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Review Article

The Reasons Behind the Salubrious of Colostrum on the Cognitive Functions: A Systematic Review

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ABSTRACT

Bovine colostrum (BC) is rich in many vitamins, minerals, and antioxidant substances. Its supplementation provides health benefits, particularly for athletes. This systematic review was carried out to update on the benefit of BC or its formulations (e.g., colostrinin) on the cognitive functions or their related biomarkers in experimental and human studies. Full texts or abstracts of 219 articles as reports of narrative or systematic reviews, randomized controlled clinical trials, observational studies, and experimental studies (*in vitro*, *ex vivo*, and *in vivo*) were included after searches in PubMed, Europe PMC, Google scholar databases. The full texts of eligible articles (25 articles) were assessed and their results were summarized in different categories according to the study design. Bovine colostrum or its related formulations have been shown to be useful as they improve cognitive functions and their biomarkers. Compatible results were observed in experimental and human studies. Further studies are mandatory to elucidate the rationale for using (BC) in healthy subjects and patients with impaired of cognitive functions.

Keywords: Bovine colostrum, Colostrinin, Cognitive functions, Clinical studies, Experimental studies.

Introduction

Bovine colostrum (BC) is rich in protein molecules that support the growth of the newborn calf. Table 1 summarizes the constituents of the colostrum in which their concentrations vary with the time of milk production.¹ The constituents of BC, particularly the presence of vitamin B series, play an important function in the prevention or slowing of the progression of Alzheimer's disease.² The presence of niacin (vitamin B3) in the BC could play a role in reducing neuroinflammation and preventing the production of A β -protein in Alzheimer's animal models.³ Improvement of cognitive function can be achieved by using a diet rich in polyunsaturated fatty acids, zinc, and vitamins (A, B1, B12, D), which are available in considerable concentrations in BC.⁴ BC or its formulations have pleiotropic properties that could be useful in individuals with a decline in cognitive functions, which include antioxidant, anti-inflammatory, cellular survival, and inhibition of A β -fibril aggregation.⁵⁻¹⁰ Several studies have shown that reactive oxygen species, neuroinflammation, and senescent cells are involved in the pathogenesis of impairment of cognitive function.¹¹ Colostrum was investigated in a small number of clinical studies, and the authors reported the beneficial effect of using colostrum in mild-moderate impairment of cognitive functions in Alzheimer's disease.^{12, 13} Therefore, the aim of this systematic review is to look for evidence that supports using BC as a nutraceutical to improve cognitive function.

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Table 1: Constituents of colostrum

Protein
Whey protein (soluble) contained:
Immunoglobulin (IgG1, IgG2, IgM, IgA, IgD, IgE)
Lactoferrin
α -lactoalbumin
β -lactoglobulin
Lactoperoxidase
Glycomacropeptide
Growth factors
Casein (phosphoprotein, insoluble)
Carbohydrate
Lactose
Oligosaccharides; sialylated oligosaccharide
Glycolipids
Glycoproteins
Nucleotide sugars
Lipids
ω -3 and ω -6 polyunsaturated fatty acids
Conjugated linoleic acid
Short chain fatty acids
Gangliosides
Phospholipids
Vitamins and Minerals
Vitamin A, D, E, B(B1, B2, B3, B12)
Zinc, Phosphorus, Calcium, Magnesium, Sodium, Potassium

Materials and Methods

This systematic review included the experimental and clinical studies that have been published up to January 2022. The method (PICO) of searching for the articles is composed of four frames:

Frame 1 (population): the humans (healthy or non-healthy), and the animals (*in vivo*, and *ex-vivo* studies).

Frame 2 (intervention): administration of BC in any pharmaceutical formulation or dosage schedule that provides improvement of cognitive functions.

Frame 3: (control); the control group is considered when there was no treatment or treatment with a placebo.

Frame 4 (outcome): the primary outcomes included improvements in cognitive functions using different applicable cognitive tests, learning, and memory. In experimental observation studies, improvements in cognitive functions as well as biochemical and immunohistochemical changes were considered.

The following databases were used for literature searches: PubMed, European PMC, and Google Scholar. The keywords that were used in the literature search were “bovine colostrum” Colostrinin” “Cognitive function”, “Learning”, “memory”, “A β -amyloid”, and “Clinical trials. The records from 1 January 1990 to 31 January 2022 were included in the study, and full-text articles were considered in the analysis.

Experimental (*in vitro*, *ex-vivo*, and *in vivo*) and clinical studies (observational, non-randomized, and placebo-controlled studies) related to the cognitive functions in healthy subjects or in patients with cognitive impairments, e.g. Alzheimer’s dementia, were included in this systematic review. The effect of BC or its related formulations on health conditions that are not related to cognitive functions is excluded from the search. Figure 1 shows the PRISMA flowchart by which the selection process of eligible articles was included in this systematic review.

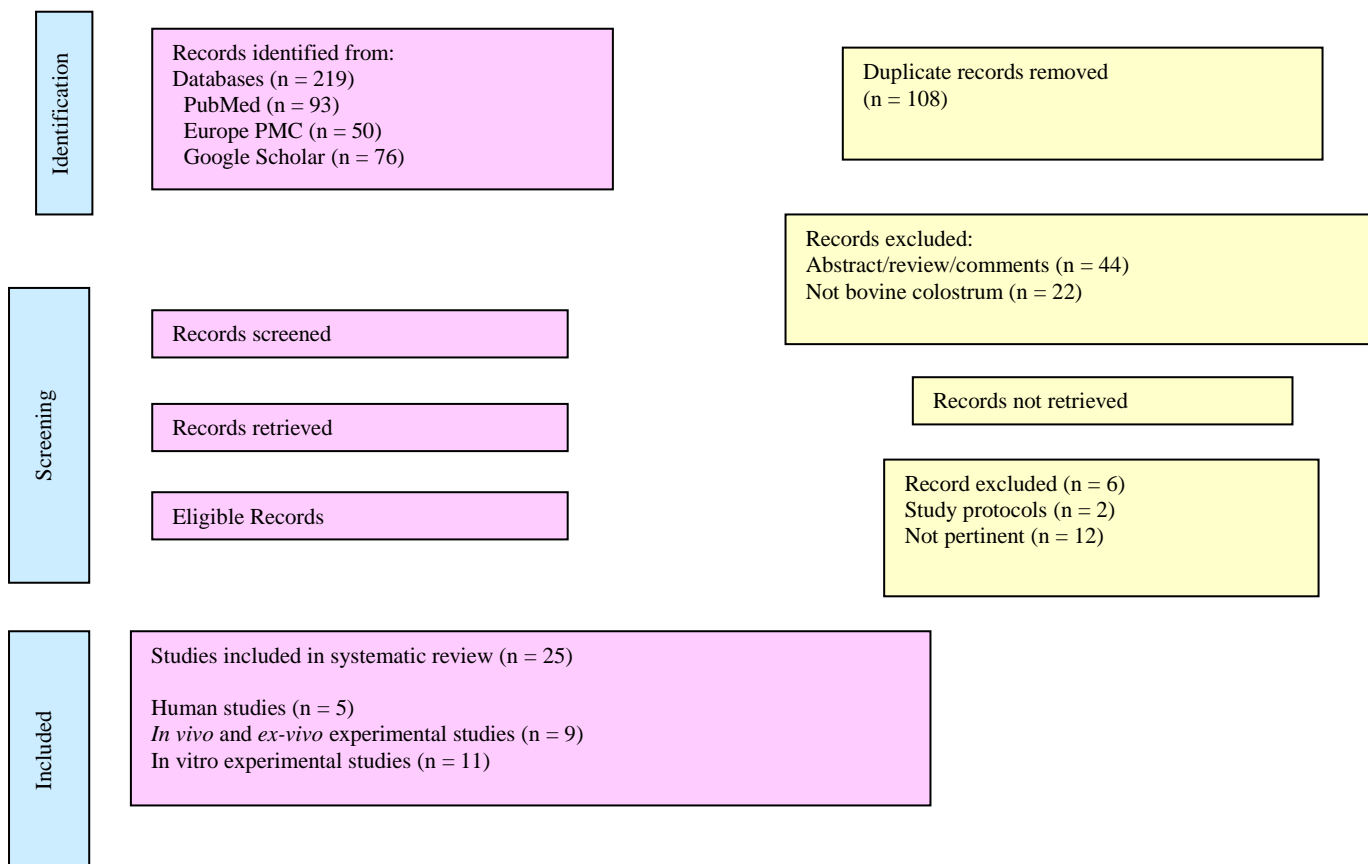


Figure 1: Flowchart of recruitment

Results and Discussion

A total of 25 out of 219 articles fulfilled the objectives of the study. Twenty of them were experimental studies, including *in vitro* studies (11), *ex-vivo* and *in vivo* studies (9), and five of them were clinical studies.

In vitro studies

Table 2 shows that colostrinin, a synthetic formulation of bovine colostrum was investigated in 6 studies that showed colostrinin exerts different pharmacological actions that indicate its usefulness in the improvement of cognitive functions. These studies highlighted two important pharmacological effects of colostrinin on cell viability and status, as well as on free radicals. The effect of colostrinin on cell viability included an increase in cell life span; a decrease in senescent cells; a decrease in cell death or apoptosis; and a decrease in A β -fibril aggregation. Its effects on free radicals included a reduction in the generation of reactive oxygen species and an elevation of superoxide dismutase activity. The effect of colostrinin on the inflammatory markers was observed in the study by demonstrating an increase in interferon- γ . The effect of BC was reported in one study by reducing reactive oxygen species and cell death, accompanied by an improvement in glutathione levels.

In three studies, nonapeptide separated from colostrum showed similar effects as colostrinin in reducing cell death, while the extracted proline-rich polypeptide complex from BC showed broad-spectrum activity against cell life span and free radical generation.

Ex-vivo and *in vivo* studies

Table 3 showed that colostrinin improved cognitive function by improving spatial, incidental, and retention memory in experimental animal models. Also, it increases cell survival and inhibits the production of reactive nitrogen species.

The effects of BC were observed in two studies that showed improvement in cell survival, and reduction of the inflammatory biomarkers and excitatory amino acids that are involved in the impairment of cognitive function. The effect of nonapeptide formulas was demonstrated in one study, which delayed the extinction of spatial memory, while proline-rich polypeptides inhibited the production of reactive nitrogen species.

Clinical studies

Table 4 shows the efficacy of colostrin (four studies) and a proline-rich polypeptide supplement (one study) on the cognitive function of patients with Alzheimer's disease. Three studies were placebo-controlled and randomized studies using different protocols, and two studies were cross-sectional observational studies. Colostrin stabilized the health of patients and showed a significant improvement in their cognitive functions by using the Clinical Global Impression of Change, Instrumental Activities of Daily Living, and Mini-Mental State Examination tests. In addition, colostrin is involved in reducing the proinflammatory markers and A β -fibril in Alzheimer's dementia. The results of this study showed that BC or its synthetic and extracted formulations are of value in the improvement of cognitive functions or the biomarkers that are linked with the impairment of cognitive functions. Moreover, literature surveys did not show the effect of BC or its related formulation on cognitive function in healthy subjects. According to laboratory and clinical evidence that was reported in 25 studies, this systematic review showed that there are multiple reasons that explain the beneficial effects of colostrum in improving the cognitive functions of the human brain, which include:

1. The ability of colostrum to cross the blood-brain barrier

BC is a lipophilic substance because it contains plenty of unsaturated fatty acids; therefore, it can cross the blood-brain barrier (BBB). Macromolecules constituents, including total protein, lactoferrin, transferrin, β -lactoglobulin, immunoglobulin G, and epidermal growth factors, were detected in the cerebrospinal fluid of newborn calves and reached peak levels after 10 hours of colostrum feeding.^{14, 15} It has been found that transportation of lactoferrin to the cerebrospinal fluid (CSF) is mediated by transcytosis via a single specific receptor located in the choroid plexus.¹⁶ Dietary lactoferrin had no significant effect on the cognitive function of young and middle-aged mice as it did not induce changes in neuroinflammation, synaptic plasticity, or A β -tangle.¹⁷ Lactoferrin is an important iron-binding glycoprotein that is involved in healthy brain function as an oral lactoferrin supplement reduces A β deposition, and improves cognitive function in patients with Alzheimer's disease.¹⁸ Human milk contained higher levels of lactoferrin compared with BC and played an important role in the cognitive function and neuronal development of the newborn.¹⁹ A randomized controlled clinical trial showed an acceleration of the neurodevelopment profile in infants supplemented with lactoferrin in the form of bovine lactoferrin.⁸ Another study found that lactoferrin supplementation for three months improves cognitive function in patients with Alzheimer's disease through several mechanisms supported by clinical and laboratory-based evidence.²⁰ The mechanisms by which lactoferrin improves cognitive function are related to the upregulation of several pathways that signal cognitive function, including brain-derived neurotrophin factor, polysialic acid that is involved in neurodevelopment, and the plasticity of neurons.²¹ In an *ex-vivo* study using newborn piglets with agammaglobulinemia who were fed with colostrum, a specific porcine immunoglobulin was observed in the CSF.²² In experimental animal models of septic shock, oral BC supplementation maintained the function of the BBB and reduced the colony numbers of the bacteria, and leukocytes in the cerebrospinal fluid.²³ ¹H-NMR-based metabolomics study showed that enteral supplementation with colostrum reduced the CSF lactate level in preterm pigs infected with *Staphylococcus epidermidis*.²⁴

2. Presence of bioactive substances that are involved in cognitive functions

BC contains many bioactive substances that are linked with cognitive function, including proline, choline, and lactoferrin. Proline is one of the endogenous metabolites that is an essential metabolite for

extranuclear signaling of sex hormone in the hippocampal region that provides preservation of cognition after global cerebral ischemia.²⁵ Colostrin is a rich polypeptide complex derived from BC, which improves cognitive functions in animals and in patients with Alzheimer's disease.²⁶ Colostrin, can slow the ageing process through its effect on the mitochondrial dysfunction of senescent cells by reducing and removing intracellular free radicals and improving glutathione activity.⁵ A recent study demonstrates that cyclic glycine-proline, which is present in milk breast, produced long-standing improvements in spatial memory due to its central effect of promoting the plasticity of the astrocytes, enhancing the cerebral vascularity, and altering the glutamate metabolism, which leads to the regulation of the function of insulin growth factor.²⁷ Choline is a precursor to acetylcholine that protects the brain from neurodegenerative diseases. It plays a role in the development of gray and white matter during the prenatal phase.²⁸ The concentration of choline in the colostrum is less than that of mature breast milk in humans, and its level is progressively increased during infancy and lactation.²⁹ In studies, dietary choline supplementation throughout life reduces the memory deficit and the cerebral amyloid β -plaque formation.³⁰ Lactoferrin is the most important substance in the colostrum that provides protection against neurodegeneration and promotes neural development. The effect of lactoferrin on the central nervous system is related to its concentration in the colostrum. Piglets fed milk with low lactoferrin concentration (155mg/kg/day) during the postnatal period extended to 38 days showed a modulation in the genes' expression that was related to cognition, while a higher lactoferrin concentration (285mg/kg/day) provides neuronal development and protection against neurological pathologies.³¹ In humans, lactoferrin supplements reduce the decline of cognitive function in Alzheimer's dementia and reduce A β -deposits, therefore it is utilized as a drug delivery system by formulating lactoferrin-based nanoparticles to treat neurodegenerative diseases associated with SARS-CoV-2 infections.¹⁸ The concentration of niacin in the BC is 0.35 μ g/mL.³² A latent improvement in cognitive functions was observed when young adulthood dietary intake contained soluble vitamins B, including niacin.³³ A recent study demonstrates that niacin supplements of 250mg daily for six months improve the motor functions of Parkinson's patients, as evidenced by a significantly lower mean score of the Unified Parkinson's Disease Rating Scale III (-1.06) compared with a placebo-treated group (-0.05).³⁴ The results of the food frequency questionnaire carried out on 815 patients aged >65 years old showed a higher food intake of niacin is associated with a low decline in cognitive function in non-Alzheimer's patients, and the relationship between the higher niacin food intake and Alzheimer's disease is inverse.³⁵

3. Counteract the oxidative and nitrative stress syndromes that are implicated in the deterioration of cognition

In human fibroblast culture studies, the addition of liposomal BC significantly ameliorated the changes induced by hydrogen peroxide as an oxidant agent and a hydroxyl radical donor by the evidence of reducing the shortening of telomerase.³⁶ In an experimental animal study using mice, BC supplements of 50mg/day/mouse (containing 6% carbohydrate, 84.7% protein, and 1.8% fat) significantly improved the total antioxidants and reduced the lipid peroxidation process induced by exercises.³⁷ Bovine colostrum elevates the skeletal muscle levels of superoxide dismutase and total antioxidants, which are associated with a decline in lipid peroxidation activity and decreases the xanthine oxidase enzyme levels in the skeletal muscles after exercise. Lactoferrin is a constituent of BC and it plays a role in counteracting the oxidative stress that is associated with heme-iron and it can abolish the overload of ferritin-binding iron molecules.³⁸ It is important to mention that the concentration of antioxidants in the BC is determined by the parity of cows, as higher concentrations of ceruloplasmin and transferrin levels are present in the BC of primiparous cows compared with multiparous cows.¹⁰ Both reactive oxygen and nitrogen species are implicated in the pathogenesis of the impairment of cognitive function, which is mediated by decreasing cell viability, loss of the function of nerve growth factor, and reducing axonal transport activity.¹¹

Table 2: Results of the beneficial effects of bovine colostrum, or colostrinin, or a proline rich polypeptide isolated from colostrum in *In vitro* experimental studies

Ref.	Model	Target	Active ingredient	Results	Conclusion
57	<i>In vitro</i> cell- induce production of cytokines	Peripheral blood leucocyte of human	Colostrinin	↑ interferon- γ	Cellular protection via inducing lymphocyte response by interferon- γ
58	<i>In vitro</i> cell line culture using lipopolysaccharide induced oxygen and nitrogen species	Human monocyte-like leukemia cell line THP-1	Proline-rich polypeptide complex (PRP) isolated from ovine colostrum	proline rich polypeptidedid not affect the production of nitric oxide or superoxide anion. Nonapeptide at high concentrations reduced the production of nitric oxide	Ovin colostrum did not have any effects on the reactive oxygen species.
59	Neuroblastoma (SHSY-5Y) cell line culture	A β (1–40)-induced cytotoxicity	Colostrinin	↓A β -fibril content ↓ cytotoxicity	Protection of neuronal cells
60	<i>In vitro</i> cultured cells model for cellular aging	Lifespan of murine diploid fibroblast cell	Colostrinin	↓senescent cells ↑life span of diploid cells ↓ reactive oxygen species in mitochondria	Improvement of mitochondrial function
61	<i>In vitro</i> amyloid (A β) fibril content using thioflavin T, using fluorescent spectroscopy	A β fibril solution	Colostrinin	↓ A β fibril content in a dose dependent fashion	Reduces the biomarker A β -fibril
6	<i>In vitro</i> cell culture using human neuronal SHSY-5Y cells	Neuronal cells	Colostrinin	↓cytotoxicity induced by A β 1-40 peptide ↓neuronal cell apoptosis	Colostrinin offers neuro-protection against A β -induced neuronal cell damage
62	<i>In vitro</i> cell culture	Rat primary hippocampal neural cells	Colostrinin	↓cytotoxicity induced by A β - peptide ↓ superoxide dismutase enzyme-1 activity	Protection of hippocampal cells against peptide induced cytotoxicity
54	Human peripheral blood cell	Reactive oxygen species and antioxidants	Proline rich polypeptide/colostrinin	↓ hydrogen peroxide ↑ glutathione activity No effect on lipid peroxidation	Stabilize the antioxidant activity
63	<i>In vitro</i> PCL12 cell culture	Rat pheochromocytoma cells	Proline rich polypeptide complex isolated from ovine colostrum	↑ production of nitric oxide ↑ cellular phosphorylation	Neurogenesis similar to the effect of nerve growth factor
44	<i>In vitro</i> cell line culture	Rat adrenal pheochromocytoma (PC12 Tet On) cells	isolated from colostrum	↓ cytotoxicity ↓6-hydroxydopamine-induced apoptosis ↑ cell survival	Neuroprotection against oxidative-cell damage

43	<i>In vitro</i> cell line culture using high doses of dexamethasone inducing apoptosis	MC3T3-E1 Osteoblastic cells	Bovine colostrum	↓ cellular apoptosis ↓ reactive oxygen species ↑ cellular glutathione	induced by 6-hydroxydopamine Counteraction against cellular apoptosis
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Table 3: Results of the beneficial effects of bovine colostrum, or colostrinin, or proline rich polypeptide isolated from colostrum in *ex-vivo* and *in vivo* experimental studies

Ref.	Model	Target	Active ingredient	Results	Conclusion
64	Animal model of assessment the functioning of spatial learning and incidental memory in rats	Cognitive functions (Learning and memory)	Colostrinin	↑ spatial memory using Morris maze water test ↑ incidental memory	Improving the cognitive function without changes in the locomotor function in aged rats
65	<i>In vivo</i> behavioral animal model using aged rats	Locomotor and spatial memory functioning	Colostrin-Val nonapeptide	No effect on the spatial memory Delay the extinction of the spatial memory	Delay the extinction of long-term memories
66	<i>In vivo</i> animal model using lipopolysaccharide-inducing reactive oxygen and nitrogen species nitrate stress	Production of nitric oxide from cultured peripheral blood cells	Proline rich polypeptide isolated from ovine colostrum, nonapeptide	↓ overproduction of nitric oxide ↓ overproduction of superoxide anion	Antioxidant properties
67	day-old domestic chicks	Retention of memory using avoidance of a bitter-tasting substance	Colostrinin	Improves retention memory	Colostrinin is a cognitive enhancer
47	Middle cerebral artery occlusion in animal (Stroke model)	Brain	Bovine colostrum	Improves the neuronal deficit ↓ infarct volume ↓ serum cytokines; IL-1 β , IL-6, and TNF- α	Attenuating the proinflammatory cytokines and protect the brain from ischemic insult
68	<i>In ex-vivo</i> experimental animal model using mice treated with lipopolysaccharide \pm colostrinin	Polysaccharide induced reactive nitrogen species- cells from intraperitoneal	Colostrinin	↓ nitric oxide release ↓ inducible nitric oxide synthetase	Antiinflammatory effect is a possible explanation of neuroprotection.
7	Intracerebral hemorrhage animal model using rats	Hippocampal cell	Bovine colostrum	↓ excitatory amino acid inducing apoptosis ↓ intracellular hemorrhage inducing neuronal cell death	Improving short term memory
69	Animal model of assessment locomotor	Cognitive function	Colostrinin	↑ spatial memory using Morris maze water	Improving spatial and episodic memory, due

	function, exploratory behaviour, and the functioning of episodic and spatial memory in rats			test	to the neuroprotective and immunomodulatory properties
9	In vivo behavioral animal model using aged and young rats	Cognitive function using Morris Maze water test	Colostrinin	↑ spatial memory using Morris maze water test	Colostrinin improves the cognitive functions of whatever age

Table 4: Results of the beneficial effects of bovine colostrum, or colostrinin, or a proline rich polypeptide isolated from colostrum in human studies

Ref.	Model	Target	Active ingredient	Results	Conclusion
49	3 week double blind placebo controlled study with 2 week hiatus, for 10 cycles	Alzheimer's patients	Colostrinin	Improves the health and the outcome of dementia (mild-to moderate) in 8 out of 15 patients	Improvement the cognitive functions
70	3 weeks supplementation non-randomized non-controlled clinical trial	Alzheimer's patients.	Colostrinin	Stabilizing the health status Transient adverse reactions; anxiety, insomnia, logorrhea	A slightly effective in stabilizing the health
12	15 week randomly double-blind-controlled clinical study	Alzheimer's patients	Colostrinin	Improving of Alzheimer's disease Assessment Scale-cognitive portion test; Clinical Global Impression of Change; Instrumental Activities of Daily Living; Mini-Mental State Examination test and ADAS-non cognitive test	Improve the cognitive functions
13	Multi-centers Clinical trials: Double blind controlled clinical study (Phase-1) and open-label clinical trial (Phase 2)	Alzheimer's patients	Colostrinin	Improvement of some cognitive function tests Down-regulation of mRNA levels for resistin (a gene involved in the production of proinflammatory cytokines) Down-regulation of A Precursor Protein (APP) mRNA levels thereby potentially decreasing levels of aggregated A β 1062	stabilizing effect on cognitive functions in mild and moderate Alzheimer's disease
71	Non-randomized non-controlled observational study	Innate immune response in Alzheimer's patients	Dietary supplement proline-rich polypeptide complex	Improves the subpopulation of circulated blood cells ↓ production of proinflammatory cytokines	Improves the innate immunity

There is a link between reactive oxygen species and the pathogenesis of Alzheimer's disease, as the hydroxyl radical is responsible for damaging the amyloid A β tangle and the surrounding tissue.³⁹

4. Counteract inflammation that is implicated in the deterioration of cognitive functions

Bovine IgG is an important globulin that protects humans against many infectious diseases, and it is available in different formulas to treat many human pathogens.⁴⁰ Diets containing anti-inflammatory substances play a role in the prevention of neuroinflammation that is associated with Alzheimer's disease and a decline in cognitive function that occurs with ageing.⁴¹ In experimental animal models of septic shock, BC supplements prevent the disruption of the BBB and neuroinflammation that is induced by intra-arterial administration of *Staph. epidermidis* in preterm pigs.²³ The anti-inflammatory effect of BC is related to its antibacterial effect against *Staph. epidermidis* by the evidence of reducing the number of leukocytes in the cerebrospinal fluid (CSF) as a result of decreasing the blood-CSF permeability, *Staph. epidermidis* and leucocyte-chemoattractants. Another study demonstrated that BC specifically reduced the neuroinflammation-related proteins in the CSF and in the prefrontal brain region, e.g., neuropeptide-Y and interleukin-18.⁴² Other studies demonstrate that BC suppressed the activity of excitatory amino acids (N-methyl D-aspartate) in the hippocampal region, which led to suppression of apoptotic neuronal cell death and thereby improved short-term memory.⁷ In *In vitro* cell line study, BC prevents dexamethasone-induced neurodegeneration of MC3T3-E1 osteoblastic cells by activating the Ras/Raf/extracellular signal-regulated kinase (ERK pathway) that mediates apoptosis and autophagy, and via modulating the heat shock proteins (Hsp70).⁴³ Another study demonstrated that the active ingredient in colostrin reduced rather than induced the neurotoxicity of adrenal pheochromocytoma cells that was induced by 6-hydroxydopamine, via transient activation of the ERK pathway.⁴⁴ Lactoferrin protects the neuronal cell by stabilizing the hypoxia-inducible factor-1 α via its up-regulatory effects on the prolyl hydroxylase enzyme and thereby prevents the formation of the abnormal isoform prion protein.⁴⁵ Other researchers demonstrated that insulin growth factor-1, which is available in the BC, plays an important role in the suppression of neurodegeneration via its effect on the generation of reactive oxygen species and improves mitochondrial function by blocking the effect of the cellular prion protein upon the mitochondria.⁴⁶ Human neuronal SHSY-5Y cells pretreated with colostrin (5 μ g/mL) are protected from neurotoxicity induced by A β 1-40 protein, indicating that colostrin is an A β -amyloid inhibitor, and will be of benefit in Alzheimer's disease.⁶

The other neuroprotective mechanism of BC is related to its effects on cytokines. As BC reduced the proinflammatory cytokines (IL-1b, IL-6, TNF-a) and improved the anti-inflammatory cytokines (IL-10) that followed the experimental model of cerebral artery occlusion, it led to reducing the percentage of infarcted cerebrum areas and improving the behavioral tasks.⁴⁷ Gladkevich et al²⁶ attributed the neuroprotective effects of proline-rich polypeptides that are available in colostrin to the following pharmacological actions:

- Regulating apoptosis via different mechanisms
- Suppression of proinflammatory cytokines, e.g., IL-b, IL-6, and TNF-a, and improvement of interferon- γ
- Promoting the expression of growth factors leads to neurotrophs
- Counteract the oxidative stress syndrome
- Direct anti-inflammatory effect

Ultimately, the above-mentioned pharmacological effect can reduce β -amyloid fibrils, which is pathological evidence of Alzheimer's disease. Janusz et al⁴⁸ found that the nanoparticle fragment of a proline-rich polypeptide inhibits the aggregation of A β aggregation, indicating that these fragments act as β -sheet breakers. In experimental animal models, colostrin (4 μ g/rat) improves significantly locomotor activity and cognitive function using the Morris water maze test compared with placebo-treated rats.⁹ In a double-blind placebo-controlled study, colostrin oral tablet (100 μ g every second day) for

two cycles, each cycle of 3 weeks separated by a 2 week washing period, provides a significant improvement in the cognitive functions assessed of patients with Alzheimer's disease by the Mini-Mental State Examination test, compared with placebo-treated patients.⁴⁹

1. Possible relation to the apoptosis and necroptosis

Several genes are expressed during the apoptosis process, including the B-cell lymphoma (Bcl)-2 family, caspases, tumor necrosis factor, p53, and apoptosis protein inhibitors.⁵⁰ In experimental cell culture models of neural apoptosis, BC showed an anti-apoptotic effect against glucocorticoids inducing neuronal damage by attenuating the apoptotic proteins including Bcl-XL, Bax, Hsp70.⁴³ The constituents of BC, including lactoferrin and its fragment lactoferricin, augmented the cytotoxic T cell and natural killer cell activity, inducing apoptosis in the epithelial cells in experimental carcinogenic animal models.⁵¹ Recent studies demonstrate that liposomal bovine colostrum improves the proliferation of fibroblast cells and attenuates markers of senescent skin cells.³⁶

2. Nutraceutical formulations are available

Several forms of pharmaceutical preparations were prepared and used for research, and many pharmaceuticals were manufactured BC. These formulations are: powder in capsule (bovine immunoglobulin concentrate)⁵²; oral bovine colostrum tablet¹⁵³¹; sublingual colostrin tablet⁵⁴ intravaginal gel containing purified (dialyzed lyophilized) bovine colostrum (ZP-025)⁵⁵; spray-dried BC⁵⁶; and liposomal bovine colostrum.³⁶

Conclusion

This systematic review highlights the significant importance of using bovine colostrum as a nutraceutical to improve cognitive function as it shows anti-inflammatory, antioxidant and anti-ageing properties because it reduces senescent cells.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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