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Review

Effect of heat treatment on micronutrients, fatty acids and some bioactive components of milk

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ABSTRACT

Milk is a nutrient-rich food with various micronutrients and bioactive components that are affected by heat treatment depending on time-temperature norm. Pasteurisation and short time ultra high temperature treatments do not cause significant changes in most micronutrients; however, intensive heat treatments such as in-bottle sterilisation can cause severe degradation of water-soluble vitamins, essential fatty acids and hormones. Exposure of heat-treated milk to light and oxygen has a more destructive effect on oxygen-sensitive micronutrients, unsaturated fatty acids and most vitamins than heat treatment itself. Therefore, losses during evaporation and drying processes can be significant and should be considered in evaluating the nutritional value of milk. Moreover, packaging material, storage temperature and duration also contribute to the losses. Application of severe heat may also cause minor losses in minerals due to precipitation in processing lines. An integral approach is recommended for retention of the nutritional value of raw milk in processed milk products.

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1. Introduction

Milk has long been known as the only source of nutrients for the newborns during the early stage of life, until weaning. On the other hand, milk is also an ideal medium for the growth of various microorganisms including pathogens due to its high water content, neutral pH and chemical composition. Therefore, considering the public health risks associated with consumption of raw milk, heat treatment is applied for ensuring food safety in milk products. In addition, heat treatment allows inactivation of spoilage microorganisms and enzymes and by this way, improves quality and extends shelf life of dairy products (de Jong, 2008; Deeth & Lewis, 2017). Depending on the heat treatment conditions, milk components may undergo chemical and enzymatic modifications at varying levels (Bezie, 2019; Gathercole et al., 2017). While heat-induced modifications of milk components are essential for the manufacture of some dairy products, i.e., the requirement of serum protein denaturation for the formation of yogurt network, heat application may lead to decrease in nutritive value of milk depending on the temperature/time norm, i.e., losses in some vitamins, essential fatty acids and other biologically active compounds (Claeys et al., 2014; Haug, Hostmark, & Harstad, 2007). As milk is vital for infant nutrition and part of a healthy diet for general population as a source of B_2 and B_{12} vitamins, calcium, phosphorus and essential fatty acids, protection of these nutrients and bioactive components in milk is of critical importance for public health. Pasteurisation and sterilisation technologies have evolved greatly over the years, and, today, the heating technologies employed in processing of milk may well be able to modify the degradation kinetics for heat-sensitive milk compounds compared with older ones. For example, a fast heating steam injection direct UHT treatment at 150–180 °C for 0.2 s, seems to cause the least thermal damage on milk components (van Asselt, Sweere, Rollema, & de Jong, 2008).

Although the influence of heat treatment on macronutrients has been investigated, especially for physical stability of dairy products (Dumpler, Huppertz, & Kulozik, 2020), information on effect of heat on micronutrients and their bioavailability is limited. This review presents an evaluation of impact of heat treatment on essential minor nutrients and bioactive compounds including minerals, vitamins, fatty acids, oligosaccharides, hormones and growth factors.

2. Heat-induced changes in minerals of milk

2.1. Mineral equilibria in milk

The mineral fraction of milk, which is an important group of micronutrients in milk, constitutes about 0.8–0.9% (w/v) of milk; however, the relative concentrations of the individual ions can significantly vary due to a number of factors such as species, breed, nutritional status of animal, stage of lactation, health condition of animal and season of the year (Table 1) (Fox, Uniacke-Lowe, McSweeney, & O'Mahony, 2015; Gaucheron, 2005). The mineral fraction of milk is composed of macroelements (calcium, magnesium, sodium, potassium, phosphorus, and chloride) and trace minerals (iron, copper, zinc, manganese, selenium, iodine, chromium, cobalt, molybdenum, fluorine, arsenic, nickel, silicon, and boron) (Cashman, 2011). Although quantitatively, the minerals are relatively minor components of milk, they have important roles in technological properties of milk and dairy products, including the conformation and stability of the proteins and buffering capacity, as well as its nutritional functions (e.g., bone and teeth growth and maintenance, serving as cofactor of vital enzymatic systems, maintenance of blood pressure and ionic equilibrium, muscle contraction) (Cashman, 2011; Gaucheron, 2011; Lucey & Horne, 2009). Inorganic calcium phosphate, calcium citrate, and complexed calcium ions comprise 6% of dry matter in the casein micelle and have a direct influence on micellar structure and stability. The high heat stability of casein micelles at the natural pH of milk is mostly due to the linkages between caseins with phosphoserine residues via colloidal calcium phosphate (Dumpler et al., 2020).

The minerals can be found in milk either as soluble in the aqueous phase or as colloidal complexes associated with casein micelles. In the aqueous phase, almost all potassium, sodium, and chloride are present as free ions. Approximately one-third of calcium is present as free ionic calcium and complexed mainly with citrate and phosphate. Two-thirds of magnesium, about 40% of inorganic phosphate ($H_2PO_4^-$ and HPO_4^{2-}), and 94% of citrate is found in the aqueous phase (Fox et al., 2015; Gaucheron, 2011). The remainder of these major mineral species is in the colloidal phase. The calcium phosphate associated with casein is generally referred as colloidal calcium phosphate (CCP). In addition, calcium can directly attach to casein via binding to phosphoserines and carboxyl groups in the absence of phosphates in milk (de la Fuente, 1998; Fox et al., 2015; Gaucheron, 2011; Holt, 2011; Holt & Jenness, 1984; Zhang & Aoki, 1996).

2.2. Heat-induced changes in the mineral equilibria in milk

The changes in physicochemical conditions (such as thermal processing, cooling, pH, concentration and dilution, the addition of chelating agents and salts) lead to alteration of the mineral equilibria in milk (de la Fuente, 1998; Fox et al., 2015; Gaucheron, 2011). Concerning heat treatment of milk, it is well known that a change in temperature causes changes in the distribution of minerals (especially calcium and phosphorus) between the aqueous and colloidal phases. The increase of milk temperature causes an increase in the dissociation of inorganic phosphate (Pi) in the aqueous phase and change in the equilibrium between $H_2PO_4^-$ and HPO_4^{2-}. The concentration of HPO_4^{2-}, which has a higher affinity for calcium, rises, and it reacts with calcium to form calcium phosphate salt. The aqueous phase becomes supersaturated with calcium phosphate, and the concentrations of ionic calcium and Pi decrease in this phase. Heat treatment results in the precipitation of calcium phosphate because the solubility of calcium phosphate is reduced as the temperature is increased. The extent of changes in mineral balance between the colloidal and serum phases depends on the intensity of heat treatment (Fox et al., 2015; Gaucheron, 2011). As the temperature of heat treatment was increased from 20 to 90 °C, concentrations of Ca and P in serum decreased by 60 and 35%, respectively (Pouliot, Boulet, & Paquin, 1989). In addition, concentrations of magnesium and citrate in colloidal phase augmented from 1.53 to 0.65 mM to 1.97 and 1.75 mM, respectively, and no change in those of sodium and potassium were observed (Pouliot et al., 1989). Holt (1995) also reported 18 and 33% reductions in the concentrations of magnesium and calcium, respectively, in the serum phase at 90 °C.

In an early study by Muldoon and Liska (1972), changes in mineral balance in milk by heat treatment at a temperature in the range of 60–94 °C were found to be irreversible, even after storage at 2 °C for 10 days. On the other hand, Pouliot, Boulet, and Paquin (1989) observed that the reversibility of the heat-induced (85 °C for 40 min) changes in Ca and P was 90–95% and 93–99%, respectively, increasing after subsequent storage at 4 °C for 24 h. Moreover, Law (1996) reported that after storage for 22 h at 4, 20 and 30 °C, the distribution of Ca and P between the soluble and colloidal phases in heat-treated milk (85 °C for 10 min) was similar to that in raw milk stored at corresponding temperature. However, severe heat treatments (above 95 °C for several minutes) caused irreversible changes in the mineral distribution, probably as a

Table 1
Mineral content of mature milk from some ruminants and human.

Mineral	Cow	Goat	Sheep	Human	Reference
Macrominerals (mg kg^{-1})					
Calcium	1043–1283				Gaucheron (2005)
		850–1980	1590–2420		Claeys et al. (2014)
				220–410	Zamberlin, Neven, Havranek, and Samarzija (2011)
Total phosphorus	930–992				Gaucheron (2005)
		790–1530	1240–1750		Claeys et al. (2014)
				120–170	Zamberlin et al. (2011)
Magnesium	97–146				Gaucheron (2005)
		100–360	160–250		Claeys et al. (2014)
				30–34	Zamberlin et al. (2011)
Potassium	1212–1681				Gaucheron (2005)
		1400–2420	940–1620		Claeys et al. (2014)
				460–550	Zamberlin et al. (2011)
Sodium	391–644	280–590	300–750	120–150	Gaucheron (2005)
					Claeys et al. (2014)
					Zamberlin et al. (2011)
Chloride	772–1207	1040–2090	990–1600	320–490	Gaucheron (2005)
					Claeys et al. (2014)
					Zamberlin et al. (2011)
Microminerals (μg kg^{-1})					
Iodine	260			20–120	Fox et al. (2015)
Selenium	17–23			12–20	Hunt and Nielsen (2009)
		7–14	17		Wijesinha-Bettoni and Burlingame (2013)
Manganese	40–100	Tr–180	Tr–180		Wijesinha-Bettoni and Burlingame (2013)
				4–6	Hunt and Nielsen (2009)
Iron	300–1000	500–1000	800–1000	400–2000	Claeys et al. (2014)
Copper	100–600			370–430	Fox et al. (2015)
		200–500	300–500		Claeys et al. (2014)
Zinc	2000–6000			2600–3300	Fox et al. (2015)
		1000–5000	5000–7000		Wijesinha-Bettoni and Burlingame (2013)

consequence of an increase in CCP and the modification in the structure of CCP (Holt, 1995).

Holt (1995) stated that the decrease of Ca and P in the aqueous phase due to heating up to 90 °C and subsequent cooling can be attributed to temperature-dependent increase in the size or number of the microgranules of CCP of the micelles rather than a simple precipitation of calcium phosphate from the aqueous phase. Boiani, Fenelon, FitzGerald, and Kelly (2018) used ^{31}P nuclear magnetic resonance (^{31}P NMR) and attenuated total refraction Fourier transform infrared (ATR-FTIR) techniques and showed that Pi and Ca precipitated within micellar casein to form new casein phosphate nanoclusters or as inorganic calcium phosphate salts in the case of low micellar casein concentration during the first heating phase (25–60 °C). During the second heating phase (60–80 °C), raising the temperature increases the negative charge of Pi leading to the micellar casein–casein phosphate nanocluster interaction. Wang and Ma (2020) also suggested that the structure of the newly formed calcium phosphate due to moderate heating of milk (below 90 °C, 15 min) was the same as native CCP nanoclusters in unheated milk, whereas the high heat treatment (100 °C, 15 min) caused the formation of a new phase of calcium phosphate with the nature of an alkaline salt unlike the acidic salt nature of the native CCP.

The heat-induced changes in the mineral balance in milk are of great importance during the processing of milk in dairy industry. The shift of the mineral balance leads to the poor coagulation of the milk in cheese production (Britten & Giroux, 2021). In addition, it should be noted that severe heat treatment may also cause some mineral losses from milk by a fouling mechanism depending on the severity of heat treatment. Jeurnink, Walstra, and de Kruif (1996) found that minerals were present at a proportion of 45% including 15.7% calcium in the deposit on the heater section of a plate heat exchanger operating at temperatures between 69 and 85 °C. They also determined that only 0.2% of the minerals transferred from serum to colloidal phase in 1 L of milk was deposited on the heater surface after heating to 85 °C for 1 min. On the other hand, heat treatment above 110 °C resulted in fouling deposits that consisted mainly of minerals (up to 80%, w/w) on the heating surface which were rich in calcium phosphate and citrates (de Jong, 2008; Deeth & Lewis, 2017; Moatsou, 2013). The loss of macrominerals by fouling mechanism by pasteurisation and UHT treatments may not be significant in terms of nutritional value since their amount in the deposit layer is too small compared with that in bulk milk.

2.3. Heat-induced changes in trace minerals of milk

There is much less information on the effects of heat treatments on the distribution and concentrations of the trace minerals in milk compared with those of the macro-elements. Trace minerals can be lost during heat treatment or other unit operations involving heat such as evaporation and drying in fouling deposits by formation of complexes with or without proteins (Foster, Chaplin, & Sumar, 1998). O'Kane et al. (2018) found no change in iodine or selenium concentrations in milk after pasteurisation. However, Foster et al. (1998) stated that pasteurisation reduced intrinsic selenium level in milk by 7.9%, and total selenium losses after pasteurisation followed by spray-drying were 49.2%. Payling, Juniper, Drake, Rymer, and Givens (2015) stated that the iodine content of the UHT milk at retail in UK was significantly lower than that of the pasteurised milk. Similarly, Stevenson, Drake, and Givens (2018) found that semi-skimmed UHT milk at retail in UK had 27% lower iodine content than conventionally semi-skimmed pasteurised milk. On the contrary, van de Kamp, Saridakis, and Verkaik-Kloosterman (2019) and Walther, Wechsler, Schlegel, and Haldimann (2018) stated that the iodine concentrations was similar in pasteurised and UHT milk samples purchased from the Dutch and the Swiss

markets, respectively. However, the studies on iodine content of heat treated milk only examined pasteurised and UHT milk at retail, therefore further investigations are needed to clearly manifest the effect of heat treatment on the iodine in milk.

2.4. Effect of heat treatment on bioavailability of minerals in milk

The bioavailability of milk minerals depends on their chemical form, applied heat treatment and other milk components such as lactose, lactulose, conjugated linoleic acid, vitamin D and casein phosphopeptides (Claeys et al., 2014). In a study with low birth weight (<1.3 kg) preterm infants, no difference in the absorption and retention of calcium, phosphorus and sodium was observed by feeding raw, pasteurised or boiled human milk for 3 weeks (Williamson, Finucane, Ellis, & Gamsu, 1978). Similarly, the intestinal absorption of calcium from raw, high temperature short time (HTST), UHT and stored UHT milk in rats was found to be similar (Weeks & King, 1985). In another study by Seiquer, Delgado-Andrade, Haro, and Navarro (2010), overheating (3 cycles of sterilisation at 116 °C for 16 min) of milk lowered the amount of soluble calcium thus its bioaccessibility by about 23.6% after in vitro digestion compared with UHT treatment (150 °C, 6 s). Reduction in solubility of calcium was attributed to heat-induced dephosphorylation of casein phosphopeptides, which protects it from precipitation in the lumen, and the formation of calcium-Maillard reaction products (MRP) chelates. In the same study, no significant effect of overheating on calcium absorption by rats was determined when food intake was controlled in comparison with UHT treatment. Similarly, Furniss, Vuichoud, Finot, and Hurrell (1989) found that urinary Zn loss was found to be increased by 2-fold by the presence of casein-lactose MRP in the diet, but the authors stated that this could be only a minor excretory pathway and would cause little effect on Zn bioavailability in case of individuals taking sufficient Zn with a diet.

Lactulose formed by the isomerisation of lactose during heat treatment of milk was reported to increase absorption of magnesium and calcium (Oh & Deeth, 2017). In a study with adult males, Seki et al. (2007) observed that concentrations of calcium and magnesium in the urine collected for 8 h after the ingestion in the placebo group were 68.2 and 39.9 mg whereas the concentrations were 71.7 and 41.4 mg in the test group fed with the test food containing 2 g lactulose, respectively. A similar increasing effect of lactulose on the absorption of calcium was reported in post-menopausal women where intake of 10 g day^{-1} of lactulose enhanced calcium absorption by 16% (van den Heuvel, Muijs, van Dokkum, & Schaafsma, 1999). In another study, absorptions of calcium, magnesium and phosphate were increased by feeding lactulose from 50, 52 and 65% in the control rats to 62, 79 and 72% in test rats, respectively (Heijnen, Brink, Lemmens, & Beynen, 1993). However, considering the amount of lactulose formed by heat treatment of milk, a maximum of 600 mg L^{-1} allowed in UHT milk, the effect of lactulose on absorption of calcium would be limited.

3. Heat-induced changes in vitamins of milk

3.1. Heat-induced changes in water-soluble vitamins of milk

Vitamin B_1 is present in animal products in phosphorylated forms and is prone to decomposition by oxidising and reducing agents and thermal treatments (Godoy, Amaya-Farfan, & Rodriguez-Amaya, 2021; Voelker, Miller, Running, Taylor, & Mauer, 2018). Thermal degradation of vitamin B_1 follows first order kinetics. Pasteurisation and sterilisation cause less than 10% and 20–50% reductions in vitamin B_1, respectively (Vidal-Valverde, Reche, & Medrano, 1990). The loss in vitamin B_1 in microwave-heated milk was found to be proportional to time and temperature and after heating at 79.6 °C for 4 min, 24.2%, 61.5% and 65.9% loss in vitamin B_1 in whole, low fat and skim milk were reported, respectively (Vidal-Valverde & Redondo, 1993). The choice of heat treatment module, e.g., tubular or plate heat exchanger in UHT and direct or indirect-pasteurised extended shelf-life (ESL) has limited impact on vitamin B_1 level in milk (Gregory & Burton, 1965; Lorenzen et al., 2011). On the contrary, in in-bottle sterilised milk which is far less commonly used by dairy industry, vitamin B_1 loss may be as high as 30–40% (Ryley & Kajda, 1994). No remarkable loss of vitamin B_1 was observed when opened UHT milk was stored under refrigeration conditions for 10 days (Lalić et al., 2014). However, as the storage period was extended to six weeks, the loss of vitamin B_1 in UHT milk was around 10% (Görner & Uherová, 1980). In evaporated milk, the loss in vitamin B_1 may be as high as 30–50% (Ottaway, 2002).

Vitamin B_2 in milk is stable to heat treatment (Guneser & Yuceer, 2012; Ottaway, 2010; Zhu, Kebede, Chen, McComb, & Frew, 2020), but its stability is reduced when exposed to light (Cardoso, Libardi, & Skibsted, 2012; Gregory, 2017). The rate and extent of vitamin B_2 loss in milk are dependent on the light intensity, the temperature of storage and surface area of the packaging material (Ottaway, 2002). Saidi and Warthesen (1995) demonstrated that heating of skim milk at 80, 100 or 120 °C led to a reduction in the rate constant for vitamin B_2 photolysis possibly due to whey protein denaturation and/or increase in casein micelle size obstructing the light. Aminoreductone which is generated during Maillard reaction seems to be the primary compound improving photostability of vitamin B_2 in UHT milk (Trang, Kurogi, Katsuno, Shimamura, & Ukeda, 2008). Moreover, the photostability of vitamin B_2 was improved by homogenisation regardless of the pressure applied (Saidi & Warthesen, 1995). Similarly, lower level of loss of vitamin B_2 in milk when subjected to ultra-high pressure homogenisation (UHPH) (0% and 13.4% loss at 300 MPa at 45 °C or 85 °C, respectively) than UHT milk (17.3% loss at 138 °C for 4 s) was demonstrated by Amador-Espejo, Gallardo-Chacon, Nykänen, Juan, and Trujillo (2015). UHPH-induced changes in particle size of fat and/or fat-protein complex may cause changes in light intensity on vitamins leading to loss in vitamin B_2 (Sharabi, Okun, & Shpigelman, 2018).

Vitamins B_3, B_5 and B_7 were found considerably stable against low temperature long time (LTLT) or HTST pasteurisation of milk and subsequent storage at 4 °C (Friend, Shahani, Long, & Agel, 1983; Zhu et al., 2020). Less than 10% reduction in vitamins B_3, B_5 and B_7 in pasteurised milk were reported in various research studies (Ball, 1994, 1998; Leśková et al., 2006; Macdonald, Brett, Kelton, Majowicz, & Snedeker, 2011; Ottaway, 2002).

Varying degrees of loss in vitamin B_6 in pasteurised (0–8%), UHT (<10%), sterilised (20–50%) and evaporated (35–50%) milk during shelf-life period were reported (Fox et al., 2015). Oamen, Hansen, and Swartzel (1989) found ~3.4% loss in vitamin B_6 after UHT treatment of milk. Heat treatment affects not only the molecular structure of vitamins (i.e., formation of 4-pyridoxic acid, a non-biologically active form of vitamin B_6) and hence destructs them at varying levels, but also causes interaction of vitamins with milk components, especially proteins, and their bioaccessibility may be reduced (Pingali & Trumbo, 1992). Vitamin B_6 in the form of pyridoxal, for example, is bound to cysteine (Bernhart, D'Amato, & Tomarelli, 1960; Srncova & Davidek, 1972) and lysine residues (Gregory & Kirk, 1977), yielding an inactive thiazolidine derivative (Godoy et al., 2021). Prydoxyllysine complexes were demonstrated to have 50% of vitamin B_6 activity in rats (Gregory, 1980). Interconversion of different B_6 forms may occur as a result of heat treatment, being more pronounced in evaporated milk. Recently,

Schmidt and Meyer (2018) has reported that UHT treatment can cause changes in the distribution of B_6 forms and proposed this as a basis for a novel time–temperature integrator for the discrimination of UHT milk from other thermally processed milk.

Vitamin B_9 (in the form of 5-methyltetrahydrofolate) is bound to folate-binding proteins (FBP) in raw milk (Wigertz, Hansen, Høier-Madsen, Holm, & Jägerstad, 1996). FBP is heat-denatured partly in the pasteurised milk and extensively in the UHT-sterilised milk, thus folate is present in free form in UHT milk. The role of FBP on the bioavailability of folate in the human body is debatable. Early reports had claimed that FBP play a role in the direct transport of folate through intestinal mucosa but more recent studies showed that FBP was ineffective on bioavailability of folate in human body (de Jong et al., 2005).

Vitamin B_{12} is fairly stable against pasteurisation and UHT treatments (Ansari, Vaid, & Ahmad, 2004; Riaz, Asif, & Ali, 2009), but more severe heat treatment to milk (i.e., in-bottle sterilisation) may cause up to 20% loss in vitamin B_{12} activity (Ottaway, 2002). Despite high heat stability of vitamin B_{12} in plain pasteurised or UHT milk, remarkable loss (33.5%) of this vitamin in chocolate flavoured milk subjected to heat treatment at 100 °C for 1 h compared with unflavoured milk (8.8% loss) was reported by Johns et al. (2015). This may have stemmed from the physical affinity of cocoa powder to vitamin B_{12} and/or strong peroxide generating capacity of cocoa polyphenols (i.e., (+)-catechin) and related products such as gallic acid, cafeic acid and (−)-epigallocatechin. Vitamin B_{12} losses in milk upon heating range from negligible at 96 °C for 5 min (Arkbage, Witthoft, Fonden, & Jagerstad, 2003) to 100% in UHT milk at room temperature for 20 wks (Godoy et al., 2021; Oamen et al., 1989). At refrigeration temperature, the stability of vitamin B_{12} in UHT milk may be protected up to 6 months. Heat treatment may not be a major destabilising factor for vitamin B_{12} and the presence of oxygen reactive compounds such as ascorbic acid and copper, and oxygen accessibility may stimulate the destabilisation of vitamin B_{12} during heating.

Thermal stability of vitamin C is influenced by a number of factors including heat treatment norm, degree of degassing of milk prior to thermal treatment and storage period. The loss of vitamin C in pasteurised cows' milk stored at 4 °C for 6–9 d may go up to 40–45% (Andersson & Öste, 1992; Khan et al., 2017). With the increase in the temperature from 63 °C to 100 °C for 30 min, the losses in vitamin C in cows' milk and dromedary camels' milk increased from 18 to 27% to 48 and 67%, respectively (Mehaia, 1994). On the contrary, Andersson and Öste (1992) demonstrated that the loss of vitamin C was negligible in UHT milk when oxygen concentration of milk was kept 3.3 ppm or less. The rate constant of vitamin C degradation is affected by the food matrix and higher rate constant for the degradation of vitamin C in milk than in fruit juice and drinks was reported (Steskova, Morochovicova, & Leskova, 2006). Oxygen exposure, presence of antioxidants and duration of heat treatment and storage are important factors in the stability of vitamin C.

3.2. Heat-induced changes in fat-soluble vitamins of milk

No significant differences in vitamin A levels in raw, pasteurised and boiled milk were noted (Bilic & Sieber, 1988). On the other hand, in the presence of air and light, some loss of vitamin A may occur if the holding time during heat treatment (Ottaway, 2010) or storage time of processed milk at room temperature (Fox et al., 2015) is prolonged. Sachdeva, Kaushik, Arora, and Khan (2021) reported that fortified vitamin A withstood pasteurisation but remarkable losses up to 37 and 23% were observed in sterilised and boiled milk, respectively. In addition, fortification of milk with iron (ferric pyrophosphate soluble or ferrous gluconate hydrate) adversely affected the heat stability of vitamin A. Evaporation following pasteurisation may also cause losses in vitamin A, but not carotene, in milk (Bezie, 2019).Vitamin A has five conjugated double bonds, making it susceptible to oxidative degradation (Godoy et al., 2021). The choice of packaging material is a critical parameter affecting the stability of vitamin A in heat-treated milk. The stability of vitamin A in heated milk stored in dark bottle was the highest followed by milk stored in polyethylene terephthalate (PET) and transparent PET bottles for 12 weeks at 23 °C, respectively (Saffert, Pieper, & Jetten, 2008). The losses of supplemented vitamin A in low fat UHT milk stored for 12 weeks at 23 °C in clear and pigmented PET bottles were 66–88% and 37–48% depending on the light intensity, respectively, while the sample stored in dark had only 5% loss (Saffert, Pieper, & Jetten, 2009). Milk fat has a protective role on the stability of vitamin A in milk against light exposure (Godoy et al., 2021). The vitamin A losses in whole, reduced fat and non-fat milk upon exposure to light for 16 h were reported as 0%, 24% and 32%, respectively (Whited, Hammond, Chapman, & Boor, 2000).

Vitamin D in milk is also stable against pasteurisation and sterilisation treatments (Ball, 1998; Davídek, Velísek, & Pokomy, 1990). Similar to vitamin A, vitamin D is more susceptible to light exposure than heat treatment. Almost 50% of vitamin D activity was reported to be lost when processed milk was exposed to fluorescent light for 12 days at 4 °C (Gregory, 2008). On the contrary, the presence of air did not affect the stability of vitamin D_3 in fortified milk (Renken & Warthesen, 1993).

Milk proteins may have a protective role against heat degradation of vitamins (especially vitamin D) via casein-vitamin complexation (Loewen, Chan, & Li-Chan, 2018). Casein micelles were shown to have a strong affinity toward binding of vitamin A in fortified commercial skim milk (Mohan, Jurat-Fuentes, & Harte, 2013). The major challenge of this interaction is the low solubility of protein-vitamin complex. A chemical modification in proteins such as succinylation may be required to improve the solubility of protein-vitamin complex (Syama, Arora, Gupta, Sharma, & Sharma, 2019). Syama et al. (2019) demonstrated that complexation of vitamin D_3 with succinylated Na-caseinate enhanced the heat stability of vitamin D_3 under pasteurisation (63 °C, 30 min), sterilisation (121 °C, 15 min) and boiling conditions. A non-specific affinity to bind hydrophobic compounds such as vitamin D_3 (Forrest, Yada, & Rousseau, 2005), and vitamin A_1 (retinol) (Dufour & Haertle, 1991) by whey proteins, was also demonstrated. Casein micelles were shown to improve heat stability of β-carotene in processed milk (Saiz-Abajo, Gonzalez-Ferrero, Moreno-Ruiz, & Roma-Hualde, 2013). High level of recovery for supplemented vitamin D_3 in HTST-pasteurised milk and UHT milk was reported by Hanson and Metzger (2010).

Vitamin E is not affected by pasteurisation or evaporation, but drying and recombination result in some losses (approximately 9%) in this vitamin (Bezie, 2019; Pandya et al., 2019). Moreover, no significant decrease in either δ- or γ-tocotrienol in UHT milk after storage was reported by Pandya et al. (2019). Some degradation of vitamin E (especially α-tocopherol) in the presence of air is evident, being more pronounced in unesterified tocopherols due to the free phenolic hydroxyl groups (Bendicho, Espachs, Arántegui, & Martín, 2002; Godoy et al., 2021; Ottaway, 2010). Similar to vitamins A and D, milk proteins contribute to the stability of vitamin E in milk products. A remarkable decrease up to 45–65% in tocopherol in protein-free liquid milk-based model infant formula after sterilisation at 120 °C for 15 min was demonstrated (García-Martínez, Holgado, & Márquez-Luíz, 2012). Similar to vitamin E, vitamin K is unlikely affected by heat treatments applied to milk (Fox et al., 2015).

Overall, common industrial practices of heat treatment of milk (i.e., HTST or ESL pasteurisation, ultra-high pasteurisation or direct or indirect UHT treatment) result in a limited level of decomposition in milk vitamins, except for vitamin C being slightly more pronounced among water-soluble vitamins (Table 2). Milk is not considered as a primary source of water-soluble vitamins except for vitamin B_2 and vitamin B_{12}, and the heat treatment (especially pasteurisation) does not cause any remarkable losses in these vitamins. Heat-triggered interactions of vitamins with milk components (i.e., proteins, fat) may well play a protective role on heat-stability of vitamins in milk.

3.3. Thermal stability of vitamins in human milk

In the absence of adequate supply of human milk, this demand is often met by human milk banks in some countries. However, donor milk must be heat-processed prior to use for infant feeding to avoid microbial transmission to the infants (Pelia et al., 2016). Holder pasteurisation (62.5 °C, 30 min) which is recommended in international regulations and 100 °C for 5 min are the most common heat treatment norms applied to human milk (Pelia et al., 2016). Romeu-Nadal, Castelotte, Gaya, and Lopez-Sabater (2008) demonstrated that upon pasteurisation of human milk at 62.5 °C for 30 min or at 100 °C for 5 min, the levels of vitamin C and vitamin E in human milk were reduced significantly, being more marked in the latter case (26% versus 41% for vitamin C; 17% versus 34% for α-tocopherol; 13% versus 32% for γ-tocopherol, respectively). Vitamin A and D were found stable against heat treatment of human milk (van Zoeren-Grobben, Schrijver, van den Berg, & Berger, 1987). Among water soluble vitamins of human milk, B_2, B_5, B_7 and B_{12} were not affected significantly by heat treatment (Goldsmith,

Table 2
Vitamin content of raw and heat−treated milk.[a]

Vitamin	Unit	Raw				Pasteurised		UHT	References
		Cow	Sheep	Goat	Human	Cow	Human	Cow	
Vit B_1	μg mL^{-1}	0.47				0.39		0.48	Lalic et al. (2014)
					0.10		0.10		Goldsmith et al. (1983)
		0.28				0.27[b]			Sierra and Vidal-Valverde (2000)
		0.45	0.80	0.68	0.17				Park, Juarez, Ramos, and Haenlein (2007)
		0.20				0.17[c]		0.18[d]	Haddad and Loewenstein (1983)
Vit B_2	μg mL^{-1}	1.33				1.32[c]		1.29[d]	Haddad and Loewenstein (1983)
							0.34[a]		Goldsmith et al. (1983)
		1.68				1.67[b]			Sierra and Vidal-Valverde (2000)
		1.60	3.76	2.10	0.20				Park et al. (2007)
		1.86						1.80[e]	Oamen et al. (1989)
	μmol L^{-1}						0.59		van Zoeren-Grobben et al. (1987)
Vit B_3	mg 100 g^{-1}				0.21		0.21[f]		Friend et al. (1983)
		0.08	0.41	0.27	0.17				Park et al. (2007)
					0.16		0.16[a]		Goldsmith et al. (1983)
Vit B_5	mg 100 g^{-1}				0.46		0.49[f]		Friend et al. (1983)
		0.32	0.41	0.31	0.20				Park et al. (2007)
					0.58		0.57[a]		Goldsmith et al. (1983)
Vit B_6	μg mL^{-1}	0.33						0.32	Oamen et al. (1989)
					0.29		0.26[a]		Goldsmith et al. (1983)
		0.4	0.8	0.4	0.1				Park et al. (2007)
	μmol L^{-1}	0.71[g]				0.65[hg]		0.73[g]	Schmidt and Meyer (2018)
							0.086		van Zoeren-Grobben et al. (1987)
Vit B_7	μg 100 g^{-1}				0.73		0.74[f]		Friend et al. (1983)
		2.00		2.00	0.70				Raynal-Ljutovac, Lagriffoul, Paccard, Guillet, and Chilliard (2008)
Vit B_9	μg mL^{-1}				0.05		0.03[a]		Goldsmith et al. (1983)
		0.005	0.005	0.001	0.005				Raynal-Ljutovac et al. (2008)
Vit B_{12}	μg L^{-1}	3.80				3.90			Andersson & Öste (1992)
					0.20		0.21[a]		Goldsmith et al. (1983)
		2.63						2.14[i]	Oamen et al. (1989)
		3.50	7.10	0.60	0.40				Raynal-Ljutovac et al. (2008)
	pmol L^{-1}						309		van Zoeren-Grobben et al. (1987)
Vit A	IU 100 g^{-1}	31.33				1.01			Cappozzo et al. (2015)
		126	146	185	190				Park et al. (2007)
	mg L^{-1}	0.79				1.06		1.26	Chotyakul, Pateiro-Moure, Saraiva, Torres, and Perez-Lamela (2014)
		0.23				0.34[a]		0.27	Panfili, Manzi, and Pizzoferato (1998)
		0.4[j]	0.8[j]	0.4[j]	0.6[j]				Raynal-Ljutovac et al. (2008)
	μmol L^{-1}						1.32		van Zoeren-Grobben et al. (1987)
Vit C	mg L^{-1}	21.32						14.29	Oamen et al. (1989)
					20−100				Jensen (1995)
		9.4	41.6	12.9	50.0				Park et al. (2007)
					3.60		3.97[a]		Goldsmith et al. (1983)
	μmol L^{-1}						141		van Zoeren-Grobben et al. (1987)
Vit D	IU	284.6							Cappozzo et al. (2015)
					20				Bae and Kratzsch (2018)
	pmol L^{-1}						143		van Zoeren-Grobben et al. (1987)
Vit E	mg L^{-1}	0.73[k]				0.81[k]			Chotyakul et al. (2014)
					5.09		3.79[f]		Delgado, Cava, Delgado, and Ramirez (2014)
		1.1[k]	1.1[k]	0.4[k]	2.3[k]				Raynal-Ljutovac et al. (2008)
	μmol L^{-1}						7.1		van Zoeren-Grobben et al. (1987)

[a] Superscript letters within the table indicate the following:[a] 72 °C, 15 s;[b] 90 °C, 30 s;[c] 72 °C, 16 s;[d] 140 °C, 3.5 s;[e] 149 °C, 3.4 s;[f] 62.5 °C, 30 min;[g] as pyridoxamin phosphate;[h] ESL+MF milk;[i] 149 °C, 3.4 s;[j] as retinol;[k] as α−tocopherol.

Eitenmiller, Toledo, & Barnhart, 1983; Hamprecht et al., 2004), but some heat-induced losses in vitamins B_1, B_2 and B_6 were evident (Erb, Brice, Lhopitault, & Assy Seka, 1981; Goldsmith, Eitenmiler, Toledo, & Barnhart, 1983; Moltó-Puigmartí, Permanyer, Castelotte, & Lopez-Sabater, 2011; van Zoeren-Grobben et al., 1987).

4. Heat-induced changes in fatty acids of milk

4.1. Fatty acids in milk and their effect on health

Milk fat, especially ruminant fats comprise a large variety of fatty acids (approximately 400 fatty acids). However, a great majority of these fatty acids are present at trace amounts in milk (<0.01%). The major fatty acids in milk are composed of about 15 fatty acids. The varieties and concentrations of fatty acids in milk fat depend on a number of factors such as species, breed, stage of lactation, daily pattern, and quality and quantity of feed. A vast amount of the fatty acids (98%) in bovine milk fat is esterified in triacylglycerides (TAG). The remaining part of the fatty acids are esterified to diacylglycerols, monoacylglycerols, and phospholipids, and also are found as free fatty acids (FFAs) (0.1%) in milk (Fox et al., 2015; Jensen, 2002; MacGibbon, 2020; Taylor & MacGibbon, 2011). The saturated fatty acids (C4:0-C18:0) constitute about 70–75% of the total fatty acids. The short-chain fatty acids, C4:0 and C6:0, are regarded as present in the milk fat at high level if their proportions are expressed as molar percentages (approximately 10 and 4.5%, respectively). The short (C4:0–C6:0) and medium-chain fatty acids (C8:0–C12:0) are unique to milk fat providing flavour or off-flavour depending on their concentrations (MacGibbon, 2020; Taylor & MacGibbon, 2011). Short chain fatty acids and lauric acid were shown to possess antiviral, antibacterial and anticarcinogenic activities (Haug et al., 2007; MacGibbon, 2020). The major monounsaturated fatty acid of the milk fat is oleic acid (cis-9-octadecenoic acid; 9c-18:1) that accounts for 17–25% of total fatty acids and promotes human health due to its antiatherogenic effect. The other monounsaturated fatty acids in the milk fat are C14:1, C16:1 and vaccenic acid (trans-11-octadecenoic acid; 11t-18:1) of which concentrations are lower. While polyunsaturated fatty acids in milk fat, linoleic (9c, 12c-18:2) and linolenic (9c, 12c, 15c-18:3) acids, are essential for human, high level of oleic acid and the ratio of ω-6 to ω-3 fatty acids being close to the ideal (1–2:1) also renders it a good fat source for cardiovascular health (Haug et al., 2007). Feeding cows with forage-based diets and less grain can reduce the ω-6/ω-3 ratio from 2.2-5.8 to 1 and increase the level of ω-3 fatty acids and conjugated linoleic acids (CLA) in bovine milk (Benbrook et al., 2018; Davis, Chatzidimitriou, Leifert, & Butler, 2020). The milk fat contains CLA at a proportion of approximately 1%. The term of CLA is defined as a mixture of positional and geometrical isomers of octadecadienoic acid with conjugated double bonds, and these double bonds can be either in the cis- or in the trans-configuration (Fritsche & Steinhart, 1998). The principal isomer of CLA in milk fat is 9c, 11t-C18:2 that constitutes of 80–90% of total CLA (MacGibbon, 2020). CLA has been claimed to have positive effects on health such as cytotoxic effect on tumour cells, anti-obesity effect, enhancement of the immune functions, and control of atherogenesis and diabetes (Aminot-Gilchrist & Anderson, 2004; Bauman et al., 2020; Belury, 2002; MacDonald, 2000).

4.2. Heat-induced changes in fatty acids in milk

Thermal degradation of milk fat is generally not observed in the conventional heat treatments of milk (Table 3), since the non-oxidative decomposition of the fatty acids occurs above 200 °C (Claeys et al., 2014; van Boekel & Walstra, 1995). The release of FFAs in heat treated milk occurs mostly due to the enzyme activity. The hydrolysis of milk fat (lipolysis) is catalysed by the lipases from mainly two sources in milk; lipoprotein lipase, which is naturally found in milk, and bacterial lipases, which are produced by contaminant bacteria (Deeth, 2020). In addition, lipases originating from somatic cells can cause lipolysis in milk (Azzara & Dimick, 1985). The milk lipoprotein lipase is inactivated by HTST or more severe thermal treatments, whereas most of bacterial lipases are heat-resistant (Deeth, 2020).

LTLT or HTST pasteurisation did not change concentrations of FFAs in bovine, cow and human milk were reported in the studies by Cappozzo, Koutchma, and Barnes (2015), Dias et al. (2020), Moltó-Puigmartí et al. (2011) and Pereira, Martins, and Vicente (2008). On the other hand, Khan et al. (2017) reported release of FFA in pasteurised (65 °C, 30 min) and boiled (for 1 min) cow and buffalo milk where the concentrations of short- and medium-chain fatty acids increased by 2–100% depending on the fatty acid, while those of unsaturated long-chain fatty acids (C18:1-C18:3) decreased by 5–50% proportional to the degree of unsaturation and heat treatment. Furthermore, Zhu et al. (2020) reported increase in concentrations of some FFAs during refrigerated storage (about 2-fold in oleic acid, 4-fold in arachidonic acid after 12 days) of LTLT-pasteurised milk which was explained by residual milk lipase and somatic cell lipase activity.

Release of FFAs in UHT-treated milk is also possible by heat-resistant lipases of contaminant bacteria. Damage to milk fat globule membrane (MFGM) by UHT treatment can augment lipolysis by allowing exposure of milk fat to lipase. Xu et al. (2020) recently showed that FFA concentration in indirect UHT-treated milk (135 °C, 15 s) was 1.31- and 1.14-fold higher than those in raw milk and pasteurised milk (85 °C, 15 s), respectively. However, this slight change does not cause a defect in UHT milk manufactured from good quality raw milk with low level of FFAs. Apart from heat treatment, homogenisation can lead to hydrolysis of milk fat by damaging the integrity of MFGM. Especially, when homogenisation is applied before heat treatment, milk fat is exposed to active lipases. van Hekken, Tunick, Ren, and Tomasula (2017) found that homogenisation (60 °C, 17.2/10.3 MPa) caused higher levels of C8 to C14 saturated fatty acids in bovine milk. Lu, Pickova, Daniel, and Langton (2020) investigated the effect of different stages of UHT milk production on fatty acid concentrations and found that double stage homogenisation-preheat treatment (200–40 bar, 80–95 °C, 120 s) and UHT treatment 143 °C, 4 s) caused gradual reductions in total fatty acid concentrations up to 4–5% and 11–12%, respectively, compared with those in the initial pasteurised milk. While FFAs exhibited an increase up to 5% by homogenisation, 22% by preheat treatment and 33% by UHT treatment, TAG-bound FAs showed a decrease up to 10% by homogenisation-preheat treatment and 19% by UHT treatment. Tunick and Van Hekken (2017) also reported slight decreases (<20%) in TAG-bound vaccenic, rumenic and α-linolenic acids by homogenisation/pasteurisation and homogenisation/UHT treatments.

Heat treatment could result in oxidation and decomposition of PUFAs that lead to the formation of oxidised intermediates, hydroperoxides and oxylipids (hydroxy, epoxy, dihydroxy, trihydroxy or ketone fatty acids), and finally aldehydes and ketones (Li, Wang, Zhang, Shao, & Guo, 2019). The methyl ketones are produced by decarboxylation of β-keto saturated fatty acids whereas the aldehydes are formed via oxidation of unsaturated fatty acids to hydroperoxides. These volatile compounds are responsible for rancid flavour, which is also described as tallowy, coconut-like or cardboardy (Deeth, 2020).

Decomposition of PUFAs by oxidation depending on the intensity of heat treatment of milk can reduce the nutritional value of milk fat. Pitino et al. (2019) did not find any significant change in

Table 3
Essential and some functional fatty acids in raw and heat−treated milk.[a]

Fatty acid (%, w/w, in fat)	Raw				Pasteurised		Sterilised		Reference
	Cow	Sheep	Goat	Human	Cow	Human	Cow	Human	
C4:0	3.75				3.82[d]		3.94[e]		Khan et al. (2017)
	3.9	3.5	2.2						Gomez−Cortes et al. (2018)
C6:0	2.28				2.87		3.35		Khan et al. (2017)
	2.5	2.9	2.4						Gomez−Cortes et al. (2018)
C18:1				35.8		35.7[c]			Pitino et al. (2019)
	21.18				19.23		18.66[c]		Khan et al. (2017)
	23.89				24.15		24.23		Tunick and Van Hekken (2017)
				28.5					Samur, Topcu, and Turan (2009)
	21.1	21.1	21.4						Gomez−Cortes et al. (2018)
C18:2				13.3		13.5[b]			Pitino et al. (2019)
	1.98				1.72		1.37[e]		Khan et al. (2017)
	3.74				3.52		3.36		Tunick and Van Hekken (2017)
	1.2−3.0	1.6−3.6	1.9−4.3	6.0−17.7					Claeys et al. (2014)
C18:3				0.10		0.11[b]			Pitino et al. (2019)
	0.48				0.35		0.22[e]		Khan et al. (2017)
	0.77				0.69		0.63		Tunick and Van Hekken (2017)
	0.3−1.8	0.5−2.3	0.2−1.2	0.6−3.4					Claeys et al. (2014)
MUFA				41.93		41.80[b]			Pitino et al. (2019)
	27.79				28.79[f]		29.06[g]		Pestana, Gennari, Monteiro, Lehn, and Souza (2015)
	22.7−30.3	23.0−39.1	21.8−35.9	33.2−45.1					Claeys et al. (2014)
PUFA				17.06		17.28[b]			Pitino et al. (2019)
	2.48				2.62[f]		2.46[g]		Pestana et al. (2015)
	2.4−6.3	2.5−7.3	2.6−5.6	8.1−19.1					Claeys et al. (2014)
ω−6:ω−3				6.74		6.70[b]			Pitino et al. (2019)
	3.51				3.47[f]		3.49[g]		Pestana et al. (2015)
	2.1−3.7	1.0−3.8	4.0	7.4−8.1					Claeys et al. (2014)
CLA	0.2−2.4	0.6−1.1	0.3−1.2	0.2−1.1					Claeys et al. (2014)
					0.55[h]		0.48[j]		Herzallah et al. (2005)
					0.53[i]				

[a] Superscript letters within the table indicate the following: [b] Holder 62.5 °C, 30 min;[c] Retort 121 °C, 5 min;[d] 65 °C, 30 min;[e] Boiling, 1 min;[f] 75 °C, 15 s;[g] 140 °C, 3s;[h] 85 °C, 16 s;[i] 63 °C, 30 min;[j] 140 °C, 4s.

FFA and oxidised lipids in human milk by batch or flash pasteurisation. van Hekken et al. (2017) also found that HTST pasteurisation and UHT treatment had no effect on the concentrations of CLA and α-linolenic acid in milk. However, Fritsche and Steinhart (1998) determined that the concentrations of CLA in raw, pasteurised, UHT and condensed milk were 1.16, 0.98, 0.80 and 0.63% of total fatty acids. Likewise, the concentration of unsaturated fatty acids was found to decrease by 53% in UHT milk compared with that in raw milk by Xu et al. (2020). Gathercole et al. (2017) reported that the concentrations of FFAs (C4:0−C18:0, C18:1) were reduced by 30−60% by increasing intensity of heat treatment ranging from Holder pasteurisation to UHT treatment. This reduction was explained by loss or modification of free fatty acids by the heat treatment. The authors also found that the concentrations of methyl ketones and oxidised fatty acids (3-hydroxy fatty acids) were directly proportional to the intensity of heat treatment increasing by 30−50%. Khan et al. (2017) also detected a 54 and 77% increase in peroxide value (POV) by boiling treatment of buffalo and cow milk, indicating a potential for oxidation. UHT treatment caused formation of more aldehydes such as hexanal and heptanal derived from unsaturated fatty acids UHT milk compared with raw, thermised and pasteurised milk (van Hekken, Iandola, & Tomasula, 2019). Similarly, Li et al. (2019) found that the concentration of oxidised flavour compounds (heptanal, nonanal, 2-heptanone, and 2-nonanone) increased with increasing the intensity of heat treatment. They also found that the total antioxidative activity decreased by 23%, and the POV increased by 37% when raw milk was heated at 90 °C for 20 min.

In another study, batch pasteurisation, HTST pasteurisation and UHT treatment did not significantly change hydroperoxide and thiobarbituric acid-reactive species (TBARS) content of milk compared with those in raw milk (Dias et al., 2020). Furthermore in this study, HTST and UHT treatments were determined to decrease oxidised products of linoleic acid and α-linolenic acid by 51−64%, concentration in milk compared with those in raw and batch pasteurised milk, which was explained by their conversion to secondary oxidation products. Zhang et al. (2018) reported that the presence of 7 oxylipids (hydroxy fatty acids) differentiated UHT milk from raw and pasteurised (85 °C, 15 s) milk using LC-MS in a metabolomics approach.

Pasteurisation had no impact on the CLA content of milk but UHT treatment caused 15% decrease (Herzallah, Humeid, & Al-Ismail, 2005). In another study, HTST pasteurisation resulted in a significant decrease in the concentrations of cis-9/trans-11 isomer and other minor CLA isomers in CLA-enriched fluid milk (Campbell, Drake, & Larick, 2003). Similarly, Rodríguez-Alcalá and Fontecha (2007) detected that heat treatment (indirect UHT, 142 °C, 6s) caused significant decreases or disappearance of some of the minor CLA isomers and a significant increase of trans−trans isomers from cis−trans, trans−cis, and cis−cis isomers in a CLA-fortified dairy product. Herzallah et al. (2005) found that pasteurisation (85 °C, 16 s or 95 °C, 5 min) and UHT treatment (140 °C, 4 s) did not cause any significant change in total trans fatty acid concentration, whereas LTLT pasteurisation (63 °C, 30 min) resulted in 19% increase.

4.3. Digestion of fatty acids in heat-treated milk

Influence of heat treatment along with homogenisation can impact digestibility of milk fat in human body. Zhao, Du, and Mao (2019) reported that while homogenisation led to an increase in the release of medium- and long-chain fatty acids, homogenisation-

HTST caused the release of unsaturated fatty acids, and homogenisation-UHT increased the release of all types of fatty acids under in vitro gastrointestinal digestion. Similarly, homogenisation, homogenisation-HTST and homogenisation-UHT treatments increased the FFA release during in vitro gastro-intestinal digestion, which was attributed to damages in the structure of the milk fat globule membrane by heat exposing lipids and increased surface area by homogenisation for lipase action (Tunick et al., 2016). In another in vitro study, the release of the C18 fatty acids, oleic acid, linoleic acid, CLA, and linolenic acid, in homogenised-HTST-treated milk and homogenised-UHT-treated milk was determined to be about 2-fold higher than those from milk either pasteurised or homogenised, or with no treatment (Tunick & Van Hekken, 2017).

In an in vivo study with rats by Gallier et al. (2013), more of fatty acids were released from cream of pasteurised milk compared with that of raw or pasteurised-homogenised milk after gastric digestion. Moreover, Nuora et al. (2018) concluded that homogenisation, pasteurisation or UHT treatment of milk did not affect intestinal absorption of TAG from a study in which postprandial plasma levels of C14–C18 fatty acids were followed for 4 h after consumption of milk in milk sensitive human subjects. In an in vitro study with human gastric enzymes, homogenisation and UHT treatment were not found to improve the lipolysis of milk fat compared with pasteurised milk (73 °C, 20 min) but rather the size of fat globules was found to be effective (Garcia, Antona, Robert, Lopez, & Armand, 2014). Homogenised and UHT-treated milk exhibited the same level of lipolysis as pasteurised milk with 9.5% in gastric, 57–64% in gastroduodenal and 59–63% in duodenal media. On the other hand, small milk fat globules (d_{43}, 1.75 μm) that are separated by microfiltration were 37 and 45% more efficiently lipolysed in gastric medium than homogenised and homogenised-UHT treated fat globules (d_{43}, 0.34 μm) respectively. While there was no difference between levels of lipolysis of small sized fat globules and homogenised fat globules in gastroduodenal medium, small sized fat globules were 26–35% more lipolysed than homogenised fat globules in duodenal medium. The differences in extent of lipolysis was attributed to the larger surface area and phospholipid layer in small sized globules compared with additional protein in homogenised fat globules by Garcia et al. (2014).

5. Heat effect on oligosaccharides in milk

Oligosaccharides have been recognised as bioactive components of human milk that are important in development of gut microbiota and immune system of infant. While they are the third abundant component of human milk (20–30 g L^{-1} in colostrum, 10–15 g L^{-1} in mature milk), they are present 20–100 fold lower levels in animal milk depending on species (for bovine, 1 g L^{-1} in colostrum, 0.03–0.06 g L^{-1} in mature milk) (Table 4) (Bode, 2012; Carr et al., 2021; Cheng, Akkerman, Kong, Walvoort, & de Vos, 2021; Martinez-Ferez et al., 2006). Oligosaccharides are derived from lactose and composed of galactose, glucose, N-acetylglucosamine, L-fucose and N-acetylneuraminic acid (sialic acid). Milk contains free and conjugated oligosaccharides bound to glycoproteins, including κ-casein, α-lactalbumin, lactoferrin, immunoglobulins, serum albumin, lysozyme and MFGM proteins, and glycolipids (gangliosides) (Peterson, Cheah, Grinyer, & Packer, 2013). Functional properties of oligosaccharides include prebiotic activity for beneficial bacteria in the colon, anti-pathogenic effect, improvement of gut barrier function and immune system (Carr et al., 2021; Cheng et al., 2021; Zivkovic & Barile, 2011).

Excess human milk has been heat-treated for long term storage in milk banks. Since oligosaccharides are valuable components for infant nutrition, determination of effect of heat treatment of oligosaccharides in human milk have been of interest. Daniels et al. (2017) reported no adverse effect of LTLT (62.5 °C, 30 min) or HTST (72 °C, 15s) pasteurisation on human milk oligosaccharides. In another study, milk samples from different milk banks applying sterilisation or pasteurisation were analysed for concentration and type of oligosaccharides (Meredith-Dennis et al., 2018). Retort-sterilised (121 °C, 5 min) human milk contained the lowest level (5.73–7.18 g L^{-1}) of oligosaccharides compared with vat (63 °C, ≥30 min) or Holder (62.5 °C, 30 min) pasteurised human milk (8.14–8.35 g L^{-1} in vat and 12.0–13.5 g L^{-1} in Holder heated sample) where raw human milk had a concentration of 8.05 g L^{-1}. This trend was explained by Maillard reaction that can take place with increasing severity of heat treatment. In addition, Holder pasteurised milk samples had higher fucosylated, sialylated and neutral oligosaccharides than vat-heated and sterilised samples. Yang et al. (2022) reported that oligosaccharides in reconstituted demineralised bovine cheese whey powder were stable against heat treatment at temperatures equal to or below 100 °C for 120 min. Although the heating time was long for regular heat treatments, this finding showed that the oligosaccharides would endure during processing.

Interestingly, heat treatment of bovine colostrum at 60 °C for 60 min increased the concentration of free oligosaccharides by 1.5–3.6 fold depending on their structure (Fischer, Malmuthuge, Guan, & Steele, 2018). This increase was explained by the release of oligosaccharides from glycoproteins and glycolipids. One of the glycopeptides in milk is caseinomacropeptide (CMP), which is released to whey from κ-casein by coagulation with chymosin during cheese making. Half of the CMP in milk is glycosylated (gCMP) with N-acetylgalactosamine, galactose and N-acetylneuraminic acid (Saito & Itoh, 1992; Thomä, Krause, & Kulozik, 2006). pH is the major factor affecting the breakdown of these glycoconjugates and their heat stability is high at neutral pH. Release of sialic acid from cheese whey was enhanced by reduction in pH from neutral to 3.8 (Lieske, Konrad, & Kleinschmidt, 2004). Complete release of sialic acid was achieved by heat treatment at 98 °C for 1 h at pH 3.0 (Saito, Yamaji, & Itoh, 1991). Nakano and Ozimek (2000) found that amounts of free sialic acid, galactose and galactosamine from sweet whey increased approximately by 2.0, 2.8 and 2.6 fold, respectively, as the pH was decreased from 4.0 to 2.5.

Table 4
Oligosaccharides in raw and heat–treated milk.[a]

Component (g L^{-1})	Raw				Pasteurised Human	Sterilised Human	Reference
	Cow	Sheep	Goat	Human			
Sialylated oligosaccharides	0.03		0.07	0.75–1.69			Monti, Cattaneo, Orlandi, and Curadi (2015)
Total oligosaccharides	0.03–0.06	0.02–0.04	0.25–0.30	5.0–8.0			Martinez-Ferez et al. (2006)
				8.05	8.14–8.35[a] 12.0–13.5[b]	5.73–7.18[c]	Meredith-Dennis et al. (2018) Meredith-Dennis et al. (2018)

[a] Superscript letters within the table indicate the following:[a] Vat 63 °C, ≥30 min;[b] Holder 62.5 °C, 30 min;[c] Retort 121 °C, 5 min.

Siegert, Tolkach, and Kulozik (2012) reported that up to 72% of sialic acid was released from gCMP at pH 2 by heat treatment at 120 °C for 90 s. Kilic-Akyilmaz and Karimidastjerd (2018) found that 79% of bound sialic acid was released from bovine cheese whey by heat treatment at 90 °C for 1 h at a pH of 3 compared with about 40% at a pH of 5. Heating at near neutral pH and then acidification of cooled whey resulted in about 10% less release in sialic acid. Taylor and Woonton (2009) showed that only 33% of gCMP in milk was recovered in cheese whey after high temperature long time (100 °C, 10 min) while 87 and 85% of it recovered by LTST (65 °C, 15 s) and HTST (72 °C, 15 s) treatments, respectively. Low release was explained by inhibition of chymosin action on casein by complex formation with denatured whey proteins.

6. Effect of heat treatment on hormones and growth factors of milk

Milk contains hormones originating from anterior pituitary gland (e.g., prolactin, somatotropin), from hypothalamus (e.g., somatotropin-releasing hormone and somatostatin) and from gastrointestinal tract (GIT) (e.g., vasoactive intestinal peptide, gastrin and substance P) (Fox et al., 2015). A number of growth factors including insulin-like growth factors-I and II (IGF-I and IGF-II), IGF-binding proteins, epidermal growth factors (EGF), transforming growth factor (TGF-β) and biologically active compounds including prostoglandin $F_2\alpha$ and E, insulin and lactoferrin (Lf) are also present in milk. The concentrations of such compounds are high in colostrum and decrease to normal values with lactation (Fox et al., 2015).

A few studies have addressed the effects of heat treatment on the stability of milk hormones so far. In an early study, Wolford and Argoudlis (1979) showed that the concentrations of steroid hormones of estrone (E1) and 17β-estradiol (E2) -major estrogens- were reduced in commercial whole milk (55.8 pg E1 mL^{-1} in raw milk versus 33.7 pg E1 mL^{-1} in processed milk, and 10.3 pg E2 mL^{-1} in raw milk versus 6.4 pg E2 mL^{-1} in processed milk). Total E1 (free and conjugated) and E2 concentrations in 3.5% fat processed milk were reported as 0.13 μg kg^{-1} and less than 20 μg mL^{-1}, respectively (Hartmann, Lacorn, & Steinhart, 1998). Both pasteurisation and homogenisation did not affect the E1 and E2 concentrations in conventional skimmed, 1% fat, 2% fat and whole milk (Pape-Zambito, Roberts, & Kensinger, 2010). Riahi-Zanjani, Heiderzagedan, Badibostan, and Karimi (2019) analysed totally 160 samples (40 high fat and 40 low fat commercial pasteurised milk samples, and 40 high fat and 40 low fat UHT commercial milk samples). Authors found no difference between pasteurised and UHT milk in terms of oestradiol levels but high fat samples had slightly higher levels of E2 compared with low fat milk.

IGF-I and IGF-II are peptide growth factors that contribute to the growth-promoting properties of human milk. Heat treatment did not influence the IGF-I and IGF-II levels in human milk (Donovan, Hintz, & Rosenfeld, 1991). Mann et al. (2020) found an approximately 10% reduction in IGF-I level of bovine colostrum upon heating. In other studies reported by Collier et al. (1991), Elfstrand, Lindmark-Månsson, Paulsson, Nyberg, and Åkesson (2002), and Kang, Kim, Imm, Oh, and Kim (2006) thermal treatments did not influence IGF-I level of bovine colostrum and cows' milk. Milk processing (pasteurisation and homogenisation) did not affect the glucocorticoid level in milk (Schwalm, Kirk, Secrest, & Allen-Tucker, 1978).

Lower levels of melatonin was reported in UHT milk (5.62 pg mL^{-1}) compared with that in raw milk (6.98 pg mL^{-1}) (Schaper, Koethe, & Braun, 2015; Romanini, Volpato, dos Santos, de Santana, & Ludovico, 2019). Heat treatment of bovine colostrum at 60 °C for 60 min caused 7–45% reduction in insulin concentrations (Mann et al., 2020). While thermal treatments did not affect the TGF-β_2 concentration of bovine colostrum (Elfstrand et al., 2002) and cows' milk (da Silva et al., 2017), the TGF-β_2 content of whey was reduced by heat treatment at 72 °C for 15 s (Rocafi et al., 2011). The TGF-β_2, EGF, adiponectin and ghrelin concentrations in donor human milk were not affected by continuous HTST (70–75 °C, 5–25 s) or Holder pasteurisation (62.5 °C, 30 min) (Escuder-Vieco Espinosa-Martos, Rodriguez, Fernandez, & Pallas-Alonso, 2018). In conclusion, slight losses in concentrations of steroid hormones E1 and 17β-E2 occur during HTST or UHT treatment of milk. Both pasteurisation and UHT treatment do not affect the stability of IGF-I and IGF-II in milk. On the contrary, with the increase in heating intensity, the melatonin and insulin concentrations in milk decrease.

7. Conclusions

Milk contains a wide variety of micronutrients and bioactive compounds. Although they are present at low levels, their impact on human, especially infants, health is substantial. Our understanding of the functions and importance of these minor components have been improved by the developments of analysis techniques with more sensitivity and precision. Heat treatment is essential to ensure microbiological safety and keeping quality of milk. On the other hand, heat can cause loss of micronutrients by decomposition or inducing oxidation.

In general, pasteurisation has no effect on stability of micronutrients, however, as the degree of heat treatment is increased especially in the case of in-bottle sterilisation, partial degradation of some nutrients including water soluble vitamins B_1, B_6, B_{12} and C, unsaturated fatty acids and some hormones. Moreover, evaporation and drying operations can be detrimental to oxygen sensitive components including most water and fat soluble vitamins and unsaturated fatty acids.

In addition, packaging technique preventing exposure to oxygen and light, and storage temperature and duration are important factors for protection of micronutrients of milk. Milk matrix components especially protein and fat can protect some micronutrients, especially vitamins. Severe heating conditions can also cause some mineral losses by precipitation on heating surfaces via chemical or physico–chemical interactions with the other milk components. On the other hand, heat may also cause release of some components from bound structures and improve their availability, i.e., oligosaccharides.

Although heat-induced changes on the micronutrients and bioactive compounds of milk have been revealed, bioaccessibility and bioavailability of these components after heat treatment are not known to a sufficient extent. More in vitro and in vivo studies are required to understand how heat treatment of milk influences their benefit for human health. This would provide basis for fine adjustment of heat treatment parameters for better protection and utilisation of these components from dairy streams. In addition, innovative thermal and non-thermal treatments can be developed for production of milk products with a rich micronutrient and bioactive composition and a long shelf life.

CRediT authorship contribution statement

Meral Kilic-Akyilmaz: Conceptualization, Methodology, Investigation, Supervision, Resources, Writing-original draft, Writing-review & editing.

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Declaration of competing interest

None.

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