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Current progress of emerging technologies in human and animals' milk processing: Retention of immune-active components and microbial safety

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Abstract

Human milk and commercial dairy products play a vital role in humans, as they can provide almost all essential nutrients and immune-active components for the development of children. However, how to retain more native immune-active components of milk during processing remains a big question for the dairy industry. Nonthermal technologies for milk processing are gaining increasing interest in both academic and industrial fields, as it is known that thermal processing may negatively affect the quality of milk products. Thermosensitive components, such as lactoferrin, immunoglobulins (Igs), growth factors, and hormones, are highly important for the healthy development of newborns. In addition to product quality, thermal processing also causes environmental problems, such as high energy consumption and greenhouse gas (GHG) emissions. This review summarizes the recent advances of UV-C, ultrasonication (US), high-pressure processing (HPP), and other emerging technologies for milk processing from the perspective of immune-active components retention and microbial safety, focusing on human, bovine, goat, camel, sheep, and donkey milk. Also, the detailed application, including the instrumental design, technical parameters, and obtained results, are discussed. Finally, future prospects and current limitations of nonthermal techniques as applied in milk processing are discussed. This review thereby describes the current state-of-the-art in nonthermal milk processing techniques and will inspire the development of such techniques for in-practice applications in milk processing.

KEYWORDS
microbial survival, milk components, nonthermal processing, nutrients

1 | INTRODUCTION

Milk, a natural fluid secreted by the mammary gland of female mammals, is considered to be the optimum feeding regime and meets the complete nutritional requirements of their neonates (van Lieshout et al., 2020). Milk not only provides vital nutrients but also provides immune-active components which facilitate, among others, the development of the intestinal tract and immune system (Lyons et al., 2020). However, owing to its vulnerability to pathogens and spoilage micro-organisms, thermal treatments are widely used in both the dairy industry and human milk banks. In the dairy industry, cow and goat milk are the most popular and available milk sources globally; high-temperature short time (HTST) pasteurization, extended shelf-life (ESL), and ultra-high temperature (UHT) treatments are most frequently applied to reduce their bacterial loads. In Europe and the United States, people generally consume HTST-treated milk while UHT-treated milk is more popular in developing regions and specific regions with scarce milk sources, where logistics and sales need a longer shelf-life or ambient temperature storage conditions. In human milk banks, donor human milk (DHM) is usually pasteurized to make sure it is microbiologically safe for which, currently, holder pasteurization (HoP) is the most common method being utilized. With this method, DHM is usually heated at 62.5°C for 30 min, destroying all high-risk viruses and non-spore-forming pathogen bacteria (Escuder-Vieco et al., 2018).

In general, the heating of milk is associated with changes in organoleptic properties, like changes in flavor or color (Al-Attabi et al., 2008). Recently, increasing evidence shows that the heating of milk leads to a loss of the inherent host defense capacity, through damage to the immune-active proteins, enzymes, cytokines, and other components (Brick et al., 2017; Escuder-Vieco et al., 2018; Liu et al., 2020a; Xiong et al., 2020). On top of that, many epidemiological investigations have revealed that consuming raw (unprocessed) milk protects infants and children from common upper respiratory infections, asthma, and allergies (Braun-Fahrländer & Von Mutius, 2011; Brick et al., 2020; Loss et al., 2011, 2015; Wyss et al., 2018), and this protective effect seems to be associated with the proteins damaged or modified upon heat treatment (Loss et al., 2015). Additionally, Abbring et al. (2020) and Xiong et al. (2020) found that heating above 70°C would significantly decrease the allergy-protective capacity and bacteriostatic properties of bovine milk, respectively, showing that damage to immune-active proteins already occurs at relatively low heat processing temperatures. Moreover, it is generally reckoned that goat milk is more susceptible to heat-induced damage in comparison with bovine milk owing to its higher content of ionic calcium and lower content of citrates. Consequently, nonthermal processing would be of even larger benefit for goat milk treatments (Barłowska et al., 2011).

With societal modernization and global economic development, both the global milk production and demand for consumption of dairy products are increasing rapidly. Meanwhile, consumers are more and more demanding for natural or minimally processed foods with the flavor and nutritive properties of fresh foods. On top of that, greenhouse gas (GHG) emissions and global warming are increasingly aggravated. Consumers are becoming more and more aware of the effect of individual dietary behavior on the environment; this may thus change their consumption habits and preferences. Within the dairy industry, there are various processes that require energy for operating plant facility systems and processing equipment, and thermal processing is a multistep, energy-intensive process (Nutter et al., 2013; Xu & Flapper, 2009). It was reported that the average GHG emissions for processing, packaging, and distribution were 0.077, 0.054, and 0.072 kg CO_2 equivalent kg^{-1} packaged fluid milk, respectively (Nutter et al., 2013), even though the detailed information on heat processing-induced GHG emission is still limited and fragmented. However, it is necessary to save the energy use associated with milk processing.

Given those heat-induced changes to native proteins, inferior organoleptic quality, and high energy consumption from thermal treatments, there has been growing interest in seeking alternative methods to process dairy products, aiming for retention of nutritive and immune-active components and better organoleptic quality (Masotti et al., 2021; Rodriguez-Gonzalez et al., 2015). Also for DHM, processing aimed at retention of immune-active components is studied extensively, as it may lead to quality improvement of such milk (Wesolowska et al., 2019a). Nonthermal treatments are thus gaining more and more attention in the dairy industry and human banks in recent years. The term “non-thermal processing” is often used to designate technologies that are effective at ambient or sublethal temperatures. These emerging techniques provide environmentally friendly and sustainable food processing methods that have the prospect of lowering energy consumption, reducing water consumption, and overcoming some limitations of current food manufacturing practices (Singh & Huppertz, 2020). Among those nonthermal treatments, ultraviolet-C radiation (UV-C), high-pressure processing (HPP), ultrasonication (US), pulsed electric field (PEF), and cold plasma (CP) are the most investigated (Figure 1). Research on using these emerging techniques in liquid milk processing is increasing. This review summarizes the current state-of-the-art of these most promising emerging techniques in dairy processing, including human, bovine, goat, sheep , camel , and donkey milk with a focus on retention of immune-active components and microbial inactivation, which differs from the other reviews focused on the physicochemical properties of milk. As far as we know, a comprehensive review focused on retaining immune-active components by nonthermal techniques has not been reported. This review will inform the dairy industry and human milk banks to manufacture clean, safe, and highly nutritive milk with simultaneous retention of immune-active components.

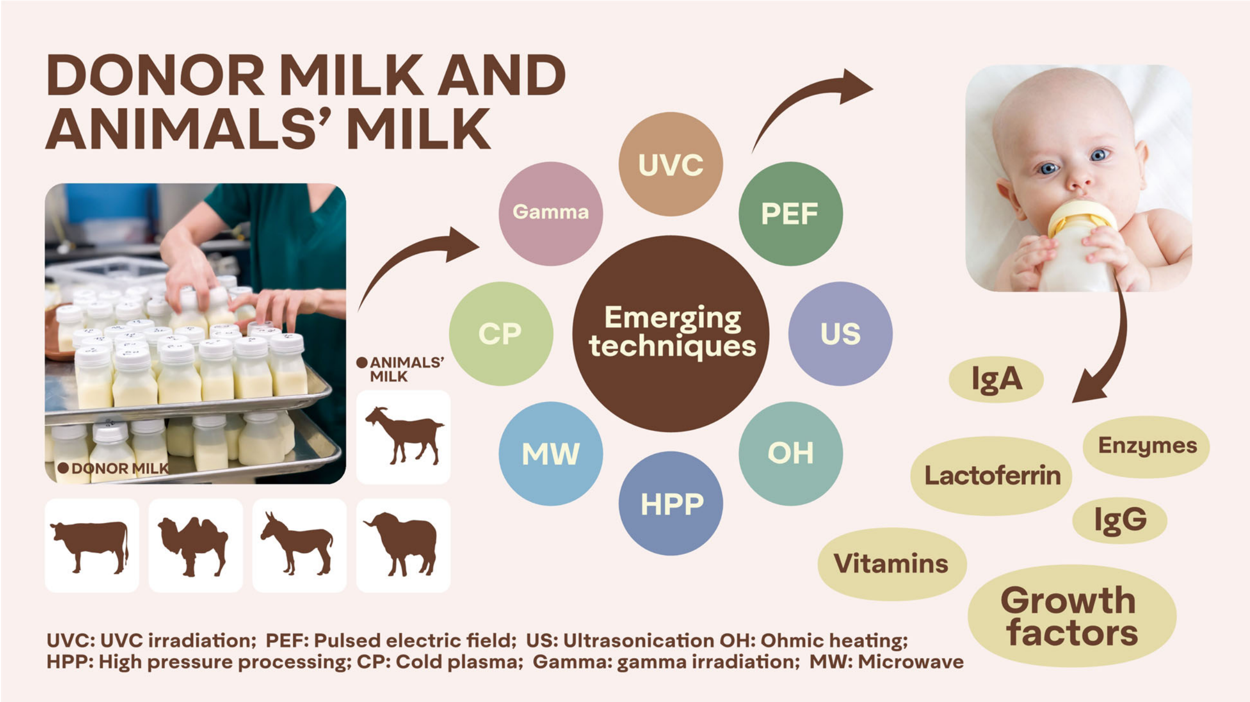


FIGURE 1 Promising emerging technologies for dairy processing

2 | FUNDAMENTALS AND DEVELOPMENTS OF NONTHERMAL MILK PROCESSING

2.1 | UV-C

Ultraviolet (UV) treatment is a physical disinfection technique that can be used to kill harmful bacteria in foods, beverages, and environments. Since 1985, UV radiation has been commercialized for water disinfection and purification, brewing, soft drinks, and cheese-making (Chawla et al., 2021; Tran & Farid, 2004). In 2016, the European Food Safety Authority (EFSA) already approved the UV-C treated pasteurized milk (whole, semi-skimmed, or skimmed) as a novel food (EFSA Panel on Dietetic Products, 2016) for use. UV-C irradiation (1000–2000 J/L) would not change the milk composition or give rise to safety concerns. However, as far as the authors know, this technology is not actually used in practice yet. As shown in Figure 2, the disinfection effect of UV irradiation was attributed to its ability to damage the genetic material (DNA bases) and form pyrimidine dimers, which would inhibit the synthesis of new DNA in cells, so that viruses, bacteria, molds, and other microorganisms are not able to reproduce, leading to cell death (Shama, 1999). UV radiation can be classified into UV-A (320–400 nm), UV-B (280–320 nm), UV-C (200–280 nm), and Vacuum-UV (100–200 nm) according to its wavelength (Delorme et al., 2020). The maximum UV absorption efficiency for DNA lies between 250 and 280 nm (Bintsis et al., 2000). UV-C, therefore, has the most potent antimicrobial activity. Further, UV-C does not require high investment and maintenance costs or bring environmental problems when compared to other processing techniques (Keyser et al., 2008). Nowadays, UV-C has been considered one of the most promising food processing technologies with great commercialization potential, including in the area of beverages and dairy products (Delorme et al., 2020; Jermann et al., 2015). For its application, several factors are important, such as the solids content, turbidity, geometry of the UV device, and microbial species that need to be inactivated (Delorme et al., 2020). However, a unified calculation of UV-C dosage is difficult in practice as various types of UV-C installations were used in those reports. A detailed overview of this will be given in section 2.1.7. Recently, the health-promoting effects of UV-C processed milk have been reported by Schaefer et al. (2018), who found that UV-C treated milk has a better immune-stimulating effect than pasteurized milk, which has the potential to counteract the immunosenescence in the elderly when tested for vaccine response efficiency.

2.1.1 | UV-C treatment for donor human milk

Christen et al. (2013a) tried to use UV-C irradiation as an alternative treatment for DHM, and found that bacterial decimal reduction dosage increases with the solids

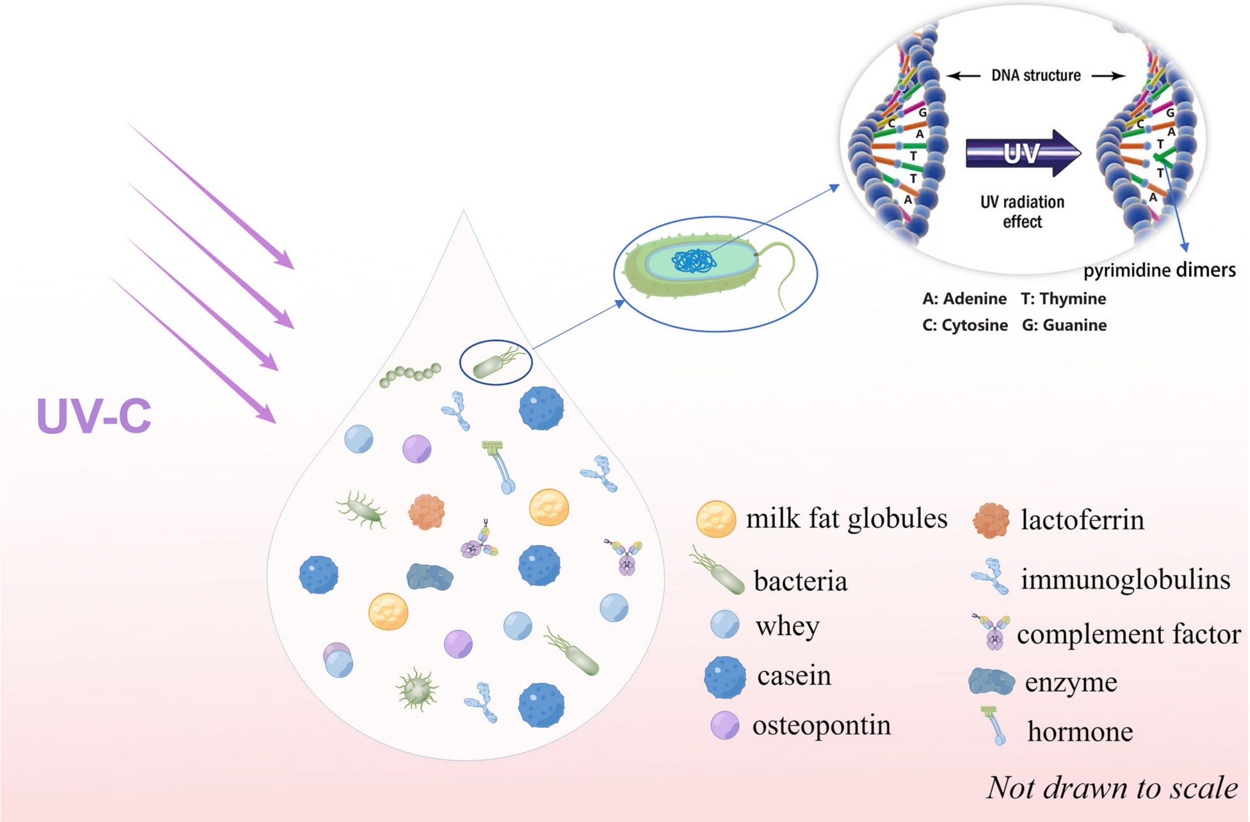


FIGURE 2 UV radiation-induced inactivation mechanism of microbes

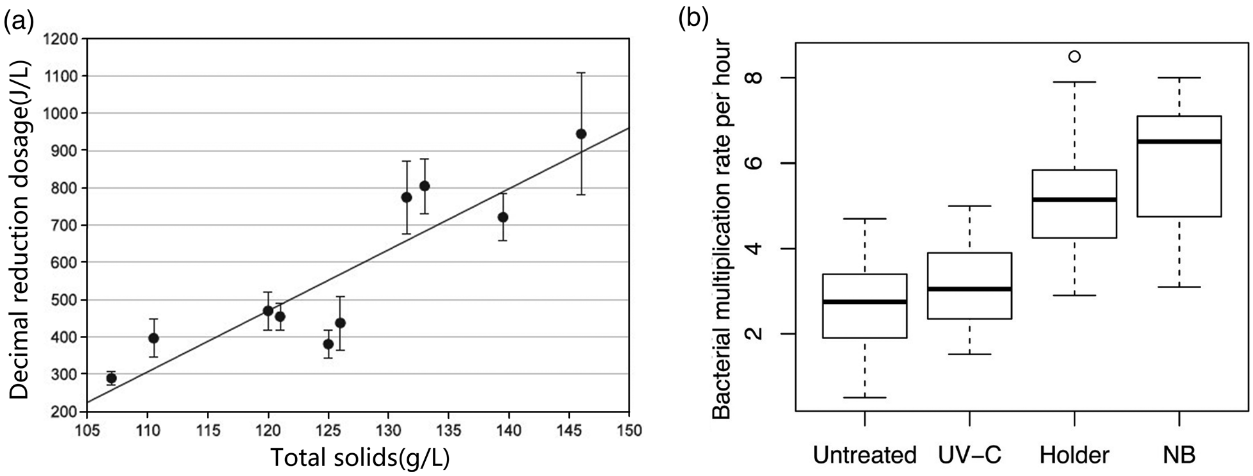


FIGURE 3 (a) Relationship between decimal bacterial reduction and total solids concentration of human milk samples from Christen et al. (2013a) and (b) bacterial growth for untreated, UV-C irradiated, and Holder pasteurized human milk and nutrient broth (NB) from Christen et al. (2013b)

content, as shown in Figure 3a. In addition, UV-C irradiation can achieve microbial safety in human milk according to the requirements of human milk banking guidelines (a 5-log reduction of bacteria for most human banks) without loss of bile salt stimulated lipase (BSSL) and alkaline phosphatase (ALP) activity. The same authors then compared the effect of UV-C on immune-active proteins and bacteriostatic activity of DHM and concluded that UV-C irradiation retained more of these proteins than HoP, without compromising the bacteriostatic properties compared with untreated human milk, as shown in Figure 3b. Pitino et al. (2019a) studied the effects of thermal and nonthermal (UV-C and HPP) pasteurization on the fatty acid composition of human milk. It was reported that UV-C and HPP treatment did not alter the fatty acid composition, but both increased the oxylipin concentration; higher concentrations of 18-carbon-derived oxylipins were found after UV-C irradiation, indicating the occurrence of oxidation. However, the biological relevance of an increased oxylipin concentration is still unclear.

2.1.2 | UV-C treatment for bovine milk

There has been a lot of research focused on UV-C treatment for bovine milk over the past decades. Recently, Atik and Gumus (2021) investigated the effects of UV-C dosage (from 60 J/L to 216.9J/L) on the microbiological quality of bovine milk and found that a ∼2 log reduction in total mesophilic aerobic bacteria count and a ∼4 log reduction in yeast/mold count was achieved in raw milk after a 107.8 J/L UV-C treatment. Moreover, Liu et al. (2020b) reported that UV-C treatment (4,500 J/L) was able to retain 80% of lactoferrin and almost 100% of IgG and lactoperoxidase (LPO) activity compared with raw milk. Zhang, Liu, Li, Xu, Hettinga, et al. (2021) developed a nonthermal device that combined microfiltration (MF) and UV-C and found that MF (1.4 μm pore size) combined with UV-C treatment prolonged the shelf-life of skimmed milk to at least 40 days. Moreover, the contents of lactoferrin and immunoglobin G in milk did not change greatly during refrigerated storage with retention of >95% (relative to the raw skimmed milk on the first day of storage).

2.1.3 | UV-C treatment for goat milk

The popularity and consumption of goat milk are increasing all over the world. Until now, the studies of UV-C treatments applied on goat milk are relatively rare. Kasahara et al. (2015) evaluated the inactivation of *Escherichia coli* in goat milk by UV-C and found that a 6-log reduction was achieved when using 10,000 mJ/cm^2 of pulsed UV. Sensory evaluation indicated that goat milk irradiated with >5,000 mJ/cm^2 showed significant differences in aroma compared with raw milk, but no significant differences in the overall flavors. Other studies showed that a more than 5-log reduction in *L. monocytogenes* was achieved when goat milk received a cumulative UV dosage of 15.8 mJ/cm^2 (Matak et al., 2005). This dosage simultaneously increased the levels of free fatty acids and aldehydes, but not enough to cause detectable differences in the odor of milk (Matak et al., 2007). Besides, UV-C was also combined with other nonthermal techniques, such as high pulsed electric field (HPEF) to realize a better bactericidal effect (Hariono et al., 2020). Studies focusing on retention of bioactive components by nonthermal techniques have not been reported; however, Saipriya et al. (2021) studied the influence of several unit operations on immunoglobulins and lactoferrin and reported that thermal treatments (pasteurization and boiling) decreased the contents of lactoferrin and immunoglobulins in goat milk to a large degree.

2.1.4 | UV-C treatment for camel milk

Camel milk has gained attention and popularity due to its specific bioactivities, such as potential antidiabetic (Han et al., 2022) and autism prevention functionality (Deshwal et al., 2020). Dhahir et al. (2020b) investigated the effects of UV-C dosage on the viability of *E. coli O157:H7* and *S. Typhimurium* and changes to camel milk components and found that UV-C treatment at 12.45 mJ/cm^2 resulted in a 3.9 log reduction in *E. coli* and *S. Typhimurium*, and this dosage did not change the main protein profile or induce lipid oxidization, as determined by secondary lipid peroxidation products.

2.1.5 | UV-C treatment for sheep milk

Studies related to UV-C treatment alone for sheep milk are relatively rare until now. Only, Ansari et al. (2019) evaluated the efficacy of UV-C radiation combined with thermal treatment on the inactivation of *Bacillus subtilis* spores in bovine milk and sheep milk and reported that UV-C pretreatment (D_{Act} 2.37 ± 0.126 J/ml) followed by thermal treatment at 110°C for 30 s resulted in a 1.1 log CFU/ml in sheep milk. UV-C irradiation could sensitize spores, making the following thermal treatment more efficient in inactivating *B. subtilis* spores.

2.1.6 | UV-C treatment for donkey milk

Donkey milk has received much attention due to its close chemical composition to human milk as well as to its unique functional properties (Polidori & Vincenzetti, 2013). However, very few studies on the nonthermal processing of donkey milk were reported. Recently, Papademas et al. (2021) evaluated the effect of UV-C on the inactivation of six foodborne pathogens inoculated in raw donkey milk, including *Listeria inoccua, Staphylococcus aureus, Bacillus cereus, Cronobacter sakazakii, E. coli*, and *Salmonella enteritidis*. It was reported that *L. innocua* was the most UV-resistant, requiring 1100 J/L for complete inactivation while the other bacteria were destroyed in the range of 200–600 J/L.

2.1.7 | Summary of UV-C treatment

Detailed information about research involving UV-C treatment in human and animal milks is summarized in Table 1. By reviewing studies where UV-C was applied in dairy processing, it is clear that the UV-C dosages and units are quite different between these reports, which can be attributed to the differences between in-house made or customized devices, as well as different calculation methods. Before realizing a large-scale industrialization of UV-C for dairy processing, several factors should be taken into account, such as the shape of UV-C lamp, output power, and radiation mode. Until now, most reported UV-C devices are simply in-house made devices operating in batch-mode, which cannot guarantee a standardized or continuous processing. In addition, relevant national regulations also need to be issued to guarantee the safety of UV-C processed milk. These are the main challenges that hinder the comparability between studies, as well as the standardization and commercialization of UV-C. Besides, another potential downside of UV-C applied in dairy processing is that oxidization of milk fat and proteins may occur, due to the high abundance of photosensitive lipids and amino acids (Dyer et al., 2017). Thus, an appropriate UV-C dosage that prevents oxidations or pre-fractionation of photosensitive components before UV-C irradiation should be taken into account.

2.2 | Ultrasonication

In the food and pharmaceutical industry, US is widely used for extraction, purification, meat tenderization, synthesization, catalyzation, modification, sterilization, and so on. (Dai et al., 2020; Wang et al., 2021; Wu et al., 2020). Generally, the frequency of ultrasound ranges from 20 kHz to 10 MHz, which could be divided into three regions: low-frequency, high-power ultrasound (20–100 kHz, intensity >1 W/cm^2); intermediate-frequency, medium-power ultrasound (100 kHz–1 MHz); and high-frequency, low-power ultrasound (1–10 MHz, intensity <1 W/cm^2), (Chandrapala & Leong, 2015). Depending on the specific application, an appropriate frequency range is selected. Low-frequency US induces strong cavitation, which affects the physical, chemical, and biochemical properties of foods, while high-frequency US creates a relatively gentle physical force and can be utilized for non-invasive analysis and monitoring of foods, and non-destructive separations of multicomponent mixtures (Chandrapala et al., 2012; Leong et al., 2013). The application of US for microbial inactivation could be traced back to the 1920s (Wood & Loomis, 1927), when its bactericidal effect on algae was first reported. Since then, several studies using US have been conducted, displaying a broad-spectrum antimicrobial activity (Dai et al., 2020). Specific mechanical vibration, acoustic streaming, and cavitation generated from US are responsible for its bactericidal effect. During US, the asymmetric collapse of cavitation bubbles leads to liquid jets rushing through the center of the collapsing bubbles with a speed as high as a few hundred meters per second. This micro streaming can erode cell walls and thereby inactivate microorganisms (Hughes & Nyborg, 1962). Figure 4 shows SEM pictures of *Anoxybacillus flavithermus* before and after US, and it is obvious that initially, the cells were in their regular rod shape whereas, after US, they were disintegrated into small pieces. Next, the sonochemistry effects of localized heating, high pressure, and highly reactive intermediates produced (e.g., free radicals or reactive oxide species, ROS production) causes DNA damage as well as thinning of cell membranes, which also contributes to the microbial inactivation (Bermúdez-Aguirre et al., 2011; Chandrapala et al., 2012). An overview of the US -induced microbial inactivation mechanism is shown in Figure 5.

Recently, US has been utilized as an alternative treatment to traditional thermal approaches in food processing (Chávez-Martínez et al., 2020; Dai et al., 2020).

2.2.1 | Ultrasonication treatment for donor human milk

For human milk, it was reported that US combined with heating at 45°C or 50°C strongly increased the inactivation rates of both *E. coli and Staphylococccus epidermidis*, compared with US alone. However, with the ongoing process of US treatment, the actual temperature of the milk increased as well, resulting in decreased retention of secretory immunoglobulin A (sIgA), lysozyme, lactoferrin, and BSSL, of which BSSL was the most vulnerable component (Czank et al., 2010). Recently, Mank et al. (2021) tried to use several nonthermal techniques to preserve insulin in DHM and found that US retained 97% of insulin in human milk, which is higher than both HoP (67%) and HTST (78%). In addition, Parreiras et al (2020) studied the effects of thermo-US on the microbial quality, antioxidant capacity, and retinol level of DHM and reported that thermo-US induced a greater decimal reduction in microorganisms than heat treatment alone; thermo-US enhanced the antioxidative capacity of DHM while HoP negatively affected it. However, in a study on the blood

TABLE 1 Summary of UV-C technology applied in human and animals' milk

Milk species	Objective	UV-C device/parameters	Results	References
Human milk	Inactivation of *S. enterica*, *E. coli*, non-pathogenic *E. coli, P. aeruginosa, L. monocytogenes, S. aureus*	In house-made device: power 1.37 mW/cm^2, wavelength 253.7 nm, time 0-60 min.	Linear and biphasic inactivation patterns were observed, 2.63–3.88 log reduction.	(Gabriel & Marquez, 2017)
	Retention of vitamin C, catalase, lysozyme, and antioxidant capacity; inactivation of *E. coli, S. aureus*, *E. faecalis*, and *E. faecium*	Dosage:85–740 J/L	Total inactivation of *E. coli* and *S. aureus*, partial for *Enterococcus*; increased oxidation products of lipids, decreasing vitamin C content and lysozyme activity.	(Martysiak-Żurowska et al., 2017)
	Sterilizing effect (*E. coli, S. epidermidis, E. cloacae, and B. cereus*, and *S. aureus*), and bioactive enzymes (BSSL, and ALP activity), and fatty acids.	253.7 nm, 380 ml milk, output power at 1.1 W, 500 rpm	Decimal reduction dosage was 289 and 945 J/L for total solids of 107 and 146 g/L, respectively. No significant changes in the fatty acid profile, BSSL activity, or ALP activity up to dosage are required for a 5-log reduction.	(Christen et al., 2013a)
	sIgA, lactoferrin, lysozyme, and bacteriostatic properties (*E. coli* and *S. aureus*)	The same as shown above	Retention of sIgA, lactoferrin, and lysozyme was 89%, 87%, and 75% respectively; better bacteriostatic properties.	(Christen et al., 2013b)
	Insulin retention	Dosage: 4863 J/L	93 ± 7 % retention relative to untreated DHM	(Mank et al., 2021)
	Vitamin C, BSSL activity, lysozyme activity, lactoferrin, and total bacterial load	The same device as shown above; 250 nm, ~15 min 2.3 Watt, 125 ml milk	48% reduction in BSSL, 44% reduction in Lysozyme, 48% reduction in lactoferrin, 25% reduction in folate, 5-log reduction in bacterial load	(Pitino et al., 2019b)
	Total bacterial load, lactoferrin, Igs, LPO activity, low-abundant whey proteins	The same device as shown above; 1.1 W, wavelength of 254 nm, 1000−5500 J/L	UV-C (4500 J/L) achieved a 5-log microbial reduction, no loss of LPO and IgG, 80% retention of lactoferrin, no change of the whey proteome.	(Liu et al., 2020b)
Bovine milk	Microbiological quality (*S. aureus, E. coli, L. monocytogenes*, and *S. Typhimurium*)	60-217 J/ml flow rate (5–18 mL/min) and temperature (4−25°C)	Approximately 2-log reduction in total mesophilic aerobic bacteria count and approximately 4-log reduction in yeast-mold count	(Atik & Gumus, 2021)
	Microbiological quality and aroma compounds in milk	254 nm wavelength, 13.87 J/mL (per single pass)	2-log reduction in mesophilic aerobic counts completely destroyed *E. coli* and *Staphylococcus* spp.	(Engin & Karagul Yuceer, 2012)
	Inactivation of *E. coli* and *B. cereus* endospores in raw and skimmed milk	Perfluoroalkoxy (PFA) tubes with internal diameters of 1.6 and 3.2 mm, 8.7 W, 110 V, the wavelength of 253.7 nm	Inactivation efficiency with 1.6 mm is higher than with 3.2 mm. Reduction of 7.8-log and 2.7-log in *E. coli* and *B. cereus* in skim milk; by 4.1 log and 2.7 log in raw milk.	(Choudhary et al., 2011)

(Continues)

TABLE 1 (Continued)

Milk species	Objective	UV-C device/parameters	Results	References
	Bacterial contaminants (*L. innocua, M. smegmatis, S. Typhimurium, E. coli, S. aureus, S. agalactiae, and A. baumannii*) in mature milk and colostrum	Pilot-scale UV light machine with pump unit (65 L/min), lamp control module (65 J/cm^2).	3.2 log reduction of *L. innocua*, 3.7 log *Salmonella* spp., 2.8 log reduction of *E. coli*, 3.4 log reduction of *Staph. aureus*, 3.4 log reduction of *Streptococcus spp.*, and 2.8 log of *A. baumannii*, 1.8 log reduction of *M. smegmatis*; the efficiency of UV-C in colostrum is worse than milk, with a 50% IgG reduction in colostrum.	(Pereira et al., 2014)
	Impacts of UV-C on vitamins A, B$_2$, C, and E in bovine milk	A customized UV-C system, a corrugated Teflon tube coiled around quartz sleeve, and 9 UV lamps (254 nm; 28 W UV-C output). Dosage of 12.6–88.2 J/ml	UV-C decreased the Vitamins in bovine milk. UV-C sensitivity: Vitamin C > E > A > B$_2$.	(Guneser & Karagul Yuceer, 2012)
Bovine milk whey	Molecular characterization of the protein and amino acid content, *Enterobacteriaceae* and total viable counts	254 nm wavelength, 30 m^3/h for skimmed whey and 7.9 m^3/h for concentrated whey	No amino acid loss, UV treatment equivalent to thermal pasteurization for microbiology and better whey quality.	(Buhler et al., 2019)
Goat milk	Inactivation of *L. monocytogenes*	A commercial UV fluid processor (CiderSure 3500A, Inc., Rochester, NY)	Able to achieve more than 5 log reduction when UV-C dose of 15.8 mJ/cm^2 is applied.	(Matak et al., 2005)
	Chemical and sensory properties	The same device as mentioned above. Dosage of 15.8 ± 1.6 mJ/cm^2	UV-C increased the acid degree value and TBA values. Increased free fatty acids did not change the odor.	(Matak et al., 2007)
	Inactivation of *E. coli*	Lambda PhysikCOMPex 110 pulsed laser, monochromatic exciplex laser device (Coherent, Inc.) The wavelength at 248 nm, frequency, 20 Hz.	A 6-log reduction was achieved when using 10,000 mJ/cm^2 of pulsed UV-C, 5000–10,000 mJ/cm^2 changes the aromatic property, but no significant compositional differences	(Kasahara et al., 2015)
	Reduction in water- and fat-soluble vitamins	The same device and parameters as shown in the bovine milk section.	Sensitivity of goat milk vitamins: C > E > A > B$_2$.	(Guneser & Karagul Yuceer, 2012)
Camel milk	Effects of ultraviolet-C dosage on the microbial reduction and components of camel milk	Dosage of 4.15, 8.30, and 12.45 mJ/cm^2 for camel milk, 253.7 nm.	UV-C dosage of 4.15, 8.30, and 12.45 mJ/cm^2 achieved 1.9, 3.3, and 3.9-log reductions in *E. coli* and 0.9, 3, and 3.9-log reductions in *S. Typhimurium*, respectively. UV-C treatment did not change the native protein profiles, including a-lactalbumin, and lactoferrin.	(Dhahir et al., 2020)
Sheep milk	Efficacy of UV pretreatment on thermal inactivation of *Bacillus subtilis* spores	UV-C pretreatment at D_{Act} 2.37 ± 0.126 J/ml, 254 nm.	UV-C pretreatment (D_{Act} 2.37 ± 0.126 J/ml) followed by a thermal treatment at 110°C for 30 s resulted in a 1.1 log CFU/ml in sheep milk.	(Ansari et al., 2019)
Donkey milk	Determining the feasibility of the UV-C to inactivate foodborne pathogens	A pilot scale SurePure Turbulator™ UV-C device; Dosage: 0, 91.8, 275.4, 459, 642.6, 826.2, 1000.8, 1100, 1200, and 1300 J/L.	UV-C resistance: *L. innocua* (~1100J/L) >*B. cereus* and *S. aureus* (~600 J/L) > *E. coli* and *Cronobacter sakazakii* (~400J/L) > *Salmonella enteritidis* (~200 J/L)	(Papademas et al., 2021)

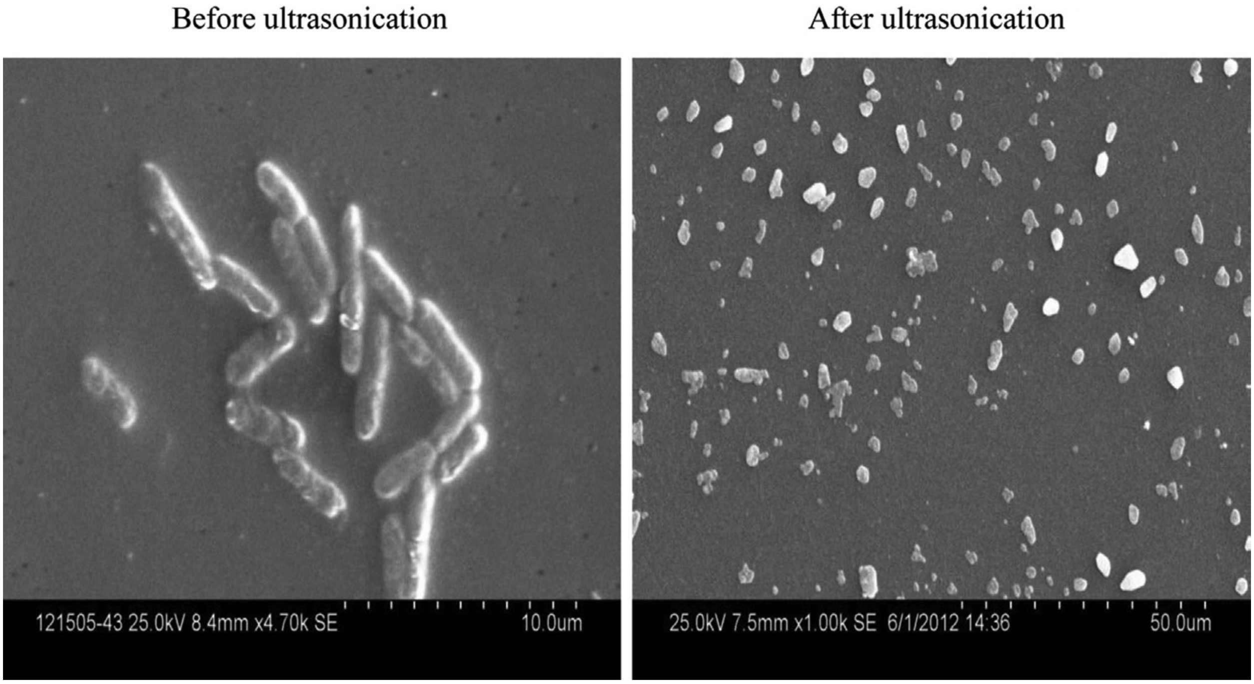


FIGURE 4 Micromorphology (SEM) of *Anoxybacillus flavithermus* before and after ultrasonication treatment from Khanal et al. (2014)

plasma-clotting capability of DHM, US was shown to be almost equally detrimental as HTST, indicating that this technique is not completely harmless to human milk's bioactivity (Hu et al., 2022).

2.2.2 | Ultrasonication treatment for bovine milk

The effects of thermo-US on aflatoxin M1 contents and physicochemical and microbial properties of milk were studied by Hernández-Falcón et al. (2018), who found that treatments at 45°C for 10 and 15 min exhibited similar microbiological quality to heat pasteurized milk (85°C/15 s). In addition, thermo-US for 10 and 15 min greatly reduced the levels of aflatoxin M1 in milk due to the US-induced hydrolysis of the molecular structure of mycotoxins. Recently, Liu et al. (2020b) found that US (308 J/ml) not only reduced the microbial load by 5-log but also better preserved more native milk serum proteins compared with thermal pasteurization. Next, Zhang, Liu, Li, Xu, Zhang, et al. (2021) developed an MF device combined with US to further reduce the microbial load and extend the shelf-life of skimmed milk and found that MF combined with US (1296 J/ml) could remove all the bacteria and extended the shelf-life up to >40 days when stored at 4°C.

The application of US in milk processing is, however, limited, as it is usually a batch-mode process. To overcome this, Van Hekken et al. (2019) developed a continuous ultrasound system and characterized the physicochemical and microbiological properties of sonicated raw bovine milk, which is conducive to commercial scale-up.

2.2.3 | Ultrasonication treatment for goat milk

The application of US in goat milk processing usually aims to modify the physicochemical properties (Hashemi & Gholamhosseinpour, 2020; Koirala et al., 2021), whereas studies especially focused on microbial inactivation or retaining bioactive components are rare. Ragab et al. (2019) studied the effects of thermo-US treatment on physicochemical properties and microbial load of goat milk and concluded that thermo-US >300 W achieved the lowest microbial load. Ultrasonication decreased the particle size of fat globules and casein micelles without affecting the main compositions of casein micelles and mineral balance. In addition, de Souza Soares et al. (2020) studied the effects of US on lipase activity in goat cream hydrolysis and reported that US did not induce cream hydrolysis, but increased lipase activity and hydrolysis rate. In addition, US at lower temperature (25°C) showed a better ultrasound effect than at 55°C, suggesting that US may act as an interesting alternative for goat cream hydrolysis to remove unpleasant flavor or obtain shorter chain fatty acids for specific purpose.

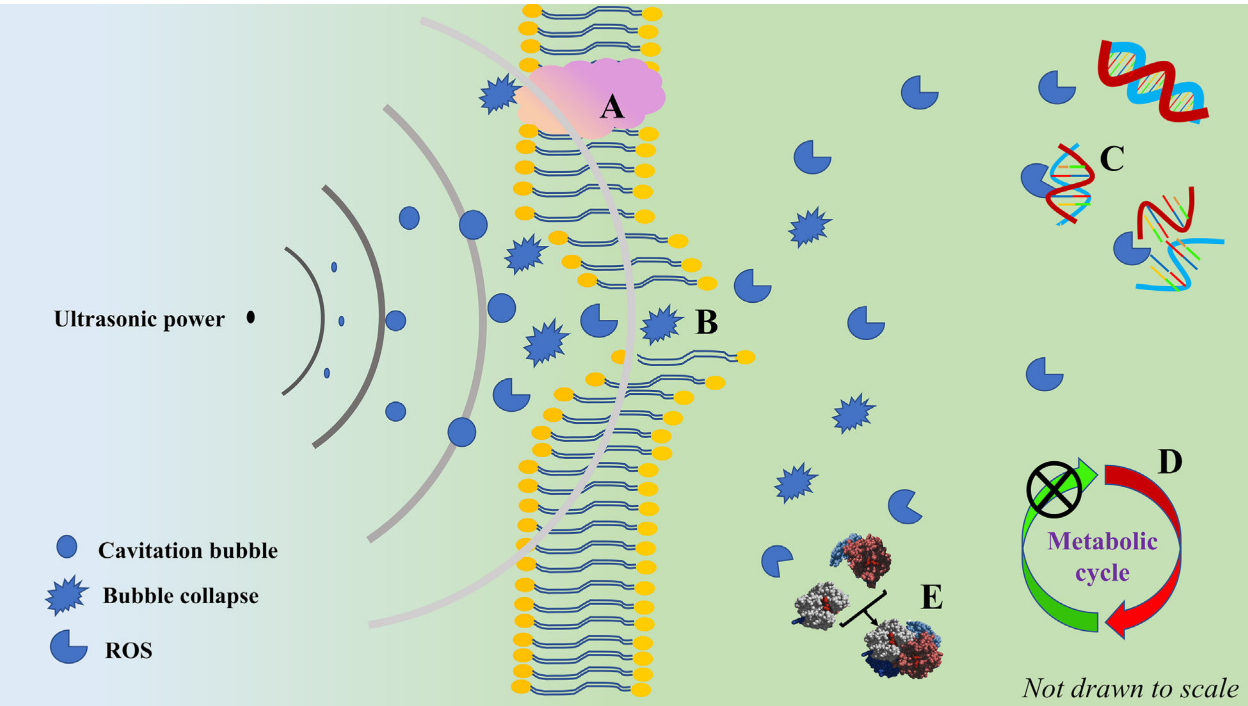


FIGURE 5 The overview of antibacterial mechanism induced by ultrasonication (not drawn to scale) adapted from Dai et al. (2020); A represents transmembrane protein damage, B represents membrane perforation, C represents DNA breakage, D represents metabolism inhibition, E intracellular protein denaturation, and enzyme inactivation

2.2.4 | Ultrasonication treatment for camel milk

Gammoh et al. (2020) evaluated the effects of US and lactic acid fermentation on the physicochemical and bioactive properties of camel caseins and whey fractions. It was reported that US decreased the average particle size of both casein and whey nanoparticles; in addition, US and fermentation both enhanced the antioxidative and angiotensin converting enzyme (ACE)-inhibitory activities of casein and whey (Gammoh et al., 2020). In addition, Dhahir et al. (2020a) investigated the effects of US on the milk-borne microorganisms (*E. coli O157: H7* and *S. Typhimurium*) and several components in camel milk and found that US treatment for 15 min significantly reduced the microbial load of these two bacteria, and US did not show detrimental effects on the composition of fatty acids, lipid peroxides, and protein fractions. Recently, Mudgil et al. (2022) investigated the influences of US treatments on microbial load, protein compositions, and bioactive properties of camel milk and reported that US at >160 W for 10 min could realize a microbial safety for public consumption without affecting its bioactive properties, such as antioxidative capacity and cholesterol esterase inhibition.

2.2.5 | Ultrasonication treatment for sheep milk

Sheep milk, one of the main bioactive dairy foods, is claimed to have many health benefits (Mohapatra et al., 2019). However, studies related to US have not been widely reported. Balthazar et al. (2019) investigated the microbiological and physicochemical quality of semi-skimmed sheep milk treated by US and found that US treatment significantly lowered the total coliform count, inactivating the *Staphylococcus* spp., and lactobacilli in semi-skimmed sheep milk, while it kept an acceptable number of lactic bacteria.

2.2.6 | Ultrasonication treatment for donkey milk

To our knowledge, studies focusing on microbial inactivation or immune-active components while using US have not been reported for donkey milk. Miao et al. (2020) investigated the effects of US on the physical stability of donkey milk, and reported that caseins are more sensitive to ultrasonic treatment in comparison with whey proteins. In addition, centrifugal precipitation rate and surface

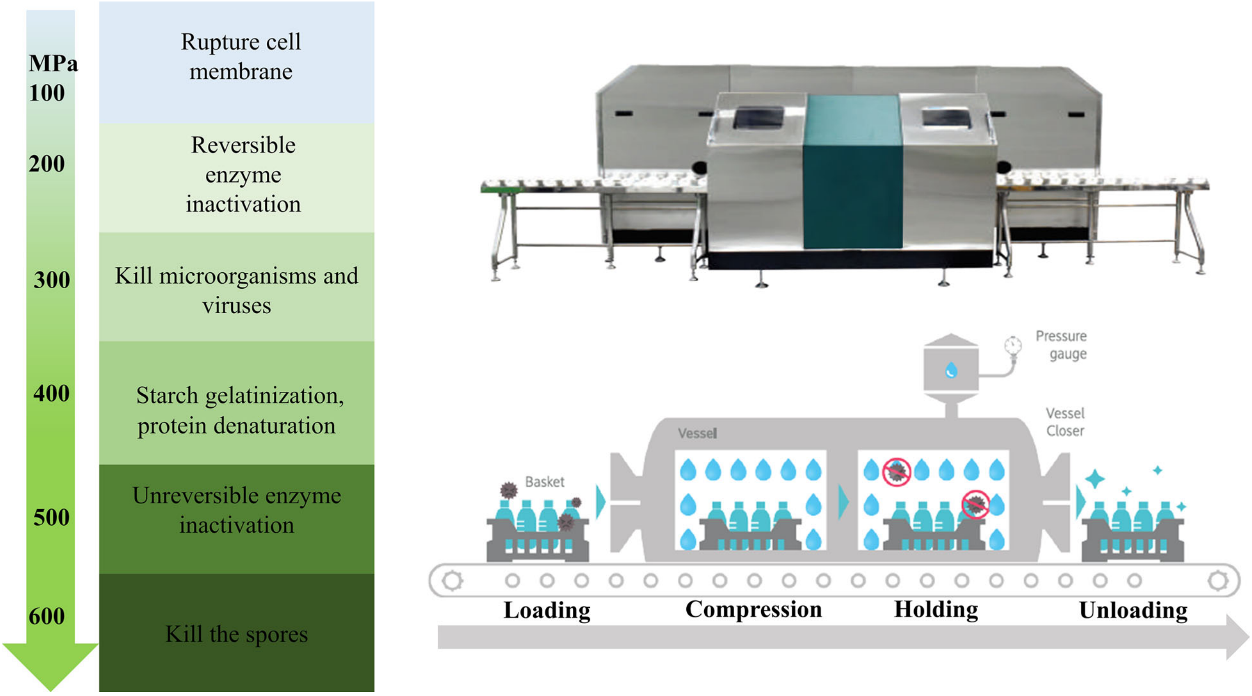


FIGURE 6 Schematic diagram and workflow of HPP processing

hydrophobicity increased with the increasing ultrasonic power.

2.2.7 | Summary of ultrasonication treatment

A detailed description of applications of US in milk processing is listed in Table 2, and most of these studies are related with bovine milk processing. As an efficient and novel microbial inactivation technique, US has huge potential in milk processing. In addition, not all studies show retention of milk immune-active components. Thus, future research is needed to get a better understanding of the effect of US on milk quality and find ways to implement it such that safety can be balanced with the retention of milk's beneficial components.

2.3 | High-pressure processing

High-pressure processing (HPP) is a well-known cold sterilization technique in food processing, where foods are treated under high hydrostatic pressure up to 900 MPa at chilled or mild temperature conditions to inactivate enzymes, pathogens, and/or spoilage microorganisms, and thereby increase safety and extend shelf-life (da Cruz et al., 2010; Matser et al., 2004). Generally, the HPP is generated through three ways: direct compression by dynamic pressure in pistons; indirect compression by static pressure seals; and through heating of the pressure medium (Huang et al., 2014). A schematic diagram and workflow of HPP processing are shown in Figure 6. HPP not only retains the natural flavor and taste and some health-promoting components like vitamins and lactoferrin but also is an environmental-friendly technique (Penna et al., 2007). The use of HPP treatment in raw milk sterilization has been commercially available in Mexico since 2014 and was first legally approved in Australia later in 2016 (Yang et al., 2020). A Mexican company Villa de Patos produced the first HPP milk products (Leche de vaca *de Libre Pastoreo* and Leche de Oveja) in the world (https://villadepatos.com/leches), and then another Australia company "Made by Cow™" located in New South Wales also developed HPP milk using raw milk from the Jersey cow breed (http://www.madebycow.com.au/; Alc antara-Zavala et al., 2018). Recently, the application of HPP in both human milk and milk of other mammals has achieved great progress (Roobab et al., 2021).

2.3.1 | HPP for donor human milk

Until now, HPP is the most common nonthermal technique applied in human milk research, where it has been studied much more extensively than in industrial dairy processing. On the one hand, this is attributed to the susceptibility of immune-active proteins in human milk; on the other hand, a batch-mode process is more suitable for DHM in human banks (Sousa et al., 2016) than for industrial dairy processing. Viazis et al. (2007) first

TABLE 2 Summary of ultrasonication technology applied in human and animals' milk

Milk species	Objective	Device/parameters	Results	References
Human milk	Microorganisms (*S. aureus*, *E. coli, and S. spp.*), antioxidant activity, and retinol content.	Ultrasound bath equipment (BRANSONIC, model CPX3800H) 40 kHz and a power of 100 W. 40 ml of milk, 14.69 mW/ml	Thermo-ultrasonication (60°C) led to greater reductions of microorganisms than heat pasteurization, and increased antioxidant activity; retinol level remained stable in both pasteurization and thermo-ultrasonication.	(Parreiras et al., 2020)
	Bioactive components (sIgA, lysozyme, lactoferrin, and BSSL) and microbial quality (*E. coli, S. epidermidis*)	An ultrasonic cell disruptor (Branson Ultrasonics, CT, USA) 12 mm disruptor horn, 20 kHz, output power 150 W, 60 ml milk at 4°C, 45°C, and 50°C	Thermo-ultrasonication inactivates more pathogens and retains more bioactive components than Hop	(Czank et al., 2010)
	Insulin retention	Branson Digital Sonifier 450 20 ml milk incubated at 40°C, 60 W for 6 min	Complete retention relative to untreated milk.	(Mank et al., 2021)
Bovine milk	Total bacterial load, lactoferrin, Igs, LPO activity, low-abundant whey proteins.	The same device as shown above. 360 J/ml	A 5-log microbial reduction, no loss of LPO activity, ~10% and 20% IgG and lactoferrin loss, respectively, compared to raw milk.	(Liu et al., 2020b)
	Aflatoxin M1 content, physicochemical properties, and microbial quality of milk.	A 1500 W ultrasonic processor (Sonics & Materials, Inc, VCX 1500 HV., Connecticut, USA) constant 20 kHz for 10 and 15 min at 95% amplitude, 400 ml milk at 45°C	Treatments for 10 and 15 min exhibited similar microbiological quality to pasteurized milk (85°C/15 s).	(Hernández-Falcón et al., 2018)
	Physicochemical properties, microbial, and enzyme inactivation of raw milk	A similar device as shown above. (Unique, Desruptor, Indaiatuba, Brazil), frequency of 20 kHz, equipped with a 13 mm diameter probe, 200–400 W for 4–8 min	Less than 1-log reduction in total bacteria count, yeast, and mold, increase in protein hydrolysis, and decrease in ALP activity.	(Pegu & Arya, 2021)
	Inactivation of thermoduric aerobic spore formers from *B. coagulans, B. licheniformis, G. stearothermophilus, B. sporothermodurans*, *and A. flavithermus*	A 20 kHz Vibra-Cell high-intensity ultrasonic Processor VC 505 (Sonics & Materials, Inc., CT, USA) equipped with a 13 mm Titanium solid probe, 20 ml milk at 80% amplitude for 1, 5, and 10 min.	Inactivating the *B. coagulants* and *A. flavithermus* in skimmed milk by 4.5, and 4.3 log, respectively, at 80% amplitude for 10 min.	(Khanal et al., 2014)
	Microbial and enzymatic inactivation	13-mm ultrasonic probe at 19 kHz (Unique, Desruptor, Indaiatuba, Brazil) 1, 3, 5, 7 kJ/ml with different power (100 and 475 W)	A 3.9 log of aerobic bacteria reduction from 5 kJ/ml at 475 W. 100 W would not inactivate the enzymes, but 475 W did.	(Scudino et al., 2020)
	Microbial inactivation and sensory quality	22 mm diameter probe at 24 kHz (UP400S, Hielscher Inc., Ringwood, NJ, USA). 160 W for 50–300 s, amplitude at 70 and 100% for 100 ml milk.	The treatment (100% × 300 s) resulted in 4.6, 2.8, 2.1, and 0.6 log reduction for *D. hansenii, P. fluorescens, E. coli*, and *S. aureus*, and caused milk sensorial deterioration.	(Marchesini et al., 2015)

(Continues)

TABLE 2 (Continued)

Milk species	Objective	Device/parameters	Results	References
	Physical, microbiological, and chemical properties	DRC-8-DPP-FGS (Advanced Sonic Processing Systems, Oxford, CT) with 2.4 kW dual-frequency reactor cell, 20 kHz, inlet temperature at 42°C and 54°C.	Inlet temperature at 54°C improved the microbial inactivation, protein–protein, and protein–lipid interactions altered.	(Van Hekken et al., 2019)
Goat milk	Physicochemical properties and microbial load of pasteurized goat milk	200 ml pasteurized goat milk were treated at f 150, 200, 300, 400 W for 10 min at 20 kHz by using a cell disruptor (JY92-IIN, Ningbo Scientz, Zhejiang, China)	Thermo-ultrasonication >300 W resulted in a significant reduction in in microbial load.	(Ragab et al., 2019)
Camel milk	Effects of ultrasonication on antioxidative and antihypertensive activities of camel milk proteins	3% (m/v) protein solutions were sonicated for 45 min using a benchtop sonicator at 30 kHz and 400 W at room temperature (Omni Sonic Ruptor 400 Ultrasonic Homogenizer, Kennesaw, GA, USA).	Ultrasonication enhanced the antioxidative capacity and angiotensin I-converting enzyme (ACE) inhibitory activity of camel whey and casein proteins.	(Gammoh et al., 2020)
	Inactivation of *E. coli O157: H7* and *S. Typhimurium;* effects of ultrasound on native components in camel milk.	70 ml milk treated at 900 W for 15 min using an ultrasonic processor (Ultrasonic Processor FS-900N, Hanchen Instrument, China), at 20 kHz.	6.0 log and 4.4 log reduction of *E. coli* and *S. Typhimurium* were achieved after ultrasonication 15 min, ultrasonication did not change the cis-9, trans-11 conjugated linoleic acid (CLA) and trans-10, cis-12 CLA contents or protein fractions.	(Dhahir et al., 2020)
	Effects of ultrasonication on microbial load, protein pattern, and bioactive properties of camel milk	100-ml milk were ultrasonicated with a Sonifier SFX550 (Branson Ultrasonics) at different power levels ranging from 105 to 210 W at 20 kHz.	Milk subjected to US power >160 W for 10 min could realize a complete reduction in microbial load, without changing protein patterns. US enhanced the cholesteryl esterase and pancreatic lipase inhibition, and antioxidative capacity.	(Mudgil et al., 2022)
Sheep milk	Microbial quality, protein and amino acids	40 mL semi-skim sheep milk were treated by a VC Vibra Cell Ultrasound (Sonics and Materials Inc., Newtown, CT, USA), at 78 W for 6 and 8 min, 104 W for 4 and 6 min at 20 kHz	No change in amino acid profile; inactivated or eliminated the total aerobic mesophilic bacteria, total coliform count; *Staphylococcus* spp., while maintaining lactic bacteria.	(Balthazar et al., 2019)

investigated the influences of HPP on total IgA and lysozyme activity in human milk compared with HoP and found that HPP retained ∼80% of total IgA, while pasteurized milk retained only ∼50%. Pitino et al. (2019b) compared the changes in DHM composition after thermal pasteurization, UV-C irradiation, and HPP and concluded that HPP (500 MPa for 8 min) best preserved the nutrients and immune-active proteins. Recently, Mank et al. (2021) found no loss of insulin after HPP treatment (500 MPa for 5 min), while thermal treatments reduced this by 20–25%. Similarly, another study reported that HHP treatment at 400–500 MPa at 20°C could reduce the counts of coliforms and total aerobic bacteria to undetectable levels ($<$ 1.0 log CFU/ml) while retaining almost all Igs, lysozyme activity, s-CD14, and TGF$\beta-2$ (Irazusta et al., 2020). In addition, HHP treatment below 350 MPa and 38°C allowed the retention of almost 100% of BSSL while this enzyme was absent after HTST or HoP treatments (Billeaud, 2021). However, it was also challenged if HPP is the best way to preserve human milk, as HPP at lower pressures (below 500 MPa) may not achieve comparable microbiological safety as thermal pasteurization, such as HoP. Besides, high costs associated with an investment in HPP equipment should also be considered (Malinowska-Pańczyk, 2020).

2.3.2 | HPP for bovine milk

Currently, studies focused on HPP are mainly concerned with microbial inactivation, enzyme activities, and physicochemical properties of bovine milk products, while they have focused less on bioactive components, such as immune-active proteins, in bovine milk, which may be due to the fact that bovine milk has a relatively low level of these components compared to human milk. Stratakos et al. (2019) reported that HPP treatment at 600 MPa for 3 min effectively reduced multiple bacteria by 5 log CFU/ml, whereas most were not obviously reduced after HPP treatment at 400 MPa for 3 min. Except for the dose-dependent manner, Yang et al. (2020) found an interesting phenomenon that using two cycles of HPP (2 × 2.5 min) was more effective for microbial inactivation than a single cycle of HPP (1 × 5 min) at the same pressure (600 MPa). This may be attributed to the iterative compression and decompression cycles during the process generating a stronger percussive and lethal action on the microbes.

2.3.3 | HPP for goat milk

So far, most studies on HPP treatment of goat milk studied the reduction in microbial load and the modification of its physiochemical properties (Deshwal et al., 2021); the latter is out of scope for this review. In terms of microbial safety, Razali et al. (2021) reported that microbial count in raw goat milk is below detectable levels after HPP treatment >400 MPa for 5 min at room temperature while 200 MPa for 5 or 10 min would achieve about 2 log reduction. Tan et al. (2020) reported that HPP-treated goat milk achieved a microbial shelf-life of 22 days at 8°C storage with no increase in *B. cereus*, mesophilic aerobic spores, coliform, yeast, and mold, but a slight increase in psychrotrophic bacteria and total plate count.

2.3.4 | HPP for camel milk

The studies on HPP treatments for camel milk have not been extensively reported yet. Omar et al. (2018) compared the effects of several industrial processing methods on the chemical composition of camel milk and found HPP treatment caused the least whey protein denaturation and retained more native α-lactalbumin and lactoferrin than HTST and UHT treatments.

2.3.5 | HPP for sheep milk

Compared with HPP treatments for camel milk, the studies on HPP treatments for sheep milk have been largely reported in earlier years (Alonso et al., 2012; Sakkas et al., 2019), and most of these reports focused on the physicochemical properties of cheese and yogurt. Recently, Tsevdou et al. (2020) studied the influences of enzymatic/HPP treatment on the quality and bioactivities of sheep milk yogurt and reported that HPP treatment both solely or followed by transglutaminase improved the textural attributes of yogurt; moreover, the HPP and transglutaminase treatments both improved the anti-hypertensive activity of yogurt and elicited an anti-inflammatory gene expression profile, respectively.

2.3.6 | HPP for donkey milk

Giacometti et al. (2016) assessed the feasibility of HPP treatment for raw donkey milk and found that a single HPP treatment at 600 MPa for 180 s would cause protein aggregation and form flocks. Then the authors tried to combine a milder HPP treatment at 400 MPa for 100 s with low temperature pasteurization (65°C for 30 min) and obtained a satisfactory microbiological quality during storage.

2.3.7 | Summary of HPP treatment

Table 3 lists the detailed information of HPP application in human and other animals' milk. It could be found that

TABLE 3 Summary of HPP technology applied in human and animals' milk

Milk species	Objective	Device/Parameters	Results	References
Human colostrum	Igs content, lysozyme, and LPO activity	Unipress Model U33 (Warsaw, Poland), 200, 400, and 600 MPa for 2.5, 15, and 30 min	200/400 MPa had no/small effect on Igs; 44% loss of lysozyme activity after pasteurization but not affected by HPP	(Sousa et al., 2014)
Human milk	IgA immunoreactivity and lysozyme activity	Stansted Fluid Power FPG 5740 Micro (Harlow, Essex, UK); 300-650 MPa for 1-7, 10, 15, and 30 min	Lysozyme activation after >400 MPa for 30 min, LTLT would not affects lysozyme, < 450 MPa for 30 min provided better results than LTLT for lysozyme and IgA.	(Mayayo et al., 2016)
	Insulin retention	10 ml milk, 500 MPa for 5 min	Full retention relative to untreated milk	(Mank et al., 2021)
	Immune-active and antioxidant activity	Multi-vessel Resato Unit (Roden, The Netherlands); 200, 400, 600, and 800 MPa for 1 s (flash treatments) at an initial temperature between −15 and 50°C	Treatments at 800 MPa decreased the Igs, HPP did not affect IL-6, IL-10, and antioxidant activity, but reduced IL-8 and TNFα at 50°C.	(Ramírez et al., 2021)
	Preservation of immune-active components (IgA, IgG, IgM, CD14, and TGF-β2)	S-IL-100−250−09 W (HP Food Processor, Stansted Fluid Power, Ltd., Harlow, UK); 400, 450, and 500 MPa for 5 min at 20°C	400 and 500 MPa inactivated coliform and total aerobic bacteria with full retention of immunological components.	(Irazusta et al., 2020)
	Inactivation of *B. cereus* spores and *S. aureus*	55 L Hiperbaric Wave 6000/55 (Hiperbaric, Burgos, Spain) with a maximum pressure of 600 MPa.	The estimated maximum bacterial inactivation was at 593.96 MPa for 233 s, reaching a decrease of 5.8 and 6.9 log in *S. aureus* and vegetative *B. cereus*, respectively.	(Rocha-Pimienta et al., 2020)
	Lipid Profile, BSSL activity, and lipophilic antioxidant content	U 4000/65 by Unipress Equipment, combined or separate treatment of 100–600 MPa for 10 or 15 min at 20°C	BSSL was decreased at >600 MPa, totally inactivated by pasteurization; HPP significantly decreased the lutein level, did not change the fatty acid composition.	(Wesolowska et al., 2019b)
	Leptin, adiponectin, insulin, hepatocyte growth factor (HGF), lactoferrin, and IgG contents	Same as above	HPP leads to the preservation of adipokines, growth factor, and lactoferrin, IgG much better or comparable with Holder Pasteurization.	(Wesolowska et al., 2018)
	Inactivation of *S. aureus* and *B. cereus*; preservation of bioactive compounds	Unclear device; 350 MPa, 38°C, compression rate at 1 MPa/s, 4 cycles of 5 min.	microbial decontamination of 6 log for both *S. aureus* and *B. cereus*, retention 60-100% of lipase, a-lactalbumin, casein, lysozyme, lactoferrin, and sIgA.	(Demazeau et al., 2018)
	Denaturation of lactoferrin	Stansted Fluid Power FPG 5740 (Micro Food Lab, Harlow, Essex, UK), treatment for 15 min at 20°C	300, 400, 500, and 600 MPa denatured 9%, 23%, 34%, and 48%, respectively, HoP denatured 80%	(Mayayo et al., 2014)

(Continues)

TABLE 3 (Continued)

Milk species	Objective	Device/Parameters	Results	References
Bovine milk	Microbiological properties and shelf-life	Kara F&B Productions, Sdn. Bhd.; 450 MPa and 600 MPa for 5 or 7 min at 15° C.	Shelf-life to 22 days at 8 °C with no increase in *Bacillus cereus*, mesophilic aerobic spores, coliform, yeast, and mold, a minor increase in *psychrotrophic* bacteria, and total plate count.	(Tan et al., 2020)
	Physicochemical properties and microbiological inactivation	Food Processing Press QFP-6 (Avure Technologies AB, Vesterås, Sweden) at 600 MPa for 3 or 5 min at 23°C. Compression rate of 450 MPa/min	Two cycles of HPP kill more bacteria than a single cycle with the same total time.	(Yang et al., 2020)
	Safety (*E. coli, Salmonella*, and *L. monocytogenes*), shelf-life, and quality	Quintus 35 L (Avure Technologies, U.S.A.); 400–600 MPa for 1–5 min	HPP (600 MPa for 3 min) significantly reduced the total viable counts, Enterobacteriaceae, lactic acid bacteria, and *Pseudomonas spp.* in milk and prolonged the shelf-life by 1 week.	(Stratakos et al., 2019)
	Protein denaturation and immunogenicity of native milk proteins	Stansted ISO-LAB FPG11501 3.6 L unit (Stansted Fluid Power Ltd, Essex, UK); 400, 500, and 600 MPa for 15 min at ~30°C, compression, and decompression rates were 600 and 1200 MPa/min	HPP at 600 MPa resulted in protein aggregation, involving mainly β-LG and κ-casein, through thiol-disulfide, and diminished the immunogenic capacity of milk proteins.	(Bogahawaththa et al., 2018)
Goat milk	Bacterial inactivation and milk quality	Avure 2L-700 HPP Laboratory Food Processing System, 200, 400, and 600 MPa were used for 5, 10, and 15 min at 25°C	>400 MPa for 5 min would inactivate all bacteria, give a higher viscosity, higher total soluble solids, and pH than pasteurization.	(Razali et al., 2021)
	Physicochemical changes, microbiological properties, and shelf-life.	A 55 L unit manufactured by Hiperbaric (Spain), 450 and 600 MPa for 5 or 7 min at 15°C	450 MPa–7 min and 600 MPa–5 min achieved a shelf life of 22 days at 8°C storage with an only a slight increase in psychrotrophic bacteria and TPC.	(Tan et al., 2020)
Camel milk	Physical and chemical properties, and proximate composition.	HPP treatment at 200, 400, 600, and 800 MPa for 30 min using a Stansted Iso-Lab 900 High Pressure Processor (Stansted Fluid Power, Stansted, Essex, UK)	HPP treatments induced the least whey protein denaturation and retained moreα-lactalbumin and lactoferrin.	(Omar et al., 2018)
Sheep milk	Enzymatic/high Pressure processing on the quality and bioactivity of yoghurt	HPP at 600 MPa and 55° C for 10 min or combined with transglutaminase.	HPP or combined with transglutaminase treatments showed higher anti-hypertensive (ACE-inhibitory activity) and immunomodulatory (inflammation-related) properties.	(Tsevdou et al., 2020)
Donkey milk	Effects of HPP on the microbial quality of pasteurized donkey milk	HPP at 400 MPa for 100 and 180 s using Quintus Food Press QFP350L-600 device.	HPP treatment after pasteurization further decreased the counts of *Pseudomonas spp*. and total mesophilic count during storage.	(Giacometti et al., 2016).

HPP treatments were most applied in human milk pasteurization, followed by bovine milk. The application in other animals' milk processing is relatively rare. Until now, HPP treatment has been considered as the most promising and feasible nonthermal technique for dairy processing due to its superiority in retaining bioactive components without deteriorating the sensory and nutritional quality of milk, although the necessity to perform it batch-wise is an important limitation for animal milk.

2.4 | Other nonthermal treatments and emerging techniques

Besides these three common nonthermal techniques that have been frequently studied for dairy processing, there are some other techniques that have been studied not as frequently, such as PEF, gamma irradiation, and CP, which may still be useful for dairy processing (Soni et al., 2021). However, no research has been done for these techniques regarding the retention of immune-active proteins or the bioactivity of milk. It is speculated that the immune-active components in milk are of low abundance, which is usually neglected in animals; on the other hand, the detection expense is relatively higher by ELISA or LC-MS/MS-based proteomics. Even though the commercial ELISA kits for immune-active milk protein quantification of mammals, such as camel and goat, are becoming available in certain countries, these are still not commonly used.

PEF applies high electric field intensities (1–60 kV/cm) for an extremely short duration (μs) at moderate temperatures, to reduce the counts of both pathogenic and spoilage microorganisms (Bendicho et al., 2002; Franco et al., 2018). Sharma et al. (2014) applied PEF to whole milk and found that PEF treatments at 22–28 kV cm^{-1} for 17–101 μs at 50°C induced a 5–6 log reduction, resulting in counts below the detection limit for *P. aeruginosa*, while *E. coli, S. aureus*, and *L. innocua* were reduced to below the detection limit at 55°C. McAuley et al. (2016) compared the effects of PEF (30 kV/cm, 22 μs at 53 or 63°C) and thermal pasteurization (63 or 72°C for 15 s) on microbiological and physicochemical stability of milk and found that shelf-life of PEF treatment of milk at 63°C was similar to HTST pasteurization and PEF did not affect the physicochemical properties of milk. The application of PEF processing of milk has been reviewed by Bendicho et al. (2002), including microbial and enzyme inactivation, and reduction of micronutrients.

The application of ionizing radiation to reduce the risk of pathogenic bacteria in foods is becoming increasingly accepted by consumers. Gamma irradiation extends the shelf-life of food products by destroying bacterial nucleic acids (DNA) leading to the elimination of microbial contamination. de Oliveira Silva et al. (2015) investigated the effect of gamma irradiation (1, 2, and 3 kGy) on the bacteriological and sensory quality of raw milk, and found that milk irradiated at 2 and 3 kGy had a significantly ($p < 0.05$) lower bacterial load. In addition, they recommended a 2 kGy dose for raw whole milk because of the positive effects on bacterial quality and minimal sensory changes. As gamma irradiation is usually used for surface disinfection of foods, such as vegetables, fruits, and meat, it may potentially be used for powdered infant formula. In general, the inactivation effects from ionizing irradiation are related to several factors, such as irradiation manner, food matrix, and food components (Osaili et al, 2007). Direct irradiation should be more effective than indirect irradiation; however, milk and infant formula are complex systems with protein, fat, and carbohydrate. It has been reported that compositional complexity may reduce the radiation damage to microorganisms by interaction with generated oxidative radicals during irradiation (McCarthy & Damoglou, 1996). Moreover, water activity (a_w) plays an important role in radiation damage, as a low a_w may reduce the generation of free radicals, reducing the indirect irradiation damage to the nucleic acid of micro-organisms. To evaluate the efficiency of gamma irradiation in inactivating *E. sakazakii* in infant formula, Osaili et al. (2007) used 0~1 and 0~9 kGy irradiation dosages to treat dehydrated and rehydrated infant milk formula and found that the D10-value (dosage needed to inactivate 90% of the bacterial population) were 0.3 and 1.0 kGy, respectively. Based on this, the lowest irradiation dose to achieve a 3-log reduction of *E. sakazakii* in infant milk formula was suggested to be 5.13 kGy. Additionally, a recent study investigated the effects of gamma-irradiation on the antibacterial properties of DHM and showed that a hybrid method of freeze-drying followed by 2 kGy of gamma-irradiation had a better antimicrobial effect on *S. aureus, S. Typhimurium*, and *E. coli* compared with HoP (Blackshaw et al., 2021).

Cold plasma, the fourth state of matter, is an electrically energized matter in a gaseous state and can be applied as a nonthermal food processing technology. The resulting charged particles, free radicals, and some radiation generated at 30–60°C by an electrical discharge under atmospheric or vacuum conditions are able to inactivate microorganisms by etching of cell surfaces by reactive species, volatilization of compounds, and intrinsic photodesorption of ultraviolet (UV) photons, and destruction of genetic material (Laroussi, 2005). As nonthermal technology, CP processing of milk and dairy products has been reviewed by Coutinho et al. (2018). More recently, Wu et al. (2021) evaluated the sterilizing properties of dielectric barrier discharge CP on milk and found that a voltage over 70 V sustained for 120 s was similar to UHT treatment. In addition, another study showed that CP treatment reduced the antigenicity of bovine casein and whey proteins (Ng et al., 2021). Based on this, it can be speculated that CP treatment may damage the immune-active proteins by structure modifications, although related studies have not been reported yet.

In addition, microwave heating is also applied in milk processing, especially in human banks. Edyta et al. (2019) found that microwave heating could obtain a lower D-value than HoP, and heating at 62.5 or 66°C for 5 or 3 min allowed the inactivation of the human milk microbiota. Recently, Martysiak-Żurowska et al. (2022) studied the influence of microwave heating on the nutrients of human milk and found that microwave heating (62.5°C, 66°C, and 75°C for 1–10 min, respectively) did not cause protein degradation. An intact protein pattern including bile salt activated lipase, lactoferrin, β-casein, lysozyme, and α-lactalbumin was observed by SDS-PAGE analysis. It was also reported that the fatty acid composition did not change after microwave heating.

Ohmic heating utilizes electrical conductivity for heating and is characterized by rapid and uniform heating of fluid food by generating alternating current through the food material. Balthazar et al. (2022) assessed the energy consumption and bactericidal effect of ohmic heating. It is reported that ohmic heating (8.33 V/cm) has a great potential for raw sheep milk pasteurization, which allowed a shelf-life up to 2 weeks under 4°C with 72–73 % less energy consumption than conventional heating.

3 | PROSPECT AND CHALLENGES

Nowadays, there is a trend for more fresh and nutritious food around the world. The increasing global demand and consumption of fresh milk and dairy products, as well as the environmental issues surrounding its production, have driven the dairy industry to explore innovative food processing technologies. Besides, more and more evidence is available showing that lower heat treatment of milk retains more health-promoting components than that of highly processed milk (Brick et al., 2020; Loss et al., 2015; Wyss et al., 2018). There are therefore multiple places around the world, where interest in raw milk consumption is increasing due to perceived health benefits. However, there is an inherent safety risk to such raw milk consumption, such as pathogenic microorganisms. Nonthermal techniques may be a solution to this problem, as they can achieve the production of safe milk while keeping the immune-active components intact. Except for these benefits resulting from nonthermal treatments, it should be noted that such treatments might also bring some challenges. For example, nonthermal treatments may not inactivate the endogenous enzymes, such as proteases and lipases in milk, which could have negative effects on the sensory properties, such as the flavor (Wang et al., 2019).

3.1 | UV-C

UV-C irradiation, an efficient sterilization method, displays a variety of advantages over conventional dairy thermal treatment. Firstly, it is able to effectively inactivate a wide range of pathogenic and spoilage microorganisms while realizing a minimal loss of heat-sensitive immune-active components in milk. In addition, UV-C radiation is more cost-effective and energy-efficient compared to thermal processing (Gayán et al., 2011). It was reported that the total energy consumption of UV systems can be up to 10,000 times lower compared to heat pasteurization (Rodriguez-Gonzalez et al., 2015). UV-C radiation is a simple and inexpensive technology, which does not have high maintenance costs. Last but not least, it has no toxic effects or waste generation (Gayán et al., 2014). Also, implementation of this technology at an industrial scale is already possible, as large units with continuous processing can be used. However, there are also some limitations to its application in milk processing, such as its lower penetration efficiency in opaque liquids. To overcome this problem, inducing turbulence in the UV-C equipment may be applied, or UV-C may be combined with other treatments such as MF (Zhang, Liu, Li, Xu, Hettinga, et al., 2021).

3.2 | Ultrasonication

Similar to UV-C, US also has a wide range of potential advantages for milk processing. First of all, it inactivates bacteria efficiently at a mild temperature, which avoids or alleviates the heat damage to the heat-sensitive components in milk (Liu et al., 2020b). In addition, US belongs to an environmentally friendly, highly efficient, non-toxic, and low-cost technology (Dai et al., 2020). Liu et al. (2021) found that US retains more native MFGM protein compared to equivalent shear-homogenization. For its application in dairy processing, there are currently still some challenges. One of the biggest concerns is the formation and release of metal particulates during US, as well as potentially increased oxidation (Reis et al., 2020). Studies have shown that particulates from transducer erosion did occur, but its level remained below accepted drinking water limits, even after excessively long exposure to ultrasound, suggesting that there are no actual health implications (Mawson et al., 2014). Undesired volatile compounds generated due to US are another concern for their application in milk. Local high temperature and

TABLE 4 Comparison in advantages of UV-C, US, and HPP

Techniques	Advantages	Disadvantages	Commercial status	Representative Products
UV-C	Cheap, convenient, and efficient in killing most bacteria, can be implemented as a continuous process	UV penetrability is limited for opaque liquids such as milk, which may induce photooxidation of proteins and lipids.	Commercialized on a small scale for milk protein concentrate (MPC) in the United States	TruActive ^{TM} MPC 85, TruActive ^{TM} WPI 90, TruActive ^{TM} LTF (Lactoferrin), The company Tamarack Biotics in the United States.
US	Easy to handle, able to inactivate some endogenous enzymes	Batch-mode process, not quite suited for industrial processing, may cause local overheating	Not commercialized yet	-
HPP	Efficient in killing most bacteria, good retention bioactive components, inactivates some endogenous enzymes	High cost of installation, maintenance, and repair, batch-mode process	Commercialized successfully	 The company Made By Cow in Australia.

pressure originating from the collapse of bubbles generates highly reactive hydrogen, hydroxyl radicals, and subsequent reactive oxygen species (ROS), which would result in redox reactions with solutes, such as milk fat and protein, and thereby may lead to the formation of undesired flavors in milk (Abrahamsen & Narvhus, 2022; Riener et al., 2009). Finally, US is often limited to batch mode processing, which is another challenge that does not favor its application in practice. Although there is a wide range of advantages to applying US for milk processing, more research is needed to enable its efficient large-scale use.

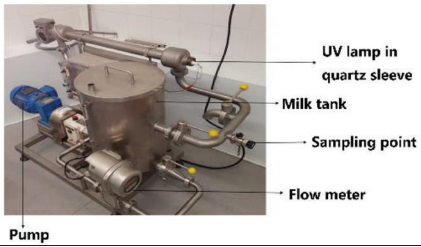
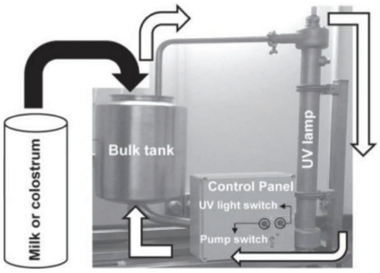
3.3 | High-pressure processing

The application of HPP in foodstuffs has been successfully commercialized for different foods like dairy, meat, juice, seafood, and jams (Pottier et al., 2017). The health, taste, and environmental benefits have led to more positive consumer attitudes toward HPP-treated foods (Olsen et al., 2010). Compared with UV-C and US treatments, HPP is better at retaining nutritional components and flavors of milk, such as preventing the vitamins loss that may occur by UV-C and the metal-associated flavors that may originate from US. During HPP treatment, the generated pressure is continuously and uniformly passed through the foods without influence on the covalent bonds of small molecules like vitamins, amino acids, and flavor compounds. From the perspective of energy use, HPP is not as good as UV-C; but much better in processing capacity than US (Rodriguez-Gonzalez et al., 2015). Finally, it is important to realize that the equipment required for HPP is much more expensive than that for other nonthermal technologies, making the costs of milk processing

TABLE 5 Detailed information of commercial or large-scale UV-C, HPP facilities, and milk products

<table>
<tr><th>Technique</th><th>Facilities</th><th>Corporation</th><th>Commercial Products</th></tr>
<tr><td>HPP</td><td></td><td>Thyssenkrupp, Hagen, Germany</td><td>

Bovine milk products</td></tr>
<tr><td>HPP</td><td>
</td><td>Hiperbaric HPP, Burgos, Spain</td><td>

Colostrum and yoghurt</td></tr>
<tr><td>HPP</td><td></td><td>Large-scale HPP device by Hippo, Korea</td><td>-</td></tr>
<tr><td>UV-C</td><td>
</td><td>“SurePure Turbulator™” UV-C device, SurePure, Switzerland</td><td>TruActive ™ MPC 85,
TruActive ™ WPI 90,
TruActive ™ LTF (Lactoferrin),</td></tr>
<tr><td>UV-C</td><td>
</td><td>GEA Farm Technologies, IL, USA</td><td>-</td></tr>
</table>

"–"represents not available data.

much higher, especially if done at a small-scale milk processing, like in human milk banks.

3.4 | Comparison of nonthermal technologies

Table 4 provides an overview of the advantages and disadvantages of the three main nonthermal processing techniques. For the time being, the use of dairy products treated with HPP has been improved enormously, and HPP is the most successfully commercialized emerging nonthermal technique for dairy processing (as shown in Table 5). However, it has a relatively high cost of installation and maintenance, which limits its further promotion. UV-C has a low cost, low energy consumption, and has just been commercialized in the US and European countries but it still needs to be further studied to overcome its limited penetrating ability in opaque liquids. Ultrasonication has the most problems to be solved before it can be industrially applied for milk processing, such as large-scale instrument developments and lipid oxidation.

4 | CONCLUSIONS

In conclusion, with an increasing demand for natural and minimally processed foods from customers, nonthermal technologies have a great potential for use in the food industry, especially for thermosensitive foods, such as dairy products. This review summarizes the current progress of nonthermal techniques applied in dairy processing in the perspective of retaining immune-active components and microbial inactivation both regarding scientific research and application in practice. Generally speaking, these nonthermal techniques all showed better protective effects on immune-active components in milk. Among those nonthermal techniques, UV-C, US, and HPP were the most investigated; HPP has been already commercialized on a relatively large scale while the application of UV-C is still at a start-up time, and the US is still in the research stage. For HPP treatment, large-scale production is limited by the costs; for UV-C treatment, a commercial UV-C device and a uniform calculation of UV-C dosage are urgently needed before it is able to be used in industry; for US, some adverse aspects must be taken into consideration, such as oxidation on proteins and milk lipids. Other nonthermal techniques are still in a primary lab-research stage.

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AUTHOR CONTRIBUTIONS

Yaowei Liu: Conceptualization; Visualization; Writing – original draft. **Kasper Hettinga**: Conceptualization; Supervision; Validation; Writing – review & editing. **Dasong Liu**: Conceptualization; Validation; Writing – review & editing. **Lina Zhang**: Funding acquisition; Validation; Writing – review & editing. **Peng Zhou**: Conceptualization; Funding acquisition; Supervision; Writing – review & editing.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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