Aging is a consequence of the dysfunction and impairment of many different mechanisms in the body (71). It is a complex process that involves a wide range of brain changes, beginning on the molecular level to ending on the functional level, with clear genetic and biophysical links (18, 72). Aging has a strong impact on a number of genes and biological pathways that are also linked with neurodegenerative diseases (70). Glorioso et al., 2011 reported a large overrepresentation of genes related to brain aging (27). Age-related genes include genes encoding neuropeptides (SSZNPY, CCK, CRF), trophic factors (BDNF, IGF1, FGF), receptors (HTR2A, DRD1, CB1R, GABRAA5, FGF2R), and numerous other disease-related genes, including those related to neurodegenerative diseases (MAOB, PER3, CLU, SYN, HTT, NRG1, RLN, TAU, PARK, PINK1, NFKB, SOD2, RGS4) (27). As we age, the brain undergoes significant changes in structure, function, and metabolic processes, often associated with cognitive decline and behavioral changes (18, 72). During aging, the brain shows characteristic signs of impaired bioenergetics at the cellular and molecular levels, including abnormal neural network activity, impaired DNA repair mechanism, mitochondrial dysfunction, disturbed neuronal Ca$^{2+}$ homeostasis, and accumulation of inflammatory and oxidatively modified organelles (9, 71). An excessive and abnormal accumulation of aging cells in body tissues can negatively affect the regenerative capacity and promote the onset and progression of various age-related diseases (69). The brain has a higher metabolic rate than the rest of the body and consumes a large proportion of the total oxygen intake, thereby increasing the potential for the production of reactive oxygen species and subsequent oxidative stress (66). Oxidative stress mediates specific neuronal damage, including modifications to lipids, proteins, and DNA, which leads to inflammation and altered neuronal function (70). A characteristic feature of the aging process is also a disturbed homeostasis of iron (45), manifested by excessive deposits of this element in the brain, which contributes to cognitive dysfunction (85). Aging is also associated with a significant decline in immunity and persistent inflammatory responses (67). Brain aging is characterized by degradation processes at the level of cells, tissues, and organs that lead to morphological changes, such as...
The importance of diet

Current treatments for AD focus mainly on the administration of symptomatic drugs that provide little relief to patients and may cause various side effects (38). That is why preventing or delaying the onset of the disease is so important in improving the health and quality of life of older people (73). Certain nutrients help prevent the onset and development of neurological diseases, such as AD. Thus, nutritional and neurological problems are linked with each other, which could lead to the development of new treatments (76). A promising strategy could be to use an appropriate diet (28), which can eliminate the problem of side effects of medication and reduce the number of patients requiring medical care. A diet rich in fatty acids, especially monounsaturated fatty acids (MUFA) and n-3 polyunsaturated fatty acids (PUFA), may play an important role in the prevention of cognitive decline associated with aging or dementia (73). The available literature reports that some diets may limit the risk of AD (20, 73). The most appropriate model to follow seems to be the Mediterranean diet including large quantities of MUFA-rich olive oil (60, 73). The latest research by Bagalagel et al., 2022 showed that the extract from *Olea europaea* L. cv. Picual (an olive variety from Saudi Arabia) had neuroprotective and anti-amnestic effects *in vivo* against cognitive decline and brain damage in a mouse AD model (9). In addition, the Mediterranean diet is also based on the consumption of large amounts of dairy products, mainly cheese. Cheese is a dairy product made by coagulating casein, mainly from the milk of cows, goats, and sheep (39). Mixed sheep’s and goat’s milk cheeses are common in many countries. In Greece, sheep’s milk is used mainly to produce feta, which is made from sheep’s milk or a mixture of sheep’s and goat’s milk and is the most important export product (62). Other traditional Greek cheeses made from sheep’s milk include pecorino, manchego, and roquefort (62). The main sheep cheese produced in Italy is pecorino romano cheese, which is the leader in the international trade in sheep milk cheeses (62). Many biologically active substances have been found in fermented sheep’s milk products, such as yogurt and cheese (34, 66, 68, 75). Sheep’s milk and its products, which naturally contain bioactive substances, may be promising ingredients for the production of health-promoting functional food (25). Sheep’s milk contains a favorable profile of fatty acids, especially essential fatty acids (EFAs), n-6, and n-3, and the highest content of conjugated linoleic acid (CLA) isomers (53). The pro-health qualities of sheep’s milk are also evidenced by its high content of minerals, fat-soluble vitamins, and B-group vitamins (10). Sheep’s milk proteins have antioxidant, antimicrobial, antihypertensive, and antithrombotic properties that affect many physiological processes (23). Moreover,
sheep’s milk contains peptides that have a regenerating effect in neurodegenerative diseases and a number of multifunctional peptides with a comprehensive effect.

The importance of proteins

A major challenge in the treatment of AD is the very low efficacy of drugs due to the blood-brain barrier, which allows only a few types of molecules to penetrate from the circulation to the central nervous system. The solution seems to be the use of lactoferrin (LF), which penetrates the blood-brain barrier and can form micelles with other biologically active molecules and thus precisely deliver drugs to the brain. LF penetrates the brain parenchyma by absorption from the sublingual mucosa (30). LF is a multifunctional glycoprotein with high affinity for iron. LF plays a vital role in anti-inflammatory, antibacterial, and antiviral modulators of reactive oxygen species, anticancer immunity, and antiapoptotic processes (41). Because of its properties, LF can be used in AD both as an active therapeutic compound and as a drug nanocarrier (41). Research by Agwa et al., 2020 has shown that LF-CLA micelles show enhanced biodistribution in vivo in brain tissue because of the active targeting potential of LF (4). Moreover, CLA exhibited sustained release, good hemocompatibility, and no in vivo toxicity for the liver and kidneys. Additionally, LF-CLA micelles reduced oxidative stress, inflammation, and apoptosis, and increased cognitive performance in a mouse model of aluminum chloride-induced AD (4). Studies show that exogenous administration of LF reduces memory impairment and Aβ aggregation in a mouse model of AD (2) and improves cognitive performance in a model of naturally aging C57/BL6J mice (84). In addition, LF reduces the production of reactive oxygen species in the hippocampus, which is associated with the mitigation of oxidative stress and inflammatory reactions, as well as the reduction of iron deposits in brain tissues (84). Dietary LF administered to AD patients limits cognitive decline by modulating the p-Akt/PTEN pathway and thus reducing inflammation and oxidative stress that are involved in AD pathology (50). An important marker of early AD is an abnormal iron metabolism. Studies have shown that AD patients have elevated iron levels in the cerebral cortex, subcortex, and white matter of the brain (32). Sheep’s milk is richer in LF (0.7-0.9 g/L) than cow’s milk (0.02-0.5 g/L) (51). LF may be useful in treating brain pathologies related to iron accumulation because of its anti-inflammatory and antioxidant properties and its ability to bind and modulate iron (32). These protective effects of LF may represent promising targets for the prophylaxis and therapy of AD in the future (50). Milk protein comprises approximately 80% of caseins and 20% of whey proteins (8). Whey protein is a by-product of the production of cheese and other dairy products. Whey protein consists of, among others, β-lactoglobulin, α-lactalbumin, immunoglobulins, serum, glycomacropeptides, and smaller proteins, such as lactoperoxidase, lysozyme, and LF (8). Importantly, sheep’s milk is the richest source of whey protein (1.02 g/100 g) (17). Recent studies have shown that a short-term administration of whey protein hydrolysate to mice with scopolamine-induced amnesia resulted in a significant improvement in their memory and neuronal protection by reducing the aggregation of Aβ plaques (19). Whey proteins contain bioactive compounds that can reduce oxidative stress on the brain and restore normal cognitive function. Research by El-Beeh et al., 2022 showed that the administration of whey protein syrup to older Wistar albino rats (Rattus norvegicus) caused, among others, increased antioxidant activity while reducing Aβ deposits in brain tissue (22). Peptides in fermented milk products may also remedy memory disorders. Ano et al., 2019 identified the peptide KEMPFPKYPVEP from β-Casein present in fermented milk products. Studies have shown that administration of that peptide prevents cognitive decline in a mouse model of scopolamine-induced amnesia (7). The level of KEMPFPKYPVEP in Roquefort cheese made from sheep’s milk (11.6 pmol/g) is higher than it is in cow cheddar cheese (1.52 pmol/g) (7).

PD is the second most common neurodegenerative disorder (80). It is characterized by, among others, increased oxidative stress and progressive loss of dopaminergic neurons derived from the substantia nigra pars compacta (35). Research by Ubaid et al., 2020 on a cellular model of PD induced by rotenone PC12 showed that a complex of camel α-lactalbumin and oleic acid (CLOA) may be a candidate for the development of future therapeutic drugs for PD (80). Moreover, treatment with the CLOA complex reduced oxidative stress and increased cell viability by increasing dopamine levels and the expression of SIRT1, FOXO3a, HIF-1α, and HSFI (80). Sheep’s milk contains more α-lactalbumin (1.2-2.6 g/L) than cow’s milk does (1.5 g/L) (51) and may therefore be another good alternative as a nutraceutical supplement for the neurological functions of older adults in the PD risk group.

Importance of fatty acids

The fatty acids in milk have a number of biological effects and health benefits. A characteristic feature of ruminant milk fat is the presence of CLA, which is a mixture of positional and geometric isomers of octadecadienoic acid C18:2. CLA has a broad health-promoting effect on the body and can prevent the occurrence of type 2 diabetes, AD, and cancer (24). Research by Kawecka and Pasternak in 2021 showed that bundz (traditional Polish fresh cheese) made from sheep’s milk had a higher content of fat (24.92%) and protein (18.06%) than bundz made from goat’s milk (21.33% fat; 16.74% protein) (33). Moreover, the content of CLA was also significantly higher (2.23%) in
traditional sheep cheese than in goat cheese (0.28%) (33). Sztker et al., 2022 also studied the amount and profile of fatty acids in various original sheep, cow, and goat cheeses (75). Studies showed that Polish seasonal sheep cheeses (oscypek) were characterized by the highest content of health-promoting fatty acids: CLA 2.1-3.1%, trans-MUFA 3.5-6%, branched chain fatty acids (BCFA) 2.7-2.9%, and short-chain fatty acids (SCSFA) 12-18% (75). CLA reduces pathological changes due to AD in a mouse model of this disease by Nrf2-mediated adaptive upregulation and upregulation of the brain glucose transporter (15). Sheep’s milk is rich in CLA (53), and particularly important isomers are t-10, c-12-CLA, and c-9, t-11-CLA. In sheep’s milk yoghurts, the content of the c-9, t-11-CLA isomer is higher (0.47-0.76 g/100 g of fat) than it is in cow’s milk yoghurts (0.24-0.45 g/100 g of fat) (68). Moreover, research by Serafeimidou et al., 2013 showed that during a 14-day storage of products at 5°C, the CLA content in sheep’s milk yoghurts significantly increased, while in cow’s milk yoghurts it significantly decreased (68). Recent studies show that c-9, t-11-CLA may also prevent neurodegenerative diseases in the elderly because of its role in protecting neurons from the damaging effects of Aβ (29). However, in the same mouse model study, treatment with t-10, c-12-CLA had no effect on Aβ production (29). The role of c-9, t-11-CLA was also confirmed by Fujita et al., 2021 whose research on a mouse model of AD showed that the presence of c-9, t-11-CLA in the diet reduced inflammation as well as the amount of Aβ aggregates in brain tissues (26).

Importance of vitamins and antioxidants

Sheep’s milk is an excellent source of B vitamins, which ensure the proper functioning of the nervous system (25). Vitamins from this group, and in particular vitamins B1 (thiamine), B6 (pyridoxine) and B12 (cobalamin), increase the speed of nerve conduction because they are involved in the synthesis of myelin, and their deficiencies can lead to the development of many neurodegenerative diseases (16). Recent research shows that increasing the daily intake of B vitamins in regular meals can help minimize the risk of dementia (54). The content of B vitamins in sheep’s milk, amounting to 650-800 µg/l for vitamin B1 (thiamine), 600-800 µg/l for vitamin B6 (pyridoxine), and 6-7.1 µg/l for vitamin B12 (cobalamin), is much higher than it is in cow’s milk (B1: 300-450 µg/l, B6: 390-600 µg/l, B12: 3.5-4.0 µg/l) or human milk (B1: 140-200 µg/l, B6: 100-110 µg/l, B12: 0.1-0.5 µg/l) (51). Decline in the levels of vitamin B1 is related to age and strongly correlates with the deterioration of cognitive functions, and its supplementation may have positive effects on the treatment of AD and other neurodegenerative diseases (64, 82). Research by Ramamoorthy et al., 2022 showed that expression levels of thiamine transporters (THTR-1 and THTR-2) are significantly downregulated in the brain of AD patients and in an animal model of AD (65). Moreover, their findings implicate neuritis in the dysfunction of thiamine transporters and suggest a beneficial effect of optimizing thiamine levels in brain tissues of AD patients, which can be achieved by administering pharmacological doses of B1 (65). Dietary vitamin B6 restriction plays a functional role in neuronal degeneration by disturbing the gamma-aminobutyric acid (GABA) balance, increasing oxidative stress and endoplasmic reticulum stress, and inducing Aβ accumulation and tau protein deposition (36). Research by Xu et al., 2022 showed that an adequate dietary intake of vitamins B9 and B12 is significantly associated with better cognitive performance in older adults (83). The team of Rampazzo et al., 2022 analyzed the vitamin B12 content of different types of ripened cheeses made from cow’s, sheep’s, and goat’s milks (66). This study showed that the concentration of vitamin B12 in sheep cheese (29.0 ng/g on average) was higher than it was in goat cheese (12.5 ng/g on average) or cow cheese (6.5 ng/g on average) (66).

An advantage of sheep’s milk over cow’s milk is its higher content of vitamin D (0.2 µg/100 g vs. 0.15 µg/100 g) (55). Vitamin D may reduce AD symptoms by modulating Aβ pathology. Research by Kang et al., 2022 showed that vitamin D deficiency caused memory impairment and an increase in the amount of Aβ aggregates in the brain of 5xFAD mice (33). In contrast, vitamin D supplementation improved memory function by alleviating amyloidopathies and gliopathy (33). In another study, long-term vitamin D3 supplementation alleviated cognitive impairment and cortical pathology in APP/PS1 transgenic mice (42). The neuroprotective properties of vitamin D3 have been associated with the inhibition of oxidative stress by activating the PI3K/AKT/Nrf2 pathway (42). Studies show that vitamin D3 supplementation can be proposed as a both preventive and therapeutic supplement in high-risk AD patients (11). A common comorbidity of AD is osteoporosis, in which patients show reduced bone mineralization and have a higher risk of bone fractures (46). Studies by Lines, et al., 2021 suggest that the dysfunction of the astrocyte network in mice with advanced AD may disturb the electrical activity of the cerebral cortex and contribute to cognitive decline (43). Moreover, according to Tsai et al., 2022, astrocyte dysfunction promotes calcium ion imbalance in vivo, leading to osteoporosis (78). Calcium ions released into the blood can cause ectopic calcifications in the pineal gland, which further promotes the development of AD. Studies on the effect of AD on bone quality have shown a lower volumetric bone mineral density in 5xFAD transgenic mice compared to control mice (46). Physical activity and proper nutrition, including an adequate intake of vitamin D and calcium, are highly recommended for osteoporosis prevention and early intervention (14). Sheep’s milk
contains more calcium (197.5 mg/100 g of milk) than goat’s milk (130 mg/100 g of milk) or cow’s milk does (112 mg/100 g of milk) (55). Moreover, pecorino cheese also contains a large amount of calcium (almost 1%) in a highly bioavailable organic form (49). As little as 30 grams of pecorino can meet nearly 30% of the daily requirement of an adult woman for calcium (49).

Conclusions

There is ample evidence that the consumption of fermented milk products can prevent neurodegenerative diseases, especially AD in the elderly (5, 6, 57, 58). Studies (58, 59) conducted in a group of over 1,000 Japanese people aged 60-79 showed that the introduction of milk or fermented milk products, such as yogurt, kefir, or buttermilk, into the diet reduces the risk of dementia in the general Japanese population. Another clinical study showed that AD patients with cognitive deficits who consumed kefir for 90 days showed marked improvements in memory, executive/language function, and visuospatial/abstract abilities (77). Moreover, kefir consumption had a reparative effect on systemic inflammation (by reducing pro-inflammatory cytokines) and systemic oxidative stress (77). Therefore, in the era of functional foods, sheep’s milk and its products may play an important role as a promising therapy, providing benefits to human health (52). Previous studies on the health-promoting properties of dairy products and their effect on neurodegenerative diseases and the aging process focused mainly on cow’s milk. The evidence presented here suggests that sheep’s milk and its products may also be valuable in the study of AD and the related aging process. Nevertheless, further research is warranted to use the available information for future clinical trial design.

**References**


**Table 1. The amount of selected nutrients in sheep’s milk and in other products of animal and non-animal origin (3, 37, 40, 47, 51, 55, 63, 81)**

<table>
<thead>
<tr>
<th>Bioactive substance</th>
<th>Foods</th>
<th>Sheep’s milk (51, 55)</th>
<th>Cow’s milk (51, 55)</th>
<th>Pork (81)</th>
<th>Chicken (81)</th>
<th>Salmon (47, 40)</th>
<th>Red tomato (63)</th>
<th>Spinach (63)</th>
<th>Sweet potato (37)</th>
<th>Apple juice (3, 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.7-0.9 g/L</td>
<td>0.02-0.5 g/L</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Lactoferrin</td>
<td></td>
<td>1.2-2.6 g/L</td>
<td>1-1.5 g/L</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>α-lactalbumin</td>
<td></td>
<td>300-450 µg/L</td>
<td>90-180 µg/L</td>
<td>0.98 mg/100 g</td>
<td>0.14 mg/100 g</td>
<td>0.037 mg/100 g</td>
<td>0.078 mg/100 g</td>
<td>0.156 mg</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Vitamin B1 (thiamine)</td>
<td></td>
<td>600-800 µg/L</td>
<td>390-600 µg/L</td>
<td>0.54 mg/100 g</td>
<td>0.38 mg/100 g</td>
<td>0.046 mg/100 g</td>
<td>0.08 mg</td>
<td>0.195 mg</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Vitamin B6 (pyridoxine)</td>
<td></td>
<td>6-7.1 µg/L</td>
<td>3.5-4.0 µg/L</td>
<td>1 µg/100 g</td>
<td>Trace amounts</td>
<td>0.0028 mg/100 g</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Vitamin B12 (cobalamin)</td>
<td></td>
<td>0.2 µg/100 g</td>
<td>0.15 µg/100 g</td>
<td>0.5 µg/100 g</td>
<td>0.1 µg/100 g</td>
<td>2.56 µg/100 g</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Calcium</td>
<td></td>
<td>197.5 mg/100 g</td>
<td>112 mg/100 g</td>
<td>7 mg/100 g</td>
<td>6 mg/100 g</td>
<td>–</td>
<td>10 mg</td>
<td>99 mg</td>
<td>37 mg</td>
<td>2.95 mg/L</td>
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