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Review

Role of Milk Micronutrients in Human Health

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Abstract

The aim of this review is to provide an overview of different compositions, in terms of main minerals and vitamins, of milk from animal species that represent the most common source of this food for humans, highlighting the uniqueness of nutritional qualities linked to animal species. It is known that milk is an important and valuable food for human nutrition, representing an excellent source of nutrients. Indeed, it contains both macronutrients (proteins, carbohydrates, and fat) that contribute to its nutritive and biological value and micronutrients represented by minerals and vitamins, which play a relevant role in the body's various vital functions. Although their supply is represented by small quantities, vitamins and minerals are important components for a healthy diet. Milk composition in terms of minerals and vitamins differs between various animal species. Micronutrients are important components for human health as their deficiency is causes of malnutrition. Furthermore, we report on the most significant metabolic and beneficial effects of certain micronutrients in the milk, emphasizing the importance of this food for human health and the need for some milk enrichment procedures with the most relevant micronutrients to human health.

Keywords: milk; minerals; vitamins; nutrition; food-fortification

1. Introduction

Milk is an essential component of the human diet. The term "milk" is associated with cow's milk since it represents 83% of world's milk production [1]. However, milk of other animal species is also used, whose properties are arousing increasing interest, for some beneficial effects on human health [2,3]. Human milk, according to the World Health Organization (WHO), is the first and extremely valuable food for infants up to 6 months of age. Although breast milk is strongly recommended, it is not always possible use it and therefore it is substituted with formula milk. Formula milk mimics the nutritional composition of breast milk, and cow's milk formula is among the three major classes of infant formulas [4]. However, this substitute is not suitable for children with cow's milk protein allergies [5], and a replacement with suitable alternatives is required, such as hydrolyzed cow's milk protein, hydrolyzed rice or soy protein, and amino acid–based formula [6]. Nevertheless, milk provides an excellent source of all the nutrients and its nutritive value has long been recognized; indeed, it contains both macronutrients (proteins, carbohydrates, and fat) (Table 1, Ref. [7]) that contribute to its nutritional and biologic value and micronutrients represented by minerals and vitamins, which play an important role in the body's various vital functions [8–10]. Among the bioactive molecules that have a major influence on the biological effects of milk are butyrate, conjugated linoleic acid, and omega 3 essential fatty acids. Butyrate, a short-chain fatty acid, has been known for its involvement in food allergy, inflammation, oxidative stress, and diabetes [11–14]. Conjugated linoleic acids are mainly effective against inflammation, obesity and cancer [15–17], while omega-3 polyunsaturated fatty acids are known to reduce inflammation and oxidative stress, playing a protective role in the cardiovascular and nervous systems [18–20]. The mineral content of milk and dairy products is composed of macroelements (calcium, phosphorus, magnesium, sodium, potassium, and chloride) and numerous microelements present in trace quantities. Both are concentrated in the ash, the inorganic part of the milk nutrients, present in various forms associated with different structural components. Conversely, vitamins are biologically active substances and together with other nutrients are the organic part of the milk nutrients, consisting of lipophilic vitamins (A, D, E, and K) and hydrophilic vitamins (B-complex vitamin and vitamin C). Factors influencing the milk composition are divided in genetic factors, e.g., the breed of cow, and in environmental factors, such as type of dietary regimen, seasonal modifications and milking systems. Furthermore, the composition of milk in terms of minerals and vitamins differs between various animal species. Although they are usually taken as trace amounts, vitamins and minerals are critical components of food and healthy nutrition. The inability of the body to synthesize vitamins makes their consumption indispensable for growth and maintaining health. Compared with other foods, milk offers a cheap and valuable source of vitamins and minerals [21]. Micronutrients are important for human health; indeed, their deficiency is a cause of malnutrition, which primarily affects the health of the most vulnerable groups in the population, as kids and pregnant women, especially in poorest countries. Some important micronutrient deficiencies with adverse health effects involve vitamin A, vitamin D and calcium [22]. Consequently, it is necessary to introduce into the market, milk with minerals (in particular calcium) and vitamins (mainly vitamins A and D) [23]. In this regard, a range of strategies have been put in place for increasing the mineral and vitamin content of milk, both acting on animal nutrition [24] and on direct enrichment "fortification". Fortification is defined as the process of incorporating micronutrients like essential vitamins into foods [25]. Milk is a good product for the process of fortification because is a staple food well accepted by the population. The aim of this review is to provide an overview on the micronutrients of milk from animal species that represent the most common source of this food for humans, highlighting the uniqueness of nutritional qualities linked to animal species. Furthermore, we report on the most relevant metabolic and beneficial effects of the major micronutrients of the milk, emphasizing the importance of this valuable food for human health. Finally, we report on the influence of raw milk processing on drinking milk micronutrients and provided an insight into some milk enrichment strategies with the most relevant micronutrients to human health.

Table 1. Macronutrient content of milk from different animal species.

	Human	Donkey	Cow	Sheep	Goat
(g/L)					
Proteins	9–19	14–20	30–39	45–70	30–52
Fat	21–40	3–18	33–54	50–90	30–72
Lactose	63–70	58–74	44–56	41–59	32–50

Source adapted and modified from Claeys *et al*. [7], 2014.

2. Review Methodology

Specific and comprehensive articles or reviews, mainly from the last decade, were considered in this narrative review, using PubMed database. The keywords used to find the right articles are the following: cow milk, donkey milk, sheep milk, goat milk, human milk, micronutrients, food-fortification, cow feeding techniques. A brief overview of the reviewed literature is reported in Table 2 (Ref. [7,26–37]). Limitations: aspects of only a few major micronutrients were considered in this review. In addition, only the types of milk considered to be of greatest interest for human consumption were considered. Strengths: the work done for this review is of a multidisciplinary nature, taking into consideration different research fields and different fundamental aspects in the composition of the milk as a final product.

3. Minerals and Vitamins in Milk of Different Animal Species

3.1 Minerals in Milk

Calcium (Ca) is the main mineral found in milk, divided into the soluble and micellar phases. In the watery phase, Ca is present in its free form combined with citrate, inorganic phosphate and whey proteins. Two thirds of Ca is bound to casein in the micellar phase, related to organic phosphate (phosphoseryl residues of casein molecules) [26]. Partitioning of this mineral between these phases is complex, highly dynamic and influenced by different factors, such as temperature, ionic strength and pH. The Ca is thermodynamically equilibrated between the water and micellar phase, in relation to the chemical condition. Biological acidification processes such as lactose fermentation, during processing of dairy products, are primarily responsible for moving Ca into the water phase [38]. Ca bioavailability in milk is high [39] and certain milk components, e.g., lactose and phosphopeptide may improve the uptake of this mineral [40]. Ca milk content is lower in human and donkey milk compared to cow's milk, while in sheep's and goat's milk is present a higher concentration (Table 3, Ref. [7,36,41–44]). Milk represents an important source of Ca to the human diet.

Phosphorus (P), an important component of milk and dairy products, is present in different forms of organic and inorganic phosphates and in various localizations. The organic form of P binds various molecules, mainly to casein molecules, in the micellar phase. The inorganic form of P is divided between the water and micellar phase. This mineral is transferred into the water phase mainly during acidification processes. P is mostly abundant in goat's and sheep's milk (Table 3) and is present in various animal foods [45]. Therefore, there is no shortage of this mineral for humans.

In contrast to Ca and P, magnesium (Mg) is not a very abundant component in milk and milk products. The effects of Mg on physiochemical stability of whey protein are similar to those for Ca. It is present in the micellar phase bound to casein proteins, while in the water phase is associated with citrate and P. Two thirds of Mg is present in the soluble part of milk [46]. This distribution, as well as Ca and P, depends on the physiochemical condition. Mg is found in higher concentrations in sheep's and goat's milk (Table 3). Milk and dairy products are good contributors of dietary Mg.

Sodium (Na) and potassium (K) are present mainly as free ions in the water phase of milk and milk products and

Table 2. Brief overview of the reviewed literature.

Authors	Title	References
Barone G, *et al*. *Int Dairy J*. 2021	Calcium fortification of a model infant milk formula system using soluble and insoluble calcium salts	[26]
Cobo-Angel C, *et al*. *Animal Frontiers*. 2014	Selenium in milk and human health	[27]
Vincenzetti S, *et al*. *Beverages*. 2020	B-Vitamins Determination in Donkey Milk	[28]
Vincenzetti S, *et al*. *Nutrients*. 2021	Vitamins in Human and Donkey Milk: Functional and Nutritional Role	[29]
Gentili A, *et al*. *J Agric Food Chem*. 2013	Comprehensive profiling of carotenoids and fat-soluble vitamins in milk from different animal species by LC-DAD-MS/MS hyphenation	[30]
WL Claeys, *et al*. *Food Control*. 2014	Consumption of raw or heated milk from different species: An evaluation of the nutritional and potential health benefits	[7]
Saeterdal, *et al*. *Cochrane Database Syst Rev*. 2012	Fortification of staple foods with vitamin A for vitamin A deficiency	[31]
Kay JK, *et al*. *J Dairy Res*. 2005	A comparison between feeding systems (pasture and TMR) and the effect of vitamin E supplementation on plasma and milk fatty acid profiles in dairy cows	[32]
Woźniak D, *et al*. *Foods*. 2022	Reasonableness of Enriching Cow's Milk with Vitamins and Minerals	[33]
Polzonetti V, *et al*. *Nutrients*. 2020	Dietary Intake of Vitamin D from Dairy Products Reduces the Risk of Osteoporosis	[34]
Itkonen ST, *et al*. *Nutrients*. 2018	Vitamin D Fortification of Fluid Milk Products and Their Contribution to Vitamin D Intake and Vitamin D Status in Observational Studies-A Review	[35]
Niero G, *et al*. *J Dairy Sci*. 2019	Validation of a gold standard method for iodine quantification in raw and processed milk, and its variation in different dairy species	[36]
Perales S, *et al*. *J Agric Food Chem*. 2006	Fortification of Milk with Calcium: Effect on Calcium Bioavailability and Interactions with Iron and Zinc	[37]

Table 3. Mineral content of milk from different animal species.

	Human	Donkey	Cow	Sheep	Goat
(mg/100 g)					
Ca	28–34	33–115	112–123	159–242	130–197
P	14–43	32–73	59–119	124–175	79–153
Mg	3–4	2–8	7–12	16–25	14–36
Na	10–18	10–27	42–58	30–75	28–59.4
K	53–62	24–75	106–163	94–162	140–242
Fe	0.04–0.2	0.04–0.26	0.03–0.1	0.08–0.1	0.05–0.3
(μg/100 g)					
Se	1.8	trace	1.7	1.7	1.1–17
(μg/kg)					
I	144	7.26	66.82	243.16	591.06

Source adapted and modified from Claeys *et al*. [7], 2014; Niero *et al*. [36], 2019; Verduci *et al*. [41], 2019; Balthazar *et al*. [42], 2017; Barłowska *et al*. [43], 2011; Fernández-Sánchez *et al*. [44], 2007.

their concentrations are increased by salting [47]. These minerals contribute to the cheese's physical-chemical properties [48], to the micro-organism's selection and to enzymatic activities throughout maturation processes. Na is a mineral quite present in milk and found in different concentration in animal species. Indeed, it is in twice the concentration in goat's, sheep's and cow's milk than in human and donkey milk, as reported in Table 3. Similarly, K, the most abundant mineral in milk, is present especially in ruminant milk, while its concentration is lower in human and donkey milk (Table 3). Iron is deficient in milk; indeed, is present in low concentration and associated with casein and whey proteins [49,50]. Selenium (Se) is a mineral found particularly in milk and dairy products [51], and mainly present bound to casein molecules and whey proteins [52]. Se can be found in two distinct forms: inorganic and organic. Inorganic forms include selenate (Na_2SeO_4) and selenite (Na_2SeO_3), whereas the organic form includes selenomethionine (SeMet) and selenocysteine (SeCys). The organic forms of selenium are better absorbed by animals and humans [53]. Studies demonstrated that its content in milk depends largely on selenium supply in feed ration for cows [54]. Animal products, such as milk, are considered the basic source of this micronutrient in the diet of human, representing a good source of Se for human needs [27]. Milk and milk products are the main sources of iodine (I) for human in a large number of countries [55,56]. The concentration of this micronutrient in milk is affected by different factors, such as: iodine content of the animal' diet, sanitation practices used for teat dipping, season, farming system and dietary supplement [57]. I compounds are soluble in water, and it is likely that milk I increases in partially skim milk. Recent evidence showed that this micronutrient might be partially associated with casein micelles [36]. Furthermore, the analysis of the I content in different milk showed that goat milk and donkey milk provided a greatest and a lowest iodine content, respectively [36] (Table 3).

In milk from different animal species, the minerals are distributed differently in soluble and non-soluble fractions (mainly casein micelles). K and Na are present in the water phase, while P, Ca, Mg, Se and I are partly linked to casein micelles. Mineral composition in milk is regarded as relatively constant, but the mineral content can vary mainly according to the lactation stage, the nutritional and health status of the animals [58]. In summary, milk is a food rich in precious minerals with mineral composition varying according to the animal species. Comparing the different animal species considered, it appears that sheep's and goat's milk are the richest in minerals compared to other types of milk, as reported in Table 3.

3.2 Vitamins in Milk

Vitamins play an important role in intermediate metabolism as co-factors in many enzymatic reactions or in non-enzymatic physiologic functions, and do not function as structural components within the cell. The vitamin content in milk varies considerably among mammals and is closely related to the type of feeding given to the animals. In particular, increased vitamin E and carotenoids have been observed in milk and dairy products obtained from pasture-fed cows compared with those obtained from milk of cows on corn silage feeds [59]. Milk and milk products contain both water-soluble vitamins (vitamins B-complex and vitamin C), and liposoluble vitamins (A, D, E and K) [60]. The water-soluble vitamins are situated in the watery phase of milk and therefore present in skim milk; while the liposoluble vitamins found in the lipidic phase, as in whole milk, cream and cheese. B complex vitamins perform numerous and important cellular functions, being implicated as cofactors in anabolic and catabolic reactions. Thiamine or vitamin B_1 and riboflavin or vitamin B_2, are produced from plants and micro-organisms [61]. In particular, riboflavin is produced especially from bacteria present in the rumen and is thus very present in the milk of ruminants. In general, both vitamin B_1 and vitamin B_2 are present in higher levels in ruminant animals compared with non-ruminant species. However, both these vitamins have also been found in abundant quantities in donkey's milk (Table 4, Ref. [7,29,41]) and are relatively stable to heat treatment and acid condition. Niacin or vitamin B_3 is primarily produced by microbial organisms of the rumen [61] and found in high concentrations, especially in sheep's milk. Recent investigations have also found a good concentration of vitamin B_3 in donkey milk [28]. Pyridoxine or vitamin B_6, synthesized from plants and micro-organisms, is involved in several biochemical pathways, such as in the metabolism of amino acids, lipids and glucogenesis [62]. The concentration of this vitamin is higher in sheep's and cow's milk than in milk of other animal species reported in Table 4. Folic acid or vitamin B_9 is a micronutrient involved in nucleic acids synthesis, is very sensitive to different physicochemical conditions [63] and is found in a higher content in cow's milk and human milk, compared to other species (Table 4). Milk provides a significant source of folic acid to humans [29]. Cobalamin or vitamin B_{12} originates from microorganisms in the digestive tract, through microbial synthesis in the rumen [64,65]. It is involved in various important functions of the organism and in milk is mainly bound to proteins. Vitamin B_{12} is mostly present in ruminant milk, which contributes largely to human intake. In particular, the vitamin is found in higher concentration in cow's and sheep's milk. Ascorbic acid or vitamin C has been known as an antioxidant molecule [66], found in milk but not in milk derivatives, as a result of its degradation during their processing. Vitamin C has a high sensitivity to light and heat treatments and milk cannot be considered an interesting source.

The fat-soluble vitamin content of milk is related to the overall fat content of milk. Vitamin A is found in various forms: retinol, retinal and retinoic acid and is highly sensitive to oxidation, light or different oxidant factors [67]. The concentration in milk declines after heat-treating and acidification processes [68]. The content of vitamin A is higher in breast and sheep's milk compared to other ani-

Table 4. Vitamin content of milk from different animal species (μg/100 mL).

	Human	Donkey	Cow	Sheep	Goat
(μg/100 mL)					
Thiamine	14–17	21–60	28–90	28–80	40–68
Riboflavine	20–60	30–97	116–202	160–429	110–210
Niacine (B_3) (mg/100 g)	0.18	0.09	0.13	0.41	0.24
Piridoxine (B_6)	11–14		30–70	27–80	7–48
Folic acid (B_9)	5.2–16		1–18	0.24–5.6	0.24–1
Cobalamin (B_{12})	0.03–0.05	0.11	0.27–0.7	0.30–0.71	0.06–0.07
Vitamin A	60	58	41	64	48
Vitamin D	0.06	2.23	0.08	0.18–1.18	0.25
Vitamin E	300–800	5.1	20–184	120	
Vitamin K	0.2–1.5		1.1–3.2		

Source adapted and modified from Claeys *et al.* [7], 2014; Verduci *et al.* [41] 2019; Vincenzetti *et al.* [29] 2021.

mal species listed in Table 4. In western countries, there is no lack of vitamin A, and milk may be regarded as a good source of the vitamin. Vitamin D is a group of components, the most important are ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3), synthesized by plants and in the animals' skin under the effect of the sun, respectively. This vitamin exerts many important physiologic functions for human health, is unstable to light, oxidation factors, heat and acidic conditions [30]. As illustrated in Table 4, milk contains a very low amount of vitamin D, and the lowest level is found in breast milk. Therefore, milk should not be regarded as a major source of this vitamin. The term vitamin E refers to a group of eight molecular forms with antioxidant activity, produced by plants and divided into 2 groups: tocopherol and tocotrienol. The main vitamin E in milk is alpha tocopherol, is found in higher concentration in breast milk, representing a good source compared to other animal species (Table 4). Phylloquinone or vitamin K_1 and menaquinone or vitamin K_2 are vitamins produced by plants and by micro-organisms present in the rumen, and its content is higher in cow's milk [69] as reported in Table 4. Vitamin K content is low in milk, but in fermented products is present in significant quantities. Nevertheless, both milk and milk derivatives are not considered to be an important source of the vitamin. As reported in Table 4, ruminant milk is a good source of B-complex vitamins, while human milk is distinguished by its vitamin A and vitamin E content.

4. Role and Beneficial Effects of Certain Milk Micronutrients on Human Health

4.1 Calcium

Ca is the major mineral in the human body and plays different structural and functional roles. Indeed, it is important to proper skeletal development [70] and many cellular metabolic processes, such as nerve and muscular cells and for normal blood pressure maintainance [71]. This ion helps to form and maintain the excitability of tissues and conduction of nerve tissue stimuli [72]. Ca plays an important role in the blood coagulation processes. Maintenance of a constant concentration is therefore of vital importance. Vitamin D, lactates and citrates support its absorption in the digestive tract. Dietary Ca derives from milk and milk products, primarily from cheese. Therefore, the main sources of this mineral are skim milk, yogurt and semi-skim cheese, since the lactose they contain promotes its absorption.

Despite milk and dairy products being sources of calcium, the bioavailability of this mineral is influenced by several factors, such as the physiological intestinal barrier, the ratio of calcium to phosphorus, the presence of lactose, vitamin D, oxalates, phytates or some fiber components [73]. In particular, plant foods contain considerable antinutritional factors, such as oxalates and phytates. These bind to calcium and form insoluble salt complexes, resulting in lower absorption [74].

As well as for other micronutrients, in some conditions such as aging and during pregnancy, the need Ca intake increases and it is quite difficult to meet recommended Ca levels, leading to the necessary use of Ca-fortified dairy-based products. In fact, the lack of calcium mainly has repercussions on bone health at all ages, since it causes rickets in infants, delays the acquisition of proper bone mass at the time of skeletal development in adolescents and is responsible for accelerated bone loss in adulthood in both women and men, leading to the development of osteoporosis [75].

4.2 Selenium

Selenium (Se) is an essential trace element for humans and animals. Most of the Se in milk is protein bound [76]. Indeed, this mineral is often found in the form of selenoprotein and is involved in various physiological functions, such as the enhancement of immunity and oxidation resistance [77]. Se is important as enzymatic cofactor in various biological systems and plays an important role in antioxidant enzyme processes [78]. The absorption of Se is mainly through the diet and the dietary levels of antioxidant agents, such as vitamins C and E, methionine and total protein can increase the bioavailability of Se. Milk and its products contribute over 4% of the total dietary Se consumed by humans [79]. In milk, about 60–80% of Se is bound to caseins. Se content of forages/feeds generally depends on the season and agro-ecological conditions, which can subsequently affect its milk content. Studies have been conducted in different places around the world in order to document the Se content in milk from dairy cows, evidencing a considerable variability, depending mainly on the amount of this element in the soil. The selenium content in cow's milk from European countries is in a wide range: in Greece, 110 μg/L; in Hugary, 41–90 μg/L; in England, 12–43 μg/L and in Scotland, 30–60 μg/L [54,80,81]. Therefore, the levels of Se within human tissue depends on dietary intake, which is related to Se availability in the soil and its geographical distribution [82]. Findings obtained in Finland showed that Se content of milk was doubled, increasing its content in the mineral fertilizers [83]. Se is a common ingredient in food supplements, allowing for adequate dietary intake. Both excessive Se intake and Se deficiency can have adverse effects on human health. Indeed, the excessive consumption can also lead to gastrointestinal disturbances, skin lesions, liver cirrhosis and pulmonary edema [53]. The deficiency for this element in the body may contribute to some issues related to cancer, cardiovascular disease, and nervous system alterations [84].

4.3 Iodine

Iodine (I) is an important element in human health, as it is key component of thyroid hormone [85]. Thyroid hormones are essential for the cellular metabolism and the proper fetal development [86]. In addition to being a structural and functional component of thyroid hormones, it also plays a significant role as a bactericidal because of its oxidative properties [87]. The amount of I in natural foods is highly variable and mainly depends on the soil where plants and animals grow [88]. Milk and milk products can have a significant I concentration and therefore considered among the most common dietary sources of this mineral [89]. Several studies showed that a low I intake results in poor development of neurological and physical functions in children [90]. Furthermore, in adults mild-to-moderate I deficiency increases the incidence of hyperthyroidism due to toxic goiter [91]. On the other hand, the excess I intake has been associated with the development of autoimmune thyroiditis and hypothyroidism [92].

4.4 Vitamin A

Vitamin A represents a group of organic compounds represented by two principal forms in foods: retinol, found in animal-sourced foods; and provitamin A, known as beta-carotene, present in animal and vegetable foods [93]. Vitamin A is an important nutrient required throughout life, which generally functions as a mediator in various metabolic and physiological processes within the body. Vitamin A is one of the key components involved with visual function, but also in development and cellular differentiation, primary epithelial cells and bone tissue [94]. It also sustains fetal development and embryonic growth [95]. Furthermore, it keeps the immune system active and strengthens its humoral and cellular components [96]. Vitamin A represents one of the most efficient substances in delaying aging, as is involved in maintenance, regulation, and repair of adult tissues [97]. It accelerates skin regeneration by influencing protein synthesis, metabolism and cell proliferation. Lack of vitamin A leads to night blindness, xerophthalmia (progressive blindness due to drying of the cornea of the eye), keratinization (accumulated keratin in the digestive, respiratory and urinary-genital tract tissues) and at last exhaustion and death [98]. A good source of vitamin A is represented from milk and milk products, and the fat content of milk facilitates the dissolving and absorption of vitamin A. Vitamin A is stored in the body and, therefore, deficiency disease is difficult. Nevertheless, the lack of vitamin A is a serious public health problem in many low- and middle-income countries. This primarily concerns young children, women of reproductive age and pregnant women [31]. Especially in this context the intake of milk and milk products fortified with vitamin A can have a positive impact on the functioning of the immune system [99].

4.5 Vitamin D

The term vitamin D refers to a group of fat-soluble secosteroids: the two main forms are vitamin D_3 (cholecalciferol) of animal origin and vitamin D_2 (ergocalciferol) present in fungi and certain plants [100,101]. Vitamin D_3 is synthesized by sunlight into the skin of humans and animals. These two forms of vitamin share essentially the same metabolism. Vitamin D actives several molecular pathways and mediates a multitude of functions. The classic role of vitamin D is the regulation Ca and P homeostasis and bone metabolism, regulating the mineralization and remodeling during growth [102]. Indeed, it increases the uptake of Ca and phosphate in the gastro-intestinal tract, promoting bone mineralization processes [102]. Also, vitamin D plays an important role in the innate and the adaptive immune system [103,104]. In addition, it plays an important potential protective effect against cancer development and progression [105]. Vitamin D overdoses occur less frequently than deficiencies. In adults, a lack of vitamin D causes disorders of bone structure, such as osteomalacia a disease characterized by the incomplete mineralization of osteoid, whereas in children, it is responsible for rickets. Rickets is a disease characterized by a decrease in the mineralization of bone tissue and growth plates, resulting in weak bones in infants and children [34]. Chronic lack of vitamin D dietary intake is the cause of secondary hyperparathyroidism, which is a cause for increased bone turnover, with consequent progressive bone loss and finally an increased risk of bones fracture [106]. Several studies showed that vitamin D deficiency is evident in a large part of the population, a concern prevalence rate, requiring public health intervention [107] and in certain countries (e.g., United States, Canada, Finland, Poland), some vitamin D-enriched foods are used to compensate for shortages. Vitamin D content in milk is low, and various foods on the national market are already improved by manufacturers with the vitamin, such as milk and milk beverages, yogurt [108].

4.6 Vitamin E

Vitamin E (primary its isoform a-tocopherol) is an essential antioxidant, which protects cell and sub-cell membranes against attacks of endogenous and exogenous free radicals [109]. The main role of vitamin E is the protection of lipids against oxidative damage. It has been demonstrated that vitamin E acts not only as an antioxidant but also, as a modulator of signal transduction and a regulator of genetic expression. Indeed, some isoforms regulate gene expression in different tissues and cell types [110,111] and are essential in preventing cardiovascular diseases, especially in coronary artery disease and atherosclerosis. The non-antioxidizing functions of vitamin E can involve several cell- signaling pathways which cause inhibition of the proliferation of smooth muscle cells, platelet adhesion, and aggregation of adhesion molecules. Signs of vitamin E deficiency include ataxia, retinopathy, peripheral neuropathy, musculoskeletal myopathy, and immune response disorders [112]. Vitamin E content in animal foods is generally low, but such products can provide important sources of the vitamin for humans due to their high intake. While the vitamin E content of milk is low, fortification of milk with this vitamin may have an important impact on public health.

4.7 B-Complex Vitamins

Vitamin B is a complex of a broad array of compounds which are essential for maintaining good health and well-being [113]. Vitamin B_1 or thiamine is regarded as one of the least stable vitamins [114]. It is a cofactor of several critical enzymes, linked to the metabolism of carbohydrates and branched-chain amino acids [115]. Indeed, vitamin B_1 is a coenzyme implied in transketolation reactions of the pentose-phosphate pathway, and pyruvate dehydrogenase catalyzed oxidative decarboxylation. In addition, thiamine is important for many other cellular processes, such as nucleic acid precursor synthesis, myelin, and neurotransmitters [116]. Thiamine deficiency can affect the cardiovascular, nervous, and immune systems, both severely and chronically as beriberi or Wernicke-Korsakoff syndrome [117]. Vitamin B_2 or riboflavin is the precursor of flavin mononucleotide and flavin adenine dinucleotide. The flavoprotein coenzymes are implicated in oxidation-reduction reactions which enter into numerous metabolic pathways, affecting cell respiration in fats, protein, and carbohydrate metabolism [118]. In addition to increasing energy, riboflavin acts as an antioxidant for a healthy immune system. Its deficiency may be linked to numerous developmental abnormalities, growth delay, cardiac disease and anemia [119]. The term niacin is frequently used to refer to a group of related chemicals, mainly nicotinamide (pyridine-3-carboxamide) and its derivatives. Vitamin B_3 has a broad spectrum of functions, as cofactor of many oxidoreductase enzymes involved in glycolysis, lipid metabolism, protein metabolism and detoxifying processes. Vitamin B_3 deficiency causes a condition called pellagra, which is characterized by photosensitive dermatitis, diarrhea, dementia and death [120]. Vitamin B_6 consists of a variety of compounds, implicated as coenzyme in different biochemical reactions. It is a coenzyme of many reactions linked to protein metabolism, in particular involving decarboxylation and transamination reactions. Vitamin B_6 is also involved in metabolizing carbohydrates, lipids, amino acids, and nucleic acids, and contributes to cell signaling. Several of the B_6 vitamers have been reported to have potent antioxidant activity [121]. Vitamin B_9 or folic acid naturally exists in multiple forms and plays a role as cofactors in essential biochemical reactions critical for cell division [122]. It is critical for the synthesis, replication, and repair of nucleotides for DNA and RNA and is therefore necessary for cellular proliferation and survival [123]. Also, this vitamin has a protective effect against neural tube defects, ischemic events and cancer [124]. Vitamin B_9 deficiency also decrease lymphocyte proliferative response and natural killer cell activity [123]. Among B vitamins, vitamin B_{12} occupies a very special niche. It is a molecule containing ion cobalt and involved in multiple metabolic reactions. This vitamin is only produced if the cobalt supply is adequate [125]. Vitamin B_{12} functions primarily as a coenzyme in the intermediate metabolism, in particular in transmethylate reactions. It is essential to the health of nerve tissue, the functioning of the brain and the production of red blood cells [126]. Higher levels of vitamin B_{12} are found in ruminants, indeed, is biosynthesized by rumen microorganisms and related to the cow's cobalt consumption [127]. Major effects of vitamin B_{12} deficiency in humans include pernicious anemia and neuropathy, due to its important function on cell division [128]. Among the B vitamins, milk is a particularly rich source of riboflavin or vitamin B_2 and vitamin B_{12}.

4.8 Vitamin C

Vitamin C or ascorbic acid exhibits many biological functions, such as antioxidant, collagen, and neurotransmitter synthesis [129]. Vitamin C is important to maintain the integrity of the intracellular matrix and to improve the immune system [130]. Vitamin C deficiency manifests symptomatically with irritability and anorexia, poor wound healing, gingival swelling with loss of teeth, mucocutaneous petechiae, bruising, and hyperkeratosis [131]. Milk is not usually considered an important source of vitamin C, mainly because concentrations are significantly reduced during handling and storage.

5. Bioactive Peptides in Milk

Protein-mineral interactions in milk are essential for the functionality of milk and the nutritional benefits that provides. The protein or peptides of milk can function as carriers, chelators of various minerals and thus enhance or inhibit bioavailability [132]. Milk and milk products provide a wide range of bioactive compounds, among them proteins such as caseins, whey proteins, and other minor constituents, have been seen to exhibit important biochemical and physiological functions on human metabolism and health [133–135]. The caseins, which accounts for about the 80%, are divided in α-caseins, which in turn comprise s1-, s2-, β-, and k-caseins. The whey proteins are a heterogeneous group of heat labile globular protein constituted mainly by α-lactalbumin, β-lactoglobulin, serum albumin and immunoglobulins, and to a lesser extent by lactoferrin and lysozyme [136,137]. In particular, lysozyme is a peptide with bactericidal action, since it breaks the bacterial cell wall. In the whey protein fraction, there are also enzymes, hormones, nutrient transporters, growth factors, disease resistance factors, and others. Bioactive peptides have been defined as specific protein fragments that have a positive influence on physiological and metabolic functions or condition of the body and may have ultimate beneficial effects on human health [138]. Bioactive peptides are released during gastrointestinal digestion and fermentation of food materials by lactic acid bacteria. The caseins, αs1-, αs2-, β- and k-casein, are most often reported as precursors of peptides containing binding sites, phosphoseryl and carboxyl, for different minerals [139]. Indeed, caseinophosphopeptides has the function of carriers for different minerals by forming soluble organophosphate salts, especially Ca^{2+} ion. Lactoferrin is among the whey proteins most involved in forming mineral bonds; in fact, it is an iron-chelating glycoprotein, which plays an important role in iron absorption in the intestine [140].

6. Effects of Thermal Treatments on Milk Micronutrients

Drinking milk is produced from raw milk through a series of steps that include: collection, normalization that allows reaching the right fat content based on the type of milk to be produced (skimmed, partially skimmed or whole), homogenization to break up the fat globules suspended in the milk to distribute them throughout the entire volume avoiding the accumulation of fat on the surface, heat treatments such as pasteurization or ultra-high temperature (UHT) sterilization and finally spillage into commercial packaging for storage and sale [141]. It is well known that heat treatments of milk affect both mineral distribution (especially calcium and phosphorus) between its aqueous and colloidal phase, e.g., a reduction in the solubility of calcium phosphate is observed [142,143], and on the concentrations of micronutrients in milk. While no substantial loss of B complex vitamins as vitamin B_2, B_3, B_5, B_6 and B_7 by heat treatment was observed (only a reduction of less than 10%) [144], losses of vitamin B_1, B_{12} and C increased from 10–20% in pasteurization and UHT treatment to 90% loss of B_{12} in bottle sterilization and evaporation [145,146]. The fat-soluble vitamins of milk are not much affected by heat treatment. Indeed, no significant differences in vitamin A and carotene content in raw, pasteurized and boiled milk were observed [147]. Since Vitamin A is susceptible to light exposure, the choice of packaging material is a critical parameter affecting vitamin stability in heat-treated milk, which shows major stability in milk stored in dark bottle and transparent polyethylene (PET) bottles [148]. Similar to vitamin A, vitamins D, E and K are more susceptible to light exposure comparing to heat treatment (especially vitamin D) [142,149]. Overall, current industrial practices for heat treatment of milk result in limited decomposition of milk vitamins as heat-triggered interactions of vitamins with milk components (i.e., proteins, fat) may well play a protective role on their heat-stability [150].

The milk processing objective is to reduce microbial pathogens in raw milk, but several multiple evidence showed that homogenization and pasteurization, through disruption of fat globules and casein micelles, alter the milk fat and protein molecular structure, increasing the allergenicity of processed milk [151]. The casein, beta-lactoglobulin and alpha-lactalbumin are mainly involved in cow's milk protein allergy. The exclusion of milk and derivatives from the diet is known to cause nutritional deficiencies in macro and micronutrients [152,153]. However, not excluding these products from the diet in people allergic to proteins or also lactose intolerant (due to the deficiency of the lactase enzyme), produces a wide spectrum of adverse symptoms that mainly affect the gastrointestinal tract but also causes dermatitis and respiratory problems [154,155].

7. Systems to Enrich Milk in Minerals and Vitamins

Different factors influence the micronutrient concentration in milk, both genetic factors, such as animal breed and environmental factors, like seasons, soil, and feeding regimens. One of the major factors that affect milk composition is the animal's diet. A number of studies have shown that increased grazing intake from cows effects on milk quality, indeed, increased levels of n-3 fatty acids, vitamins A, E, carotenoids, and phenols in milk was observed [32,156]. For example, higher consumption in pasture (usually associated with lower consumption of concentrate feed) has been associated with higher concentrations of polyunsaturated fatty acids [157–159]. In addition, production systems that are more dependent on grazing have produced milk with higher levels of antioxidants and vitamins [160]. The concentrations of minerals and trace elements show wide variations [161], influenced by various factors, including lactation stage, season, soil type, race, food and contaminants. Actually, diet correlates with small variations in the mineral content of cow's milk. Indeed, dairy cows feeding has relatively small impact on the content of Ca and P in milk, as the cow's skeleton serves as a mineral reservoir [162]. Regarding selenium, higher levels were found in food products derived from monogastric animals which were fed with grain feed, as well as dairy cows administered with feed rations containing more mixed feeds enriched in mineral additives. In addition, the selenium content of milk used in different countries is unknown and depends on its content in soils [54]. Moreover, elevated Se concentrations appear in soils rich in iron compounds and organic matter in saline soils [163]. The variations in essential trace element concentrations in milk are mainly influenced by animals' concentrate intake due to the systematic supplementation of these elements to concentrate feeds [164]. Feeding has a high effect on liposoluble vitamins, which concentrations are lower when the animals are fed with grass silage, corn silage or hay than fresh forage. In particular, in these conserved forages the vitamins and carotenoid concentrations (vitamin A precursor such as β-carotene) are lower compared to fresh grass [165]. Indeed, carotenoids are abundant in vegetable material and appear in milk because they are ingested by cows. β-carotene is present in vegetative material and therefore forage is a good source of this compound, whereas cereals and their by-products contain very little or no β-carotene. However, concentrations of β-carotene in silage may be retained if silage is of high quality [166]. Studies have shown that seasonal and regional variations in the concentrations of retinol and carotenoids in milk are common, reflecting the nature of the forage used for animal feeding [160]. Thus, in order to obtain a high β-carotene content in the milk, a cow's diet with high-quality forage is needed, in particular silage or pasture. The most important feed source of vitamin E is forage, especially fresh forage. The significant factors influencing the vitamin E content in forage are the phase of maturity and conservation conditions. Silage is preferable to hay because storage losses may be significant [160]. Therefore, quantitative changes in dietary intake of carotenoids and vitamin E explain the differences in concentrations of these compounds in milk from cows fed by different types of forages or different forage-to-concentrate ratios [160]. The content of vitamin D depends principally on seasonal variations; indeed, the exposure of the animal's body to ultraviolet sunlight positively correlates with a higher concentration of vitamin D in milk in summer than produced in winter [167].

Also, with respect to water-soluble vitamins, and in particular B-vitamins complex, correlations with dietary intake were demonstrated. Ruminal synthesis of B-vitamins is modified by diet composition. In particular, it is affected by dietary forage and the unfermented carbohydrate content of dairy cow diet, indeed, it was observed that increasing dietary forage content decreased ruminal synthesis of pyridoxine, folic acid and vitamin B_{12}. Instead, increasing unfermented carbohydrates content in the diet, increases ruminal synthesis of nicotinic acid, nicotinamide, niacin, pyridoxal, B_6, and folic acid, but decrease the B_{12} synthesis [168]. Changes in the forage-to-concentrate ratio of the diet alter the microbial activity of the rumen [169] and are therefore likely to influence the quantity of B vitamins produced. Indeed, milk concentrations of B vitamins seem generally poorly related to vitamin intake [170] likely due to processes of degradation of these vitamins in the rumen. Vitamin B_1, vitamin B_2 and vitamin B_{12} were found in higher proportions in milk derived from pasture diets. It has been shown that increasing the forage-to-concentrate ratio of the animal's dietary intake increases vitamin B levels in milk. The vitamin B_{12} concentrations in milk are highly variable and are affected by cobalt supply and feeding regimens [171]. Forage growing on soils with a low cobalt content can lead to vitamin B_{12} deficiency [172]. Several studies showed that inclusion of oat silage increased milk concentrations of vitamin B_{12} compared with corn silage [171]. Furthermore, other studies comparing different production systems, mainly characterized by their forage system (grassland or corn silage) showed an increase in milk concentrations of vitamin B_{12} after corn silage intake [173], whereas milk produced when diets were based on hay in winter or pasture during the grazing period were richer in vitamin B_2 [174]. A higher content of vitamin B_3 (in the form of nicotinic acid and nicotinamide) was observed in milk from diets at high concentrates content, as a result of cereal grains being a major food source of vitamin B_3 [175].

It is also noteworthy that among milk production systems, the organic system is the one that most ensures high quality milk from the perspective of micronutrient composition. Indeed, this system combines the preservation of a high level of biodiversity, protection of natural resources and high standards of animal welfare. The animal feeding choices adopted by this system ensure a source of a variety of bioactive substances that become part of milk [176].

In addition to animal feeding strategies adopted to increase the minerals or vitamin content in milk, the enrichment of this food can be carried out by a process of "fortification", a necessary practice since some important micronutrient deficiencies have a detrimental effect on human health. As reported by Woźniak and colleagues [33], it is difficult to meet the needs of calcium, iron, vitamin A and D, particularly in the diet of young children. In fact, in many cases supplementation of these components is necessary to avert health problems especially in the most vulnerable groups. This leads to the conclusion that, not only should milk consumption be encouraged, but fortification of milk with these micronutrients to balance its deficiencies due to both different treatments of milk itself and poor milk consumption, can be of great help [33]. Shortages of vitamin A, vitamin D and Ca (even in high- latitudes countries) have been reported to be a major concern [177,178]. Food fortification is one of the public health actions aimed at improving the content of essential micronutrients, i.e., vitamins and minerals (including trace elements) in a food, representing a good choice to improve the nutritional quality of the food. In certain countries, especially populations at high latitudes such as Finland, Sweden and Canada, the fortification of milk with vitamin D is strongly recommended [35]. Indeed, in Northern latitudes, particularly in winter, ultraviolet B radiation is too weak for the dermis to synthesize vitamin D [179] and its supplementation is required to prevent deficiency [180], because many foods commonly consumed by humans contain low levels of vitamin D. Vitamin A can be found in large quantities in whole milk, as it is mainly related to the fat phase of milk. As a result, vitamin A should be added to dairy products whose fat has been removed, in the amount needed to restore the quantity of these vitamins lost in fat removal. In contrast, whole milk is not considered as an important source of vitamin D, and therefore the elimination of fat does not make milk less nutritious if we consider the amount of this vitamin [181]. Milk and dairy products contain high levels of Ca with high bioavailability. However, milk consumption is decreasing in industrialized countries, resulting in inadequate intake of Ca. This is one of the reasons for the industrial development of Ca-fortified foods, ensuring an adequate consumption of this mineral. Indeed, studies showed an excellent Ca bioavailability in Ca-fortified milk, but all that glitters is not gold as the Ca fortification has a negative impact on iron absorption percentages [37]. Despite this inhibitory effect on iron uptake, consumption of Ca-rich foods should be encouraged, considering that fortification of milk with vitamin D and Ca nearly eliminated the public health concerns related to rickets in the 19th century. In Table 5, micronutrients were classified according to milk enrichment practices.

Table 5. Milk enrichment practices.

	Micronutrient-fortified milk	Grazing and feeding techniques
Calcium	√	
Vitamin A	√	
Vitamin D	√	
β-carotene		√
Vitamin E		√
B-vitamins complex		√
Selenium		√

8. Economic Impact of Fortifications versus Grain Feed Practices

Food fortifications are a cost-effective strategy for improving the population nutritional state [182] and were associated with strong economic advantages [183]. Indeed, cost effectiveness, considering deaths averted or disabilities cured, has helped to give fortification high priority as a preventive health-care intervention. The prerequisites for food fortification include modern food-processing facilities, quality control and monitoring systems, distribution facilities, and regulatory support, which certainly drive up the cost of the final product. However, this price increase, can be considered insignificant compared to the high return in terms of health and disability prevention [184]. On the other hand, the different types of selected feeds and forages, which ensure a nutritionally quality product, have significant economic and environmental impacts. To date, factors such as scarcity of land, soil, and water, ongoing global warming and frequent drastic climatic variations, and increased competition for arable land can pose serious economic and environmental challenges to the sustainability of feed production systems and fodder cultivation [185]. In addition, the production, processing and transport of feed account for ~45% of the anthropogenic greenhouse gas emission from the livestock sector [186]. Therefore, food fortification remains an efficient economic and environmental strategy for human health.

9. Conclusions

Over the past few years, researchers' attention to the quality of foods consumed by humans to prevent the onset of malnutrition has significantly increased. A number of studies have been carried out to analyze the composition and nutritional quality of foods. Of these, a large space is occupied by milk, a food rich in all nutrients, which makes it particularly valuable. The particularly interesting nutritional components of milk are minerals and vitamins, which despite their presence in small amounts, are essential compounds because their consumption is crucial for the growth and maintenance of human health. The mineral and vitamin profile in milk varies according to animal species, making each unique. In this review, we examined the main differences in terms of minerals and vitaminic profile of milk from different animal species, observing more marked differences in micronutrient content between ruminant and non-ruminant animal species. In detail, it appears that sheep's and goat's milk are the richest in minerals and complex B vitamins, while human milk is distinguished by its vitamin A and vitamin E content. In addition, we focused on the main effects of certain minerals and vitamins on human health, emphasizing the adverse effects due to the lack of these valuable milk components, which make it a valuable food for humans. Fortunately, the current industrial practices of processing raw milk in drinking milk lead to limited alteration in micronutrients, except in special cases. Finally, we analyzed certain strategies adopted to increase micronutrient content in milk. Animal feeding type is known to play an important role in determining higher or lower levels of micronutrients in milk, and thus milk quality. It has become apparent that higher consumption in pasture associated with lower consumption of concentrate feed is the optimal strategy for enriching milk with micronutrients. Also, to date, the fortification systems of milk with certain micronutrient, is a preventive practice on the development of malnutrition-related diseases. Vitamin A, vitamin D and Ca deficiencies have been identified as a major public health concern, primarily in the poorest countries. The problem is partly addressed through the formulation of fortified milk.

The further exploration of effective systems to produce milk rich in essential ingredients for human health should therefore be encouraged and strengthened.

Author Contributions

GC and FC contributed to the conception of this manuscript. GC, FC, AC, RT and IV contributed to manuscript writing-original draft preparation. GC contributed to manuscript writing-revision and editing. FC and LP contributed to manuscript visualization. GC contributed to manuscript supervision. All authors read and approved the final manuscript.

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Conflict of Interest

The authors declare no conflict of interest. GC is serving as Guest Editor of this journal. We declare that GC had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to JJ.

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