The anticarcinogenic potential of milk fat

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Abstract

Introduction and objective. The anticarcinogenic potential of milk fat can be attributed to its antioxidant, anti-inflammatory, immunostimulatory properties as well as the presence of compounds with antimutagenic effects. In view of the high incidence of cancer the aim of this article was to review the literature concerning the biological activity of milk fat components.

Brief description of the state of knowledge. Conjugated linoleic acid (CLA), coenzyme Q10, phospholipids, β-carotene, and vitamins A, D and E play an important role in the pro-oxidant/antioxidant homeostasis. The anti-inflammatory properties of milk fat can be attributed to the presence of phospholipids and short- and medium-chain saturated fatty acids. Conjugated linoleic acid has immunostimulatory properties, and it influences the proliferation and activity of lymphocytes and macrophages. Saturated (C10 and C12) and unsaturated (C18) fatty acids, as well as sphingolipids, exert bactericidal effects in the gastrointestinal tract. Vaccenic acid, CLA and sphingomyelin possess antimutagenic and anticarcinogenic properties. Butyric acid promotes the apoptosis of cancer cells in the liver, and delivers positive effects in the treatment of breast and colorectal cancer. Alkylglycerols activate macrophages, stimulate phagocytosis and, most importantly, the apoptosis of cancer cells.

Conclusions. The health benefits of milk fat are not fully exploited due to its low consumption. Therefore, only some epidemiological studies have shown a negative correlation between the consumption of high-fat dairy products and the incidence of cancer. More research is needed involving human clinical trials to allow a better understanding of the anticancer biochemistry related with milk fat compounds.

Key words

milk fat, antioxidant properties, immunostimulatory and anticancerogenic potential

INTRODUCTION

Milk fat has unique properties due to its specific fatty acid profile that fully meets the nutritional needs of humans, as well as the sterosepecific structure of triglycerides which resembles that of human breast milk fat. Milk fat globules are coated with a phospholipid-protein layer which stabilizes the fat emulsion in the aqueous phase of milk, protects triglycerides against hydrolysis, and prevents the autoxidation of unsaturated fatty acids [1, 2].

All milk fat components, including saturated fatty acids (considered to exert atherogenic effects), are biologically active. The Western diet is deficient in active lipophilic antioxidants (CLA, phospholipids, coenzyme Q10, β-carotene, vitamins A, D and E). Antioxidant deficiencies disrupt the pro-oxidant and antioxidant homeostasis, which leads to chronic inflammation and increases the risk of cancer.

The type of consumed fat significantly influences pro-oxidant/antioxidant homeostasis. In diets abundant in vegetable fats, the demand for antioxidants increases proportionally (logarithmically) to the content of polyunsaturated fatty acids (PUFAs) and the number of unsaturated bonds. In contrast, milk fat promotes antioxidant homeostasis and is a source of unique ingredients with documented anti-inflammatory and anticarcinogenic properties. Despite the above, the health-promoting properties of milk fat have been discredited in the scientific community due to the high content of saturated fatty acids and cholesterol.

OBJECTIVE

In view of the high and steadily growing incidence of cancer, including in progressively younger ages, the aim of this article was to review the literature concerning the biological activity of milk fat components. The significance of milk fat components in cancer treatment is discussed.

Antioxidant potential of milk fat components. Milk fat is one of the most abundant sources of lipophilic antioxidants in the human diet. Conjugated linoleic acid (CLA) which is synthesized by ruminal microbiota from vaccenic acid (trans-11 octadecenoic acid) is the most active antioxidant in milk fat [3]. The CLA content of milk ranges from 2 – 37 mg/g of fat, and is determined by cattle breed, diet, age of the animal, age, season (CLA content is higher in May, June and July), and processing parameters, such as pasteurization, duration and conditions of storage. Fermented dairy products are much more abundant in CLA than non-fermented products [4].

Conjugated linoleic acid includes 28 positional and geometric isomers. The isomers with the highest levels of biological activity are cis-9, trans-11 and trans-10, cis-12 isomers. The cis-9, trans-11 isomer is predominant in the CLA complex (75–95%), and delivers health benefits on account...
of its very high antioxidant potential [5]. In vitro and in vivo studies have demonstrated that the cis-9, trans-11 isomer is more effective in protecting structural lipids against free radicals than α-tocopherol, even at low concentrations [6, 7].

Dairy products are rich in carotenoids and vitamin A which prevent the oxidation of LDL-cholesterol and inhibit lipid peroxidation in tissues with low partial pressure of oxygen. β-carotene is a much more effective scavenger of singlet oxygen and lipid peroxides than vitamins A, E and C [8, 9, 10]. Vitamin E, one of the key antioxidants in milk fat, and complements the antioxidant properties of vitamin A and its derivatives [1]. Dietary sources contain eight chemical forms of vitamin E, including four tocopherols (α, β, γ, δ) and four tocotrienols (α, β, γ, δ), where α-tocopherol is the main biologically active form of vitamin E [12, 13].

The above can be attributed to the fact that α-tocopherol is activated at body temperature and that α-tocopherol transfer protein (αTTP), a specialist protein produced by the liver, specifically binds and transports only this form of tocopherol [11, 13].

Milk fat contains only α-tocopherol which, despite low concentrations (13 – 30 µg/g fat), effectively protects milk fat against auto-oxidation. The chemical structure of α-tocopherol, which comprises a chromanol ring (head) and an isoprene side chain (tail), makes it the most active lipophilic antioxidant in the human body. In lipid bilayers, the hydrophobic tail is inserted between hydrocarbon chains, whereas the polar head is exposed to a hydrophilic environment. Cell membranes and blood plasma lipoproteins α-tocopherol are protected against ROS by scavenging organic free radicals, terminating lipid peroxidation and extinguishing singlet oxygen. These reactions produce a relatively non-reactive tocopheryl radical which can interact with other free radicals, or undergo regeneration to the basic structure of vitamin E in the presence of a reduced form of coenzyme Q10, or vitamin C. Vitamin E also supports the activity of glutathione-dependent enzymes and interacts with selenium and sulfur-containing amino acids in cell membranes to prevent the peroxidation of structural phospholipids. It exerts a protective effect on vitamin A and regenerates β-carotene [12, 13, 14]. Vitamin E maintains the healthy structure and permeability of cell membranes, which is particularly important for cells and tissues most exposed to oxidative stress, such as erythrocytes and alveoli [15].

Coenzyme Q10 found mainly in butter (7.1 mg/kg) and ripened cheeses (1.2–1.3 mg/kg) [16], transports electrons in the respiratory chain and participates in the formation of ATP in cells [17]. Coenzyme Q10 is a highly active antioxidant, and ubiquinone – its reduced form – protects cell membranes and LDL lipoproteins against peroxidation more effectively than α-tocopherol and β-carotene. Ubiquinol prevents the initiation and propagation of peroxidation of polyunsaturated fatty acids in lipids and phospholipids in mitochondrial membranes.

Coenzyme Q10 binds with proteins to stabilize mitochondrial membranes and guarantee their optimal fluidity. Ubiquinol enhances the antioxidant properties of vitamin E by participating in the regeneration of tocopherol radicals to tocopherol. Direct antioxidant effects in cells are induced by the reduced form of coenzyme Q10, whereas indirect effects are associated with vitamin E regeneration [17, 18]. The content of different antioxidants in milk fat is generally low.

Despite the above, these compounds stimulate the endogenous antioxidant systems in the human body. They prevent the oxidation of structural lipids by exerting pleiotropic and synergistic effects [19].

Immunostimulatory potential of milk fat components. Experimental evidence indicates that CLA influences the proliferation and activity of lymphocytes and macrophages, increases the cytotoxicity of T-cells and the phagocytic ability of leukocytes, and neutralizes bacterial endotoxins. It regulates eicosanoid transformations, modulates interleukin and leukotriene activity. The cis-10, c-12 isomer prevents the conversion of n-6 AA to E, prostaglandins, thus inhibiting the production of proinflammatory cytokines [20].

A randomized trial revealed that diets supplemented with a combination of cis-9, trans-11 and trans-10, cis-12 CLA isomers at a 1:1 ratio (3 g/day for 12 weeks) increased IgA and IgM levels and decreased the concentration of IgE. The analyzed isomers also induced a decrease in the concentrations of proinflammatory cytokines (IL-1) and tumour necrosis factor-alpha (TNF-α), and contributed to an increase in anti-inflammatory cytokine levels (IL-10) [21]. By modifying the fluidity and permeability of cell membranes, CLA exerts bacteriostatic and immunomodulatory effects, prevents hypertriglyceridaemia, and improves bone mineralization [22, 23, 24].

Short-chain and medium-chain saturated fatty acids which are found in milk fat and are synthesized from fibre by gut microbiota also exert indirect immunomodulatory effects. Both short-chain and medium-chain SFAs induce the growth, maturation and differentiation of colonocytes, which contributes to the formation of healthy epithelial structure in the gastrointestinal tract [25]. They are absorbed in the small and large intestines, regulate water and electrolyte adsorption, and stimulate colonic motility and contractility. By controlling the blood flow, SFAs supply nutrients and regenerate colonic mucosa. Short-chain SFAs which are supplied with food and produced by probiotic lactic acid bacteria, play equally important roles in the regeneration of the intestinal epithelium. They enhance the ionization of mineral compounds and increase their bioavailability [26].

Milk fat contains small amounts of PUFAs which are precursors of biologically active long-chain PUFAs. The ratio of n-6 linoleic acid to n-3 α-linolenic acid in milk fat (3.5–5: 1) is optimal for health. The dietary n-6/n-3 PUFA ratio determines the fatty acid composition of membrane phospholipids.

The above contributes to the differentiation of eicosanoids produced by n-6 arachidonic acid (AA) and n-3 eicosapentaenoic acid (EPA). The transformation of n-6 arachidonic acid leads to the production of proinflammatory and prothrombotic eicosanoids that weaken the immune system [27]. Excessive levels of n-6 PUFAs, which are found mostly in vegetable oils, increase the risk of cardiovascular disease and inflammatory conditions. The 5- and 12-lipoxygenases metabolize n-6 arachidonic acid to hydroxyeicosatrienoic acid (HETE), which decreases with a combination of trans-9, cis-11 CLA isomers at a 1:1 ratio (3 g/day for 12 weeks) increased IgA and IgM levels and decreased the concentration of IgE. The analyzed isomers also induced a decrease in the concentrations of proinflammatory cytokines (IL-1) and tumour necrosis factor-alpha (TNF-α), and contributed to an increase in anti-inflammatory cytokine levels (IL-10) [21]. By modifying the fluidity and permeability of cell membranes, CLA exerts bacteriostatic and immunomodulatory effects, prevents hypertriglyceridaemia, and improves bone mineralization [22, 23, 24].

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Vitamin A influences innate immunity by preserving the integrity of mucosal membranes, stimulating the synthesis of lysozyme and mucin, and enhancing the production of white blood cells. Vitamin A deficiency significantly
The antiproliferative activity of CLA has been confirmed and in studies of various cancer cell lines. The supplementation of animal diets with 0.05–1.5% CLA inhibited the progression of chemically-induced skin, gastrointestinal tract, and the highest consumption of ripened cheese, a rich source of CLA, breast cancer mortality rates were lower than in countries where ripened cheese was less popular.

Conjugated linoleic acid from milk fat exerts anticarcinogenic effects by entering into synergetic interactions with other compounds, including α-tocopherol, β-carotene, vitamins A and D₃, phospholipids, short-chain saturated fatty acids, vaccenic acid, coenzyme Q₁₀, and ether lipids. Natural cis and trans isomers of vaccenic acid (C18:1) play a unique biological role in membrane phospholipids and glycolipids by promoting the adaptation of microorganisms and macroorganisms to the surrounding environment. These isomers also participate in signal transduction from the cytoplasm to cell membranes, and activate membrane enzymes and receptors which protect the host’s cells and maintain cellular homeostasis. Vaccenic acid isomers significantly slowed down the proliferation of colorectal cancer cells in vitro, and the trans isomer was twice as effective as the cis isomer. The analyzed isomers preserved the healthy structure of cell membranes in the gastrointestinal tract.

Carotenoids quench singlet oxygen and effectively protect DNA against oxidation. Beta-carotene intensifies the synthesis of IL-12 which stimulates the proliferation, activation and cytotoxicity of NK cells. These mechanisms prevent skin tumours caused by exposure to UV radiation, whereas vitamin A – in particular retinoic acid – prevents the onset of carcinoogenesis, and β-carotene protects the body against the progression of cancer.

Plasma vitamin D levels higher than 30 ng/ml decrease the risk of lung, breast, intestinal and prostate cancer by 30–50%. By inhibiting the proliferation and differentiation of cancer cells and inducing apoptosis, vitamin D prevents carcinoogenesis and cancer metastasis.

Vitamin K₂ (menaquinone) induces apoptosis. Studies of brain, stomach and colon cancer cell lines have shown that vitamin K₂ inhibits the cell cycle. It enhances the expression of the protein responsible for DNA degradation, thus suppressing repair processes in cancer cells. Recent research into bile duct cancer and leukemia has shown that vitamin K₂ is capable of inducing autophagy. It also participates in oncosis, a form of cell death caused by ischemia, to which cancer cells are particularly susceptible. Menaquinone interacts with vitamin K₃ to inhibit angiogenesis which slows down the development of neoplastic cells. Vitamin K₂ modifies growth factors and their receptors by weakening their stimulatory effect on tumour initiation and progression. By inducing oxidative stress without toxic consequences for tissue health, K₂ contributes to the death of cancer cells.

Laboratory experiments and epidemiological research have demonstrated that vitamin K₂ has immense potential for treating various types of cancer. Vitamin K₂ inhibits the initiation, promotion and progression of human hepatocellular carcinoma cells. In various types of lung cancer, including small-cell carcinoma, squamous-
cell carcinoma and adenocarcinoma, vitamin K2 induces apoptosis by activating ‘suicide’ proteins [53]. A study of 11,000 male subjects has revealed that increased consumption of vitamin K2 can reduce the risk of prostate cancer by 35%. The health benefits of vitamin K2 were most apparent in patients with advanced prostate cancer [54].

Milk phospholipids, in particular sphingomyelin (which is found in the membrane of milk fat globules), protect skin cells against UV radiation [55]. Sphingomyelin exerted chemopreventive or even chemotherapeutic effects in mice with chemically-induced colorectal cancer [56]. Sphingolipid digestion products, ceramides and sphingosines, influence the growth, differentiation and apoptosis of cells, in particular in the intestinal epithelium [57].

The health benefits of MFGM lipids, in particular in the treatment of colon cancer, have been recently confirmed [58]. Research into other cell types indicates that sphingolipids can prevent damage caused by γ radiation and chemical compounds [59]. Due to the presence of long-chain SFAs in its structure, sphingomyelin is able to interact with cholesterol to create rigid domains known as lipid rafts, which compromises the survival of cancer cells and metastatic ability [60].

Milk fat phospholipids contain alkylglycerols and alkyl glycerophospholipids. Alkylglycerols activate macrophages: they increase the fluidity and responsiveness of cell membranes by mediating changes in surface receptors. These processes enable macrophages to secrete more than 60 substances that inhibit acute and chronic inflammations. Activated macrophages are capable of recognizing cancer cells. Alkylglycerols inhibit kinase C and cancer promotion. These potent antioxidants protect tissues against the toxic effects of hydroxyl radicals which are generated in large quantities during radiation therapy [61, 62].

13-methyltetradecanoic acid, a unique component of milk fat with an odd number of carbon atoms and a branched carbon chain, is capable of inducing the apoptosis of cancer cells [2, 63, 64].

Controversy surrounding the anticarcinogenic potential of milk fat. All milk fat components have antimicrobial, anti-inflammatory and immunostimulating properties, and they exert protective effects on gastrointestinal and respiratory mucosa. The anticarcinogenic potential of CLA, vaccenic acid, phospholipids, 13-methyltetradecanoic acid, and vitamins D₃ and K₂ has also been documented.

Despite the above, the results of epidemiological studies comparing the incidence of three types of cancer in people consuming low-fat and high-fat dairy products are inconclusive, non-replicable and highly controversial [65, 66, 67, 68, 69]. Epidemiological studies have revealed potential correlations between the consumption of milk fat and the risk of bladder cancer, but the results are ambiguous and inconclusive [70]. In a cohort study of Dutch women, a positive correlation was found between the consumption of butter and full-fat milk and the risk of bladder cancer [71].

According to other studies, high consumption of milk fat containing high levels of SFAs and cholesterol enhances the production of endogenous estrogens, and contributes to the initiation and promotion of cancer. On the other hand, several epidemiological and cohort studies have shown that dietary milk fat does not increase the risk of breast cancer [72, 73, 74]. In vitro experiments and animal studies have failed to provide convincing evidence that milk fat has carcinogenic properties. It should be noted that milk fat components, such as CLA, are renowned for their immunostimulatory and antioxidant potential. A meta-analysis has revealed that animal fats do not contribute to the risk of breast cancer [75]. Prospective studies have demonstrated that dairy products not only do not increase, but actually reduce the risk of breast cancer [76].

A study investigating the health status and diets of 64,904 Norwegian women revealed that overall consumption of dairy products, including milk, yogurt, various types of cheeses and ice-cream, is not correlated with the risk of breast cancer. Regular intake of cheese in the daily amount of 25 g minimized cancer risk by 50% in premenopausal women and by 20% in postmenopausal women [77]. High-fat dairy products are abundant in vitamins D₃ and K₂, Vitamin D regulates hormone levels and prevents the estrogen-induced proliferation of cancer cells by lowering progesterone and estradiol concentrations [78]. It has antiproliferative, proapoptotic and pro-differentiating effects on many types of neoplastic cells [79, 80].

According to a review of epidemiological research conducted by Barrubés et al. (2018), the consumption of dairy products, including full-fat milk products, is not correlated with the risk of colorectal cancer (CRC) [82]. A meta-analysis of the relevant literature did not reveal any correlations between the consumption of milk with different fat content and the risk of breast cancer [83]. However, the risk of aggressive prostate cancer was 74% higher in men who consumed the largest quantities of whole milk relative to subjects who did not consume whole milk [84]. Despite the fact that high consumption of dairy products has been linked with the risk of prostate cancer, the accumulated evidence is ambiguous, mainly due to statistical inconsistency [85].

The discrepancy between the results of research studies investigating the correlations between the consumption of dairy products and the risk of cancer could be attributed to the quality of the milk. Milk from cows affected by mastitis is characterized by high concentrations of inflammatory cytokines, eicoosanoids and acute phase proteins (produced by somatic cells). These parameters are correlated with higher levels of transforming growth factors (TGF) and insulin-like growth factor IGF-1, which plays a key role in the regulation of cell proliferation, differentiation and apoptosis [86]. The concentration of IGF-1 is several-fold higher in the milk of cows simulated with bovine somatotropin (rbGh) which radically increases milk yield and was approved for use in the USA in 1994 [87]. High blood levels of IGF-1 increase the risk of prostate and breast cancer [84, 88, 89]. For this reason, the use of rbGh in dairy cattle has been banned in all EU member states, Canada, Australia, New Zealand and Japan. In addition to compounds with documented anticarcinogenic potential, milk fat may contains compounds that contribute to the development of cancer, such as aflatoxins, pesticides and estrogens [90, 91, 92, 93]. The composition of milk fat is also determined by animal nutrition. The synthesis of bioactive compounds increased 3-5-fold in the milk of grass-fed cows (due to the predominance...
of cellulyotic bacteria in the rumen) than in the milk of cows fed TMR throughout the year [94, 95]. It should also be noted that only the milk of grass-fed cows supplies the daily CLA dose that is effective in cancer prevention.

Carcinogenesis is a complex process with many etiologic agents, which is why the influence of one or several nutrients on neoplasia is difficult to confirm or rule out with certainty. The presence of correlations between selected dietary components and increased risk of cancer does not constitute sufficient scientific evidence, especially since most nutrients exert pleiotropic effects.

The above can explain the different and often contradictory results of studies investigating the significance of milk fat in cancer prevention.

CONCLUSION

Milk fat is a rich source of lipophilic antioxidants (conjugated linoleic acid – CLA, phospholipids, vitamins A, E and D). These compounds occur in small quantities, but they effectively prevent oxidation processes in the human body due to their high thermostability and pleiotropic and synergistic interactions.

Many milk fat components deliver immunostimulatory effects. Phospholipids and long-chain saturated fatty acids have antiviral and antimicrobial properties. Short-chain and medium-chain SFAs regulate water and electrolyte adsorption, they contribute to the regeneration of the intestinal epithelium by promoting the growth, maturation and differentiation of colonocytes, and enhance the ionization and bioavailability of minerals. Eicosanoids derived from α-linolenic acid (n-3), as well as lipophilic vitamins, have anti-inflammatory properties. Conjugated linoleic acid directly contributes to an increase in IgA and IgM levels and a decrease in IgE levels and proinflammatory agents.

The unique components of milk fat (CLA, vaccenic acid, phospholipids, including ether lipids, 13-methyltetradecanoyl acid) and vitamins A, D₃ and K₃ have antioxidant, anti-inflammatory and immunostimulating properties and exert anticarcinogenic effects. However, milk fat can contain persistent organic pollutants (polychlorinated biphenyls, dioxins and pesticides) with mutagenic and carcinogenic properties of conjugated linoleic acids. The above can explain the different and often contradictory results of studies investigating the significance of milk fat in cancer prevention.

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