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NEW TRENDS IN THE BIOACTIVE COMPOUNDS OF MILK: A REVIEW OF THE FUNCTIONAL ACTIVITIES AND PROCESSING EFFECTS

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Review

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ABSTRACT

Milk has a complex highly variable nutritional composition based on the different species and animal breeds, together with the strategy and management of the animal feed. It is the first food consumed by children, exclusively for the initial months because it contains all the nutrients necessary for body growth and the development of cognitive functions. Considering the Mediterranean diet, cow and goat milk is consumed fresh or used for the production of dairy products, while sheep and buffalo milk is used exclusively for cheese production. In developing countries, sheep milk or milk from particular animal species such as the yak is also used for fresh consumption and is a low-cost food source for consumers. Milk is the only raw food with a complete profile of all nutrients, from proteins to fats, carbohydrates, water, minerals, and vitamins. Several bioactive compounds are present in milk or originate during protein digestion and fat fraction. Thus, milk can be defined as a functional food because it adapts to the definition "any food or food ingredient that can provide a health benefit over the traditional nutrients it contains".

INTRODUCTION

Human eating habits have evolved differently depending on the availability of food and the cultural or climatic differences of countries (Elthon, 2008). The most important nutritional change was the introduction of milk and meat into the diet, and the birth of agriculture (Rotilio and Marchese, 2010). Several studies have investigated the dietary history of man and how changes in diet are linked to the anatomical and cultural evolution. These studies are important as they provide insights into the evolution of modern diets, and thus help identify the pathophysiological mechanisms from which modern diseases related to diet derive. Researchers have focused on genetics, nutrigenomics and on the link between gene expression, and nutritional metabolites originating from different food regimens (Pritesh et al., 2018). Agriculture and animal breeding began 12,000 years ago and, after this important event, man discovered the nutritional value of milk and its derivatives (Figure 1).

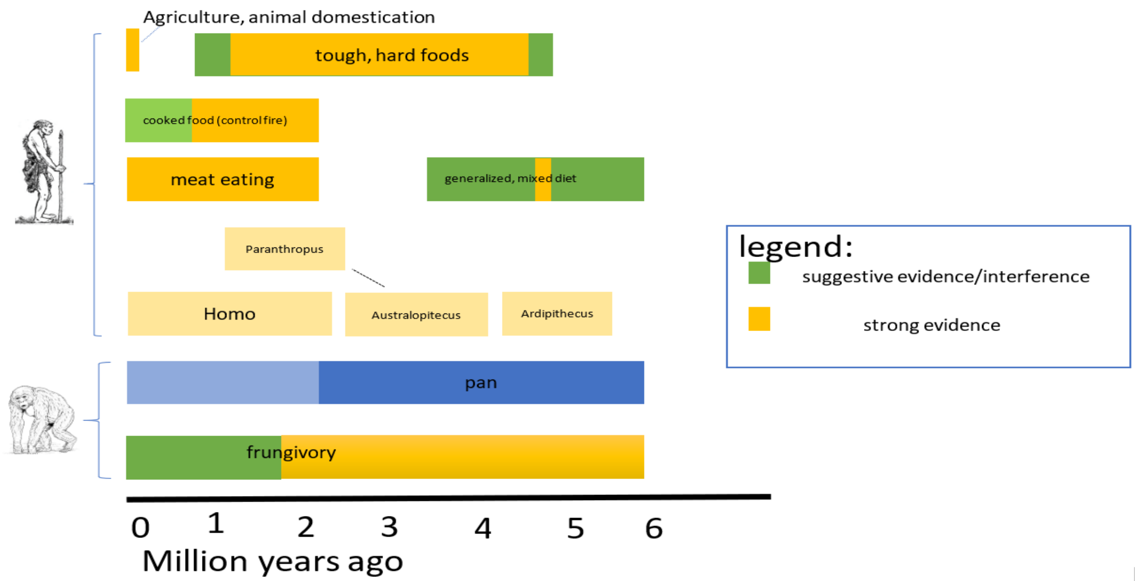

Figure 1. Timeline of the main dietetic changes during human evolution (adapted from Luca et al., 2010).

When nomadic gatherers became stable farmers, their eating habits changed drastically with a heavy repercussion on their metabolism. This change represented an important pressure on insulin signaling and the human metabolism from a selective and interesting evolutionary point of view (Luca et al., 2010). One example of how the change in eating habits of our ancestors has had an influence on genetics and metabolism is the persistence of lactase.

Originally, lactase stopped being produced because the synthesis of an unneeded enzyme in post weaning is metabolically disadvantageous. When human beings returned to consuming foods containing lactose, a strong selective pressure induced a genetic mutation which led to the production of lactase even in adulthood. Today, only 25% of the world's population do not digest lactose, and lactose tolerance seems to be more common in populations with a longer history of livestock, rather than in populations that started to practice it more recently (Krebs, 2009). As a result, our genetic predisposition strongly influences our food preferences and responses after exposure to certain foods. However, it does not limit our cultural influences, changes and the resulting development.

Presence of bioactive molecules in milk

Milk has a complex nutritional composition that varies greatly based on the different species, breed, feeding, animal management and environmental conditions of the farm. It is the first food consumed by children, exclusively for the first months because it contains all the substances necessary for the growth and optimal development of all bodily and cognitive functions. Milk fits the definition of a functional food as "any food or food ingredient that can provide a health benefit over the traditional nutrients it contains". It is also an important ingredient in the Mediterranean diet. Cow milk is the animal milk most consumed by adult populations in the world, while sheep milk is mainly used for cheese production. Milk is generally regarded as part of a balanced and healthy diet plan, as its composition and lipid profile are associated with beneficial functions for the human body. Its proteins have a high biological value, and the easily absorbed minerals and vitamins are fundamental for the regular progress of metabolic functions. Today, more attention has been paid to the biologically active molecules present in milk both in the lipid and protein fraction due to their fundamental role in human health (Korhonen, 2009).

Lipid bioactive compounds

The lipid fraction of milk is mainly represented by spherical globules, originating from alveolar epithelial cells, consisting of a "nucleus" of triglycerides (95-98% of total milk lipids) and a thin membrane of phospholipid lining (0.5 -1% of total milk lipids). Milk fat is considered the most complex of naturally-occurring fats, containing more than 400 fatty acids (FA) and more than 43 different triglyceride species in cow milk and 137 in goat milk (Fraga et al., 2000; Mansson, 2008). The position of the single fatty acid in the triglyceride structure is the main factor determining the nutritional characteristics of milk fat (Thormar and Hilmarsson, 2007). Sn2 monoglycerides are absorbed more rapidly from the intestinal walls, and the molecular structure of FA bound to this position has great nutritional importance. Several studies have shown that different FAs have a different affinity for the Sn-2 binding site and that C16: 0, C14: 0, C12: 0 and C18: 1 are often esterified in this position (DePeters et al., 2001). Monoglycerides originate during the digestion of milk triglycerides in the intestine and are potent antimicrobial agents (Thormar et al., 2007; Colin et al., 2018).

Hyldgaard et al. (2012) demonstrated the antimicrobial mechanism of monocaprilated against *Escherichia coli*, *Staphylococcus xylosus* and *Zygosaccharomyces bailii,* while Ruzin and Novick (2000) showed the inhibitory effect of monolaurate on the virulent expression of Staphylococcus aureus. The milk lipid fraction consists of 70% saturated fatty acids (SFA) and 30% unsaturated fatty acids (UFA). One part of SFA (11%) consists of short chain fatty acids (SCFA), in particular butyric (C4: 0; BA; 4.4%) and caproic acid (C6: 0; 2.4%) which creates the pungent taste of milk from different species such as sheep or goats (Pereira, 2014; Mele et al., 2015). Butyric acid is an SCFA (C4: 0), and in monogastrics, including humans, it is naturally produced by the fermentation of fibrous food components from intestinal microbiota. This FA is mainly used as a source of energy from colonocytes, and secondly is metabolized in the liver.

Studies on animal models have shown that fiber-rich diets help to prevent cancer due to the high production of BA, while other studies have shown that patients already suffering from colorectal cancer have a lower concentration of this FA in the intestine (Parodi, 2004). The mechanisms of its antitumor activity are not yet clear, but are probably related to its anti-inflammatory abilities. When BA is associated with other biologically active molecules such as vitamins A and D, resveratrol and aspirin, its anti-carcinogenic activity increases. The most active chemical form is tributirine, a triglyceride with three moles of BA bound to glycerin, which is naturally present in milk (Parodi, 2004; Gill et al., 2018). Studies conducted on animal models show that BA also has different antimicrobial effects on bacteria in the intestine, as it counteracts the toxic activity of Clostridium perfringens and the proliferation of coccidia (Tenella, Acervulina and Maxima), and as a growth factor for the development of intestinal villi in growing animals (Antongiovanni et al., 2007; Timbermont et al., 2010).

Cow milk contains BA, normally about 4 g / 100 g of total lipids, while sheep milk contains about 7 g / 100 g which is quantitatively transferable in cheese. Another interesting FA of milk with functional properties is conjugated linoleic acid (CLA), which is a pool of positional and geometric isomers produced exclusively by ruminants (Table 1). The most important isomer for its beneficial effect on human health is C18: 2 *cis*9 *tran*s11 (Rumenic acid, RA). RA has a double origin because it is formed in the rumen by the isomerization of linoleic acid (C18: 2 *cis*9 *cis*12; LA) and for 9-desaturation of vaccenic acid (C18: 1 *trans*11; VA) in the mammary gland from StearoilCoA. The mammary gland activity is strongly influenced by the presence of metabolites or nutrients enhanced by blood flow, including alpha-linolenic acid (C18: 3 *cis*9 *cis*12 *cis*15; -LNA), as reported in

Table 1. Conjugated linoleic acid isomer profile

Isomer	Composition (g/100g CLA)		
	Bovine	Caprine	Ovine
cis-8, *trans*-10	< 0.01 - 1.70	< 0.01	NR
cis-9, *trans*-11	65.6 - 88.9	62.1 - 75.1	80.0 - 80.9
cis-11, *trans*-13	< 0.01 - 0.23	0.16 - 0.69	NR
cis-12, *trans*-14	< 0.01 - 1.06	0.00 - 0.13	1.69 - 1.83
trans-7, *cis*-9	2.63 - 9.49	4.57 - 11.7	5.96 - 6.08
trans-8, *cis*-10	< 0.01 - 2.33	1.85 - 3.48	NR
trans-9, *cis*-11	< 0.01 - 3.93	< 0.01 - 4.21	NR
trans-10, *cis*-12	< 0.01 - 1.61	< 0.01 - 0.90	0.55 - 0.57
trans-11, *cis*-13	0.06 - 9.33	0.22 - 0.48	2.14 - 2.38
trans-6, *trans*-8	< 0.01 - 1.40	0.12 - 1.91	< 0.01
trans-7, *trans*-9	0.02 - 2.80	0.42 - 1.08	0.40 - 0.42
trans-8, *trans*-10	0.19 - 0.67	0.36 - 1.47	0.34 - 0.42
trans-9, *trans*-11	1.31 - 1.40	2.99 - 5.77	1.40 - 1.60
trans-10, *trans*-12	0.31 - 1.40	0.76 - 4.16	0.53 - 0.85
trans-11, *trans*-13	0.89 - 6.00	0.58 - 1.14	3.04- 3.18
trans-12, *trans*-14	0.35 - 3.55	0.72 - 1.90	1.90 - 2.20
trans-13, *trans*-15	< 0.01 - 0.16	< 0.01	NR

Adapted from: Mele M. and Pulina G., 2015. Alimenti di origine animale e salute.

Considering the metabolic pathways of RA synthesis, only foods derived from ruminant breeding contain RA. This is because its precursor, VA, is mainly formed during the biohydrogenation of LA and -LNA. Figure 2 shows the pathways for the biohydrogenation of LA and -LNA rumen. Plant products do not contain RA and VA because the plant's metabolism is not able to synthesize them. The alleged beneficial effects related to RA were discovered about thirty years ago, and several studies have shown that the biological activities are linked to the suppression of f cancer, a slowing of body fat accumulation, improvement in bone mineralization and modulation of the system immune system, delayed onset of type II diabetes, and the development of atherosclerosis (Murru et al, 2018; Pintus et al., 2013; Wannamethee et al., 2018).

The profile of the monounsaturated fatty acids of milk (MUFAs) is very interesting because it consists mainly of VA and oleic acid (OA). It is derived from the mobilization of lipids, the absorption of LCFA in the diet from blood or from endogenous synthesis through the 9-desaturation of stearic acid (C18: 0; SA). This FA is the main MUFA in milk, and provides over 30% of the diet requirements when olive oil is not present. The literature reports that a diet rich in high oleic acid favorably alters the low-density lipoprotein cholesterol, triglycerides and coagulant activity of factor VII (Allman-Farinelli et al., 2005; Liu et al., 2018). Unlike margarine, milk fat is low in trans fatty acids (TFA), the main one being VA. Figure 3 shows the TFA profile of milk. The bioactive properties of VA are related to anti-inflammatory properties, such as a reduction in the tumor necrosis factor and interleukin-6 in human epithelial colorectal colon cancer cells, as observed in a study carried out in the Republic of Ireland (Reynolds et al., 2008).

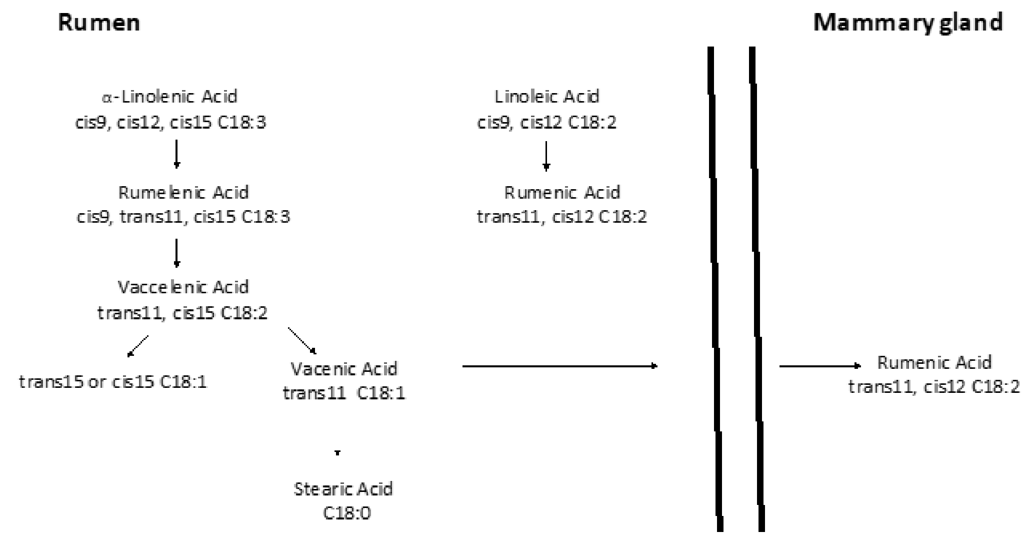

Figure 2. Biohydrogenation pathway of LA and a-LNA in the rumen and endogenous synthesis of rumenic acid in the mammary gland (adapted from Harfoot and Hazlewood, 1988; Bauman et al., 2003).

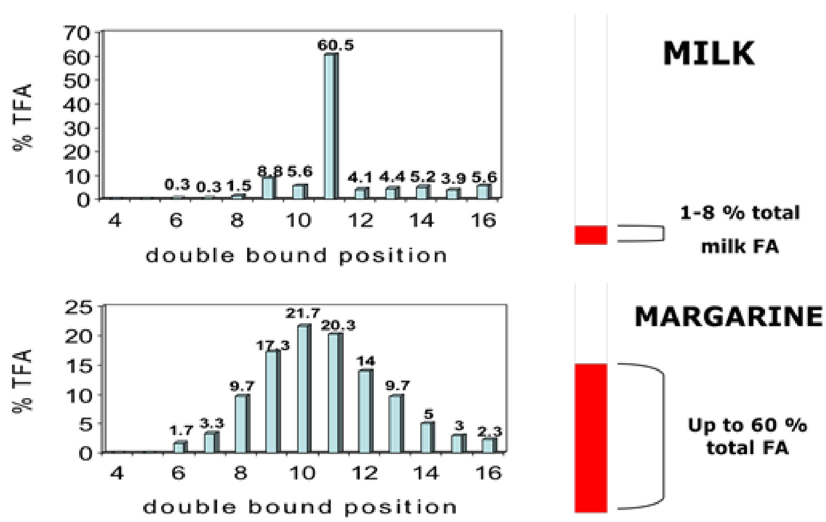

Figure 3. Trans fatty acid profile of milk and margarine (adapted from Sébédio and Christie, 2009. Trans *Fatty Acids in Human Nutrition* Eds. F. Destaillats, J.L. Sébédio, F. Dionisi and J.M. Chardigny, Oily Press, Bridgwater).

These results are supported by another study (Jacome-Sosa et al., 2016), which monitored the anti-inflammatory effects in animal models and concluded that VA together with the lipid molecule of oleoylethanolamide signaling can activate anti-inflammatory activity by lipopolysaccharides through PPAR. The biological activity of a molecule is due to its chemical structure. It is interesting to note that the structure RA (C18: 2 *cis*9 *trans*11) mirrors that of VA (C18: 1 *trans*11) and of OA (C18: 1 *cis*9) (Figure 4). Another particular feature of ruminant milk is the presence of branched fatty acids (BCFA) with 14, 15, 16 and 17 carbon atoms derived from the microbial activity in the most active rumen compared to the monogastric intestine.

Trivial name	Systematic name	Empirical formula	ω/n position	Structure
Oleic Acid	*cis*9 octadecenoic acid	$C_{18}H_{34}O_2$	9	
Linoleic Acid	*cis*9 *cis*12 octadecenoic acid	$C_{18}H_{32}O_2$	6	
Vaccenic Acid	*trans*11 octadecenoic	$C_{18}H_{34}O_2$	7	
Rumenic Acid	*cis*9 *trans*11 octadecadienoic acid	$C_{18}H_{32}O_2$	7	
10-CLA	*trans*10 *cis*12 octadecadienoic acid	$C_{18}H_{32}O_2$	6	
α-Linolenic	*cis*9 *cis*12 *cis*15 octadecatrienoic acid	$C_{18}H_{30}O_2$	3	
Stearic Acid	octadecanoic acid	$C_{18}H_{36}O_2$	-	

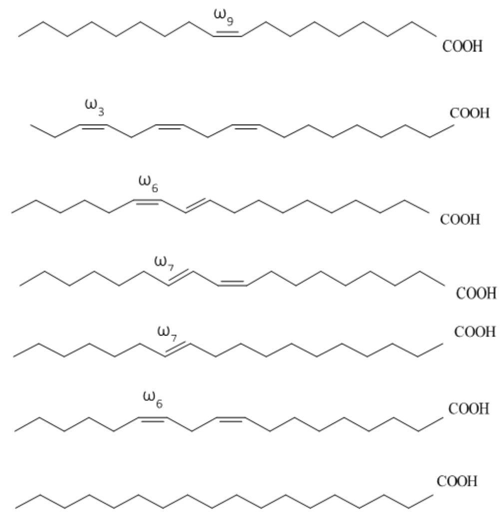

Figure 4. Main fatty acids of interest with their common names, systematic names and chemical structures (adapted from Benjamin et al., 2015).

Their biological activity is often compared to the antitumor activity of the RA. The *iso*-C15: 0 isomer is of particular interest which, in experiments in vitro, seems to be particularly active against leukemia (De Stefani, 2013). Considering w-3 FA, milk fat naturally contains small amounts of eicosapentaenoic acid (EPA, C20: 5 *cis*5 *cis*8 *cis*11 *cis*14 *cis*17) and docosahexanoic acid (DHA; C22: 6 *cis*4 *cis*7 *cis*10 *cis*13 *cis*16 *cis*19) but has a good content of α -LNA considered by the EFSA to be healthy for its hypotensive and anticholesterolemic activity (EFSA, 2009, EFSA 2010). A feeding strategy has also been created for ruminants to improve the di-LNA content in milk (Mele et al., 2015).

Bioactive protein and derivatives in milk

Milk proteins are classified as having a high biological value on the basis their amino acid profile, high digestibility, bioavailability and the human body's requirements,. Cow milk contains about 32 g / 100 g of protides, represented by casein (80%) and whey protein (20%). The amino acid profile differs between these two fractions and whey proteins are rich in branched amino acids such as leucine, isoleucine and valine and lysine, while caseins are the richest in histidine, methionine and phenylalanine (Pereira, 2014). The protein content of milk is one of the factors determining the purchase price of milk because the production of cheese is closely linked to the content of milk casein, which is responsible for the formation of curd. Recent studies have shown that peptides derived from the digestion of milk proteins play a protective role in human health, and phosphorylated peptides are essential for the transport and absorption of other nutrients such as zinc and calcium (Bhat et al, 2015; Mele et al., 2015).

Milk proteins are recognized for their high nutritional quality, however many of these macromolecules have been associated with various biological activities including satiating potency, antimicrobial properties, mineral absorption, antilipidemic activity and antitumor properties (Anderson et al., 2004). In addition, peptides originating from their digestion also have interesting biological activities because they are positively correlated with inflammatory markers, hypertension, diabetes and osteoporosis (Nielsen et al., 2017; Nongonierma et al., 2015; Pal and Ellis, 2010; Rajput et al., 2018). The main bioactive proteins or derivatives in milk are shown in Table 2.

Table 2. Bioactive peptides present in milk

Bioactive peptides	Protein precursor	Bioactivity
Casomorphin	α-, β-Casein	Oppioid agonist
α -lactorfin	α-Lattalbumin	Oppioid agonist
β-lactorfin	β-Lattoglobulin	Oppioid agonist
Lactoferroxin	Lattoferrin	Oppioid antagonist
Casoxin	k-Casein	Oppioid antagonist
Casochinins	α-, β-Casein	ACE-inibitor
Immunopeptides	α-, β-Casein	Immunomodulator
Lactoferricin	Lattoferrin	Antimicrobial
Casoplatelin	k-Casein, Transferrin	Antitrombogenic
Phosphopeptide	α-, β-Casein	mineral chelant

Adapted from: Mele M. and Pulina G., 2015. Alimenti di origine animale e salute.

Carbohydrate component

Lactose is the main carbohydrate of milk (4-10 g per 100 g of milk). It is a disaccharide consisting of 1 mole of glucose and 1 mole of galactose. Lactose digestion occurs by means of β-galactosidase, more commonly known as lactase. This enzyme is located at the edge of the human intestine brush and hydrolyses lactose into glucose and galactose, which are then absorbed by the intestinal wall and transported to the liver through the portal vein. In mammals, the activity of this enzyme decreases significantly after weaning, however this does not happen in humans, where its activity continues into adulthood as a result of the intake of milk in adulthood. Lactose intolerance is linked to the reduced activity or lack of this enzyme in the intestine (Pereira, 2014).

Mineral component

Milk has a very particular micronutrient composition. It is generally recognized as a primary source of calcium, but there are many other elements, such as phosphorus, magnesium, zinc and selenium, which play an important role in the vital functions of the human body. The percentage of minerals in milk is about 1g / 100g of the total dry matter (DM). These minerals are in the form of cations (Ca^{2+}, Na^{2+}, K^{+}, Mg^{2+}), and anions in the case of inorganic phosphorus (PO_4^{-2}), chloride (Cl^-) and citrate ($C_6H_6O_7^{-2}$). Their molecular form influences the absorption capacity of the body and of milk lactose, increasing the absorption of calcium, and keeping it in a soluble form (Rajput et al., 2018).

Milk is therefore an excellent source of absorbable calcium (about 1200 mg / l). As a consequence of the innate capacity of animals to mobilize their body reserves, compensating for any lack of micronutrients in the ration, the animal diet does not influence the content of microelements in the milk (Ca, P, Mg, K, Na, Cl, S), as reported by Pulina et al. (2007). The only exception is iodine (I^-), whose quantity in milk seems to be strongly related to the diet (Schwendel et al., 2015). By observing the mineral content of different species of ruminants, goat and sheep milk have a higher content of Calcium, Phosphorus, Magnesium, Zinc and Chloride than cow milk and a lower content of Sodium, Potassium, Sulfur, Manganese and copper (Park et al., 2007).

Vitamin profile

The vitamin profile of milk includes both fat-soluble vitamins (A, D, E) and water-soluble vitamins (vitamin B complex and vitamin C). Fat-soluble vitamins are bound to the lipid fraction and, therefore, in partially and totally skimmed milk, their content is greatly or completely reduced. The concentration of vitamins in milk strongly depends on the animal diet. Grazing animals collect retinol in their milk, derived from carotenes, while animals fed on a hay diet show a 70% reduction in carotenoid intake, which is reflected in the milk (Mele et al., 2015). Water-soluble vitamins are important enzyme cofactors needed in many metabolic processes, such as the production of nutrient energy and the synthesis of hormones. They can be synthesized by rumen microorganisms if the conditions are favorable.

Vitamin B2 (riboflavin) is found in clear concentrations in milk, while vitamin B3 (vitamin PP) is present in the form of nicotinamide. Milk is also a particularly rich food in vitamin B5 (pantothenic acid) and vitamin B8 (biotin). Vitamin B6 is found in milk mainly in the form of pyridoxamine phosphate, while vitamin B9 (folic acid) is mainly linked to the protein component that makes it absorbable.

Effects of conventional and innovative techniques to reduce the microbiological hazards of milk nutritional components.

The pH and water activity make milk an optimal medium for microbial growth, and thermal treatments are needed such as pasteurization and Ultra High Temperature processing (UHT) to ensure microbial safety. Thermal treatments such as pasteurization reduce microbiological hazards and improve the shelf life of milk. In the last few years, research has focused on non-thermal processing technologies in order to manufacture products with a high nutritional quality.

The pasteurization procedure kills microbial vegetative cells, but is not capable of controlling the spores (Novak et al. 2005). Moreover, some studies have shown that the germination of aerobic spores can be started by the pasteurization process (Hansonet al. 2005). However, pasteurization causes the disruption of the tertiary structural environment of whey proteins and the degradation of vitamin C (Michalski and Januel, 2006; Qi et al., 2015).

In contrast, riboflavin is heat stable but very sensitive to light, therefore the packaging is fundamental in order to protect against oxidation (Sharabi et al., 2018). Ultra-high temperature processing decreases the B group vitamins by 10-20% (Sharabi et al., 2018).

The ultra-high-pressure homogenization method (UHPH) combines homogenization and pasteurization into one single process, reducing the negatives aspects of thermal treatments. It preserves vitamin C and the riboflavin degradation is lower compared to UHT and pasteurization in bovine milk (Amador-Espejo et al., 2015).

High intensity pulses (HILP) is a novel technique that uses light pulses of a short duration (among 100-400 µs) for product decontamination. This method inactivates pathogenic microorganisms because the UV light induces a modification in the DNA structure, damaging the genetic information including gene replication and transcription (McDonald et al 2002). Another mechanism of microbial inactivation is the damage of membranes and proteins causing the death of the cell (Takeshita et al. 2003). HILP inactivates bacteria such as *Aspergillus niger*, *Escherichia coli* and *Listeria monocytogenes* (Palgan et al., 2011).

UV light is known to generate free radicals through a wide variety of photochemical reactions, which can damage vitamins and induce lipid oxidation (Koutchma, 2009). However, in the literature no adverse effects of HILP have been reported on milk or fruit juices.

Another emerging technology is ultrasound (combined with mild pressure and/or temperature (manothermosonification, MTS). In milk, ultrasound exerts a lethal effect on several pathogenic bacteria such as coliform and *L. monoytogenes*. This method leads to the disintegration of milk fat globule membrane, producing smaller fat globules and a destabilization of casein micelles, reducing the rate of coagulation (Soria et al., 2010; Paniwnyk e al., 2017). This technique is efficient in reducing the cells and spores (about 100%) of *Pseudomonas fluorescens*, *E. coli*, *L. monocytogenes* in milk with no loss of bioactive peptides and an increase in angiotensin converting enzyme inhibitory peptides (ACE inhibitory) or antioxidant peptides (Paniwnyk e al., 2017). However, Soria et al. (2010) reported that ultrasound may alter bovine serum albumin leading to the undesirable formation of sulfinic and sulfonic acid.

CONCLUSIONS

Milk is needed for the optimal growth and development of humans and a very interesting food for adults, and is recommended as part of a balanced daily diet. It is an excellent source of high biological value proteins, essential vitamins and minerals, and for the transport and absorption of other nutrients. Numerous scientific studies have been conducted to clarify the dose-response of specific healthy molecules contained in milk. The lipid component presents an interesting fraction in terms of its antimicrobial activities due to monoglycerides and SCFA, its anticarcinogenic activities due to BA and CLA, and its antiaterogenic activities due to OA.

Peptides derived from the digestion of milk proteins play a protective role in human health, and phosphorylated peptides are essential for the transport and absorption of other nutrients such as zinc and calcium.

Milk is also considered a good source of absorbable calcium which protects against osteoporosis. The animal management including the feeding strategy, is fundamental in increasing the bioactive components of milk. In addition, the choice of techniques to reduce the microbiological hazards is crucial because the treatment can affect the nutritional quality of the milk. However, little information is available in the literature on the effects of these methods on specific bioactive components.

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