions often face the double burden of both infectious and chronic diseases. There is currently no single drug that can effectively treat both infectious and chronic diseases, highlighting the potential need to complement existing drugs with nutraceuticals like lactoferrin.

To our knowledge, there have been few, if any, systematic reviews of the literature that have investigated the effects of lactoferrin on a broad spectrum of diseases. Therefore, this study highlights the multifunctional role of lactoferrin in infectious diseases such as parasitic, bacterial, and viral infections. Additionally, this study explores the role of lactoferrin in certain cancers, diabetes, cardiovascular diseases, and its mechanisms of action. Overall, this study seeks to shed light on the potential benefits of lactoferrin in combating a variety of diseases and improving overall health outcomes.

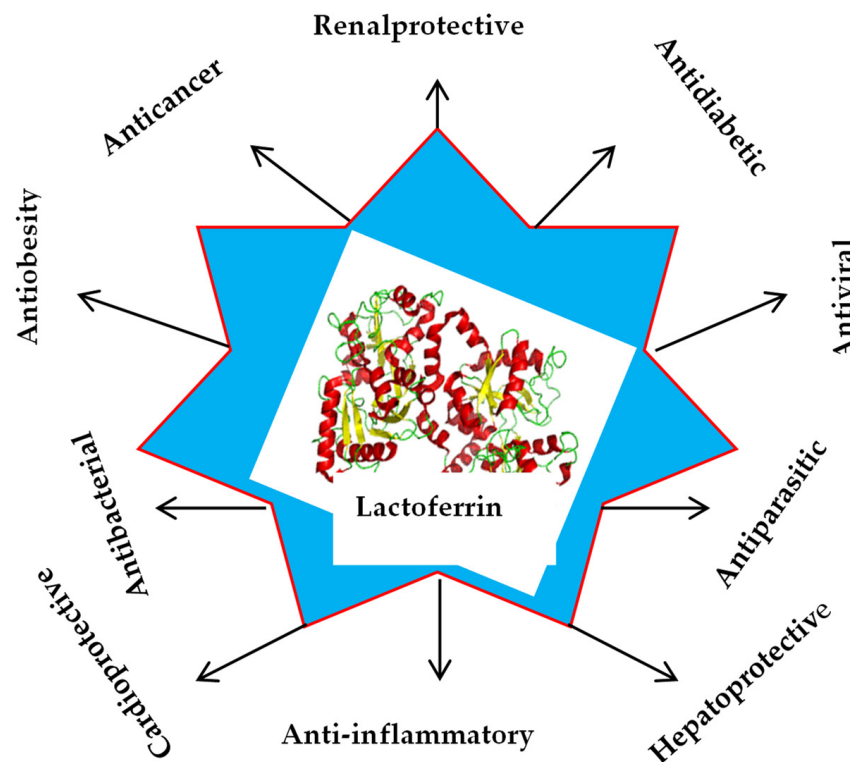


Figure 1. Schematic diagram showing some health benefits of lactoferrin.

2. Method

In this study, major databases such as PubMed, Scopus, Google Scholar, and the Directory of Open Access Journals were searched to obtain relevant information. Key words and combined keywords such as lactoferrin and inflammation, lactoferrin and bacterial infections, lactoferrin and viral infections, lactoferrin and parasitic infections, lactoferrin and cancer, lactoferrin and diabetes, lactoferrin and cardiovascular diseases, lactoferrin and ulcer, and lactoferrin and neurodegenerative diseases were used.

3. Anti-Bacterial Effects of Lactoferrin

Lactoferrin can be used as a therapeutic treatment for diseases caused by bacterial infections [14]. The antibacterial potential of lactoferrin against bacterial strains may depend on the specific strain–lactoferrin pair [15]. Purified bioactive lactoferrin has been observed to affect growth and biofilm formation in *Burkholderia pseudomallei*, *Burkholderia mallei*, and *Francisella tularensis* [16]. Lactoferrin was effective against *Staphylococcus epidermidis*, *Bacillus cereus* (Gram-positive bacteria), *Campylobacter jejuni*, and *Salmonella* (Gram-negative bacteria). However, the effect was more pronounced on Gram-positive bacteria than on Gram-negative bacteria [17]. A study demonstrated that synthetic lactoferrin has broad-spectrum antibacterial activity against four Gram-negative bacteria—*Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Salmonella gallinarum* [18]. A similar observation has been reported by Sharbafi et al. [19]. More findings from studies on the antibacterial effects of lactoferrin are shown in Table 1.

Table 1. Antibacterial properties of lactoferrin.

Studies	Key Findings	Reference
Antibacterial properties of bovine lactoferrin	Bovine lactoferrin had a good inhibitory effect against human pathogenic microorganisms. The minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC) for <i>Salmonella typhimurium</i> and <i>Listeria monocytogenes</i> were 7.562 µg/mL and 15.125 µg/mL, respectively.	[20]
Effects of purified human lactoferrin and peptides derived from its N terminus against infections with antibiotic-resistant bacteria	Human lactoferrin lacking the first three residues (hLF ^{-3N}) was less efficient in killing antibiotic-resistant <i>Staphylococcus aureus</i> , <i>Listeria monocytogenes</i> , and <i>Klebsiella pneumoniae</i> . Human lactoferrin and peptides derived from its N terminus were highly effective against infections with antibiotic-resistant <i>S. aureus</i> and <i>K. pneumoniae</i> .	[21]
Antimicrobial potential of bovine lactoferrin against the neonatal pathogen, <i>Staphylococcus capitis</i> .	At a concentration of 750 µg/mL, lactoferrin significantly inhibited the growth of the isolates tested, and the effect was based on a bacteriostatic mechanism. At the same concentration, biofilm formation was significantly inhibited.	[22]
Investigation on the potential of bovine lactoferrin, isolated from bovine milk whey against the growth of <i>Staphylococcus aureus</i> (<i>S. aureus</i>), <i>Escherichia coli</i> (<i>E. coli</i>), <i>Streptococcus agalactiae</i> (<i>S. agalactiae</i>) and <i>Pseudomonas aeruginosa</i> (<i>P. aeruginosa</i>)	The isolated bovine lactoferrin showed significant inhibitory effect against <i>E. coli</i> followed by <i>P. aeruginosa</i> , <i>S. agalactiae</i> and <i>S. aureus</i> .	[23]
Antibacterial and antibiofilm activity of the human breast milk glycoprotein lactoferrin against Group B <i>Streptococcus</i> .	It was revealed that lactoferrin inhibits Group B <i>Streptococcus</i> growth and biofilm formation by binding to free iron. Additionally, it also inhibits Group B <i>Streptococcus</i> adherence to human gestational membranes.	[24]
Analysis of antimicrobial and antibiofilm activity of human milk lactoferrin compared to bovine lactoferrin against multidrug resistant and susceptible <i>Acinetobacter baumannii</i> clinical isolates.	Both bovine and human lactoferrin inhibit <i>A. baumannii</i> biofilm formation. However, the human lactoferrin was slightly more effective than bovine lactoferrin against certain strains of <i>A. baumannii</i> .	[25]

The antibacterial mechanism of lactoferrin is based on its ability to bind to porins present in the outer membrane of Gram-negative bacteria. This binding can cause a rapid release of lipopolysaccharide (LPS) resulting in osmotic shock. This shock increases the susceptibility of bacteria to other antibacterial agents [26]. The binding of lactoferrin to porins occurs through electrostatic and hydrophobic interactions involving specific amino acid residues of lactoferrin and the porin loops. Porins are outer membrane proteins associated with the modulation of cellular permeability [27,28]. They act as barriers against molecules, contributing to drug resistance in Gram-negative bacteria [29].

Lactoferrin can also have direct effects on bacteria by disrupting their cell membranes through interactions with LPS and other surface components. This can induce the release of lipopolysaccharides and some membrane components, including phospholipids, leading to cell death [30].

Another mechanism of lactoferrin is its ability to sequester iron [31,32], making it unavailable for bacterial growth. Iron is an essential growth factor for the survival and growth of most bacterial species [33]. Lactoferrin also has other bactericidal effects, such as

preventing microbial adhesion and biofilm formation [34]. Microbial adhesion refers to the attachment of microbial cells to a material's surface or host cell. It is a host colonization strategy and a crucial first step in pathogenesis [35]. Biofilms, on the other hand, act as barriers against antibiotics and immune defenses [36].

Findings from a study showed that lactoferrin has a broad spectrum of antimicrobial activities [37]. The broad-spectrum antibacterial nature of lactoferrin suggests that it can help overcome the issue of microbial drug resistance and potentially save thousands of lives, especially if supplemented with antibiotic drugs. Combining lactoferrin with penicillin has been shown to increase the inhibitory activity of penicillin by fourfold and reduce the growth of tested *Staphylococcus aureus* strains [38]. This suggests that the lactoferrin–penicillin combination can help overcome infections caused by *S. aureus* resistant to antibiotics. Antimicrobial resistance causes at least 700,000 deaths per year worldwide [39]. It has been projected that by 2050, antimicrobial resistance could cause approximately 10 million deaths annually, especially if proactive measures are not put in place [40–43].

4. Antimalarial Properties of Lactoferrin

Parasitic infections are a significant public health issue that affects approximately 25% of the global population [44–46]. Like many other infectious diseases, treating parasitic infections is challenging because parasites can develop drug resistance.

Malaria is a significant global parasitic disease. The anti-malarial activity of bovine lactoferrin has been studied using a hemozoin formation inhibition assay. While chloroquine, an established antimalarial drug, inhibited hemozoin formation, bovine lactoferrin caused hemozoin degradation [47]. Hemozoin is a digestion product formed by parasites, particularly the malaria parasite *Plasmodium*. Its function is to counteract the toxic effects of heme released from hemoglobin degradation on the parasite [48]. One of the profound effects of heme is its ability to inhibit various enzymes, including glycolytic glyceraldehyde-3-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase, in *Plasmodium* [49]. Inhibiting these enzymes is significant because they are essential for parasite survival and proliferation, making them promising targets for novel antimalarial drugs.

Findings showed that lactoferrin is internalized through receptor-mediated endocytosis [50]. This could potentially lead to the formation of immature cysts. This process may inhibit bacterial growth. Cyst formation is a survival strategy used by the parasite, allowing it to transform into a dormant, resistant stage enclosed by a protective wall. Lactoferrin can also bind to the parasite's cytoplasmic membrane, internal membranes, and cytoskeleton, destabilizing these structures and ultimately causing parasite death [51].

5. Anti-Viral Properties of Lactoferrin

Lactoferrin plays an important role against both DNA- and RNA-viruses [52,53]. It may protect the host from viral infections by preventing the attachment of a virus to cells and inhibiting their replication [54]. Lactoferrin could also act as a receptor competitor for viruses [55]. This implies that the virus cannot successfully enter the host cell because viruses require specific receptors on the surface of a cell to bind to and gain entry.

It has been observed that bovine lactoferrin suppresses the cathepsin-dependent pathway of SARS-CoV-2 entry in vitro [56]. The study clarified that bovine lactoferrin did not suppress the entry of wild-type pseudoviruses into cells. However, it did suppress the entry of Omicron pseudo viruses into the cells [56]. Lactoferrin can also exert antiviral activity against SARS-CoV-2 through direct attachment to both SARS-CoV-2 and cell surface components [57].

A study has suggested that lactoferrin supplementation could be used as a complementary treatment against pediatric gastroenteritis, as evidenced in clinical trials [58]. Viral gastroenteritis has been recognized as one of the most common causes of morbidity and mortality worldwide, especially among children and older adults [59,60]. Therefore, the use of lactoferrin as an essential component of existing drugs may help reduce morbidity and mortality associated with viral gastroenteritis.

Lactoferrin has been shown to inhibit HIV-1 replication [61] and hepatitis B virus replication [62]. When recombinant human lactoferrin was administered intravenously, it significantly reduced the severity of hepatitis, as evidenced by lower levels of serum alanine transaminase and tumor necrosis factor alpha (TNF- α) [63].

It has been confirmed that human, camel, and sheep lactoferrin inhibit virus amplification in Hepatitis C-infected HepG2 cells, with camel milk lactoferrin showing the highest efficacy [64]. The antiviral effects of camel lactoferrin may be attributed to its ability to prevent the entry of the virus into human leukocytes [65]. The combined therapeutic effects of lactoferrin, interferon, and ribavirin in patients with chronic Hepatitis C have demonstrated its potential for use in treating patients with the viral infection [66].

Lactoferrin can also suppress oxidative stress in patients with viral hepatitis C infections. This was evident among studied respondents with chronic hepatitis C who were given lactoferrin [67]. The hepatitis C patients exhibited a significant decline in plasma 8-isoprostane levels, which correlate positively with an improvement in liver function. However, no significant change in serum HCV RNA levels was observed [67]. In a dose-response trial of lactoferrin in patients with chronic hepatitis C, it was observed that HCV RNA levels decreased by 50% in some patients after five and six months, and six to 10 months, respectively [68]. Aside from hepatitis C, lactoferrin has shown to also inhibit hepatitis B DNA in HepG2 cells [69]. Similar findings have been observed in studies as shown in Table 2.

Table 2. Anti-viral effects of lactoferrin.

Studies	Key Findings	Reference
Effect of bovine lactoferrin (BLF), lactoferrin hydrolysate, or iron-, zinc-saturated lactoferrin on hepatitis B virus (HBV)-infected HepG2 cells.	Results from fluorescent quantitative polymerase chain reaction showed that lactoferrin hydrolysate exhibited insignificant inhibition on HBV-DNA copies. However, bovine lactoferrin significantly inhibited the amplification of HBV-DNA in a dose-dependent manner in HBV-infected HepG2 cells. A similar observation was reported for iron- or zinc-saturated lactoferrin.	[70]
Investigation on the mechanism underlying the action of bovine lactoferrin.	Bovine lactoferrin stimulated the production of IL-11 in human intestinal myofibroblasts, and consequently acted protectively on the epithelial cells of the coculture. However, lactoferrin had no effect on morphogenetic protein 2 production in any cell type.	[71]
Evaluation on the efficacy of orally administered bovine lactoferrin (BLF) in patients with chronic hepatitis C	The study observed no significant difference in virologic response rates between groups given bovine lactoferrin, and placebo.	[72]
Identification of a lactoferrin-derived peptide possessing binding activity to hepatitis C virus E ₂ envelope protein.	Far-Western blot analysis using lactoferrin fragments and the E ₂ protein, expressed in Chinese hamster ovary cells, revealed that 93 carboxyl amino acids of lactoferrin specifically bound to the E ₂ protein.	[73]

Table 2. Cont.

Studies	Key Findings	Reference
Characterization of antiviral activity of lactoferrin against hepatitis C virus infection in human cultured cells	It was observed that bovine lactoferrin inhibited viral entry to the cells by interacting directly with HCV immediately after mixing of bovine lactoferrin and HCV inoculum. However, the anti-HCV activity of the lactoferrin was lost at 65 °C. Furthermore, it was observed that a basic N-terminal loop of bovine lactoferrin, an important region for antibacterial activity, did not exhibit any anti-HCV activity. This suggests that the anti-HCV activity of lactoferrin may be due to other region.	[74]
Effects of human lactoferrin and lysozyme on herpes simplex virus type 1.	The human lactoferrin inhibited the replication cycle of the virus in addition to neutralizing it.	[75]
Investigation on the role of lactoferrin in the Epstein–Barr virus (EBV) induced inflammatory response in macrophages	Lactoferrin suppressed Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF- κ B) pathway and reduced synthesis of IL-8 and monocyte chemo-attractant protein-1 (MCP-1) induced by EBV in macrophages. It also inhibited the ability of Toll like receptor 9 (TLR9) to recognize double stranded DNA (dsDNA) by binding to its co-receptor Cluster of Differentiation 14 (CD14), which blocked the interaction between CD14 and TLR9.	[76]

BLF—bovine lactoferrin; HBV—hepatitis B virus; EBV—Epstein–Barr virus; IL-11—interleukin 11; HCV—hepatitis B virus; NF- κ B—Nuclear Factor kappa-light-chain-enhancer of activated B cells; TLR9—Toll like receptor 9; MCP-1—monocyte chemoattractant protein-1; dsDNA—double stranded DNA; CD14—Cluster of Differentiation.

6. Anti-Inflammatory Properties of Lactoferrin

The anti-inflammatory role of lactoferrin is associated with the regulation of intracellular signaling pathways. Lactoferrin has the ability to reduce levels of tumor necrosis factor alpha (TNF- α), IL-6, and IL-1 β cytokines [77]. Additionally, it can inhibit the activity of Inhibitory kappa B kinase beta (IKK- β) and Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF- κ B) (p65) [78,79]. Lactoferrin can also suppress the expression of myosin light-chain kinase (MLCK) [80].

Increased neuronal inflammation stimulated by lipopolysaccharides (LPS) has been shown to be reduced by recombinant human lactoferrin, inhibiting the activation of the NF- κ B pathway [81]. Other studies have also demonstrated the anti-inflammatory properties of lactoferrin [82–84].

Lactoferrin may exhibit an anti-inflammatory role by disrupting the cleavage of p50 from p105, consequently inhibiting the Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF- κ B) pathway. NF- κ B induces the expression of various pro-inflammatory genes, making it an important mediator of inflammatory responses [85].

The NF- κ B pathway consists of two distinct pathways: canonical and non-canonical, and is composed of sub-unit proteins (p50 (NF- κ B1), p52 (NF- κ B2), p65 (RelA), c-Rel, and RelB) [86]. The p50 is a cleaved product from the N-terminus of p105, generated by the 26S proteasome-mediated removal of the C-terminal consensus sequence of p105. As a cleaved product of p105, p50 only possesses the DNA-binding domain and must form a heterodimer with RelA, RelB, or C-Rel to act as a transcription factor to regulate target gene transcription. This means that p50 cannot regulate NF- κ B downstream gene expression alone, as it lacks a transactivation domain [87].

The p52 proteins are encoded within the N-terminal regions of p100. Therefore, p100 is the precursor of the NF- κ B subunit p52 and inhibits the translocation of the NF- κ B subunit into the nucleus. Both p50 and p52 up-regulate transcription of target genes through the

formation of heterodimers with p65, c-Rel, and RelB. Specifically, p65 and c-Rel are key subunits of NF- κ B that promote inflammatory gene expression. Lactoferrin can enhance p65 phosphorylation at Ser (536) and stimulate the translocation of p65 into the nucleus [88]. Once in the nucleus, the activated p65 can bind to DNA and regulate the expression of genes related to immune and inflammatory responses.

The NF- κ B pathway involves a cascade of events known as stimulation, activation, phosphorylation, degradation, translocation, and transcription (SAPDIT). During pro-inflammatory events, external factors like pathogens, physical or chemical tissue damage, allergens, and irritants stimulate the production of pro-inflammatory cytokines such as TNF- α , IL-1, and IL-6, leading to receptor activation. The stimulated molecules then bind to their respective receptors, initiating the activation of the I κ B kinase (IKK) complex. The activated IKK complex phosphorylates I κ B α [89]. Lactoferrin has been shown to inhibit the phosphorylation of I κ B α and IKK β (I κ B kinase β) [90], potentially preventing phosphorylated I κ B α from undergoing ubiquitination.

Ubiquitination is a complex post-translational modification process where a small protein called ubiquitin is covalently attached to a target protein, and marking it for degradation [91]. The degradation of I κ B α releases the NF- κ B complex, allowing it to translocate into the nucleus. Inside the nucleus, NF- κ B binds to specific DNA sequences, triggering the transcription of target genes that promote inflammation. This promotion of inflammation by NF- κ B can be mitigated by lactoferrin [78,92].

It has been revealed that exogenous lactoferrin can shorten the chromatin fibers found in released Neutrophil Extracellular Traps (NETs). This indicates that lactoferrin could be used to control the release of NETs in inflammatory diseases [93]. Neutrophil Extracellular Traps (NETs) are fibrous web-like structures released by neutrophils in response to pathogenic infections or inflammatory stimuli. NETs consist of DNA, histones, neutrophil elastase (NE), high-mobility-group protein B1 (HMGB1), myeloperoxidase (MPO), and a variety of primary and secondary granular proteins. DNA and histones are the major constituents of NETs [94].

7. Anticancer Effects of Lactoferrin

Cancer is a significant global issue. Approximately one in five men or women may develop cancer in their lifetime, with around one in nine men and one in twelve women dying from it [95]. While advances in cancer treatment like radiotherapy, chemotherapy, and immunotherapy are beneficial, they can also have side effects that compromise patients' quality of life [96]. Therefore, alternative therapeutics may help manage these side effects.

Increasing evidence suggests that lactoferrin can induce anti-cancer effects [31,97–100]. Lactoferrin has been shown to trigger apoptosis in breast cancer cells by inhibiting Vacuolar-type H⁺-ATPase (V-ATPase) [101]. V-ATPase is a crucial proton pump that plays a vital role in maintaining intracellular pH homeostasis [102]. In highly metastatic cancer cells, V-ATPase migrates to the plasma membrane, contributing to the acidity of the tumor microenvironment [103]. The tumor microenvironment consists of normal cells, molecules, and blood vessels that surround and nourish a tumor cell. An acidic microenvironment reduces the effectiveness of anti-tumor drugs [104], especially weak base drugs that become ionized and neutralized in the microenvironment [105,106]. This transformation can prevent these drugs from entering cancer cells. As a result, the drugs may not reach their target site to inhibit cancer cell growth or induce cell death. This could lead to treatment failure. Inhibiting the activity of V-H⁺ ATPase by lactoferrin has been shown to reduce the acidity of the tumor microenvironment [107] and potentially enhance the efficacy of anticancer drugs (see Figure 2).

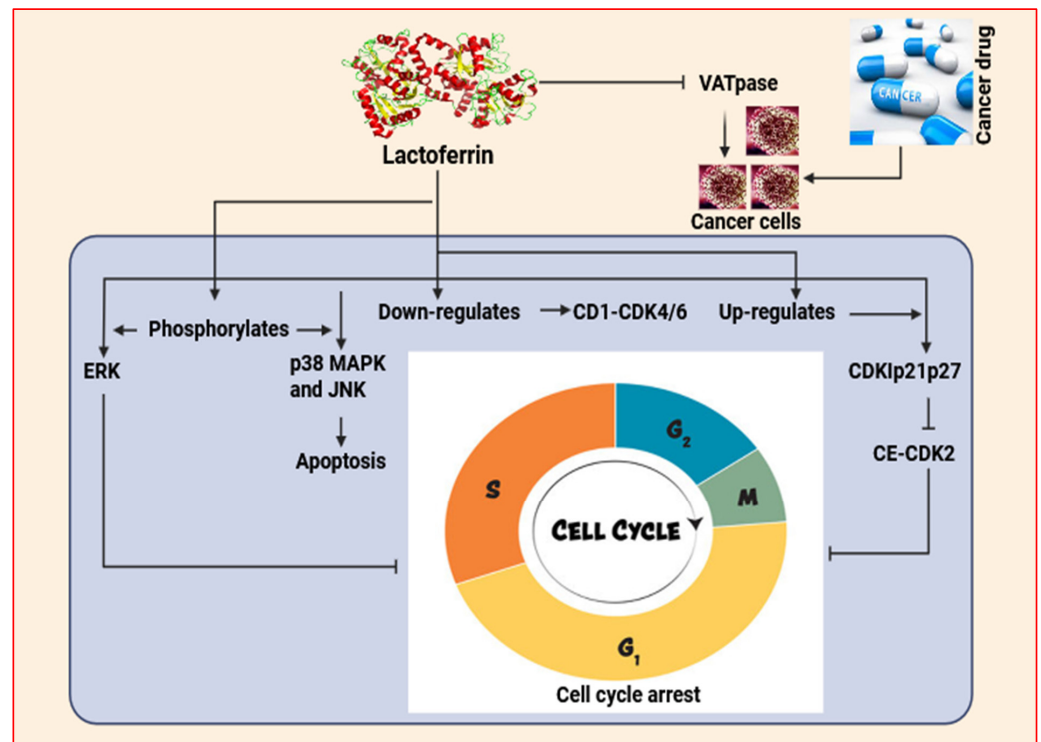


Figure 2. Schematic diagram showing anticancer mechanism of lactoferrin. Created in BioRender. CD1-CDK4/6—cyclin D1-Cyclin-dependent kinase 4 and 6 complex; CDKip21p27—Cyclin-dependent kinase 4 and 6p21 and p27; CE-CDK2—Cyclin E-Cyclin-dependent kinase 2; VATpase—Vacuolar-type Ht-ATPase; ERK—Extracellular signal-regulated kinase; p38 MAPK—p38 mitogen-activated protein kinases; JNK—c-Jun N-terminal kinase.

Bovine lactoferrin induces cell cycle arrest at the G0/G1 phase in human prostate cancer cells through increased oxidative stress [108] (Figure 2). In a study that investigated the effect of lactoferrin against head and neck squamous cell carcinoma, the G0/G1 phase arrest appeared to be modulated by the down-regulation of cyclin D1 [109].

Lactoferrin may provide beneficial treatment for hepatocellular carcinoma [110]. It has shown to induce apoptosis and G0/G1 cell cycle arrest in hepatocellular cancer cells [111]. The increased phosphorylation of p38 mitogen-activated protein kinases (p38 MAPK) and c-Jun N-terminal kinase (JNK) may be responsible for the apoptosis, while phosphorylation of Extracellular signal-regulated kinase (ERK) may be associated with cell cycle arrest. Additionally, lactoferrin's effects on the Intelectin-1 receptor have been shown to inhibit the progression of hepatocellular carcinoma [111].

A study observed that treatment of a human lung cancer cell line with lactoferrin decreased the expression of vascular endothelial growth factor (VEGF) protein in a dose-dependent manner, which consequently reduced the proliferation of A549 cells [112].

Lactoferrin has been shown to suppress human colon tumors by activating the Vascular Endothelial Growth Factor Receptor 2-Phosphoinositide 3-kinase (PI3K)/Protein Kinase B (Akt)—Extracellular signal-regulated kinases 1 and 2 (VEGFR2-PI3K/Akt-Erk1/2) pathway [113]. In tumor-bearing mice, orally administered recombinant human lactoferrin, alone or in combination with chemotherapy, inhibited tumor growth by stimulating cytokines such as IL-18 [114].

Another mechanistic insight into the role of lactoferrin against cancer cells is its ability to inhibit the activity of the cyclin D1-cyclin-dependent kinase 4 and 6 (CDK4/6) complex (Figure 2), resulting in cell cycle arrest in the G1 phase. Additionally, lactoferrin has been shown to upregulate Cyclin-dependent kinase inhibitors (CDKIs) p21 and p27,

subsequently inhibiting the cyclin E-CDK2 complex [115]. If this complex is not inhibited, it may slow or stall DNA replication. Consequently, this can lead to genomic instability and contribute to human carcinogenesis [116].

8. Anti-Diabetic Effects of Lactoferrin

To date, effective management of type-2-diabetes remains a significant challenge, especially among the impoverished. Studies suggest that lactoferrin may help overcome this challenge. The anti-diabetic effect of camel milk-derived lactoferrin has been confirmed among young obese patients with type 2 diabetes. After treatment with the camel milk-derived lactoferrin, the patients showed increased expression of Peroxisome Proliferator-Activated Receptor gamma (PPAR- γ) and Sirtuin 1 (SIRT-1) [117]. PPAR- γ has been recognized as a strong therapeutic target for type-2-diabetes, as it plays a key role in regulating glucose metabolism. This role has been shown to improve insulin sensitivity [118–120].

The action of PPAR-gamma on glucose metabolism is associated with genes involved in insulin-stimulated glucose disposal [121]. One of these genes is Solute Carrier Family 2-member 4 (SLC2A4). The gene SLC2A4 codes for the synthesis of Glucose Transporter 4 (GLUT4), a protein that facilitates insulin-stimulated glucose uptake in muscle and fat cells. When blood sugar levels rise, particularly after a carbohydrate-rich meal, insulin signals muscle and fat cells to take up glucose from the bloodstream. This uptake of glucose is aided by GLUT4, as it moves to the cell surface to allow glucose to enter. The translocation of GLUT4 to the cell surface is stimulated by Protein Kinase B [122]. Purified lactoferrin from camel and bovine milk has been shown to induce phosphorylation of Protein Kinase B (PKB) and Extracellular signal-regulated protein kinases 1 and 2 (ERK1/2) in diabetic cells [123].

The anti-diabetic effects of lactoferrin may be linked to increased activities of glucokinase and glucose-6-phosphate dehydrogenase. It may also be associated with decreased activities of phosphofructokinase and fatty acid synthase in the liver [124]. Increased activity of glucokinase promotes glucose metabolism and reduces blood glucose levels [125]. Furthermore, Glucokinase plays a role in insulin secretion in pancreatic β -cells and glycogen synthesis in the liver. Mutations in the gene that codes for glucokinase synthesis have been linked to diabetes [126], highlighting the enzyme's importance in glycemic balance and diabetes management [127]. Lactoferrin may also indirectly affect pancreatic alpha cells and glucagon secretion by reducing inflammation. These effects can contribute to glycemic balance and better control of diabetes (Figure 3).

Experimental rats fed a high-fat diet for 15 weeks and injected with streptozotocin (STZ) for five consecutive days exhibited insulin resistance and abnormal glucose and lipid metabolism [128]. After 12 days of treatment with lactoferrin, decreased serum concentrations of glycated serum protein, fasting insulin, and increased liver insulin sensitivity were observed. Upregulation of the insulin receptor, phosphatidylinositol 3-kinase (PI3K), and protein kinase B (AKT) in the liver by lactoferrin has been reported [128]. This upregulation of these proteins is crucial for insulin sensitivity [129].

One of the complications associated with diabetes is brain tissue damage [130,131]. A study on the protective effect of lactoferrin against brain damage in diabetic rats revealed that administration of lactoferrin improves brain pathological changes [132]. Lactoferrin administration to the diabetic rats also corrected aberrant levels of serum Neuron-Specific Enolase (SNE), brain-derived neurotrophic factor (BDNF), and tissue necrosis factor-alpha (TNF-Alpha).

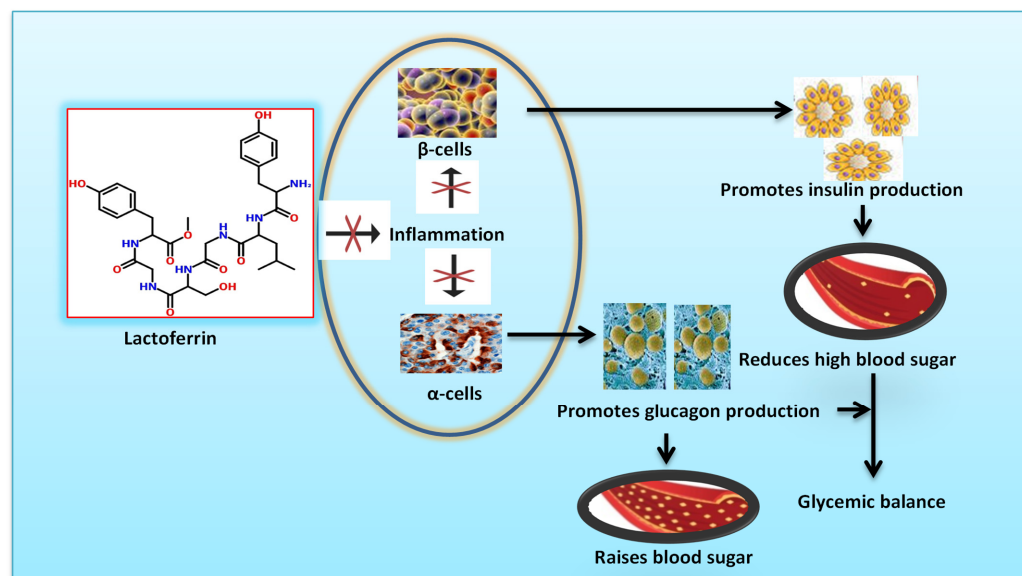


Figure 3. Schematic representation showing anti-diabetic role of lactoferrin.

9. Cardioprotective Role of Lactoferrin

The cardio-protective role of enteral lactoferrin has been observed in experimental rats [133]. A recent study by Omiya et al. [134] revealed that enteral lactoferrin significantly increased serum glucagon-like peptide-1 (GLP-1) levels, consequently mitigating myocardial ischemia–reperfusion. Findings showed that oral lactoferrin counteracted azithromycin-induced cardiac toxicity by downregulating cardiac biomarkers including creatine kinase, lactate dehydrogenase, and alkaline phosphatase [135]. It has also been shown to restore cardiac oxidant/antioxidant balance. Decreased cardiac Toll-like receptor 4 (TLR4), Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF- κ B), and increased IL-10 and Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2) expression were also observed [135]. Injection of lactoferrin to rats intoxicated with nicotine was shown to reduce cardiac inflammatory indices such as interleukin-6 (IL-6) and C-reactive protein (CRP) [136].

10. Hepatoprotective Attributes of Lactoferrin

The liver performs over 500 functions including synthesis, detoxification, metabolism, and storage. Therefore, liver damage may compromise these functions and could lead to conditions such as liver cirrhosis, cancer, and liver failure among others. Evidence from a study revealed that lactoferrin may prevent the progression of liver cirrhosis. This was demonstrated in nonalcoholic steatohepatitis (NASH) model rats with metabolic syndrome, fed a high-fat diet and intraperitoneally injected with dimethylnitrosamine. Treatment using lactoferrin significantly protected the liver against steatosis [137]. It was also evident that lactoferrin down regulated fibrosis-related cytokines such as Transforming Growth Factor-beta 1 (*Tgf- β 1*), Tissue inhibitor of metalloproteinase-2 (*Timp2*), and Collagen Type I Alpha 1 Chain (*Col1a1*) [137].

Lactoferrin has been shown to improve levels of alpha-fetoprotein in Thioacetamide-intoxicated rats [138]. Similarly, the protective role of lactoferrin has been observed in Carbon tetrachloride-induced liver fibrosis [139]. Organ fibrosis is gradually becoming a human health and safety problem [140]. A study suggests that lactoferrin may offer protection against D-Galactosamine and lipopolysaccharide-induced acute hepatic failure [141]. The impact of lactoferrin on the hepcidin–ferroportin (FPn) axis may increase hepatocellular iron output, ultimately maintaining liver oxidative balance and suppressing hepatocyte

death [142]. More findings from studies on the hepatoprotective effects of lactoferrin are shown in Table 3.

Table 3. Hepatoprotective effects of lactoferrin.

Studies	Findings	Reference
Investigation on lactoferrin mechanisms in thioacetamide (TAA)-induced liver fibrosis in rats and TGF- β 1-treated HSC-T6 cells	It was revealed that treatment with lactoferrin decreased mRNA expression of inflammatory factors such as <i>Il-1β</i> and Intercellular Adhesion Molecule 1 (<i>ICAM-1</i>), as well as fibrogenic factors including alpha-smooth muscle actin (α -SMA), <i>Collagen I</i> , and Connective Tissue Growth Factor (<i>CTGF</i>) in TAA-treated liver tissues.	[143]
Assessment of lactoferrin in treatment of bile duct ligation-induced hepatic fibrosis in rats: impact on inflammation and TGF- β 1/Smad2/ α SMA signaling pathway.	The bile duct ligation caused inflammation and fibrosis of the liver by up-regulation of transforming growth factor-beta 1 (TGF- β 1)/Mothers against decapentaplegic homolog 2 (Smad2)/ α -smooth muscle actin (SMA) signaling pathway. However, treatment with lactoferrin improved these effects by down-regulation of the TGF- β 1/Smad2/ α -SMA signaling pathway.	[144]
Assessment of hepatic and immune ameliorating potential of extracted bovine lactoferrin (LF), Selenium nanoparticles (SeNPs) or their combination (LF/SeNPs) against bleomycin induced hepatic injury	Hepatic lipid peroxidation and nitric oxide increased significantly in rats given bleomycin. On the other hand, hepatic glutathione, Na ⁺ /K ⁺ -ATPase, and glutathione peroxidase were significantly reduced. Additionally, bleomycin injection resulted in marked histopathological alterations and severe expression of caspase 3. Treatment with lactoferrin attenuated the bleomycin induced hepatic dysfunction.	[145]
Protective effects of lactoferrin against acetaminophen-induced liver injury in mice	Lactoferrin treatment significantly reduced acetaminophen-induced liver sinusoidal endothelial cell dysfunction and ameliorated hepatic microcirculation disorder through activation of Kupffer cells.	[146]
Preventive effects of lactoferrin on acute alcohol-induced liver injury via iron chelation and regulation of iron metabolism	It prevents alcohol-induced liver injury by chelating excess iron, thus mitigating iron overload and ferroptosis.	[147]

11. Effects of Lactoferrin on Interstitial Cystitis (Painful Bladder Syndrome)

Interstitial cystitis, also known as painful bladder syndrome, is a chronic and debilitating condition characterized largely by pelvic pain, urinary urgency, and frequency [148]. This condition can persist for more than six weeks in the absence of infection or other identifiable causes [149]. The prevalence of interstitial cystitis is higher in females (52 to 500/100,000) compared to males (8–41/100,000) [150]. The global incidence of interstitial cystitis (IC) is increasing, and its management and treatment remain challenging as the precise causes are still unknown [151].

Lactoferrin may serve as a potential therapeutic option for treating IC. The effects of lactoferrin on women affected by IC were reported in a retrospective pilot study. Among the women studied, who had experienced six episodes of IC in the six months prior to the study, 20 had hereditary thrombophilia, while 11 did not. After treatment with the traditional capsule Valpalf, which contains lactoferrin, 28 of the women experienced no episodes of IC, while three women had one episode during the follow-up period [152].

12. Effects of Lactoferrin in the Prevention and Treatment of Ulcer

Lactoferrin can be used in the treatment and prevention of ulcers [153]. The gastroprotective effect of lactoferrin in an ethanol-induced gastric ulcer rat model showed significant healing of gastric mucosal damage. Reduced levels of tumor necrosis factor α (TNF- α), interleukin-1 β (IL-1 β), myeloperoxidase (MPO), intracellular adhesion molecule-1 (ICAM-1), and gastric malondialdehyde (MDA) were also observed in rats

with gastric ulcers treated with lactoferrin [154]. Pathological evaluation of lactoferrin against indomethacin-induced gastric ulcers in rats showed suppressed elevation of lactate dehydrogenase activity, tumor necrosis factor- α , and nitric oxide. This suggests that lactoferrin may play a promising role in preventing stomach tissue ulceration [155].

Results show that the addition of lactoferrin to traditional therapy improves the *Helicobacter pylori* infection eradication rate. This was evident among 50 patients. Twenty-five of the patients received traditional therapy (clarithromycin, omeprazole, amoxicillin, or metronidazole), while the other 25 patients received the traditional therapy plus lactoferrin [156]. This suggests that lactoferrin may be used as an adjuvant to traditional therapy in the treatment of *H. pylori* [157]. Similar observations have been revealed in other studies [158,159]. *Helicobacter pylori* are a type of bacteria that lives in the stomach and can cause inflammation, leading to peptic ulcers and gastric cancer [160].

13. Effects of Lactoferrin on Obesity

Obesity is a significant global health issue that is on the rise. In 2022, more than one billion people were classified as obese [161]. It has been projected that by 2050, over 3.80 billion adults will be obese or overweight [162]. Therefore, the use of therapeutics to combat obesity will be crucial in maintaining population health. Lactoferrin possesses anti-obesity properties. However, the effectiveness of lactoferrin may vary depending on individual genetic differences. A study suggests that single-nucleotide polymorphisms contribute to the individual variations in the anti-obesity effects of lactoferrin [163].

Obesity contributes to low-grade chronic inflammation, which leads to a variety of chronic diseases [164]. Research shows that lactoferrin can reduce chronic low-grade inflammatory responses and increase the expression levels of zonula occludens 1 and occludin proteins in the intestines of obese mice. Additionally, it can alter the intestinal microbial structure of obese mice [165]. In obese mice, lactoferrin has been found to have beneficial effects on glucose tolerance, reduce adipose tissue inflammation, and improve fatty liver formation [166].

A study observed that lactoferrin has no beneficial impact on weight gain; however, it stimulates leptin secretion and alters plasma corticosterone [167]. When lactoferrin was used in combination with inulin, decreased body weight, fat, and lean mass, as well as plasma leptin concentrations, were observed [168].

14. Effect of Lactoferrin on Neurodegenerative Diseases

Neurodegenerative diseases such as Multiple Sclerosis, Alzheimer's, and Parkinson's are incredibly challenging to treat, as current therapies have not been successful in halting the progression of these diseases [169]. One reason for this may be the blood–brain barrier, which prevents effective drug delivery. Lactoferrin has the potential to overcome this barrier due to its ability to cross the blood–brain barrier via receptor-mediated transcytosis [170,171].

The use of Lactoferrin as a novel pharmacological target for Alzheimer's disease (AD) is gaining attention as it modulates the processing of amyloid precursor protein (APP) [172]. This modulation of APP is believed to occur through the activation of α -secretase, an enzyme that cleaves the amyloid precursor protein (APP) and prevents the accumulation of amyloid-beta ($A\beta$) in the brain. Accumulation of amyloid-beta can lead to several complications, including neuronal damage and death [173].

The modulation of APP is also believed to occur through the activation of a-disintegrin and metalloprotease10 (ADAM10) as observed in experimental mice. This modulation increased the cleavage of the α -COOH-terminal fragment of APP and consequently reduced

amyloid-beta ($A\beta$) generation. This improvement in amyloid-beta levels led to enhanced spatial cognitive learning ability in the AD mice [174].

Lactoferrin-induced reduction in $A\beta$ levels in the brains of mice, mediated by increased apolipoprotein E (ApoE) secretion and ATP-binding cassette transporter A1 (ABCA1) protein levels, has been reported [175]. A study observed that lactoferrin administration improved the activities of phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) and protein kinase B (PKB or Akt) in peripheral blood lymphocytes. Furthermore, lactoferrin also significantly reduced the increased expression of tau, Mitogen-activated Protein Kinase 1 (MAPK1), and Tensin Homolog deleted on Chromosome 10 (PTEN) in AD patients. A decrease in elevated levels of serum amyloid β ($A\beta$) 42 in AD patients was also observed [176]. In fact, lactoferrin is gaining momentum as an important biomarker of Alzheimer's disease [177–179]. However, a study revealed otherwise, stating that lactoferrin in cerebrospinal fluid is not a diagnostic biomarker for Alzheimer's disease [180].

Inflammation in the brain is a crucial factor in the onset and progression of various brain diseases, such as Alzheimer's, Parkinson's, and multiple sclerosis. Studies have confirmed the effectiveness of lactoferrin in reducing inflammation in the brain [181–183]. This ability of lactoferrin to protect the brain from inflammation may help prevent the development of neurodegenerative diseases.

Lactoferrin plays a protective role against Parkinson's disease [184], a neurodegenerative disorder of the central nervous system characterized by tremor, muscle rigidity, and slowness of movement [185]. The protective role of lactoferrin in patients with Parkinson's disease is associated with the up-regulation of levels of brain-derived neurotrophic factor (BDNF), hypoxia-inducible factor 1 α (HIF-1 α), activation of extracellular regulated protein kinases (ERK) and cAMP response element binding protein (CREB). Lactoferrin could decrease 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-triggered apoptosis of dopaminergic (DA) neurons [186].

The effects of lactoferrin on DA neurons could be attributed to its ability to bind to heparan sulfate proteoglycans on the cell surface of DA neurons, leading to partial inactivation of focal adhesion kinase (FAK) [187]. A significant reduction in DA content in the striatum is an important feature of neurodegenerative disorder. Therefore, a therapeutic approach that could mitigate the reduction in DA content has become essential for neurodegenerative improvement. It has been revealed that lactoferrin not only mitigated 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced DA depletion in the striatum but also prevented iron deposition and apoptotic processes in the substantia nigra [188]. A similar study demonstrated that pre-treatment with lactoferrin significantly reduced MPTP-induced neuronal toxicity, as manifested in improved motor functions in experimental mice [189].

15. Effects of Lactoferrin Against Chronic Kidney Disease

The global burden of kidney disease is increasing [190]. In fact, approximately 10% of the global population is affected by chronic kidney disease (CKD) [191]. Unfortunately, awareness of kidney disease at the population level is low, with nine out of every ten people with kidney disease being unaware that they have it [192]. The high number of individuals affected by CKD highlights the need for improved prevention and treatment [193].

Emerging research suggests that lactoferrin could be a potential candidate against chronic kidney disease [194]. Protective and preventive effects of lactoferrin on chronic kidney disease in experimental mice have been studied. Administration of lactoferrin to a mouse model of adenine-induced renal failure showed improvement in renal function and mitigated tubulointerstitial damage. These effects contributed to delayed progression of sarcopenia [195]. Sarcopenia is a progressive and systemic skeletal muscle disorder

characterized by low muscle strength [196,197]. Low muscle strength and muscle mass in patients with CKD contribute to higher mortality rates [198].

The protective effect of lactoferrin against the progression of acute to CKD has been investigated. Findings showed that lactoferrin induced autophagy via the activation of the Adenosine Monophosphate-Activated Kinase (AMPK) and inhibition of the protein kinase B/mammalian target of rapamycin (Akt/mTOR) pathway in human kidney proximal tubular cells [199]. The Akt/mTOR pathway regulates cell growth, differentiation, apoptosis, and angiogenesis. Adenosine Monophosphate-Activated Kinase (AMPK) is a cellular energy sensor that responds to low energy by activating catabolic pathways while inhibiting anabolic pathways, thereby restoring cellular energy balance. Its role is crucial, especially in kidney disease, as it helps renal cells survive during low energy states [200]. Therefore, inhibition of the Akt/mTOR pathway is an important strategy that can retard the progression of CKD [201].

Treatment with lactoferrin in a mouse model of folic acid-induced acute to chronic kidney disease transition suppressed renal fibrosis [199]. Similarly, lactoferrin-cerium oxide nanoparticles have been reported to suppress the progression of renal fibrosis [202]. Renal fibrosis is a condition where there is an abnormal accumulation of connective tissue in the kidneys, leading to excessive scarring and deterioration of kidney tissue. It is the end stage of several CKD [203].

Chronic kidney disease is often associated with anemia. The more decline in kidney function, the more severe the anemia becomes. This may be due to the fact that the kidneys produce a hormone called erythropoietin, which stimulates red blood cell production. Recent research suggests that lactoferrin, which induces erythropoietin synthesis [204], may be beneficial in improving anemia associated with kidney disease.

Studies have shown that oral administration of lactoferrin can increase hemoglobin levels in patients with advanced CKD [205]. In pediatric patients, lactoferrin has also been found to effectively treat anemia induced by CKD. A study involving 30 pediatric patients who received 100 mg of oral lactoferrin daily for three months showed promising results [206]. Improving anemia in patients with CKD not only slows the decline of renal function [207], but also significantly enhances the quality of life for these patients [208,209].

16. Effects of Lactoferrin on Intestinal Microbiota

Although lactoferrin (LF) possesses several therapeutic potentials, including antimicrobial, anti-inflammatory, and anti-chronic disease activities, its multifunctional effects may be influenced by its interactions with various gut microbes. Lactoferrin has been found to modulate microbiota as a prebiotic agent, contributing to its beneficial functions in gut health [210–212]. In fact, LF deficiency during the lactation period may increase the growth of pathogenic organisms and exacerbate dysbiosis [213]. The significant impacts of LF on gut microbiota may partially explain its therapeutic potential against certain chronic diseases. On the contrary, a study reported no impact of lactoferrin on increased gut microbiota diversity. This was evident in a study that analyzed the gut microbiota composition of 60 toddlers aged 12–18 months from Lima, Peru, who received daily oral administration of lactoferrin or placebo for 6 months since enrollment [214].

17. Toxicity of Lactoferrin

A study evaluating the reproductive toxicity of antiretroviral drugs loaded lactoferrin nanoparticles found that vaginal administration is safe and can be considered for effective delivery of antiretroviral agents through the vaginal route [215].

Oral administration of recombinant human apo-lactoferrin to Wistar rats for 28 days showed no toxicological changes in clinical signs, organ weights, pathology, or clinical

chemistry. The No Observed Adverse Effects Level (NOAEL) was found to be greater than 1800 mg/kg/day [216]. This observation was also reported in a study by Vishwanath-Deutsch et al. [217]. Therefore, Lactoferrin is generally recognized as safe (GRAS) by the FDA, with low toxicity even at high doses [217].

Another study reported that oral administration of bovine lactoferrin showed a NOAEL greater than 2000 mg/kg/day [218]. A similar study found a safe level of human lactoferrin at doses up to 2000 mg rhLF/kg/day [219]. This amount is approximately 400 times greater than the estimated daily intake at the 90th percentile for human adult use [219].

18. Conclusions

As the global population and disease incidence rise, the efficacy of existing drugs is diminishing due to the widespread problem of drug resistance and inefficacy. This issue may be attributed to various factors, including overlapping symptoms caused by comorbidity. While it is widely acknowledged that treating comorbid conditions presents significant challenges, the search for therapeutics with broad, multi-target functionality is an important area of research. Therefore, this study investigated the potential role of lactoferrin against certain human diseases. Findings from a literature search revealed that lactoferrin has a broad spectrum of potential against infectious and chronic diseases. Consequently, lactoferrin could be used in conjunction with existing medications to enhance their effectiveness. Unfortunately, traditional extraction of lactoferrin from milk cannot meet the demand for it. Therefore, there is a need for mass production through recombinant technology. This technology enables large-scale, cost-effective, and safe production of lactoferrin for use in nutrition and disease treatment.

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