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Review

Milk fat as a source of bioactive compounds

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Milk fat is a source of not only nutritionally valuable but also biologically active ingredients that are involved in various regulatory processes, thus participating in a functioning organism. These compounds have been studied and various beneficial effects on the health and development of the organism have been described. Ingredients such as fatty acids (monounsaturated fatty acids, polyunsaturated fatty acids and conjugated linoleic acid) and phospholipids (glycerophospholipids and sphingolipids) may have a beneficial effect on human health or can prevent various diseases. Some candidate genes that are significantly involved in milk fat metabolisms, such as diacylglycerol O-acyltransferase 1 and stearoyl-CoA desaturase 1, thus contribute to the composition and concentration of the individual components of milk fat. This review deals with the composition of the collected bioactive components of milk fat and their impact on health and their potential to produce functional foods.

Keywords: milk fat, phospholipids, fatty acids, bioactive compounds

1 Introduction

Milk is one of the most important foods because it is the first form of feed to provide immunological factors in addition to energy and nutrients for mammals (Verardo et al., 2017). The composition of milk fat is also important for health because milk fat contains a number of components that have functional properties (Morris et al., 2007). As one of the main constituents of milk – lipids are a complex group of chemical compounds that have an important role in the human diet (Smoczyński, 2017). Milk fat is thought to contain several thousand types of lipids, making it the most complex material in nature in terms of lipid composition (Liu et al., 2018). Milk lipids have attracted attention due to the presence of several bioactive components present in the lipid fraction, such as omega-3 and omega-6 polyunsaturated fatty acids, conjugated linoleic acid and phospholipids (Verardo et al., 2017).

2 Bioactive components of milk fat

In mammals, lipids are produced in milk-secreting mammary gland cells in the form of milk fat globules (Smoczyński, 2017), which are surrounded by a milk fat globular membrane (MFGM). The globular membrane of milk fat is composed mainly of polar lipids (Månsson, 2008), which include phospholipids (PL) (Table 1, Figure 1). Milk phospholipids have a unique composition and make up about 50% of the total MFGM (Arranz and Corredig, 2017). PLs are ubiquitous molecules found in both membranes and vesicles, and their mixture is unique in milk (Ortega-Anaya and Jiménez-Flores, 2019). They serve as bioactive ingredients with processing functions, although they represent only a small proportion of total milk lipids (Huang et al., 2019). Due to their characteristic properties, they are indispensable for the excretion of milk fat and other milk components (Smoczyński, 2017).

Another important constituent in milk are fatty acids (FA) (Table 2). They are present in the form of triglycerides, phospholipids, or free fatty acids. Milk FAs originate

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Table 1 Content (% wt/wt of phospholipid) of major phospholipids in milk fat (adapted from Bernard et al., 2018)

Phospholipids	Bovine	Caprine	Ovine
Phosphatidylethanolamine	23.4–46.7	26.9–46.1	26.1–43.0
Phosphatidylinositol	0.10–9.0	2.21–9.4	1.53–6.4
Phosphatidylserine	0.12–9.1	2.41–14.0	1.61–10.7
Phosphatidylcholine	25.9–33.2	27.4–31.6	26.4–30.5
Sphingomyelin	19.8–25.4	16.1–27.3	22.3–29.7

Table 2 Content (% of total fatty acids) of fatty acids in milk fat (adapted from Gantner et al., 2015)

Fatty acid	Bovine	Caprine	Ovine
Saturated fatty acids	55–73	59–74	57–75
Monounsaturated fatty acids	22–30	22–36	23–39
Polyunsaturated fatty acids	2.4–6.3	2.6–5.6	2.5–7.3
Conjugated linoleic acid	0.2–2.4	0.3–1.2	0.6–1.1

either from *de novo* synthesis in mammary epithelial cells or from the uptake of circulating FAs from the blood (Bernard et al., 2018). Fatty acids are classified according to the length and degree of unsaturation of the hydrocarbon chain (Glaser et al., 2011) (Figure 2).

Milk fat contains several unique fatty acids which have biological importance. The most characteristic fatty acids for cow's milk fat are fatty acids with an odd number of carbon atoms, conjugated linoleic acid and butyric acid (Hageman et al., 2019). Polyunsaturated fatty acids

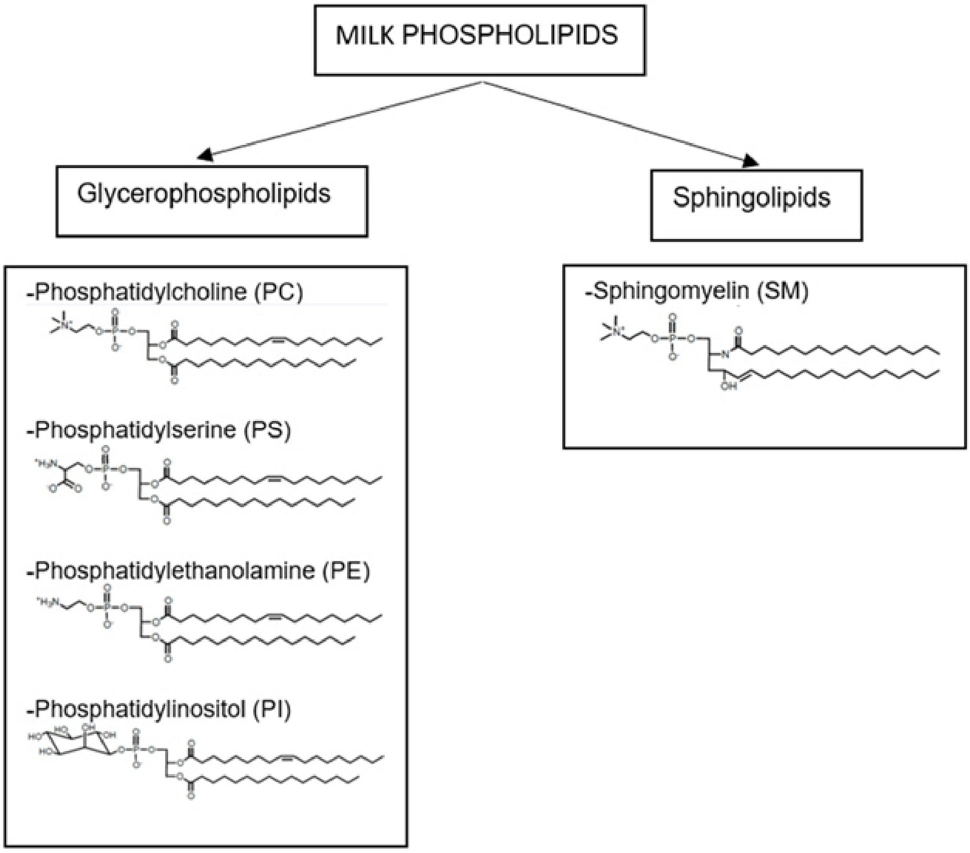

Figure 1 Structure of major phospholipids in milk fat

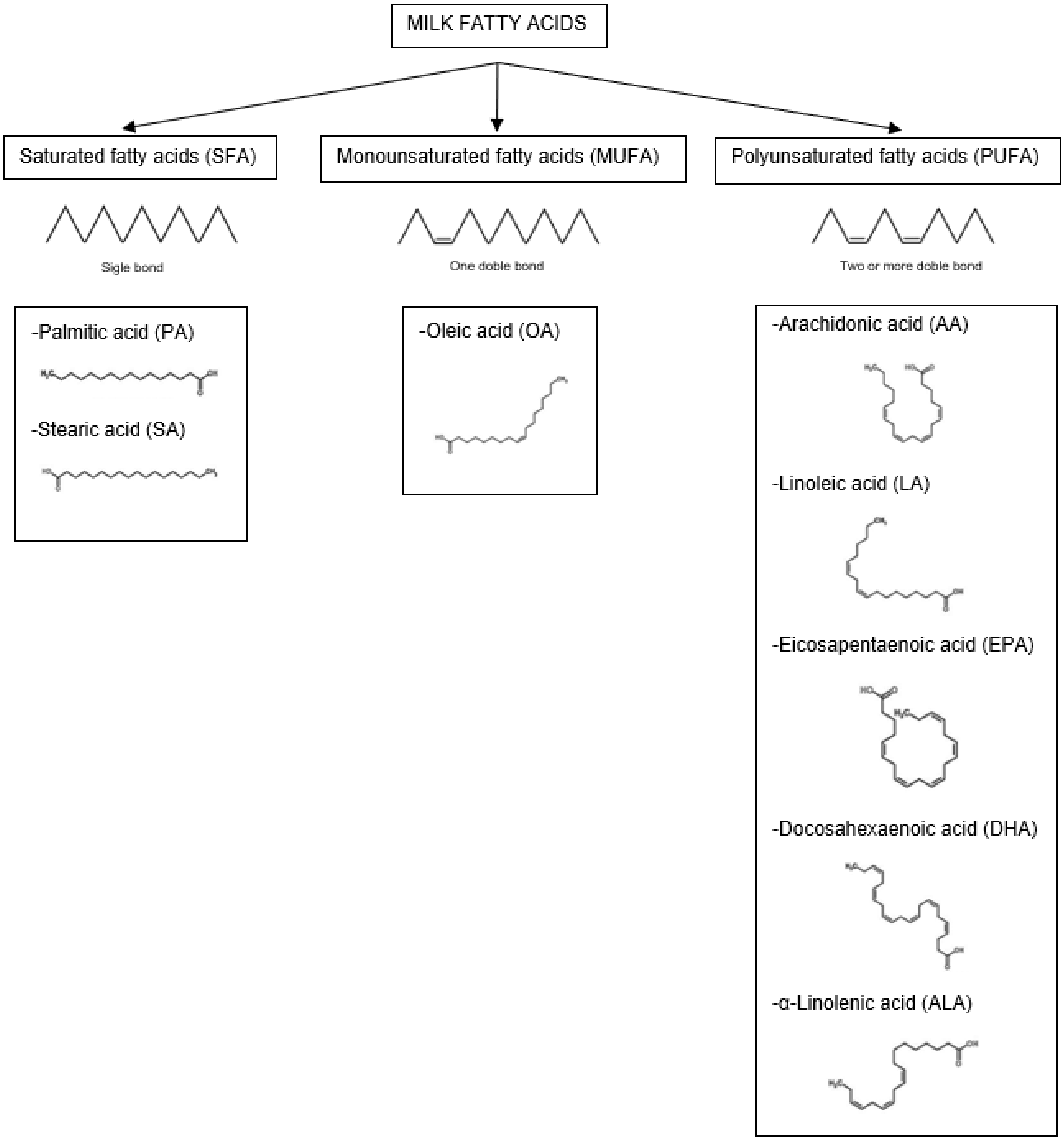

Figure 2 Classification by degree of unsaturation and structure of selected milk fatty acids

(PUFA) with 18 carbon atoms consist mainly of the group of (*cis* or *trans*) isomers of conjugated double bond linoleic acid (Ibeagha-Awemu et al., 2014). The most representative isomers of conjugated linoleic acid (CLA), which are ascribed biological importance, are 18:2 9c, 11t and 10t, 12c (Fuke and Nornberg, 2017). The two main groups of biologically other important PUFAs are n-6 PUFAs with their first double bond to C6 (linoleic acid LA 18:2, arachidonic acid AA 20:4) and n-3 PUFAs with their first unsaturated bond to C3 (alpha-linolenic ALA 18:3, eicosapentaenoic acid EPA 19:5, docosahexaenoic acid DHA 22:6) (Michalak et al., 2016).

2.1 Genes affecting lipid content and composition

Examination of a large number of candidate genes has allowed the identification of DNA polymorphisms associated with properties important for milk production (Yudin and Voevoda, 2015) that can be used to improve selection for milk fat production and milk fat components (Kumar et al., 2020). This provides opportunities to change the composition of milk fats through a genetic approach (Li et al., 2015). Milk fat synthesis is regulated by several important enzymes.

The stearoyl-CoA desaturase (SCD) gene encodes a key enzyme in the cell biosynthesis of monounsaturated

Table 3 Studies focusing on the beneficial effects of PLs and CLA

Phospholipids*		
Decrease in the incidence of colon tumours chemically induced	animal *in vivo*	Zhang et al., 2008
Decrease in postprandial lipemia, and improvement of lipid metabolism	animal *in vivo*	Lecomte et al., 2015
Lipid metabolism improvement after deleterious effects of a high-fat diet	animal *in vivo*	Norris et al., 2016
Brain and cognitive development	animal *in vivo*	Liu et al., 2014
Improvement of *in vivo* resistance to attenuated diarrheagenic *E. coli*	human	Ten Bruggencate et al., 2016
Conjugated linoleic acid**		
Suppresses cell proliferation, induces apoptosis	animal *in vitro*	El Roz et al., 2013
Reduces cell proliferation	human	McGowan et al., 2013
Lowers risk of colon cancer	human	Larsson et al., 2005

Source: adapted from *Bernard et al., 2018; **Moon, 2014

fatty acids (Li et al., 2016). FAs with 10–20 carbon atoms can be desaturated by the stearoyl-CoA desaturase enzyme which is located in the endoplasmic reticulum in mammary epithelial cells (Bernard et al., 2018). The stearoyl-CoA desaturase 1 catalyses the conversion of saturated fatty acids C16:0 palmitate and C18:0 stearate to monounsaturated C16:1 n-7 palmitoleate and C18:1 n-9 oleate fatty acids, which are the dominant components of adipocyte triacylglycerols (TAG) and phospholipids (Ralston and Mutch, 2015). Also, the synthesis of CLA (18:2 c9, t11) in the mammary glands is considered to be catalysed by stearoyl-CoA desaturase 1 (Wang et al., 2018).

Diacylglycerol O-acyltransferase 1 (*DGAT1*) is one of the major enzymes in controlling the rate of triglyceride synthesis in adipocytes. Gene catalyses the conversion of diacylglycerol and acyl-coenzyme A to triacylglycerol in the synthesis of triglycerides (Kumar et al., 2020). Many studies have described the association of *DGAT1* gene polymorphism with fat content (Bovenhuis et al., 2016; Vanbergue et al., 2016), in addition to affecting individual components of milk fat as fatty acid content and composition (Bovenhuis et al., 2016; Cruz et al., 2019). The size of the milk fat globe is related to the polar lipid composition, the milk fat content as well as fatty acid composition. The phospholipid/triacylglycerol ratio was significantly associated with fat content and with the *DGAT1* K232A polymorphism (Argov-Argaman et al., 2013).

2.2 Health benefits of phospholipids and fatty acids

It is a possible relationship between the consumption of phospholipids and the prevention of several chronic diseases (Verardo et al., 2017). Glycerophospholipids and sphingolipids have been extensively studied in recent decades because they have been found to have a variety of mechanisms and positive effects on many aspects of human health (Table 3) (Liu et al., 2018; Ortega-Anaya and Jiménez-Flores, 2019) and also have properties handily for the development of functional foods (Sánchez-Juanes et al., 2009; Huang et al., 2020). Phospholipids have a beneficial effect on health in that they may be involved in regulation of various inflammatory responses or may have a chemopreventive and chemotherapeutic effect on certain types of cancer (Contarini and Povolo, 2013). They have been shown to reduce the side effects of some medicines. The positive effect of PL on various diseases lies in their high efficacy in delivering their fatty acid residues for incorporation into cell membranes (Küllenberg et al., 2012). They are a source of unsaturated fatty acids such as long-chain polyunsaturated fatty acids (Lopez et al., 2017). Norris et al. (2016) observed the effects of milk sphingomyelin (SM) on lipid metabolism in mice. They found that SM lowered serum cholesterol also significantly reduced lipopolysaccharide serum and was associated with bifidogenic effects and changes in the distal intestinal microbiota, so milk SM may have beneficial effects in protecting against dietary harm. Sprong et al. (2002) in their study have shown strong bactericidal activities of sphingolipid digestion products. Sphingolipids may also protect against gastrointestinal infections or may increase resistance to certain types of food-borne gastrointestinal infections (Sprong et al., 2002). Sphingomyelin and its metabolites in the gut may affect the hydrolysis of TAG, cholesterol absorption, lipoprotein production and mucosal growth (Nilsson and Duan, 2006).

Monounsaturated fatty acids have a positive effect on the concentration of high-density lipoproteins (HDL) while reducing the concentration of low-density lipoproteins (LDL), which are stored in blood vessels throughout the body (Markiewicz-Kęszycka et al., 2013). Oleic acid (OA, 18:1 n-9), as the second major FA in milk fat, has been extensively studied in cell studies, where the data obtained suggest an anti-inflammatory effect (Da Silva and Rudkowska, 2015).

Polyunsaturated fatty acids are crucial nutrients that are involved in various processes associated with the regulation of human health and development (Lee et al., 2016). EPA and DHA are associated with a reduced risk of cardiovascular morbidity and mortality. These fatty acids play a key role in preventing and slowing the progression of cardiovascular disease due to their influence on a number of risk factors. EPA and DHA may also play a role as part of cancer treatment, with some recent studies showing that they increase the efficacy of some chemotherapeutic agents (Calder, 2014) and have the potential to prevent colorectal cancer in high-risk groups (Michalak et al., 2016). Increased intake of omega-3 unsaturated fatty acids such as eicosapentaenoic acid, docosapentaenoic acid and docosahexaenoic acid may also affect mental health (Hibbeln and Gow, 2014). EPA and DHA have the potential to contribute to improving mental development, reducing the burden of some psychiatric illness (Calder, 2014), and are associated with reducing the symptoms of depression (Hibbeln and Gow, 2014).

Conjugated linoleic acid is considered to be a bioactive compound that has positive effects on human health (Table 3). Dairy products account for approximately 75% of dietary conjugated linoleic acid intake (Bauman et al., 2006). CLA drew attention to itself due to the various biologically beneficial properties and health effects that have been demonstrated in animal models of various diseases. Its anticarcinogenic, antiobesity, anti-inflammatory, antiteratogenic and antidiabetic effects are attributed to it (Fuke and Nornberg, 2017; Den Hartigh, 2019). CLA is under investigation for its anticarcinogenic properties and its potential effect has been demonstrated *in vivo*, *in vitro* and clinical studies. Studies from cell and animal models suggest that CLA isomers may have various beneficial effects such as antitumor and antimutagenic activity or can be used as a chemopreventive agent (Moon, 2014; Dachev et al., 2021).

2.3 Other use

Phospholipids show good emulsifying properties and can be used as a delivery system for fat-soluble components (Contarini and Povolo, 2013) which offers extraordinary potential, especially for the encapsulation of bioactive substances because milk PL vesicles show unique stability (Arranz and Corredig, 2017). Liposome-encapsulated n-3 PUFAs target specific inflammatory sites such as lesions associated with inflammatory bowel disease or tumours. These modern drug delivery methods may be key to unlocking the true medical potential of PUFAs (Michalak et al., 2016). Huang et al. (2020) demonstrated the degree of *in vitro* antioxidant activity and the antioxidant activity of milk phospholipids that may be used to delay PUFAs oxidation. Phospholipids derived from whole milk can be used as functional products in nutritional formulations or other industrial processes (Sánchez-Juanes et al., 2009).

3 Conclusions

Milk fat is an important component of milk, which not only contributes to the nutritional quality of milk, but through the content of bioactive substances, it can also have a positive effect on health. Although there is a need to expand information and studies on effects in humans, the results of studies in cell and animal models show a positive relationship between consumption, eventual supremacy, and improvement in several disease states. Or they can act as preventive or protective components against various diseases. Through advances in the identification of genes involved in milk fat metabolism as well as the identification of individual fat components and the understanding of their metabolic pathways, opportunities to change the composition of milk fats are provided. From the point of view of human health, a change in the composition of milk, through the profile of beneficial substances, can have a positive effect on the nutritional quality of milk and dairy products. Due to the unique properties of these substances, there is the potential for the creation of functional foods and can also be used in the pharmaceutical industry.

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