Cow’s Milk

Subjects: Food Science & Technology

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Cow’s milk (CM) is a healthy food consumed worldwide by individuals of all ages. Unfortunately, “lactase-deficient” individuals cannot digest milk’s main carbohydrate, lactose, depriving themselves of highly beneficial milk proteins like casein, lactoalbumin, and lactoglobulin due to lactose intolerance (LI), while other individuals develop allergies specifically against these proteins (CMPA).

cow’s milk lactose intolerance microbiota food allergy

1. What Is Cow’s Milk Made of?

Cow’s milk (CM) is our first food, although milk and its numerous derivatives are still consumed in adulthood and old age. However, whether milk is a healthy or unhealthy food compared to others is constantly being debated in the scientific community, and its consumption is often the subject of controversy.

It is true that humans are the only adult mammals who consume milk after weaning, but it is undeniable that it is a complete food from a nutritional perspective due to its high amounts of macronutrients, such as proteins, lipids and carbohydrates, and micronutrients, such as vitamins and minerals [1] (**Figure 1**). An extensive network of production and distribution ensures that milk is available to the consumer in all forms, fresh or long-life, depending on the method of processing. According to the “Codex Alimentarius Commission” instituted by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO), “Milk is the normal mammary secretion of milking animals obtained from one or more milkings without either addition to it or extraction from it intended for consumption as liquid milk or for further processing”. (https://www.fao.org accessed on 11 December 2023).

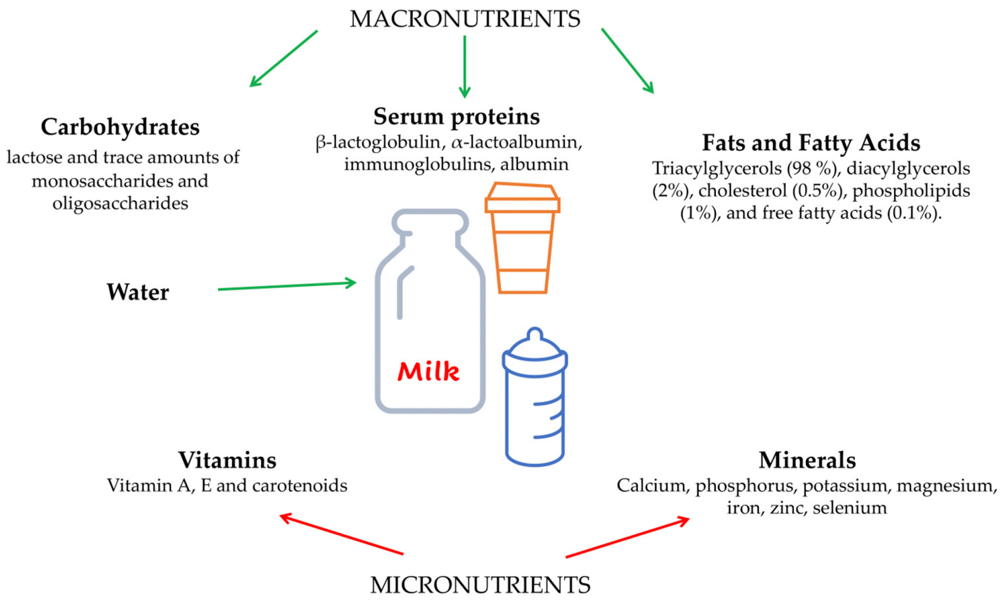

Figure 1. Schematic representation showing the components of cow milk. Parts of the figure were drawn using pictures from Server Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License.

However, there are different types of drinking milk commercially available that meet the needs of all consumers. There are, in fact, several types of milk modified in composition by the addition and/or withdrawal of some milk constituents, such as low-calorie milk, low-protein infant formula and obesity-risk milk, completely skimmed milk or milk supplemented with omega 3 fatty acids (FAs), calcium and protein. Therefore, milk products derive from different types of milk processing and may contain food additives and other functional ingredients necessary for the process. The aims of these adjustments, in terms of addition or withdrawal, are to protect the consumer and ensure the correct use of milk and milk products at all ages. It has been reported that protein intake during the first 6 months of life is higher in formula-fed infants (approximately 70%) when compared to breastfed infants [2].

It is thought that the lower protein concentration of breast milk can positively influence infant growth, possibly preventing childhood obesity- and adulthood obesity-related disorders. Currently, research is focused on understanding the underlying mechanisms of early protein intake on later health and the most appropriate infant formula for improved protein quality together with a reduced protein content for optimal growth. However, breast milk remains the gold standard of infant nutrition, providing a unique combination of nutrients and more. CM is considered by some to be the perfect food, not only for its nutritional value, but also for its hydration properties and its contribution to maintaining the stability of the intestinal microbiota and priming the immune system in infants [3].

CM and its derived dairy products play a significant role in providing a high-nutrient food source, with a positive impact on human health. The human diet typically includes milk as a source of proteins and microelements such as calcium. The composition of bovine milk can vary significantly in relation to many variables, such as cattle breed, lactation period, parity, and the animal’s health status [4]. Several environmental factors, such as nutrition type, can play a major role in the nutritional and organoleptic qualities of milk, both as a drink and as a foundation for dairy products. The chemical composition of milk includes a water content of 80% or more, as well as proteins, lipids, sugar, minerals, and vitamins (**Figure 1**).

Foroutan et al. performed a complete and exhaustive analysis on the chemical composition of commercial CM, taking into account the assessment of metabolites and macromolecules. In summary, the compositional analysis of milk reveals a set of key constituents, such as carbohydrates (lactose, glucose, and galactose), inorganic ions (potassium and calcium), organic acids (citrate) and amine-containing compounds (creatinine, choline, and urea). Smaller quantities of vitamins, triacylglycerols (TGAs) the dominant lipid components, di- and monoacylglycerols, FAs, short-chain fatty acids (SCFAs), amino acids, and other small bioactive compounds are also evident. In addition, milk also contains a number of macromolecules, including DNA and RNA, and several proteins such as the bovine casein peptides, β-lactoglobulin, and α-lactalbumin [5].

2. Cow’s Milk Proteins

The milk proteins have a high nutritional value, being rich in essentials amino acids (leucine, isoleucine, valine, lysine, histidine, methionine, and phenylalanine) [1]. Milk proteins, separated using membrane microfiltration procedures, may be found in the soluble whey fraction (20%), and in the insoluble micellar caseins fraction (80%). Whey proteins, also called serum proteins, include β-lactoglobulin (β-LG), α-lactoalbumin (α-LA), immunoglobulins (IgG1, IgG2, IgA, and IgM), serum albumin (BSA), and to a lesser extent, β-lactoferrin (β-LF), lactoperoxidase, lysozyme, vitamin-binding and metal-binding proteins, and hormones. They all possess a wide variety of biological significant functions [6][7], acting as health promoters. In particular, β-LG works as an immunoglobulin carrier during colostrum formation, α-LA may act as a lactose synthase component also having antimicrobial and anticancer activity, β-LF is a glycoprotein with iron binding and delivery functions transferrin-like and, moreover, exerting antimicrobial, antiviral, immunomodulatory, antioxidant and antitumor activity, lysozyme has antimicrobial functions, immunoglobulins protect the mammary gland from infections, BSA has anticancer and immunomodulatory activity and, finally, lactoperoxidase has antimicrobial and antioxidant properties. In the soluble fraction containing whey proteins, lactose, salts, vitamins, and trace amounts of other compounds are also found [8][9].

The insoluble micellar fraction of milk proteins is constituted by caseins that are present in milk in the form of self-assembled colloidal particles of 50–600 nm in diameter, known as “casein micelles”, and distinguished as αs1-casein, αs2-casein, β-casein, γ-casein, and κ-casein [10]. The micellar protein fraction has many bioactive functions and is responsible for several characteristics of milk, such as white color or coagulation capacity or heath resistance. Casein micelles are structurally complex and are able to carry calcium and phosphate, with κ-casein located on the globule surface, determining the size of the micelle, as well as preventing their aggregation [11].

β-casein is encoded by the CNS2 gene and 13 different allelic variants (A1, A2, A3, B, C, D, E, F, G, H1, H2, and J) have been described. A1 and A2 β-casein are the two most common variants, differing by only one amino acid at position 67. The A1 variant is only present in cattle, while the A2 variant is present in the milk of many mammals, including humans. Dairy cow breeds present different β-casein patterns in their milk and, nowadays, most milk marketed contains a mixture of A1 and A2 β-casein.

A2 milk appears to be healthier than A1 due to its natural antioxidant activity, resulting in glutathione production increase [12], and its lower amount of bioactive opioid peptide β-casomorphin 7 (BCM-7) released upon digestion, compared to A1 milk. BCM-7 is harmful for human health, due to its opioid-like activity as a result of binding to μ-opioid receptors, being responsible for pain and symptoms in the gastrointestinal tract as well as in the nervous system.

In addition, as reported in mice models, β-casein A1, compared to the β-casein A2, can increase the inflammatory response as well as intestinal permeability and IL-4 production by activation of the Th2 pathway [13]. Moreover, by measuring the TNF-α and histamine release from Human Mast Cells (HMC)-1 cells, the hypoallergenic property of A2 β-casein was demonstrated [14].

In fact, it was reported that α-caseins, β-caseins, and β-lactoglobulin inhibit cellular senescence, playing a protective role against oxidative damage of cellular components that results from the accumulation of Radical Oxygen Species (ROS), namely oxidative stress, thus preventing aging-associated diseases, or skeletal muscle loss. In addition, the enzymatic hydrolysis of several proteins generates many bioactive peptides that can exert protective functions, enhancing human well-being and health [15].

3. Cow's Milk Fats and Micronutrients

CM fats are mainly constituted by TAGs (98%), diacylglycerols (DAGs) (2%), cholesterol (0.5%), phospholipids (1%), and free FAs (0.1%). The wide presence of phospholipids in milk provides numerous benefits to human health, due to their structural and functional role in the cell membrane and in cell signaling, respectively. In milk, there are more than 30 classes of phospholipids, such as phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, and sphingophospholipid. In particular, these molecules are found within two fractions of milk: in the trilayer membrane surrounding fat globules and in nanovesicles secreted into milk by cells of the mammary gland [16]. To date, special attention has been given to milk-derived exosomes (MDEs), phospholipid bilayer nanovesicles released from breast milk. MDEs have been found in humans, cows, pigs, and rats and they seem to be involved in multiple biological processes. They are present at different lactation periods, such as colostrum or mature milk, and contain proteins, lipids, DNA, mRNA, microRNA and long non-coding RNA (lncRNA), thus protecting them against enzymatic and non-enzymatic degradation. MDEs play an emerging role as messengers between cells and, although little information is available about the role of lncRNA in MDEs, they are involved in gene expression and development [16]. Feng et al. reported that MDEs play an important role in the development and immune functions of the digestive tract thanks to their capacity to transfer their cargos to the cytoplasm of cell targets by endocytosis. Moreover, they report the hypothesis of their application as nanodevices for the development of new chemotherapeutic/chemopreventive carriers [17].

Sphingophospholipid is the major fat type present in milk [18], affecting human health in many different ways. In particular, a high concentration of sphingomyelin present in the phospholipid fraction of milk is important for neuronal development and protection from bacterial infections of neonates. In this fraction, there are also gangliosides, another kind of sphingolipid, that have potential bioactivities in brain function and the immune system [19][20].

The high complexity of fat milk derives from the wide variety of FAs bound to either the glycerol or sphingosine backbone. There are many variables that can be connected with FA amount and the composition of bovine milk, because they can be derived from either food or rumen microbiota activity and influenced by animal origin, stage of lactation, seasons and mastitis. Generally, the composition of the fat fraction is: 70% saturated (palmitic, myristic, stearic and SCFAs) and 30% unsaturated FAs (oleic, linoleic, a-linolenic) and a certain amount of trans-fatty acids (vaccenic acid).

Carbon chains length of FAs can vary from C2 to C24 and they can be saturated (SFA), monosaturated (MUFA) or poly-unsaturated (PUFA) due to the presence of single, for saturated, or at least one or more double bonds between the carbons for MUFA and PUFA, respectively. PUFA, like omega-3s, with the last double bond at the third carbon from the omega end of the chain, and omega-6s, with the double bond at the sixth carbon from the omega end of the chain, are considered “good” fats and an important part of a healthy diet because they are “essential”, since humans, and other animals, cannot synthesize them and must introduce them with the diet. The “optimal” ratio of omega-6s to omega-3s, as proposed by Benbrook et al., is suggested to be approximately 2:1 [21]. This balance is crucial, as an excess of omega-6s can prevent the effective utilization of omega-3s, consequently restricting their manifold health advantages. These benefits include mitigating the risk of cardiovascular disease, diabetes, and obesity. Although milk can be fortified with plant-based omega-3s, researchers are currently investigating the potential benefits of fortifying dairy cattle diets with omega-3s to influence the proportion of these healthy fats in milk.

The question arises whether an increased intake of omega-3s by cows corresponds to an elevation of omega-3s in their milk. While this relationship is true in humans and mammals, the dynamics between diet and milk composition in cows are complex and require further exploration [22]. As cows digest the fats in their food, the microbial activity in their rumen converts the double bonds of PUFA into single bonds, turning them into saturated FAs [21]. To this end, researchers are currently experimenting with different cow feeding with different combinations and concentrations of various vegetable sources of omega-3s and the results are promising.

Finally, in CM, there are also traces amounts of hydrocarbons, fat-soluble vitamins, flavor compounds, and a wide range of micronutrients, including minerals, such as calcium, phosphorus, potassium, magnesium, iron, zinc, selenium, as well as vitamins, such as vitamin A, E and carotenoids [23]. Some of them, like selenium, zinc, vitamin E, C, beta-carotene and sulfur, exert an important antioxidant activity themselves or as cofactors of antioxidant enzymes, like glutathione peroxidase, superoxide dismutase and catalase.

Therefore, several milk constituents have an antioxidant activity useful for preventing the consumer from metabolic and chronic ROS-related diseases such as diabetes, atherosclerosis and cancer.

Nowadays, the comprehensive association between dietary intake and diseases is not only complex but is also not easy to understand, with controversial scientific evidence. For example, although milk consumption is recommended for its high calcium content resulting in an increase in bone density and thus preventing the onset of osteoporosis, currently there is also considerable debate concerning the effect of calcium supplementation by itself in bone mass [24].

Recent studies have linked calcium supplements with an increased risk of colon polyps, kidney stones and cardiovascular disease (CVD) risk [25][26]; on the other hand, a meta-analysis of all placebo-controlled randomized trials demonstrated that there is not a significant association between calcium supplements, alone or with vitamin D, and risk for CVD and all-cause mortality [27].

In addition, in meta-analysis studies, Drouin-Chartier et al. report neutral associations between the consumption of various forms of dairy products and CVD, as well as favorable associations between total dairy intake and hypertension risk [28].

Furthermore, some studies reported that milk consumption could increase the risk of several Western diseases, including metabolic diseases such as diabetes [29][30], while other studies show that dairy consumption was inversely associated with the risk of developing cancer, including breast and colorectal cancer [31][32].

Nonetheless, it is unquestionable that, due to its chemical and biochemical composition, CM and its derivatives are a source of important macro- and micronutrients, suggesting that its consumption is crucial for development during the first years of life and still relevant in adulthood [33].

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