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SHEEP'S MILK CHEESES AS A SOURCE OF BIOACTIVE COMPOUNDS

– Review –

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Abstract: Since ancient times, sheep`s milk cheeses have been a part of a human diet. Currently, their consumption is of great interest due to its nutritional and health values. The aim of the article was to review the chemical composition of sheep's milk cheeses and its main bioactive ingredients in the context of nutritional and health values. Sheep's milk cheeses are rich in functionally and physiologically active compounds such as: vitamins, minerals, fatty acids, terpenes, sialic acid, orotic acid and L-carnitine, which are largely originate from milk. Fermentation and maturation process additionally enrich them in other bioactive substances as: bioactive peptides, γ-aminobutyric acid (GABA) or biogenic amines. Studies show that sheep's milk cheese consumption may be helpful in the prevention of civilization diseases, i.e. hypertension, obesity or cancer. However, due to the presence of biogenic amines, people with metabolic disorders should be careful of their intake.

Keywords: biogenic amines, bioactive peptides, CLA, GABA, rumenic acid

INTRODUCTION

Cheeses are one of the oldest forms of food in the world. Their production is a natural way of preserving milk. At the same time, thanks to the activity of many beneficial microorganisms, products with an increased or modified nutritional value with the desired sensory characteristics are obtained, thereby increasing the diversity of food.

The start of cheese production is connected to taming of domestic animals, mainly sheep and goats. It is believed that the first cheeses were produced in the Middle East around 10,000 years ago in the Neolithic period (Walther et al., 2008). However, the oldest known evidence for the cheese production comes from about 5,500 BC, from today's Kujawy region, Poland (Salque et al., 2013). Despite the long world tradition of obtaining milk from sheep, cow's milk and dairy food produced of it dominate the world. Regarding to cheese, in 2018 (no newer data available) the world production of sheep's milk cheese was 726,421 tons, which constitute only ~4% of cow`s milk cheese production (FAOSTAT, 2021). This is mainly the results from the marginal world production of sheep's milk as well as its regional significance. It is also related to the seasonality of ewe's milking and their relatively small individual milk yield (Ptasińska-Marcinkiewicz, 2014).

As statistics show, the highest cheese consumption is currently in Europe, North America and Oceania. In 2018-2020, the average cheese consumption (expressed in kg per capita) for European Union was 20.9, United States 17.4, Canada 13.7, Australia 12.5, while for the continents of Africa and Asia it was only 0.7 and 0.6, respectively (OECD/FAO, 2021). Nevertheless, these data apply to all types of cheeses. There are no statistics available on the consumption of sheep's milk cheeses only. However, taking into account the sheep's milk cheeses supply quantity in 2018 (no newer data available), only in Greece it reached 36 grams per capita per day, while in other countries included in the database, it was only 0-5 grams per capita per day (FAOSTAT, 2021). The same statistics for cow's milk cheeses have higher and more varied values (0-96 g/capita/day), so it can be assumed that sheep's milk cheeses consumption is relatively low. It may be related to their availability (seasonality, distribution) and prices. Sheep's milk cheeses are often traditional, artisanal cheeses, and many of them are legally protected with a certificate of authenticity. The awareness of today's consumers (mainly from developed countries) about nutrition

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and its impact on health, increases the demand for good quality "healthy foods" (Balthazar et al. 2017). Sheep's milk cheeses, due to their properties, could fill this request.

As the composition and role of the individual components of sheep's milk cheeses were exploring, it was noted that some of them, in addition to nutrition of the human body, may have effects on its functioning (both, positive and negative). They are called bioactive compounds. According to Biesalski et al. (2009), these are „essential and non-essential compounds that occur in nature, are part of the food chain, and can be shown to have an effect on human health". The sheep's milk is naturally rich in bioactive substances such as: vitamins, minerals, orotic acid, L-carnitine and a favourable profile of fatty acids. Nevertheless, some of substances are lost along with the whey during cheesemaking (Robinson and Tamime, 1996). The cheeses are also enriched with biologically active substances in the process of fermentation and maturation, by the breakdown of the main milk components – fats and proteins (Walther et al., 2008).

The aim of the article is to review the chemical composition of sheep's milk cheeses and its main bioactive ingredients in the context of nutritional and health values.

BIOACTIVE COMPOUNDS IN SHEEP'S MILK CHEESES

Figure 1 presents the bioactive compounds from sheep's milk cheeses described in this article.

Minerals and vitamins

There are about twenty minerals (macro- and microelements) considered as essential for human. They play the structural, biochemical and nutritional functions in human body, so their adequate intake is necessary for optimal mental and physical health (Zamberlin et al., 2012).

The concentration of minerals in cheeses depend on the raw material (which is affected by sheep breed, the stage of lactation, environmental conditions, pasture type, soil contamination), cheese manufacturing (type of process, contaminations from equipment) and ripening (possible migration of minerals in cheese layers) (González-Martín et al., 2011). Also the type of rennet could affect the mineral content of cheese – animal rennet retains more zinc and phosphorus in cheese (Sanjuán et al. 1998).

Borys et al. (2006), conducted a research on the content of some minerals in sheep's milk and the degree of their retention in different types of cheeses made from it. They showed that sheep's milk cheeses are richer in calcium, phosphorus and magnesium than cow's milk cheeses. This is due to the fact that these minerals in sheep's milk are associated with casein micelles fraction forming the cheese curd. However, a part of them may also be present in a soluble, free form in milk. For this reason, cheeses contain several times more calcium and phosphorus than milk (fresh cheeses 4-5x, semihard cheeses 7-8x, hard cheeses 10x) (Chia et al., 2017). Optimal calcium, phosphorus and magnesium macroelements intake are important to prevent cardiovascular disease, osteoporosis, hypertension, insulin resistance and type 2 diabetes occurrence (Malara et al., 2017). In addition, it may prevent the formation of tooth decay (Rashidinejad et al., 2017).

Minerals such as sodium, potassium and chlorine are almost completely soluble in milk and are lost along the whey during cheesemaking (Chia et al., 2017). Nevertheless, cheeses can be a good source of these minerals due to the addition of salt. In European Union countries, cheese contribute around 10% of salt intake. Sodium is an essential for normal cell function, however, its high intake could contribute to high blood pressure and consequently increase the risk of cardiovascular and kidney diseases (European Commission, 2012). For this reason, it is recommended to limit its consumption. Cheeses with reduced sodium content is develop by decreasing NaCl levels or its substitution of with KCl, $MgCl_2$ and $CaCl_2$ (Cruz et al., 2011).

The consumption of sheep's milk cheeses complements the body's need for fat-soluble vitamins, mainly A (retinol) and E (α-tocopherol). Their amount depends on their content in milk (which is mostly related with the sheep's diet, but also farm practices or mastitis) and the cheesemaking process (Milewski et al., 2016; Rashidinejad et al., 2017). In addition, along with the time of cheese ripening their amount may decrease (Revilla et al., 2014; Gutiérrez-Peña et al., 2021). In regard to water-soluble vitamins, e.g. riboflavin (B_2), niacin (B_{12}) or folate, their content in cheeses is lower than in milk. However, some B vitamins can be synthesized by microorganisms during the cheese ripening, which compensates for their loss during the cheese-making process (López-Expósito et al., 2017).

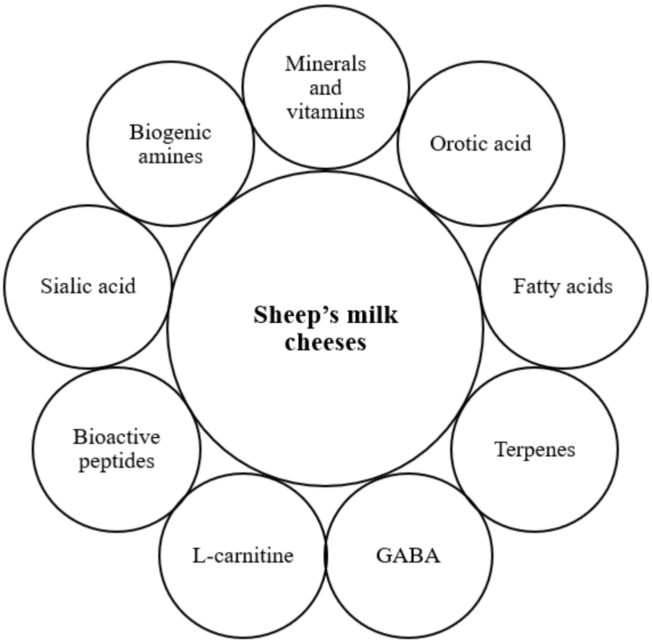

Figure 1. Schematic presentation of bioactive compounds from sheep's milk cheeses described in the article

According to Milewski et al. (2016) hard ripened rennet cheeses from sheep's milk, originating in Warmia-Masuria region in Poland, contain 2.6 µg/g of vitamin A and 2.41 µg/g of vitamin E. In the Italian Parmigiano sheep's milk cheese, these values range 0.86-6.83 µg/g of vitamin A and 1.35-3.2 µg/g of vitamin E (Perretti et al., 2004).

These two vitamins are essential for human. They can play diverse roles, however, eating food rich in these vitamins reduce the risk of occurrence cancers, can delay the body's aging (thanks to the antioxidant activity), as well as stimulate the immune system (Oruch and Pryme, 2012; Rizvi et al., 2014).

Orotic acid

Orotic acid (OA), formerly known as vitamin B_{13}, present in high level in ruminant milk, can have also a great influence on human body. In sheep`s milk its amount varies from 0.45 to 1.95 mg/100 mL (Gajos and Krezlewicz, 1974). In cheeses, its quantity depends on the amount of soluble whey solids, degree of fermentation and time of cheese ripening (Larson and Hegarty, 1979; Urbienė and Leskauskaitė, 2006). Additionally, Manolaki et al. (2006) shows that the OA content in sheep's milk Feta cheese drops drastically during the first 2 days of its maturation, which may indicate the assimilation of OA by microorganisms.

OA is an organic acid (6-carboxyuracil) formed from carbamoyl phosphate and aspartic acid, which is a precursor of nucleotide compounds (Milewski, 2006). It has been shown that OA increase metabolism of folic acid and vitamin B_{12}, improved the condition of hearts with hypertrophy (West et al. 2017) and increase the growth of *Lactobacillus* sp. (Wright et al., 1950). However, people with impaired nucleotide metabolism can suffer from orotic aciduria (caused by a buildup of OA). In addition, studies on rats indicate that a diet rich in OA reduce Low Density Lipoprotein (LDL) cholesterol level in blood, but at the same time fat accumulating in the liver lead to its damage (Creasy et al., 1961; Živný et al., 2007).

Fatty acids

The most important and best studied bioactive ingredients of sheep's milk cheeses are fatty acids. Their amount depends primarily on the content in unprocessed milk (Nudda et al., 2005; Fernández et al., 2015). It has been shown that depending on the season and lactation period, the fatty acid profile of milk (Bielińska-Nowak and Czyżak-Runowska, 2016; Balthazar et al. 2017) as well as sheep's milk cheeses (Nudda et al., 2005; Kawęcka and Sosin-Bzducha, 2014) change. In summer, saturated fatty acids are reduced in favor of unsaturated fatty acids (Walther et al., 2008). These changes are mainly caused by the way of animals feeding – with different availability of pastures and fatty acid composition of grasses (Nudda et al., 2005). The profile of free fatty acids in cheese depends also on the pasteurization process, the type of coagulant used and the parameters of cheese production (Kawęcka and Sosin-Bzducha, 2014).

Studies show that sheep's milk cheeses are naturally rich in bioactive lipids (Table 1). The main fatty acids of Italian Gran Ovino cheese are C16:0

palmitic acid, C18:1 n-9 oleic acid and C14:0 myristic acid (Gaglio et al., 2019), while in Spanish artisanal hard cheeses – C16:0 palmitic and also C18:1 n-9 oleic acids (Estrada et al., 2019). Polish Bundz cheese contains large amounts of C10:0 capric acid, C16:0 palmitic acid, C18:1 n-9 oleic acid, linoleic acid C18:2 n-6, conjugated linoleic acid (CLA) and linolenic acid C18:3 n-3 (Bonczar et al. 2009). Aguilar et al. (2014) showed that Chilean commercial sheep's milk cheeses were richer in C18:1 trans isomers (including vaccenic acid) compared to cow's and goat's milk cheeses, and had a lower thrombogenicity index.

Saturated fatty acids (SFA) constitute 60% to 70% of fatty acids in milk of ruminants and thus are the most abundant group of fatty acids in animal products (Markiewicz-Kęszycka et al., 2013). Depending on the length of the chain, we divide them into Short-Chain Fatty Acids (SCFA), Medium-Chain Fatty Acids (MCFA), Long-Chain Fatty Acids (LCFA) and Very Long-Chain Fatty Acids (VLCFA). The presence of saturated SCFA (1-6 carbon atoms in the chain) and MCFA (6-12 carbon atoms) is a unique feature of milk fat. In ruminants, their synthesis takes place de novo in the mammary gland (Rutkowska et al., 2015). They are absorbed from the gastrointestinal tract without bile acids action, quickly penetrating into the blood without esterification (Cichosz and Czeczot, 2012b). Experimental studies show that MCFAs in the diet suppress the deposition of fat due to improved thermogenesis and fat oxidation in both, animals and humans (Nagao and Yanagita, 2010).

Monounsaturated fatty acids (MUFA) constitute 20%-35% of sheep's milk fat and includes e.g. vaccenic acid (C18:1 cis-7) (Markiewicz-Kęszycka et al., 2013). However, the trans isomer of vaccenic acid (C18:1 trans-11) is mostly present in sheep's milk cheeses. It is synthesized in the rumen of animals by bacteria and is a precursor of CLA (Rutkowska et al., 2015). It does not show pro-atherosclerotic activity, which is attributed to trans fatty acids. Contrary, studies in animal models show that a vaccenic acid-rich diet (C18:1 trans-11) has a hypolipidemic effect, which may prevents the formation of atherosclerotic lesions (Bassett et al., 2010) and alleviate the features of the metabolic syndrome (Jacome-Sosa et al., 2014). In addition, it has been shown that both isomers, cis and trans, exhibit anti-carcinogenic effects (Banni et al., 2001; Miller et al., 2003; Sauer et al., 2004; Lim et al., 2014).

The group of polyunsaturated fatty acids (PUFA) with health-promoting properties contained in sheep's milk cheeses include mainly omega-3,-6,-9, CLA, as well as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). It has been shown that increasing the consumption of essential PUFAs, including linoleic acid, α-linolenic acid, EPA, DHA and γ-linolenic acid, reduces the risk of diet-related diseases (Janczy, 2012).

The most important and best-studied bioactive fatty acid found in sheep's milk cheeses is the so-called rumenic acid – conjugated dienes of C18:2 linoleic acid (Conjugated Linoleic Acid, CLA). CLA arises mainly in the mammary glands of animals as a result of the Δ9-desaturase of vaccenic acid and partly through the bioconversion of PUFA by anaerobic bacteria that takes place in the rumen (Recio et al., 2009; Cichosz and Czeczot, 2012a). Accordingly, rumenic acid is found only in the meat and milk of ruminants, including sheep. Numerous studies have confirmed its health-promoting effects. Currently market offers many dietary supplements using these properties. Their main task is to support weight loss by inhibiting enzymes responsible for the deposition of adipose tissue (Cichosz and Czeczot, 2012a).

Animal studies have shown that enrichment of diet in CLA increases the body's immunity and improves the metabolism of cholesterol and triacylglycerol in the blood plasma, thereby inhibiting the development and pathogenesis of atherosclerosis (Pariza, 1999; Roche et al., 2001). In addition, a small (1%) dose of this fat in the diet has an anti-cancer effect, causing inhibition of carcinogenesis at various stages of its development (Kowalska and Cichosz, 2013). This is mainly related to the antioxidant activity of CLA (Cichosz and Czeczot, 2012a).

Until recently, nutritionists have not recommended frequent consumption of cheese and animal products, mainly due to the high content of sodium, saturated fat and trans fatty acids. Consumption of dairy products was associated with an increased risk of obesity, atherosclerosis and cancer (Krzęcio-Nieczyporuk and Antosik, 2015). However, these assumptions are not confirmed by the latest research. Sofi et al. (2010) conducted preliminary studies that has been shown that the short-term (10-weeks) consumption of regional Italian hard Pecorino sheep's milk cheese, naturally rich in CLA cis and trans isomerism, significantly improves the value of anti-atherosclerotic markers. Additionally, Tong et al. (2017) showed that long-term consumption of cheese is not associated with an increased risk of death, as previously thought. Moreover, in countries with the highest consumption of ripening cheeses rich in CLA (France, Italy, Greece), a much lower mortality rate was observed due to, among others breast cancer (Kowalska and Cichosz, 2013).

Table 1. Mean values of fatty acids in various sheep's milk cheeses

Type of cheese	SFA	MCFA	MUFA	PUFA	CLA	Reference
	[g/100g]					
Gran Ovino	68.40	no data	22.97	8.62	1.05	Gaglio et al. (2019)
Pecorino Carmasciano	51.30	no data	19.80	4.30	0.52	Marrone et al. (2014)
Pecorino di Farindola	74.62	41.23	21.25	4.16	1.02	Schirone et al. (2011)
Pecorino	67.69	21.70	26.83	5.48	0.78	Prandini et al. (2007)
Pecorino	65.94	22.27	23.80	4.93	0.11	Prandini et al. (2011)
Roquefort	70.10	26.12	21.11	3.92	0.88	
Semi-hard ripened	66.32	13.40	28.47	4.60	0.84	Jarzynowska and Kłopotek (2013)
Hard ripened	74.07	no data	22.04	3.90	1.09	Milewski et al. (2016)
Feta	70.20	no data	21.00	4.7	0.18	Zlatanos et al. (2002)
Kefalotyri (made in December)	71.69	no data	23.33	5.00	1.09	Govari et al. (2020)
Kefalotyri (made in April)	69.20	no data	24.78	6.04	1.48	
Serra da Estrela	73.4	no data	20.3	6.3	no data	Lima et al. (2019)
Azeitão	73.8	no data	17.5	4.11	0.8	Partidário et al. (2008)
Évora	71.2	no data	19.4	4.35	0.8	
Nisa	67.9	no data	22.1	4.60	1.0	
Roja Mallorquina (fresh)	21.69	13.73	6.52	1.99	0.14	Gutiérrez-Peña et al. (2021)
Roja Mallorquina (ripened)	14.87	9.12	3.60	1.14	0.21	

SCFA – Saturated Fatty Acid, MCFA – Medium-Chain Fatty Acids; MUFA – Monounsaturated Fatty Acids; PUFA – Polyunsaturated Fatty Acids, CLA – Conjugated Linoleic Acids

The recent discoveries of the beneficial effects of cheese consumption on human health could be related with changes in milk composition over the years (different breeding systems and animal nutrition), greater knowledge of bioactive compounds, as well as improved analytical methods (Raynal-Ljutovac et al., 2008).

It is known that the fatty acid profile of sheep's milk could be modified to a greater extent than that of cow's milk (by changing animal feeding). Consequently, the creation of functional sheep's milk cheeses is simpler and in this respect, eating them may have a greater impact on our health. This is confirmed by recent studies. Pintus et al. (2013) investigated the effects of eating Italian Pecorino cheese, naturally enriched in linoleic acid (by feeding sheep`s with extruded linseed), on the health of people with diagnosed mild hypercholesterolemia. For this purpose, 42 adult volunteers were eating control or enriched cheese (90 g/day), for 3 weeks. It has been proven that, in opposite to control cheese, intake of naturally enriched cheese significantly increased the plasma concentration of CLA, vaccenic acid, the n-3 fatty acids Alpha Lipoic Acid (ALA) and EPA and decreased endocannabinoid anandamide and LDL-cholesterol. Similar research was done by Murru et al. (2018). 15 adult volunteers ate ALA and CLA enriched sheep's milk cheese (90 g/day) for 4 weeks. It resulted increasing the EPA (80%) and DHA (20%) plasma level, higher CLA incorporation (240%), as well as improving the n-3 highly unsaturated fatty acids (HUFA) score (28%). Further research consisted in administering to 36 volunteers variously enriched cheeses made from sheep's, cow's or goat's milk (50 g/day) for 2 months. Consumption of each of the cheese improved the n-3 HUFA score by increasing the DHA plasma level and the effect was proportional to their CLA content.

Terpenes

Terpenes are isoprene-based compounds, mainly of plant origin. Therefore, their amount and composition in milk and cheese is mainly determined by their content in the diet of animals. The milk pasteurization and cheesemaking process could also affect the terpene profile (Cornu et al. 2005). In addition, terpenes may undergo microbial bioconversion (Mikami, 1988).

As the qualitative and quantitative composition of terpenes in plants is influenced by such factors as: their species, growth stage, soil, climate, geographical location and the management of grassland (Poulopoulou et al., 2011), terpenes in cheeses are investigated for their potential function as biomarkers of the cheese origin according to the way the animals are fed (Favaro et al., 2005). In this way it was possible to distinguish the highland from lowland cheeses (Valdivielso, et al. 2017; Moran et al., 2019). However, Poulopoulou et al. (2011) showed that terpenes as cheese biomarkers may not be reliable.

Various terpenes have been found in sheep's milk cheeses (Table 2). Limonene and α-pinene were most frequently detected. Depending on the amount of terpenes in the product, they could affect the sensory properties of cheese, although their importance in creating the flavor of the cheese appears to be controversial (Curioni and Bosset, 2002).

Terpenes are known for their broad therapeutic properties. However, in the context of their presence in cheeses, it has not yet been investigated whether they have an impact on the health of the consumer.

Table 2. Terpenes found in various sheep's milk cheeses

Type of cheese	Terpene	Reference
Halloumi	α-pinene	Papademas and Robinson (2002)
	β-pinene	
	copaene	
	thymol	
	α-caryophyllene	
	β-caryophyllene	
	δ-cadinene	
Manchego	*D*-limonene	Barron et al. (2005)
	cymene	
Idiazabal	α-pinene	Barron et al. (2007)
	D-limonene	
Vastedda della valle del Belìce	α-pinene	Verzera et al. (2010)
	β-pinene	
	limonene	
	o-cymene	
	caryophyllene	
Gran Ovino	D-limonene	Gaglio et al. (2019)
Urfa	α-pinene	Atasoy et al. (2013)
	β-pinene	
	camphene	
	β-myrcene	
	limonene	
	o-cymene	
Piacentinu Ennese	ocimene	Horne et al. (2005)
	terpinolene	
	rose oxide	
	L-carvone	
	citronellol	
	α-terpineol	

Table 3. The content of GABA in various sheep's milk cheeses

Type of cheese	GABA[mg/kg]	Reference
Pecorino	289 – 391	Siragusa et al. (2007)
Pecorino di Farindola	554 – 672	Tofalo et al. (2019)
Spanish artisinal	100 – 980	Diana et al. (2014)
Fruhe	28.8	Murgia et al. (2020)
Roncal	271 – 986	Muñoz et al. (2003)
Roncal type	33.7 – 891	Irigoyen et al. (2007)
Serra da Estrela	238.1 – 1638.9	Tavaria et al. (2003)

γ-Aminobutyric acid

γ-Aminobutyric acid (GABA) is a non-protein amino acid, which presence in food is recently sought after due to its potential health benefits. The main source of GABA in cheese are Lactic Acid Bacteria with glutamic acid decarboxylase enzyme activity, mainly *Lactobacillus* spp. During the fermentation and proteolysis, a large amount of L-glutamate, a precursor of GABA, is released from native caseins (Tofalo et al., 2019). For this reason, except microbiota, an amount of protein in raw milk, type of coagulant used, as well as time of ripening affect this amino acid content in cheese (Santiago-López et al., 2018). In addition, research showed that with the decreases of cheese pH, the amount of GABA increases (Nomura et al., 1998).

The GABA content in cheese correlates with the increased number of cheese eyes, although it has no direct or indirect effect on its flavor (Estrada et al., 2019). The concentration of GABA in some sheep’s milk cheeses was examined (Table 3) and it is very variable.

In humans, GABA is an inhibitory neurotransmitter that can perform various functions in the central and peripheral nervous system as well as in some nonneuronal tissues (Watanabe et al., 2002). It was proved that daily consumption of GABA-containing dairy product could be helpful in regulating and stabilizing blood pressure of people with high normal pressure and mild hypertension (Inoue et al., 2003; Kajimoto et al., 2004). Furthermore, researches indicate that GABA intake could alleviate human stress and anxiety, while enhancing its immune responses (Abdou et al., 2006; Yoto et al., 2012). Due to the positive impact of GABA consumption on human health, attempts are being made to create functional GABA-enriched dairy foods, including cheese, using GABA-producing microorganisms (Linares et al., 2016; Carafa et al., 2019; Redruello et al. 2021).

L-carnitine

L-carnitine (L-β-hydroxy-γ-N,N,N-trimethyl-aminobutyric acid) is an essential cofactor of fatty acid metabolism, endogenously biosynthesized from the amino acids L-lysine and L-methionine or obtained from food sources (Goa et al., 1987). The daily requirement of L-carnitine in humans ranges between 2 and 12 μmol/kg body weight/day (0.3 and 1.9 mg/kg/day) and may even be higher for athletes and pregnant women (Demarquoy et al., 2004).

According to Bodkowski et al. (2011), sheep’s milk contains a lot of L-carnitine amino acid – on average 11.08 mg/100 mL, about 32.1% more than cow's milk. The high level of carnitine in sheep`s milk may reflect the specific fatty acid utilization needs of the newborn animal (Woollard et al.,1999). Unlike milk, sheep’s milk cheeses are its less-rich source. Due to its hydrophilicity, it is lost along with the whey during cheese production and along with the loss of water during ripening (Bodkowski et al., 2011). Nevertheless, sheep's milk cheeses contain about 50% more L-carnitine than cow's milk cheeses (Seline and Johein, 2007).

L-carnitine is widely known as a supplement supporting slimming. It transports chains of fatty acids into the mitochondrial matrix, thus enabling cells to break down and draw energy from stored fat stores, thereby helping to lose weight and detoxify cells (Pękala et al., 2011). In addition, due to its antioxidant properties, it has a potential anticancer effect. Increased levels of other antioxidants by L-carnitine were also demonstrated, as well as its ability to chelate iron, cadmium or lead (Rospond and Chłopicka, 2013).

Bioactive peptides

Bioactive peptides are short chains containing 2-20 amino acid residues, which are released as a result of proteolysis and gained new pro-healthy properties (Balthazar et al., 2017). In cheese, their source is mainly casein broken down by milk enzymes, rennet, starter cultures or secondary microbiota (López-Expósito et al., 2017). However, bioactive peptides released during cheese production may become inactive after proteolysis during its long ripening periods (Alhaj and Kanekanian, 2014). It makes their presence dependent on the type and properties of cheese (Barać et al., 2017).

Some in vitro and in vivo studies were carried out to determine the properties of bioactive peptides and their impact on the human body. It has been proven that some active peptides derived from sheep’s milk casein fragments: αs1-, αs2- and β- have antimicrobial properties, e.g. on *Escherichia coli* (Benkerroum, 2010). They can also exhibit strong antioxidant activity (Barać et al., 2017). Others, obtained from the decomposition of κ-casein and lactoferrin, inhibit thrombin-induced platelet aggregation, thus exhibiting anticoagulant effects (Marcone et al., 2017). Some peptides derived from casein β inhibit the angiotensin converting enzyme I (ACE), thereby contributing to lowering blood pressure (Balthazar et al., 2017; Zdrojewicz et al., 2017). However, there is no conclusive evidence that bioactive peptides present in food, other than di- and tripeptides, can penetrate the intestinal wall and enter the hepatic portal system in physiologically relevant concentrations (Miner-Williams et al., 2014).

Pisanu et al. (2015) compared the composition of bioactive peptides in ripening sheep's milk cheeses made from raw and pasteurized milk. They showed, that there are significant differences in the peptide profiles of the examined cheeses in terms of individual sequences and their relative amounts. In sillico analysis of the properties of bioactive peptides (BIOPEP software) showed that 69% of the identified bioactive peptides have unknown properties and the rest are likely to have immunomodulatory (11%), ACE inhibitor (8%), antibacterial (5%), antioxidant (4%), anticancer (2%) and opioid-agonistic (1%) properties. Significantly higher content of peptides with immunomodulatory properties and ACE inhibitors was found in raw milk cheese and opioid-antagonistic activity in pasteurized milk cheeses.
The biological activity of peptides, due to the complexity of research, is mostly demonstrated in vitro (Table 4), which does not always reflect the effects obtained in a living organism (Darewicz et al., 2015). Further research is needed to better understand their impact on human health.

Sialic acid

Sheep's milk is particularly rich in a sialic acid (Sia) – family of 9-carbon acidic sugars contained in oligosaccharides, glycolipids and glycoproteins (Nakano et al., 2001). Its amount in milk depends on genetics, breed of animals, their nutrition, geographical location, lactation period or a combination of these factors (Karunanithi et al., 2013). During cheesemaking, by the action of rennet, κ-casein from milk is hydrolyzed to para-κ-casein, which remains in the curd, and glycomacropeptide, which is removed with the whey with all the κ-casein sugars, including Sia (Costa et al., 2019). In literature, there is no data about its levels in sheep's milk or cheeses.
Sia occurs mainly as N-acetylneuraminic acid (Neu5Ac) and N-glycolylneuraminic acid (Neu5Gc). Neu5Ac, naturally present in human milk and body, plays an important role in infant brain development and cognition (Wang, 2009).

Table 4. Bioactive peptides derived from different types of sheep's milk cheeses and their functional effects demonstrated in vitro

Type of cheese	Sequence of bioactive peptide	CN fragment	Functional effect	Reference
Pecorino Romano	GLSPEVLNENLL	α_{S1}-CN f(10–21)	antibacterial properties against Gram positive and Gram negative bacteria	Rizzello et al. (2005)
	RFVVAPFPE	α_{S1}-CN f(22–30)		
	VVAPFPEV	α_{S1}-CN f(24–31)		
	VMFPPQSVL	β-CN f(155–163)		
Canestrato Pugliese	MPIQAF	β-CN f(183–188)		
Idiazábel	QP, FP	various fragments	angiotensin-converting-enzyme (ACE)-inhibitory activities	Gómez-Ruiz et al. (2006)
	DKIHP	β-CN f(47–51)		
	DKIHPF	β-CN f(47–52)		
Roncal	QP, PP	various fragments		
	PKHP	α_{S1}-CN f(2–5)		
	DKIHP	β-CN f(47–51)		
	DKIHPF	β-CN f(47–52)		
Cabrales	PP	various fragments		
	DKIHP	β-CN f(47–51)		
	DKIHPF	β-CN f(47–52)		
Roquefort-type	TDAPSFSDIPNPIGSENSGK	α_{S1}-CN f(189–208)	antioxidant and angiotensin-converting-enzyme	Meira et al. (2012)
	DIPNPIGSENSGKTTMPLW	α_{S1}-CN f(196–214)		

	IPNPIGSENSGKIT	α_{S1}-CN f(197–210)	(ACE)-inhibitory properties	
	YQGPIVLNPWDQVK	α_{S2}-CN f(116–129)		
	YQGPIVLNPWDQVKR	α_{S2}-CN f(116–130)		
	GPIVLNPWDQVKR	α_{S2}-CN f(118–130)		
	VLNPWDQVKR	α_{S2}-CN f(121–130)		
	NAGPFTPTVNR	α_{S2}-CN f(131–141)		
	KEMPFPKYPVE	β-CN f(122–132)		
	WMHQPPQPLPPTVMFPPQSVL	β-CN f(158–178)		
	MHQPPQPLPPTVMFPPQSVL	β-CN f(159–178)		
	HQPPQPLPPTVMFPPQSVL	β-CN f(160–178)		
	YQEPVLGPVRGPFPI	β-CN f(206–220)		
	QEPVLGPVRGPFPI	β-CN f(207–220)		
	QEPVLGPVRGPFPILV	β-CN f(207–222)		
	PVLGPVRGPFPI	β-CN f(209–220)		
	LGPVRGPFPI	β-CN f(211–220)		
Manchego	FP	various fragments	angiotensin-converting-enzyme (ACE)-inhibitory activities	Gómez-Ruiz et al. (2002)
	VVAPFPE	α_{S1}-CN f(24-30)		
	FPE	α_{S1}-CN f(28-30)		
	KQMK	α_{S1}-CN f(58-61)		
	DVPSERY	α_{S1}-CN f(85-91)		
	DVPSERYLG	α_{S1}-CN f(85-93)		
	VPSERY	α_{S1}-CN f(86-91)		
	VPSERYL	α_{S1}-CN f(86-92)		
	KKYNVPQ	α_{S1}-CN f(102-108)		
	KKYNVPQL	α_{S1}-CN f(102-109)		
	LEIVPK	α_{S1}-CN f(109-114)		
	LKKISQ	α_{S2}-CN f(165-170)		
	AWPQ	α_{S2}-CN f(176-179)		
	TQPKTNAIPY	α_{S2}-CN f(195-204)		
	VRYL	α_{S2}-CN f(205-208)		
	IPY	α_{Si2}-CN f(202-204)		
	REQEEL	β-CN f(1-6)		
	DKIHP	β-CN f(47-51)		
	VPKVKE	β-CN f(95-100)		
	VPKVKET	β-CN f(95-101)		
	GPVRGPFP	β-CN f(197-204)		
	VRGPFP	β-CN f(199-204)		

In contrast, the influence of Neu5Gc on human health is not yet clear. It is not produced in human body due to a deletion in the gene encoding the enzyme responsible for its formation – CMP-Neu5Ac hydroxylase (Karunanithi et al., 2013). However, Neu5Gc builds up in the body from food sources, such as red meat and dairy. The research of Samraj et al. (2015) indicates that long-term consumption of Neu5Gc (from red meet) could lead to chronic inflammation, resulting from the reaction of the human immune system. It can participate in the formation of cancerous changes. In addition, the long-term accumulation of this compound may result in the appearance and development of certain diseases in the elderly (Szczurek, 2004). However, more research should be done in this regard.

Biogenic amines

Biogenic amines (BA) are a low-molecular nitrogen compounds produced during the fermentation and ripening of cheeses, mainly as a result of the decarboxylation of amino acids by microorganisms. Therefore, the content of BA in cheese depends mainly on the type of microorganisms occurring during fermentation and maturation, but also on many other factors such as availability of substrates, temperature and cheese ripening / storage time, their pH, salt content, oxygen availability, redox potential, level of sugar, added herbs or used technological processes (Bonczar et al., 2017). For these reasons, the quantitative and qualitative composition of BA in sheep's milk cheeses is extremely variable, even for one type of cheese (Schirone et al., 2012). High concentration of BA in cheese could indicate poor hygienic conditions during its production and storage (Martuscelli et al., 2005).

Several studies have been done to check the level of BA in sheep's milk cheeses (Table 5). They confirm high variability. Researches show that the amount of BA in cheese increases with its ripening time, and pasteurization does not guarantee a reduction.

Table 5. The content of individual biogenic amines in various sheep's milk cheeses

Type of cheese	PHE	PUT	CAD	HIS	TYR	total BA	Reference
	[mg/kg]						
Pecorino di Farindola	0.0–127.1	9.9–394.1	26.8–276.1	0.0–21.8	52.3–1171.3	209.0–1839.0	Schirone et al. (2011)
Pecorino	nd–232.4	nd–986.0	nd–2127.6	nd–761.4	nd–1771.3	10.3–5860.6	Schirone et al. (2013)
Pecorino	24–144	22–512	2–262	nd–23	147–1132	274–2161	Torracca et al. (2015)
Manchego	nd–49.8	nd–668.3	1.8–803.1	16.1–217.9	5.6–326.8	43.7– 881.7	Poveda et al. (2015)
Terrincho	12.9–237.8	82.6–446.5	48.6–239.6	nd–10.9	nd–283.1	428.0–922.0	Pintado et al. (2008)
Zamorano	3–120	10–190	5–35	1–55	1–85	no data	Combarros-Fuertes et al. (2015)
Feta	0.77–7.04	1.6–193	0.2–82.8	0.0–84.6	0.0–246	12.2–617	Valsamaki et al. (2000)
Fiore Sardo	2–16	nd–450	6–40	4–210	60–700	170–1100	Zazzu et al. (2019)
Azeitão	no data	nd–137	161–260	414–818	72.3–445	no data	Pinho et al. (2001)
blue-veined	13.25–61.44	17.28–33.46	no data	no data	7.15–52.20	no data	Calzada et al. (2013)
bryndza	no data	22.1–60.9	16.5–42.6	24.2	34.6–107.4	73.2–222.2	Buňková et al. (2013)
smoked	no data	16.2–99.9	62.6–80.7	nd	8.9–38.3	25.1–177.1	
fresh	no data	20.7	19.6	nd	nd	nd–40.3	
unripened	no data	55.3–118.2	11.4–35.8	nd	10.2–11.1	nd–140.3	
pasta filata type	no data	nd	nd	nd	nd	nd –13.2	
brined	no data	229.5	125.6	nd	23.1–174.6	37.2–529.8	
flavoured	no data	108.8	nd	nd	114.7	nd–223.5	

PHE – phenylethylamine; PUT – putrescine; CAD – caderine; HIS – histamine, TYR – tyramine; BA – biogenic amines; nd – not detected

BAs have an ambiguous effect on human health. They play an important role in the human body including as precursors in the synthesis of hormones, proteins, alkaloids or nucleic acids, as well as by participating in the regulation of blood pressure, allergic reactions or cell growth control (Jansen et al., 2003). However, consumption of a large amount of BA may have an adversely affect the health of consumers, especially people with metabolic disorders, causing symptoms such as nausea, headaches, rash, arrhythmia or changes in blood pressure (Santos, 1996).

Research to date indicates that healthy people not taking monoamine oxidase inhibitor (MAOI) drugs could be exposed to a level of 25-50 mg of histamine and 600 mg of tyramine per person per meal (EFSA, 2011). However, currently there are none specific toxic doses for individual BA in cheeses determined, as they depend on each individual's detoxification body mechanisms (Ordonez et al., 1997).

The level of BA in cheeses can be reduced by the use of high pressure processing, γ-irradiation, applications of additives (like spices and herbs), reduction of decarboxylase activity and temperature, and the most popular way, use of a selected starter culture (Ercan et al., 2013). Renes et al. (2019) was managed to produce a sheep's milk cheese with reduced level of BA and at the same time a higher GABA content by using autochthonous *Lactococcus lactis* subsp. *lactis* and *Lactococcus lactis* subsp. *cremoris* as starters and *Lactobacillus plantarum* as adjunct culture. As sheep's milk cheeses are often produced in a traditional way, perhaps such an approach to cheese production could increase their safety, while preserving the native character and enhancing the health-promoting properties.

CONCLUSIONS

Sheep's milk cheeses contain many bioactive ingredients both derived from milk and formed during its fermentation and / or maturation, largely due to the action of microorganisms. For this reason, the content of this individual components is variable and depends mainly on the milk composition, type of cheese, time of ripening and microbiota involved in the process. Contrary to popular belief, sheep's milk cheese consumption has a proven positive effect on human nutrition and health. However, further long-term research is needed to assess its role as a functional food.

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