Journal of Animal and Feed Sciences, 31, 3, 2022, 211–216 https://doi.org/10.22358/jafs/151020/2022
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The role of sheep's milk bioactive substances in the prevention of metabolic and viral diseases

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KEY WORDS: bioactive components, COVID-19, milk, sheep

Received: 26 April 2022
Revised: 8 June 2022
Accepted: 14 June 2022

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ABSTRACT. Sheep's milk exerts a number of biological effects that influence metabolic reactions and disease resistance. Sheep's milk contains the highest level of casein, whey protein and conjugated linoleic acid isomers (CLA), which stimulate the immune system, and have "anti-obesity", "antidiabetic" and "anticancer" properties. Sheep's milk is an excellent source of protein and group B vitamins, which ensure the proper functioning of the nervous system. Proline-rich polypeptide partially reverses neurodegenerative changes and has immunoregulatory and pro-cognitive properties. CLA isomers also reduce oxidative stress and mitochondrial dysfunction in the brain, which may be important in neurodegenerative diseases such as Alzheimer's disease. Sheep's milk shows the highest inhibitory activity of angiotensin converting enzyme, which is crucial in preventing SARS-CoV-2 infection. Systemic inflammation is a common factor in atherosclerosis and COVID-19. Polar lipids present in sheep's milk lower inflammatory biomarkers and reduce the development of atherosclerosis. Therefore, dairy products can be used to help prevent COVID-19 disease. Sheep's milk and its products containing bioactive substances may be promising ingredients for the production of health-promoting functional foods.

Introduction

The high content of valuable nutrients and biologically active substances in sheep's milk affects the dietary qualities of this beverage and its products. In times of widely developing civilization diseases, malignancies and the COVID-19 pandemic, it is very important to support the body with natural products with special, bioactive properties. Ruminant milk is an important source of protein in the human diet. The demand for healthy food has increased significantly over the last decade and milk has attracted consumer interest. Due to its profile of bioactive substances, sheep's milk has many health-promoting properties for the body (Flis and Molik, 2021). One of the main sources of bioactive ingredients in sheep's milk are proteins (Vargas-Bello-Pérez et al., 2019). Sheep's milk is an important source of peptides inhibiting angiotensin-converting enzyme (ACE), as well as "antihypertensive" peptides. Proteins such as immunoglobulins, lactoferrin and lysozyme exhibit "antibacterial", "antioxidant", "anticancer" and "anti-inflammatory" effects (Moatsou and Sakkas, 2019; Flis and Molik, 2021), while proline shows neuroprotective properties (Yenkoyan et al., 2018). Sheep's milk also contains a high content of B vitamins, which are responsible for the proper functioning of the nervous system. The bioactive peptides of sheep's milk also regulate insulin metabolism, and therefore exert an "antidiabetic"

effect (Jan et al., 2016). In terms of fatty acid composition, sheep's milk is superior to cow's milk, showing a higher content of omega-3 and omega-6 fatty acids (Flis and Molik, 2021). These compounds reduce the synthesis of triglycerides and cholesterol. Additionally, they play a protective role against neurodegenerative disorders, such as Alzheimer's disease (Flis and Molik, 2021). The content of conjugated linoleic acid (CLA), polar lipids (PL) and fat-soluble vitamins (vitamins A and D) is higher and more nutritionally beneficial in sheep's milk than in cow's counterpart (Moatsou and Sakkas, 2019). CLA isomers contained in sheep's milk have positive effects on human health, as they show "anti-cancer" properties, lower triglyceride concentration and reduced blood cholesterol and glucose levels (Basak and Duttaroy, 2020). CLA isomers can also regulate the functions of the immune system (Santurino et al., 2020). The *cis*-9, *trans*-11 CLA and *trans*-10, *cis*-12 CLA isomers affect specific T cell populations and immunoglobulin subclasses. The crucial component of ruminant milk is orotic acid, which is of key importance in preventing cardiovascular diseases through its "anti-atherosclerotic" effect (Czauderna et al., 2021). High inflammation in the body caused by COVID-19 disease negatively affects the cardiovascular system (Kaye et al., 2021). Milk fat is rich in PL, such as sphingomyelin, phosphatidylcholine, and phosphatidylethanolamine (Moatsou and Sakkas, 2019; Lordan et al., 2020; Millar et al., 2020). *In vitro* and *in vivo* studies have shown that PL shows "anti-inflammatory" and "antithrombotic" properties (Tsorotioti et al., 2014). This is of particular importance in the prevention and treatment of atherosclerosis and protection against more severe course of coronavirus disease (COVID-19) in patients with comorbidities.

The studies presented in this review highlight the nutritional function of sheep's milk in the human diet and the possible role of its consumption in the prevention of many chronic conditions such as cardiovascular (CVD) and neurodegenerative diseases, cancer, obesity, diabetes and COVID-19.

Metabolic changes

Amino acids and bioactive peptides found in sheep's milk exhibit many beneficial biological properties, including stimulation of insulin secretion (Flis and Molik, 2021). Milk peptides inhibit dipeptidyl peptidase 4 (DPP-4), an enzyme that plays an important role in the development of type 2 diabetes. Consumption of dairy products inhibits DPP-4, and thus stimulates insulin secretion, which may have a beneficial effect in individuals with impaired secretion of this hormone (Vargas-Bello-Pérez et al., 2019). Therefore, reducing or inhibiting the activity of DPP-4 and α-glucosidase is one of the important strategies in the treatment of type 2 diabetes. Sheep's milk peptides were shown to inhibit α-glucosidase and DPP-4 (Jan et al., 2016). Products obtained by hydrolysis of lactoferrin from milk are capable of inhibiting the DPP-4 enzyme, and as reported by Caboni et al. (2019), sheep's milk is the richest in lactoferrin. This suggests that sheep's milk may have a DPP-4 inhibitory effect, and thus potentially improve blood glucose regulation. Casein hydrolysates from milk may also be used as food ingredients that reduce insulin resistance. A study by Jan et al. (2016) demonstrated that of the three enzyme hydrolysates (trypsin, pepsin and chymotrypsin), chymotrypsin-treated casein had the highest "antidiabetic" activity. Moreover, the "antidiabetic" effect of hydrolysed casein from raw sheep's milk exceeds that of cooked milk (Jan et al., 2016).

The feeling of satiety is a key factor in obesity prevention. Satiety is caused by the release of anorectic substances, which include cholecystokinin (CCK) (Neelima et al., 2013). CCK secretion is caused by glycomacropeptide (GMP), which is released during the cheese making process. As reported by Neelima et al. (2013), GMP accounts for approximately 20–25% of all proteins found in whey products. Sheep's milk is the richest source of whey protein (1.02 g/100 g) (Dario et al., 2008), therefore, consuming sheep's milk as a natural source of GMP can be used to control food intake and increase satiety, thereby reducing obesity. CLA isomers modulate adipose tissue deposition, making it a very important factor in the prevention and control of obesity. A study by Dahiya and Puniya (2018) in mice with diet-induced obesity showed that supplementation with CLA-enriched skim milk exerted "anti-obesity" effects. Sheep's milk has the highest concentration of CLA isomers compared to the milk of other ruminants (Molik et al., 2020). Due to the highest content of CLA isomers in sheep's milk and its products, they can be used as food ingredients supporting weight control and preventing obesity. Overweight and obesity are now recognised risk factors for cancer and cancer-related mortality (Basak and Duttaroy, 2020; Santurino et al., 2020).

Importance in the prevention and treatment of oncological diseases

A diet rich in CLA isomers, most of which are found in sheep's milk (Molik et al., 2020), may prevent cancer. The *trans*(t)-10, *cis*(c)-12-CLA isomer exerts "antitumour", "anti-obesity" and "antidiabetic" effects, while c-9, t-11-CLA has mainly "antitumour" properties. Therefore, consuming CLA supplements may play a role in inhibiting the growth and development of cancer cells. The c-9, t-11-CLA isomer mediates "anticarcinogenic" effects through apoptosis. On the other hand, the t-10, c-12-CLA isomer was shown to inhibit the growth of colon cancer cells and induce their death (Basak and Duttaroy, 2020). Additionally, casein and whey proteins and their hydrolysates were demonstrated to provide protection against colorectal cancer (Quigley, 2022). For the aforementioned reasons, sheep's milk, as the richest source of casein and whey protein (Dario et al., 2008), seems to be an appropriate product for application in colorectal cancer prevention. A study by Oguz et al. (2020) proved that proline derivatives (calixarene l-proline) showed a selective cytotoxic potential against DLD-1 human colorectal cancer cells and A549 lung cancer cells.

Immune stimulation

The most common comorbidities in COVID-19 patients, include hypertension, diabetes and cardiovascular disease (Djaharuddin et al., 2021). COVID-19 has been shown to be associated with high inflammation in the body, which has a negative impact on the cardiovascular system (Kaye et al., 2021). Therefore, people with cardiovascular diseases may be more exposed to hospitalisation and the disease may be significantly more severe. Systemic inflammation is a common factor in the course of atherosclerosis and COVID-19. This may exacerbate COVID-19 disease in patients with atherosclerosis, resulting in an increased number of cytokine-secreting immune cells. Polar lipids in dairy products, including sheep's milk, lower the levels of inflammation biomarkers and reduce atherosclerosis development (Millar et al., 2020). Therefore, sheep's milk products can be used to help prevent severe COVID-19 disease in high-risk individuals. The outbreak of the pandemic triggered a series of intensive studies on the identification and mechanism of action of the SARS-CoV-2 coronavirus. SARS-CoV-2 has been shown to bind to angiotensin-converting enzyme 2 (ACE2) in the lungs and later enter other tissues of the body (Sun et al., 2020). The renin-angiotensin-aldosterone system plays a key role in regulating the body's water and electrolyte balance (Sun et al., 2020). Stimulation of this system causes vasoconstriction and an increase in the reabsorption of sodium ions in nephrons, leading to an increase in blood pressure (Sun et al., 2020). According to Schiffrin et al. (2020), ACE inhibitors and angiotensin receptor blockers could reduce the risk of developing acute respiratory distress syndrome, myocarditis, or acute kidney injury that might occur in patients with COVID-19. The bioactive components of sheep's milk have the ability to inhibit ACE (Vargas-Bello-Pérez et al., 2019). Hence, products made from sheep's milk may potentially play a key role in preventing or recovering from COVID-19 disease. CLA isomers can also regulate the functions of the immune system. The *cis*-9, *trans*-11 CLA and *trans*-10, *cis*-12 CLA isomers can affect specific T cell populations and immunoglobulin subclasses (Santurino et al., 2020). Bioactive whey peptides contained in milk were shown to reduce autoimmune inflammatory processes and exert a protective effect against bacterial and viral infections (Flis and Molik, 2021). Among whey proteins, lactoferrin and lysozyme show the highest "antimicrobial" activity (Dario et al., 2008). Sheep's milk has a high content of proline, which is involved in the synthesis of haemoglobin (Flis and Molik, 2021) and has "antibacterial" properties. The proline-rich "antimicrobial" peptide Api137 exerted a bactericidal effect in porcine blood infected *ex vivo* with porcine or human *Klebsiella pneumonia* strains (Krieger et al., 2021). In human nutrition, milk and dairy products are the primary sources of fat-soluble vitamins. This group includes vitamin D, which improves the immune response against bacteria, fungi, parasites and viruses (Gilani et al., 2022). The outbreak of the SARS-CoV-2 coronavirus pandemic highlighted the role of vitamin D and its content in food products. Vitamin D content in sheep's milk is 0.18–0.2 μm/100 g (Moatsou and Sakkas, 2019). The risk of COVID-19 infection is associated with vitamin D deficiency. Vitamin D inhibits the cytokine storm and inflammatory processes associated with COVID-19 disease (Gilani et al., 2022), while in macrophages, it promotes the production of "antimicrobial" and "antiviral" proteins such as β-defensin 2 and cathelicidin that inhibit viral replication and promote its removal from cells by autophagy (Gilani et al., 2022). All these factors reduce the severity of the disease and shorten the

hospitalisation period. Consuming dairy products rich in vitamin D may have a preventive effect, and may be a promising treatment for COVID-19.

Importance in the prevention of heart and circulatory system diseases

Consumption of dairy products, due to their rich content of bioactive peptides, reduces the risk of metabolic syndrome and its components, such as hyperglycaemia, low high-density lipoprotein (HDL) cholesterol level or elevated blood pressure. Biologically active milk peptides, including sheep whey protein, lower blood pressure by inhibiting ACE (Vargas-Bello-Pérez et al., 2019). Studies have shown that sheep's milk has the highest ACE inhibitory activity after digestion (Tagliazucchi et al., 2018). In patients at increased risk of cardiovascular disease, consumption of naturally enriched cheese with n-3 and CLA isomers was shown to significantly improve plasma lipid profile and regulate inflammation by increasing HDL levels and decreasing blood c-reactive protein levels (Santurino et al., 2020). Due to the content of PL, sheep's milk and its products may be effective in preventing CVD. The phospholipid fraction of sheep's milk is extremely important for its "anticoagulant" properties. Administration of 2% PL milk to LDLr $^{-/-}$ mice fed a diet rich in milk fat reduced inflammation marker levels and atherogenic lipoprotein cholesterol concentration and limited the development of atherosclerosis (Millar et al., 2020). Atherosclerosis is the leading cause of CVD resulting from systemic inflammation. The lipid mediator platelet activating factor (PAF) and PAF-like lipids, which act by binding to a unique G-protein coupled receptor known as the PAF receptor, are particularly involved in the pro-inflammatory development of atherosclerosis (Megalemou and Siorika, 2017). A study by Megalemou and Siorika (2017) found that the most active inhibitors of PAF were present in yogurt made from sheep's milk. Vitamin K also belongs to the group of fat-soluble vitamins. Sources of vitamin K2 are mainly dairy products, but also egg yolks and meat. A study by Haugsgjerd et al. (2020) revealed that a higher intake of vitamin K2 was associated with a lower risk of coronary heart disease. Whole sheep's milk contains approximately 17.4 ng/g vitamin K2, while cow's milk has about 8.60 ng/g (Yasin et al., 2017). Thus, eating cheese and other sheep's milk products with a naturally higher vitamin K2 content may have a preventive effect, but may also be used in therapy against cardiovascular disease. Orotic acid is another bioactive component of milk that improves the condition of the heart muscle, and its main source is ruminant milk (Czauderna et al., 2021). Sheep's milk contains more orotic acid (20–400 mg/ml) than human milk (less than 2 mg/l) (Aguilar et al., 2009). A diet rich in orotic acid may be important for patients at increased risk of lifestyle-related cardiovascular disorders (Czauderna et al., 2021). This acid and its magnesium salt (magnesium orotate) increase the energy state of the muscle after a heart attack. In addition, magnesium orotate increases exercise tolerance in people with coronary artery disease (Aguilar et al., 2009). Orotic acid stimulates the production of erythrocytes and thrombocytes, thereby protecting the body against ischemic stress. In addition, it shows beneficial effects in cardiomyopathy and delays the symptoms of aging. It can also increase heart contractility and prevent the build-up of cholesterol plaques in blood vessels (Czauderna et al., 2021).

Influence on the functioning of the nervous system

Proline-rich dairy products also protect against amyloidogenic diseases, including Alzheimer's disease. In a rat model of Alzheimer's disease, intramuscular injection of proline-rich polypeptide (PRP) caused a partial reversal of neurodegenerative changes (Yenkoyan et al., 2018). The beneficial effects of the PRP complex are due to its immunoregulatory and pro-cognitive properties. CLA isomers were demonstrated to reduce oxidative stress and mitochondrial dysfunction in the brain, which could be important in many neurodegenerative diseases (Aydın et al., 2021). A study by Aydın et al. (2021) in rats revealed that CLA isomers protected brain cells against toxic effects of acrolein. Sheep's milk is a rich source of orotic acid (Flis and Molik, 2021), which acts as a precursor in the pyrimidine nucleotide biosynthesis pathway. Sheep's milk is an excellent source of group B vitamins (Moatsou and Sakkas, 2019), which ensure the proper functioning of the nervous system. B-group vitamin deficiencies can lead to the development of many neurological diseases such as epilepsy, Parkinson's disease or Alzheimer's disease. Vitamins B1 (thiamine), B6 (pyridoxine) and B12 (cobalamin) in particular contribute to the maintenance of a healthy nervous system. The content of these vitamins in sheep's milk is much higher than in cow's or human

milk and amounts to: vitamin B1 – 650–800 μg/l, vitamin B6 – 600–800 μg/l and vitamin B12 – 6–7.1 μg/l (Moatsou and Sakkas, 2019). Vitamin B1 plays a key role in the nerve regeneration process. A recent study by Qian et al. (2022) showed that supplementation with vitamin B1 or its analogues could have a beneficial effect in preventing cognitive decline in patients with Alzheimer's disease. Group B vitamins contribute to the increased nerve conduction velocity because they are involved in the synthesis of myelin, which plays an important role in the pathology of Alzheimer's disease.

Conclusions

Sheep's milk is an excellent source of well-balanced nutrients. It also displays a range of biological activities that influence metabolic reactions and disease resistance. This is evidenced by the content of biologically active ingredients, a favourable profile of fatty acids, especially EFA, n-6 and n-3, and the highest content of CLA isomers. The high content of fat-soluble vitamins, B vitamins and orotic acid in sheep's milk also proves its high health-promoting values. Sheep's milk proteins and bioactive peptides influence many physiological processes, and therefore can help prevent many types of cancer and cardiovascular diseases. A number of naturally formed bioactive compounds have been found in fermented dairy products such as yogurt and cheese. In addition, milk processing, especially the fermentation process, enhances the "anticoagulant" properties of PL of sheep's milk. Due to the wide range of proposed human health benefits, sheep's milk and its products may be promising ingredients for the production of health-promoting functional foods. Peptides and other active milk components have the potential to be used in the creation of health-enhancing nutraceuticals and as potent drugs with well-defined pharmacological effects.

Conflict of interest

The Authors declare that there is no conflict of interest.

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