GERONTOLOGIA POLSKA 2025; 33; 194-200 ARTYKUŁ ORYGINALNY / ORIGINAL PAPER
zgłoszono 12.08.2025 - zaakceptowano 03.09.2025

The importance of lactoferrin in therapeutic strategies of selected neurodegenerative diseases

Znaczenie laktoferyny w strategiach terapeutycznych wybranych chorób neurodegeneracyjnych

Piotr Czwałga, Patrycja Koprowska, Jakub Husejko, Kornelia Kędziora-Kornatowska

Department of Geriatrics, Ludwik Rydygier Medical College in Bydgoszcz of Nicolaus Copernicus University in Toruń

Abstract

Introduction. *Current research on potential neuroprotective factors in selected neurodegenerative diseases has focused on lactoferrin, a peptide with known antimicrobial properties. It has been found to acquire additional functions, including the regulation of adaptive immunity, inflammation, oxidative stress, as well as participation in the processes of aging and neurodegeneration.* **Aim**. *The aim of this study was to highlight the role of lactoferrin as a protein with immunomodulatory and neuroprotective properties, focusing exclusively on selected neurodegenerative diseases, namely Alzheimer's disease, Parkinson's disease, and prion disease.* **Materials and methods.** *This paper is a review of the literature from 2020-2023 (including historical materials), based on content searched in PubMed, Google Scholar, and Web of Science databases. Only English-language publications on the role and mechanisms of action of lactoferrin were analyzed.* **Results.** *It was found that lactoferrin supports the central nervous system through a variety of mechanisms of action. In Alzheimer's disease, it inhibits apolipoprotein E4 (APOE4), promotes non-amyloidogenic protein cleavage, and alleviates inflammation and oxidative stress. In Parkinson's disease and prion diseases, it restores iron homeostasis, protects dopaminergic neurons, and possibly alleviates neurotoxic effects through protein conformational changes.* **Conclusions.** *An increasing number of studies conducted using cell models, laboratory rats, and even humans confirm the beneficial effect of lactoferrin in alleviating neurodegenerative processes in patients with Alzheimer's disease, Parkinson's disease, and prion disease. However, much more in-depth research is needed before its therapeutic potential can be fully exploited. (Gerontol Pol 2025; 33; 194-200) doi: 10.53139/GP.20253328*

Keywords: *lactoferrin, neuroprotection, Parkinson's disease, Alzheimer's disease, prion disease*

Streszczenie

Wstęp. *Prowadzone obecnie badania nad potencjalnymi czynnikami neuroprotekcyjnymi w wybranych chorobach neurodegeneracyjnych skoncentrowały uwagę na laktoferynie, peptydzie o znanych właściwościach przeciwdrobnoustrojowych. Stwierdzono, iż nabyła ona dodatkowe funkcje, obejmujące między innymi regulację odporności adaptacyjnej, stanów zapalnych, stresu oksydacyjnego, jak również udział w procesach starzenia się i neurodegeneracji.* **Cel.** *Celem niniejszej pracy było przybliżenie roli laktoferyny jako białka o właściwościach immunomodulujących i neuroprotekcyjnych, koncentrując się wyłącznie na wybranych chorobach neurodegeneracyjnych - mianowicie chorobie Alzheimera, chorobie Parkinsona oraz chorobie prionowej.* **Materiały i metody.** *Praca jest przeglądem literatury z lat 2020-2023 (uwzględniono materiały historyczne), oparta na treściach wyszukanych w bazach PubMed, Google Scholar i Web of Science. Analizie poddano wyłącznie publikacje anglojęzyczne dotyczące roli i mechanizmów działania laktoferyny.* **Wyniki.** *W rezultacie stwierdzono, że laktoferyna wspiera centralny układ nerwowy poprzez różnorodne mechanizmy działania. W chorobie Alzheimera hamuje apolipoproteine E4 (APOE4), wspomaga nieamyloidogenne cięcie białek oraz łagodzi stany zapalne i stres oksydacyjny. Z kolei w chorobie Parkinsona i chorobach prionowych przywraca homeostazę żelaza, działa ochronnie na neurony dopaminergiczne i prawdopodobnie łagodzi neurotoksyczne efekty poprzez zmiany konformacyjne białek.* **Wnioski.** *Coraz to nowsze badania przeprowadzane z użyciem modeli komórkowych, szczurów laboratoryjnych, a nawet wśród ludzi potwierdzają korzystny wpływ laktoferyny w łagodzeniu procesów neurodegeneracyjnych u pacjentów z chorobą Alzheimera, chorobą Parkinsona czy chorobą prionową. Jednakże potrzeba jeszcze wielu dogłębnych badań, nim w pełni będzie można wykorzystać jej potencjał terapeutyczny. (Gerontol Pol 2025; 33; 194-200) doi: 10.53139/GP.20253328*

Słowa kluczowe: *laktoferyna, neuroprotekcja, choroba Parkinsona, choroba Alzheimera, choroby prionowe*

Correspondence address: ✉ Jakub Husejko, ul. Tymiankowa 13/25, 86-031 Osielsko ☎ (+48 52) 585 49 00 💻 kubahusejko@gmail.com
ORCID: Piotr Czwałga 0009-0001-6717-4609, Patrycja Koprowska 0009-0002-4322-922X, Jakub Husejko 0000-0002-9217-298X, Kornelia Kędziora-Kornatowska 0000-0003-4777-5252

Introduction

In recent years, lactoferrin, an antimicrobial peptide [1], has been scrutinized in the context of neurobiology. Through evolution, it has gained functions that go beyond its basic role and has become more than just a component of innate antimicrobial immunity [2]. These functions include the regulation of adaptive immunity, inflammation, and oxidative stress, as well as its active participation in the processes of aging and neurodegeneration [3]. These discoveries have led to lactoferrin gaining particular attention as a potential neuroprotective agent in the context of Alzheimer's, Parkinson's, and prion diseases.

Lactoferrin is a multifunctional glycoprotein from the transferrin protein family, with a molecular weight of approximately 80 kDa. It consists of a single polypeptide chain with two homologous N- and C-terminal domains. It was first isolated from cow's and human milk in 1939 and 1960, respectively [4]. It is produced mainly by epithelial cells of the mucous membranes and neutrophils, and secreted into glands that store and/or secrete colostrum, milk, tears, serum, or saliva [5]. The antimicrobial activity of lactoferrin results from its binding of iron, which is essential for bacterial metabolism [6]. However, it is also worth noting its various properties related to wound healing, immunomodulation, anticancer, antioxidant, osteogenic, and neuroprotective effects [7].

Aim

The aim of this study was to highlight the role of lactoferrin as a protein with immunomodulatory and neuroprotective properties, focusing exclusively on selected neurodegenerative diseases, namely Alzheimer's disease, Parkinson's disease, and prion disease.

Material and methods

The work is based mainly on articles from recent years, i.e., 2020-2023, taking into account some historical materials. The aim of the literature review was to gather comprehensive knowledge on the significance and multifaceted activity of lactoferrin (LF). The work uses methods involving querying articles found in the PubMed, Google Scholar, and Web of Science databases using the following keywords: lactoferrin, neuroprotection, Parkinson's disease, Alzheimer's disease, prion disease. Only articles published in English were included.

Results

Lactoferrin - structure and form

In humans, three forms of lactoferrin can be distinguished depending on its degree of iron saturation. Thus, there is the iron-free form (apo-lactoferrin; apo-Lf), a partially iron-saturated form with one iron ion in the C- or N-terminal lobe, and an iron-saturated form (holo-lactoferrin; holo-Lf) [8]. Thanks to its open conformation, apo-Lf exhibits stronger iron chelating and antibacterial activity, while the closed conformation of holo-Lf provides greater stability and resistance to higher temperatures and proteolytic digestion [9].

Lactoferrin enters the cell through endocytosis via clathrin. However, for this to happen, it must bind to its lactoferrin receptor (LfR), which is a protein with a molecular weight of 110 kDa. LfR is expressed in various cells and tissues, such as the small intestine, liver, brain, bones, and lymphocytes [10]. The multifunctionality of lactoferrin results from its ability to bind and interact with other receptors besides LfR [11,12]. These receptors include CD14 and Toll-like receptor 4, which enable the mediation of immune responses [13]. Other molecules that lactoferrin binds to include heparan sulfate proteoglycans, metalloproteinases, ions (copper, zinc, manganese), glycosaminoglycans, and lipopolysaccharides [12].

Parkinson's disease (PD)

There are many factors underlying Parkinson's disease, the most common of which are genetic predisposition, aging, and environmental factors. The importance of older age is evidenced by the fact that the disease most often occurs in people over 50, with the incidence increasing between the ages of 60 and 90. The symptoms mainly boil down to movement disorders, which is why stiffness, tremors, or postural instability can be observed in affected individuals [14].

The neuropathological features of PD may result from the presence of Lewy bodies, which are dopaminergic intracellular neuronal inclusions [15].

However, the development of PD is most strongly associated with the death of dopaminergic neurons in the substantia nigra of the basal ganglia. The death of dopaminergic cells leads to disturbances in dopamine flow, which in turn results in muscle structure disorders and impaired motor coordination [16].

In patients with Parkinson's disease, iron accumulation in the brain is a sign of brain dysfunction and neurometabolic disorders [17]. Increased Fe3ţ concentrations in the substantia nigra of the brain can lead to iron-dependent catalysis, which will result in the formation of free radicals and nerve cell degeneration. However, the presence of lactoferrin in the central nervous system appears to counteract these processes by preventing: dopamine loss in the striatum, iron accumulation, oxidative and apoptotic processes in the substantia nigra. In addition, lactoferrin reduces the expression of iron import protein while increasing the expression of iron export protein ferroportin, thereby reducing iron accumulation in the nigrostriatal system [18].

Rousseau and colleagues observed elevated levels of lactoferrin in dopaminergic (DA) neurons resistant to degeneration in patients with Parkinson's disease. This neuroprotective effect results from the binding of lactoferrin to heparan sulfate proteoglycans located on the surface of DA neurons, which is responsible for the inactivation of focal adhesion kinase (FAK). At the same time, it is worth noting that iron sequestration by lactoferrin prevents oxidative stress and protects DA neurons from apoptosis [19].

Gene therapy based on intravenous administration of modified lactoferrin nanoparticles containing neurotrophic factor derived from human glial cell lines (hGDNF) appears promising, as it may improve locomotor activity, reduce DA neuron loss, and increase monoamine neurotransmitter levels [20]. Lactoferrin can also lead to downregulation of transferrin receptors (TF), stimulate the expression of brain-derived neurotrophic factor (BDNF), and activate the protein kinase pathway, more specifically the mitogen-activated protein kinase ERK/MAPK. Accordingly, lactoferrin protects DA neurons by reducing α-synuclein levels and stimulating the expression of hypoxia-inducible factor-1a [18].

Alzheimer's disease (AD)

Alzheimer's disease is one of the most common forms of dementia among the elderly, and its pathology is characterized by abnormal levels of extracellular senile plaques containing β-amyloid peptides and abnormal levels of intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated Tau protein [21]. Other abnormalities observed in the brains of these patients include abnormal iron deposition and oxidative damage [22].

The underlying mechanism of AD results from the excessive production of neurotoxic Aβ42 by the amyloid-β precursor protein (APP). As a result, neurotoxic Aβ42 induces aggregation and hyperphosphorylation of Tau protein, which competes with normal Tau proteins for tubulin binding, thereby disrupting the balance between microtubule assembly and degradation, ultimately forming NFTs. These processes lead to region-specific synaptic degeneration and neuronal loss [23].

Recent findings suggest that in the pathological state, microglia and infiltrating leukocytes in the brain can synthesize lactoferrin. Hence, three neuroprotective mechanisms have been proposed [24]:

- Inhibition of apolipoprotein 4 (APOE4).
- Promotion of the non-amyloidogenic pathway.
- Suppression of oxidative stress, inflammation, and apoptosis.

3.1 Inhibition of apolipoprotein 4

Apolipoproteins (APOE) interact with LRP-1 and mediate lipid transport and metabolism in many organs, including the brain [25]. There are three isoforms of APOE in the human genome, of which APOE4 is considered to be the greatest known genetic risk factor for Alzheimer's disease [26]. APOE4 has been found to have amyloidogenic properties - it facilitates the accumulation of Aβ in neurons and increases amyloid-associated gliosis and dystrophic neurites in the brain [27].

Many studies have shown that lactoferrin can inhibit the effect of APOE on neurite growth. This is due to the similarity of the lactoferrin sequence to the APOE binding site sequence, hence the suggestion of competition for the same binding site on HSPG and LRP-1 [28].

Promoting the non-amyloidogenic pathway

APP, the amyloid precursor protein, is processed via the amyloidogenic or non-amyloidogenic pathway. In the first case, β-secretase cleaves APP into soluble APP-β (s APP-β) and the β-carboxy-terminal fragment (CTFβ), and γ-secretase cleaves CTFβ into the APP intracellular domain (AICD) and Aβ40/42 peptides. In the non-amyloidogenic pathway, α-secretase (usually ADAM10) cleaves APP into sAPP-α and CTFα, which are then cleaved by γ-secretase (mainly PS1) into P3 and AICD, and ultimately no Aβ40/42 peptides are formed [29].

Studies in transgenic mice have shown that treatment with lactoferrin improves spatial learning and reduces the number of amyloid plaques in the hippocampus and cerebral cortex. Further studies have also shown a reduction in the number of the most common APP isoform in neurons and the level of APP695 in the brain through an increase in the enzymatic activity of ADAM10 and PS1,

thereby promoting non-amyloidogenic APP cleavage [30].

Lactoferrin, specifically its apo-Lf form, is also known as a physiological mimetic of hypoxia, as it can both stabilize and stimulate HIF-1α by chelating iron, thereby preventing iron-dependent hydroxylation of HIF-1α [31].

It has also been noted that deferoxamine exerts HIF-1α-dependent inhibition of amyloidogenic APP processing in cellular and animal models, reducing Aβ accumulation and leading to cognitive preservation [32].

Suppression of oxidative stress, inflammation, and apoptosis

A study in aged mice involving lactoferrin showed its beneficial effect on cognitive function by alleviating its decline, as well as reducing hippocampal cell loss, while lowering markers of oxidative stress and inflammation in the hippocampus [33].

In a randomized pilot study, daily intake of lactoferrin (250 mg/day apo-Lf) for 3 months contributed to improved cognitive function and biomarkers related to oxidative stress (glutathione, MDA), inflammation (IL-10, IL-6), apoptosis (caspase -3) and amyloid or Tau protein pathology in patients with AD. This study also detected increased levels of phosphatidylinositol-4,5-bisphosphate 3 kinase (PI3K) and protein kinase B (Akt), which may suggest stimulation of the PI3K/Akt pathway by lactoferrin [34]. In studies on Parkinson's disease, this pathway was also shown to be involved in the preservation of dopaminergic neurons by lactoferrin via the surface proteoglycan heparan sulfate (HSPG) [19]. Hence, it is suspected that HSPG may also potentially mediate the lactoferrin-activated PI3K/Akt pathway in AD.

Prion disease

At the root of incurable prion disease lies the transformation of prion proteins in normal cells into amyloid subtypes - the result of conformational changes. Patients may present with a range of symptoms, from progressive dementia, sleep disorders, sensory disturbances, tremors, and seizures to urinary and fecal incontinence and hypertension.

Many studies have shown the beneficial effects of lactoferrin on the clinical picture of patients with prion disease. This was related to PrP(C) remaining on the cell surface, a reduction in its internalization, and the interaction of lactoferrin with PrP(C) and PrP(Sc), mediating changes in their conformation. It can therefore be said that lactoferrin exhibits functional anti-prion activity [35].

Lactoferrin can also prevent neuronal cell death by reducing the production of reactive oxygen species (ROS), reducing mitochondrial dysfunction, and ensuring the stability of HIF-1α by inhibiting the enzymatic activity of prolyl hydroxylase 2 (PHD2) [36].

Discussion

This review has highlighted the role of lactoferrin and presented it as a protein with both immunomodulatory and neuroprotective properties. However, it focused exclusively on certain neurodegenerative diseases, demonstrating the therapeutic potential of lactoferrin in Alzheimer's disease, Parkinson's disease and prion disease.

This does not mean that lactoferrin has no application in other diseases. Indeed, it does, as evidenced by studies conducted by research groups in Europe and Asia, which have demonstrated the broad spectrum of antiviral activity of lactoferrin in the context of COVID-19 infections [37]. In one study, 75 patients with COVID-19 recovered completely within 4-5 days of oral therapy with 32 mg of bovine liposomal lactoferrin, 12 mg of vitamin C and 10 mg of zinc [38].

Lactoferrin also appears to play an important role in the treatment of cancer through:

- optimisation of the iron-dependent mitochondrial oxidative phosphorylation and ATP synthesis,
- metal binding/transport and Fe3ț sequestration,
- cytotoxicity associated with cell membrane disruption, cell cycle arrest, cellular immune response, or apoptosis induction [39],
- acting as a carrier for the targeted delivery of chemotherapeutic drugs - the ability to cross the blood-brain barrier.

As if that were not enough, in a randomised study involving 109 Japanese children, consumption of a lactoferrin-enriched preparation compared to a placebo significantly improved sleep parameters and alleviated the symptoms of restless legs syndrome [40]. It is also suspected that the synergy of lactoferrin with melatonin may potentially alleviate oxidative stress and protect against neuronal damage.

Conclusions

As mentioned earlier, lactoferrin is a multifunctional glycoprotein with many properties - anti-inflammatory, immunomodulatory, and neuroprotective. More and more recent studies involving mice, cell models, and even humans confirm its beneficial effect in alleviating neurodegenerative processes in patients with Alzheimer's disease, Parkinson's disease, and prion disease.

In the case of Alzheimer's disease, its neuroprotective effect is based on three pillars, as it participates in the inhibition of apolipoprotein 4, promotes the non-amyloidogenic pathway, and suppresses of oxidative stress, inflammation, and apoptosis. In Parkinson's disease, it reduces oxidative stress, regulates iron metabolism, and protects dopaminergic neurons by influencing a number of molecular pathways. In prion diseases, it appears to influence protein conformation, thereby limiting its neurotoxicity.

Due to its multifunctionality and complexity, lactoferrin is a promising target for research, but much time and in-depth study are still needed before its therapeutic potential can be fully exploited.

Conflict of interest
None

References

1. Zhang LJ, Gallo RL. Antimicrobial peptides. Curr Biol. 2016;26(1):R14-R19.
2. Mylonakis E, Podsiadlowski L, Muhammed M, Vilcinskas A. Diversity, evolution and medical applications of insect antimicrobial peptides. Philos Trans R Soc Lond B Biol Sci. 2016;371(1695):20150290.
3. Oyinloye BE, Adenowo AF, Kappo AP. Reactive oxygen species, apoptosis, antimicrobial peptides and human inflammatory diseases. Pharmaceuticals (Basel). 2015;8(2):151-75.
4. Groves ML. The isolation of a red protein from Milk2. J Am Chem Soc. 1960;82(13):3345-50.
5. Baveye S, Elass E, Mazurier J, Spik G, Legrand D. Lactoferrin: a multifunctional glycoprotein involved in the modulation of the inflammatory process. Clin Chem Lab Med. 1999;37(3):281-6.
6. Ganz T. Iron and infection. Int J Hematol. 2018;107(1):7-15.
7. Elzoghby AO, Abdelmoneem MA, Hassanin IA, Abd Elwakil MM, Elnaggar MA, Mokhtar S, et al. Lactoferrin, a multi-functional glycoprotein: Active therapeutic, drug nanocarrier & targeting ligand. Biomaterials. 2020;263:120355.
8. Wang B, Timilsena YP, Blanch E, Adhikari B. Lactoferrin: Structure, function, denaturation and digestion. Crit Rev Food Sci Nutr. 2019;59(4):580-96.
9. Rosa L, Cutone A, Lepanto MS, Scotti MJ, Conte MP, Paesano R, et al. Physico-chemical properties influence the functions and efficacy of commercial bovine lactoferrins. Biometals. 2018;31(3):301-12.
10. Jiang R, Lopez V, Kelleher SL, Lönnerdal B. Apo- and holo-lactoferrin are both internalized by lactoferrin receptor via clathrin-mediated endocytosis but differentially affect ERK-signaling and cell proliferation in Caco-2 cells. J Cell Physiol. 2011;226(11):3022-31.
11. Kell DB, Heyden EL, Pretorius E. The Biology of Lactoferrin, an Iron-Binding Protein That Can Help Defend Against Viruses and Bacteria. Front Immunol. 2020;11:1221.
12. Suzuki YA, Lopez V, Lönnerdal B. Mammalian lactoferrin receptors: structure and function. Cell Mol Life Sci. 2005;62(22):2560-75.
13. Ando K, Hasegawa K, Shindo K, Furusawa T, Fujino T, Kikugawa K, et al. Human lactoferrin activates NF-kappaB through the Toll-like receptor 4 pathway while it interferes with the lipopolysaccharide-stimulated TLR4 signaling. FEBS J. 2010;277(9):2051-66.
14. Balestrino R, Schapira AHV. Parkinson disease. Eur J Neurol. 2020;27(1):27-42.
15. Meade RM, Fairlie DP, Mason JM. Alpha-synuclein structure and Parkinson's disease - lessons and emerging principles. Mol Neurodegener. 2019;14(1):29.
16. Fahim MA, Shehab S, Nemmar A, Adem A, Dhanasekaran S, Hasan MY. Daily subacute paraquat exposure decreases muscle function and substantia nigra dopamine level. Physiol Res. 2013;62(3):313-21.

17. Mochizuki H, Choong CJ, Baba K. Parkinson's disease and iron. J Neural Transm (Vienna). 2020;127(2):181-7.
18. Liu H, Wu H, Zhu N, Xu Z, Wang Y, Qu Y, et al. Lactoferrin protects against iron dysregulation, oxidative stress, and apoptosis in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced Parkinson's disease in mice. J Neurochem. 2020;152(3):397-415.
19. Rousseau E, Michel PP, Hirsch EC. The iron-binding protein lactoferrin protects vulnerable dopamine neurons from degeneration by preserving mitochondrial calcium homeostasis. Mol Pharmacol. 2013;84(6):888-98.
20. Huang R, Ke W, Liu Y, Wu D, Feng L, Jiang C, et al. Gene therapy using lactoferrin-modified nanoparticles in a rotenone-induced chronic Parkinson model. J Neurol Sci. 2010;290(1-2):123-30.
21. Price JL, Morris JC. Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. Ann Neurol. 1999;45(3):358-68.
22. Smith MA, Zhu X, Tabaton M, Liu G, McKeel DW Jr, Cohen ML, et al. Increased iron and free radical generation in preclinical Alzheimer disease and mild cognitive impairment. J Alzheimers Dis. 2010;19(1):363-72.
23. Reitz C. Alzheimer's disease and the amyloid cascade hypothesis: a critical review. Int J Alzheimers Dis. 2012;2012:369808.
24. Yong SJ, Veerakumarasivam A, Lim WL, Chew J. Neuroprotective Effects of Lactoferrin in Alzheimer's and Parkinson's Diseases: A Narrative Review. ACS Chem Neurosci. 2023. Advance online publication. doi:10.1021/acschemneuro.2c00679.
25. Shinohara M, Tachibana M, Kanekiyo T, Bu G. Role of LRP1 in the pathogenesis of Alzheimer's disease: evidence from clinical and preclinical studies. J Lipid Res. 2017;58(7):1267-81.
26. Di Battista AM, Heinsinger NM, Rebeck GW. Alzheimer's Disease Genetic Risk Factor APOE-ε4 Also Affects Normal Brain Function. Curr Alzheimer Res. 2016;13(11):1200-7.
27. Liu CC, Zhao N, Fu Y, Wang N, Linares C, Tsai CW, et al. ApoE4 Accelerates Early Seeding of Amyloid Pathology. Neuron. 2017;96(5):1024-32.e3.
28. Nathan BP, Jiang Y, Wong GK, Shen F, Brewer GJ, Struble RG. Apolipoprotein E4 inhibits, and apolipoprotein E3 promotes neurite outgrowth in cultured adult mouse cortical neurons through the low-density lipoprotein receptor-related protein. Brain Res. 2002;928(1-2):96-105.
29. Coronel R, Bernabeu-Zornoza A, Palmer C, Muńiz-Moreno M, Zambrano A, Cano E, et al. Role of Amyloid Precursor Protein (APP) and Its Derivatives in the Biology and Cell Fate Specification of Neural Stem Cells. Mol Neurobiol. 2018;55(9):7107-17.
30. Guo C, Yang ZH, Zhang S, Chai R, Xue H, Zhang YH, et al. Intranasal Lactoferrin Enhances α-Secretase-Dependent Amyloid Precursor Protein Processing via the ERK1/2-CREB and HIF-1α Pathways in an Alzheimer's Disease Mouse Model. Neuropsychopharmacology. 2017;42(13):2504-15.
31. Zakharova ET, Kostevich VA, Sokolov AV, Vasilyev VB. Human apo-lactoferrin as a physiological mimetic of hypoxia stabilizes hypoxia-inducible factor-1 alpha. Biometals. 2012;25(6):1247-1259.
32. Guo C, Zhang YX, Wang T, Zhong ML, Yang ZH, Hao LJ, et al. Intranasal deferoxamine attenuates synapse loss via up-regulating the P38/HIF-1α pathway on the brain of APP/PS1 transgenic mice. Front Aging Neurosci. 2015;7:104.
33. Zheng J, Xie Y, Li F, Zhou Y, Qi L, Liu L, et al. Lactoferrin improves cognitive function and attenuates brain senescence in aged mice. J Funct Foods. 2020;65:103736.
34. Mohamed WA, Salama RM, Schaalan MF. A pilot study on the effect of lactoferrin on Alzheimer's disease pathological sequelae: Impact of the p-Akt/PTEN pathway. Biomed Pharmacother. 2019;111:714-23.
35. Iwamaru Y, Shimizu Y, Imamura M, Murayama Y, Endo R, Tagawa Y, et al. Lactoferrin induces cell surface retention of prion protein and inhibits prion accumulation. J Neurochem. 2008;107(3):636-46.
36. Park YG, Moon JH, Park SY. Lactoferrin from bovine colostrum regulates prolyl hydroxylase 2 activity and prevents prion protein-mediated neuronal cell damage via cellular prion protein. Neuroscience. 2014;274:187-97.
37. Campione E, Cosio T, Rosa L, Lanna C, Di Girolamo S, Gaziano R, et al. Lactoferrin as Protective Natural Barrier of Respiratory and Intestinal Mucosa against Coronavirus Infection and Inflammation. Int J Mol Sci. 2020;21(14):4903.

38. Serrano G, Kochergina I, Albors A, Diaz E, Oroval M, Hueso G, et al. Liposomal lactoferrin as potential preventative and cure for COVID-19. Int J Res Health Sci. 2020;8(1):8-15.
39. Cutone A, Rosa L, Ianiro G, Lepanto MS, Bonaccorsi di Patti MC, Valenti P, et al. Lactoferrin's Anti-Cancer Properties: Safety, Selectivity, and Wide Range of Action. Biomolecules. 2020;10(3):456.
40. Miyakawa M, Kubo S, Oda H, Motoki N, Mizuki M, Tsukahara T, et al. Effects of Lactoferrin on Sleep Conditions in Children Aged 12-32 Months: A Preliminary, Randomized, Double-Blind, Placebo-Controlled Trial. Nat Sci Sleep. 2020;12:671-7.