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Nutritional and therapeutic perspectives of camel milk and its protein hydrolysates: A review on versatile biofunctional properties

Anahita Izadi[a], Leila Khedmat[b], Sayed Yousef Mojtahedi[c,*]

[a] Department of Pediatric Infection Disease, Tehran University of Medical Sciences, Tehran, Iran
[b] Health Management Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
[c] Department of Pediatric Nephrology, Bahrami Children Hospital, Tehran University of Medical Sciences, Tehran, Iran

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ABSTRACT

This updated review summarizes the available literature on major bio-functionalities of Ca-M and its protein hydrolysates such as antimicrobial, antioxidant, antiradical, antidiabetic, angiotensin-converting enzyme inhibitory, anticancer, anti-inflammatory, hepatoprotective, antiallergic, and anti-autism activities. The most important bioactive compounds affecting health functions are some minerals (Zn and Mg), vitamins (C and E), protective proteins (lactoferrin, lysozyme, and immunoglobulins), and antioxidant enzymes (glutathione peroxidase and superoxide dismutase). Bioactive peptides derived from Ca-M proteins during fermentation processes and hydrolysis reactions by proteolytic enzymes play protective roles for body cells through the release of amino acids such as proline. In contrast with bovine milk, Ca-M has lower antiallergic effects due to the presence of immunoglobins and its protein (free of β-lactoglobulin) profile. The short- and long-term regular consumption of Ca-M because of the suppression of oxidative/inflammation stresses significantly improves diabetes and hypertension in adults and the behavioral of children with autism spectrum disorder.

1. Introduction

In infancy and early childhood, cow's milk allergy is considered the most dominant food allergy (Rona et al., 2007). As anaphylaxis or severe allergic reactions to this dairy source in some cases is life-threatening, it is necessary to treat patients with adrenaline (epinephrine) during medical emergencies (Kim et al., 2011). However, finding a safer choice than cow milk (Co-M) for feeding children and infants can be effective in reducing this risk factor in the development of functional gastrointestinal (GI) disorders (Ehlayel, Bener et al., 2011; Izadi, Rahbarimanesh, Mojtahedi, & Mojtahedi, 2018).

Based on the most recent FAO statistics, the world population of camel to be approximately 29 million, of which around 95% are dromedary (*Camelus dromedarius*) camels (FAO, 2019). In recent years, much attention towards the consumption of camel milk (Ca-M) as an alternative to Co-M and other kinds of milk (e.g., goat, sheep, buffalo, donkey, and mare) has been attracted. 2–6% of children and infants show allergic symptoms to Co-M proteins, which can be resolved with immunoglobulins (Igs) present in Ca-M (Shabo, Barzel, Margoulis, & Yagil, 2005). Antiallergenic property of Ca-M also is due to the similar protein profile to human mother's milk in lacking β-lactoglobulin and richness of α-lactalbumin (Mojtahedi, Izadi, Seirafi, Khedmat, & Tavakolizadeh, 2018). Ca-M due to the high content of antioxidant and antimicrobial components also has a vital role in many health functions of the body such as the reduction of GI disorders, the treatment of diabetes, psoriasis, and hepatitis C and B, the efficiency enhancement of immune system, the growth inhibition of cancer cells, and the tuberculosis remedy (Kaskous, 2016). The therapeutic properties along with antimicrobial and antioxidant effects of this dairy product are mainly attributed to the presence of different bioactive peptides and

Abbreviations: Ca-M, camel milk; Co-M, cow milk; GI, gastrointestinal; ASD, autism spectrum disorder; PGRP, peptidoglycan recognition protein; Ig, immunoglobulin; NAGase, N-acetyl-β-glucosaminidase; LF, lactoferrin; LP, lactoperoxidase; LZ, lysozyme; NO, nitric oxide; FRAP, ferric reducing antioxidant power; MW, molecular weight; ACE, angiotensin-converting enzyme; CRP, C-reactive protein; TNF, tumor necrosis factor; PE, phosphatidylethanolamine; GLUT4, glucose transporter 4; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1; DPP-IV, dipeptidyl peptidase IV; HbA1c, glycosylated hemoglobin; CPT-I, carnitine palmitoyl transferase type I; IRS-2, insulin receptor substrate type 2; FASN, fatty acid synthases; HDL, high-density lipoprotein; TH2, T helper 2; ROS, reactive oxygen species; RNS, reactive nitrogen species; AERLs, aqueous extract of rosemary leaves; GTH, glutathione; GPx, glutathione peroxidase; SOD, superoxide dismutase; CMPA, cow's milk protein allergy; SPT, skin prick test; CARS, childhood autism rating scale; SRS, social responsiveness scale; ATEC, autism treatment evaluation checklist; TARC, thymus and activation-regulated chemokine

* Corresponding author.
E-mail address: Drmojtahedi@tums.ac.ir (S.Y. Mojtahedi).

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protective enzymes (Awadhi & Elain, 2013).

Autism spectrum disorder (ASD) is a set of behavioral symptoms in affected children distinguished by emotional confusion and symbolic behavior, and by difficulties with social interactions and verbal and nonverbal conversations (Ozkaya, 2013). A high prevalence rate of ASD (1–88 healthy children) with a more ratio in males (~5:1.2, boys: girls) in different investigations has been reported (Smith, 2013). Edmiston, Ashwood, and Van de Water (2017) have recently reported that the United States has the fastest growing rate of ASD in the globe with one out of 68 births. Although the autism etiology remains unclear, various factors such as genetics, environment, immunology, and neurology are involved in this lifelong, developmental disability. In recent years, some studies have been focused on the beneficial role of Ca-M consumption in ASD therapy in pediatric patients. It was hypothesized that the small and specific Igs of Ca-M after the intake by children patients get into blood streams in their body. These protective antibodies with high affinity and specificity interact with active sites and diffuse into dense parts to bind antigen molecules, indicating the potential functions of Ca-M in the treatment of this complex developmental disorder (Shabo & Yagil, 2005).

In recent years, the nutraceutical and medical importance of Ca-M as a food supplementation has been taken into consideration in some review articles (Abdel Gader & Alhaider, 2016; Dubey, Lal, Mittal, & Kapur, 2016; Kula & Tegeng, 2016; Mati et al., 2017; Shori, 2015). Shori (2015) summed up the potential of Ca-M as an effective therapy in controlling high levels of blood sugar and cholesterol, improving the wound healing process. Kula and Tegeng (2016) summarized the chemical composition of Ca-M to find their role in therapeutic efficiency. A wide span of biological activities of Ca-M was briefly summarized based on the results of a large number of relatively old studies. Abdel Gader and Alhaider (2016) reported that the Ca-M intake can be effective in four main complications of diabetes, cancer, hepatitis and food allergy mainly due to the presence of lactoferrin (LF) and Igs. According to the review of the available literature from 1957 to 2014, Dubey et al. (2016) presented a summary of bioactive components with immune functions in Ca-M to treat different diseases. Mati et al. (2017) mainly focused on the different proteins present in Dromedary Ca-M and mentioned their cellular-molecular role in health-promoting activities. In general, some of these studies reported that peptides derived from Ca-M proteins have good biological potentials in treating some of main complications and health problems due to their *in vitro* antioxidant and antimicrobial activities. However, these articles comprehensively did not review the current state of the clinical information released on the diverse biofunctional aspects of the Ca-M proteins, particularly bioactive peptides produced by bacterial fermentation and enzyme treatments of Ca-M.

Therefore, the objective of the currently updated overview was to study physicochemical and bio-functional characteristics of Ca-M and its effectiveness in the prevention and treatment of an extensive range of chronic diseases with a particular focus on the bioactive peptides and other healthy-functional compounds.

2. Camel milk: physicochemical and nutritional properties

The color, taste, and odor of Ca-M are opaque white, salty, and normal, respectively. The mean values of acidity, specific gravity, viscosity, surface tension, refractive index, freezing point, and electrical conductivity were reported to be 0.144% lactic acid, 1.029, 1.77 cp, 58.39 dyne/cm, 1.3423, −0.518 °C, and 6.08 millimohs (Mehta, Aparnathi, Yoganandi, Wadhwani, & Darji, 2014). Nonetheless, physicochemical properties of Ca-M are highly depended on the geographical origin, camel breed, and even lactation time. It was reported that Ca-M compared to Co-M has high heat stability so that the denaturation percentage of whey proteins of Ca-M at temperatures of 80 and 90 °C were 32–35% and 47–53%, respectively (Farah, 1996).

According to the meta-analysis and literature data presented by Konuspayeva, Faye, and Loiseau (2009) from 82 investigations, amounts (g/100 mL) of dry matter, fat matter, total protein, lactose, and ash in Ca-Ms collected from different parts of the world were 8.64–16.08 (12.47 ± 1.53), 0.28–6.40 (3.82 ± 1.08), 2.15–4.90 (3.35 ± 0.62), 2.40–5.80 (4.46 ± 1.03), and 0.60–1.05 (0.79 ± 0.09), respectively. Most Ca-Ms were analyzed from samples collected from two species of dromedary (*C. dromedarius*) and Bactrian (*C. bactrianus*) grown in Asia, Western Asia, Africa, East and North Africa, and the Indian subcontinent. Apart from species differences, geographical origin plays a significant role in the difference between the gross composition of Ca-Ms. Camel milks obtained from the Bactrian breed in Asia due to the specific environmental conditions showed more dry matter, fat, protein, and lactose values compared to those produced by dromedary and hybrids camels (Konuspayeva et al., 2009). It is rich of micronutrients including minerals (e.g., Na, K, Ca, Mg, Zn, P, Fe, and Cu) and vitamins (e.g., C and B-group) (Mal, Suchitra Sena, & Sahani, 2007). Stahl, Sallman, Duehlmeier, and Wernery (2006) earlier reported that despite the lower content of A, E and B1 vitamins of Ca-M compared to Co-M, vitamin C level of Ca-M is 2–3 times more than Co-M. Higher content of ascorbic acid in Ca-M because of the development of low pH value can remarkably extend its shelf life under harsh storage conditions. Higher mineral levels of Na, K, Ca, P, and Mg of Ca-M in late lactation compared to early lactation were reported. Conversely, a lower content of vitamin C of Ca-M in late lactation compared to early lactation was reported (Mal et al., 2007). Also, no detectable β-carotene quantity in this milk type was found (Stahl et al., 2006).

Ereifej, Alu'datt, AlKhalidy, Alli, and Rababah (2011) compared fat and protein composition of Ca-Ms obtained from eight Jordanian areas. They pointed out that the profile of fatty acids of Ca-Ms has not only a good balance of saturated and unsaturated fatty acids but also this nutritive source mainly composed of long-chain (~92–99%), unsaturated (35–50%) fatty acids. The best Ca-M was chosen from Al Umari region with the minimum short-chain fatty acids (i.e., butyric (C4:0), and caproic (C6:0)), and medium-chain fatty acids (i.e., caprylic (C8:0), capric (C10:0), lauric (C12:0), and myristic (C14:0)), and the maximum unsaturated long-chain fatty acids because of its consumption can substantially reduce the serum level of lipids and the prevalence of related cardiovascular diseases (Ereifej et al., 2011). Narmuratova et al. (2006) exhibited that Ca-M rich of glutamic acid compared to Co-M has higher C14:0-C18:0 levels and lower C4:0-C12:0 amounts. In general, Ca-M compared to Co-M has higher moisture and protein content. There is more β-casein and lower κ-casein in Ca-M than Co-M (Mal & Pathak, 2010). However, Ca-M has not any β-lactoglobulin (Merin et al., 2001), whereas it is considered the main whey protein in cow, caprine, buffalo, and equine milks (Hinz, O'Connor, Huppertz, Ross, & Kelly, 2012). There are functional protective proteins with known immunological, antiviral and antibacterial properties in Ca-M such as peptidoglycan recognition protein (PGRP) enzyme, Igs, N-acetyl-β-glucosaminidase (NAGase), LF (95–250 mg/dL), lactoperoxidase (LP, 2.23 U/mL), and lysozyme (LZ, 0.03–0.65 mg/dL) (Mal & Pathak, 2010). There are higher amounts of LF, NAGase, and LZ in Ca-M compared to Co-M, while no PGRP is found in Co-M (Felfoul, Jardin, Gaucheron, Attia, & Ayadi, 2017).

3. Biofunctional properties of camel milk proteins and its derivatives

Different functionalities in terms of the *in-vitro* and *in-vivo* antimicrobial, antioxidant, antidiabetic, angiotensin-converting enzyme (ACE) inhibitory, anti-inflammatory, anti-hepatic, and anticancer activities of Ca-M proteins and their hydrolysates are summarized in Tables 1 and 2.

3.1. Antimicrobial properties

Similar to human milk, the most important antimicrobial

Table 1
A summary of *in vitro* biofunctional properties of Ca-M proteins and their hydrolysates.

Ca-M proteins and their derivatives	Functionality type	Key findings	Reference
Lactoferrin	Antimicrobial	– The highest activity against *E. coli* O157:H7 compared to LFs isolated from other milk kinds	Conesa et al. (2008)
Lysozyme, Lactoperoxidase	Antimicrobial	– Increasing the microbial inhibitory against *E. coli* and *L. monocytogenes,* The low antimicrobial capacity of heat-treated Ca-M	Benkerroum et al. (2004)
Bioactive peptides (especially from caseins) having phosphorylated serine residues	Antioxidant, Antiradical, ACE inhibitory	– Increasing the antioxidative and ACE-inhibitory activity of digested Ca-M and colostrum proteins digests due to the release of 181 bioactive peptides – A higher scavenging activity for casein peptides than hydrolysates of Ca-M, colostrum and whey proteins	Jrad, El Hatmi et al. (2014) and Jrad, Girardet et al. (2014)
Bioactive peptides of Ca-M, colostrum and colostral whey proteins, Lactoferrin fragments	Antimicrobial	– The high growth inhibition of *E. coli* XL1 blue and *L. innocua* LRGIA01 cells by undigested and digested samples of Ca-M and colostrum	Jrad, El Hatmi et al. (2014) and Jrad et al. (2015)
Bioactive peptides of casein hydrolyzates	Antimicrobial, Antioxidant	– A notably higher antioxidant and antimicrobial activity of whole casein hydrolysates than their fractions – Producing the hydrolysates with remarkable antioxidant (by α-chymotrypsin) and antimicrobial (by α-chymotrypsin and alcalase)	Kumar et al. (2016a)
Lactoferrin	Antiradical, Antioxidant, Anticancer	– Inhibiting the DNA damage and growth of colon cancer cells (50% at 5 mg/mL) – Interesting FRAP with a high antioxidant capacity against DPPH˙ and NO˙ free radicals	Habib et al. (2013)
Ca-M protein hydrolysates	Antioxidant, Antiradical	– Strong antiradical (ABTS˙ and DPPH˙) potential in *in vitro* and real food systems along with great techno-functional (solubility, emulsifying and foaming) properties	Al-Shamsi et al. (2018)
Whole casein and beta-casein hydrolysates	Antioxidant, Antiradical, ACE inhibitory	– β-casein: a strong anti-hypertensive protein in Ca-M – Increasing the antioxidant and ACE-inhibitory activities after the enzymatic hydrolysis	Salami et al. (2011)
Whole casein hydrolyzates	Antioxidant, Antiradical	– A significantly more antiradical (ABTS˙ and DPPH˙) activity and FRAP at higher hydrolysis time and degree – A higher antioxidant activity of casein hydrolysates produced by chymotrypsin than the hydrolysates generated by alcalase and papain	Kumar et al. (2016b)
Peptide fractions generated during fermentation by *L. rhamnosus* PTCC 1637	Antioxidant, ACE-inhibitory	– Higher ACE-inhibitory and antioxidant activities fermented Ca-M than Co-M – The increased antioxidant activity by rising proteolytic activity during the cold-storage of fermented Ca-M	Moslehishad et al. (2013)
Hydrolysates of whey proteins (WPs)	Antimicrobial, Antioxidant	– The improved antimicrobial and antioxidant properties after the limited enzymatic hydrolysis – A significantly higher antioxidant activity of Ca-M's WP hydrolysates than Co-M's counterparts	Salami et al. (2010)
Ca-M protein hydrolysates	Antiradical, Antioxidant	– Higher antioxidant activity of fermented Ca-M compared to Co-M – Higher antiradical activity (ABTS and DPPH) of Ca-M fermented by *Leu. lactis* SM10 than samples fermented by other bacterial strains	Soleymanzadeh et al. (2016)
β-casein hydrolyzates	ACE-inhibitory, Antimicrobial	– High ACE-inhibitory and proteolytic activity of hydrolysates produced by *L. helveticus* – Higher antimicrobial activity of fermented Ca-Ms compared to Unfermented ones	Alhaj (2017) and Alhaj et al. (2018)
Whole camel casein hydrolysate	ACE-inhibitory, Antiradical	– Producing the 3 kDa-peptides with strong ACE-inhibitory and antioxidant (ABTS˙ scavenging) activities	Rahimi et al. (2016)
κ-casein hydrolysates by the GI digestion	ACE-inhibitory	– The antihypertensive effect of tripeptide isoleucine-proline-proline	Tagliazucchi et al. (2016)
Biopeptide (κ-CN f107–115) isolated from κ-casein	ACE-inhibitory	– A high ACE-inhibitory activity for Ca-M (Inner Mongolia, China) fermentated by *L. helveticus* 130B4	Quan et al. (2008)
α, β-, and κ-casein hydrolysates	ACE-inhibitory	– A strong hypotensive potential for Ca-M fermented by *L. fermentum* and *bulgaricus* (2% inoculation rate for 12 h incubation)	Solanki et al. (2017)
Whole Ca-M hydrolysates	Anticancer, Antihypertensive, Antidiabetic, Antioxidant	– The maximum antioxidant, antidiabetic and ACE-inhibitory activities for Ca-M fermented by *Lc. lactis* KX881782 – A higher *in vitro* anticancer potential of fermented Ca-M than Co-M	Ayyash, Al-Dhaheri et al. (2018)
Whole Ca-M hydrolysates	Anticancer, ACE-inhibitory, Antioxidant	– Greater ACE-inhibition (particularly for *L. reuteri* K777, > 80%), anticancer and antioxidant (DPPH˙ and ABTS˙ scavenging) activities of fermented Ca-Ms than Co-Ms	Ayyash, Al-Nuaimi et al. (2018)
Ca-M proteins	Anticancer	– The growth inhibition of HepG2 and MCF7 cells via the activation of extrinsic and intrinsic apoptotic pathways	Korashy et al. (2012)
Free α-lactalbumin and formulated with oleic acid	Anticancer, Antitumor	– A promising way for cancer remedy especially in treating breast cancer	Uversky et al. (2017) and El-Fakharany et al. (2018)
α-Lactalbumin, lactoferrin	Anticancer	– Reducing the rate of breast cancer using Ca-M and its exosomes	Badawy et al. (2018)
Protective proteins (especially, lactoferrin)	Anticancer, Antitumor	– Antiproliferative effects on human cancer cells by inducing autophagy	Krishnankutty et al. (2018) and Yang et al. (2018)

Table 2
The *in vivo* biofunctional properties of Ca-M proteins and their hydrolysates.

Ca-M proteins and their derivatives	Functionality type	Key findings	Reference
Lysozyme, Lactoperoxidase, Lysozyme, peptidoglycan recognition protein	Antimicrobial	– The strong synergistic effect with ciprofloxacin on the growth inhibition of *E. coli* and *S. aureus*	Yassin et al. (2015)
Ca-M proteins and biopeptides produced by fermentation	Hypocholesterolemic, Antihypertensive	– A significantly higher reduction in liver tissue degeneration, apoptosis/necrosis, inflammation, steatosis and fibrosis by fermented skim Ca-M compared to the unfermented one – The strong hypotensive effect of skim Ca-M fermented by skim camel milk by *L. helveticus* and *S. thermophillus at high doses* in short- and long-term times	Yahya et al. (2017, 2018)
Whole camel milk, Lactoferrin	Anti-hepatitis C virus	– A superior effect for Ca-M compared to human milk to inhibit hepatitis C virus due to the more bio-efficiency of its lactoferrins	Redwan and Tabll (2007) and El-Fakharany et al. (2017)
Whole Ca-M hydrolysates	Anti-inflammatory	– An intense decrease in the inflammatory biomarkers in obese individuals fed with fermented Ca-M	Badkook (2013)
Ca-M proteins (insulin and insulin-like protein), micronutrients	Anti-hepatic, Antidiabetic, Antioxidant	– The prevention of non-alcoholic fatty liver disease induced by high-fat diets with the regular consumption of Ca-M	Korish and Arafah (2013)
Ca-M proteins (e.g., lactoferrin)	Anti-inflammatory	– The robust inhibition of inflammatory angiogenesis via downregulation of proangiogenic and proinflammatory cytokines	Alhaider et al. (2014)
Ca-M proteins (e.g., lactoferrin)	Anti-inflammatory, Anticancer	– Ca-M consumption: a complementary way with lower incidence of side effects during the therapy of inflammatory bowel diseases	Arab et al. (2014)
Ca-M proteins (e.g., lactoferrin), vitamins C and E, minerals	Anti-inflammatory, Antioxidant	– The treatment potential of acute respiratory distress syndrome with Ca-M consumption	Zhu et al. (2016)
α-lactalbumin, lactoferrin	Anticancer	– Ca-M and its exosomes: an anticancer agent for cancer treatment (particularly, breast cancer)	Badawy et al. (2018)
Lactoferrin	Antitumor	– Strong antiproliferative effects of antitumor active fraction of TR35, isolated from Xinjiang Bactrian Ca-M	Yang et al. (2018)
Ca-M proteins	Antidiabetic, Antioxidant, Hepatoprotective	– Protecting white Albino rats against toxicity of aluminium chloride in the liver and kidney tissues	Al-Hashem (2009)
Ca-M proteins	Antidiabetic, Antioxidant	– Strong hypoglycemic effects with a significant improvement in the diabetes-induced oxidative stress	El-Said et al. (2010)
Ca-M proteins	Antidiabetic, Antiradical Anti-inflammatory	– Improving the diabetes conditions via the regulation of insulin and blood glucose levels – A significant reduction in oxidative stresses – Increasing the proinflammatory cytokines and β-defensin levels, accelerating cutaneous wound healing	Badr (2013)

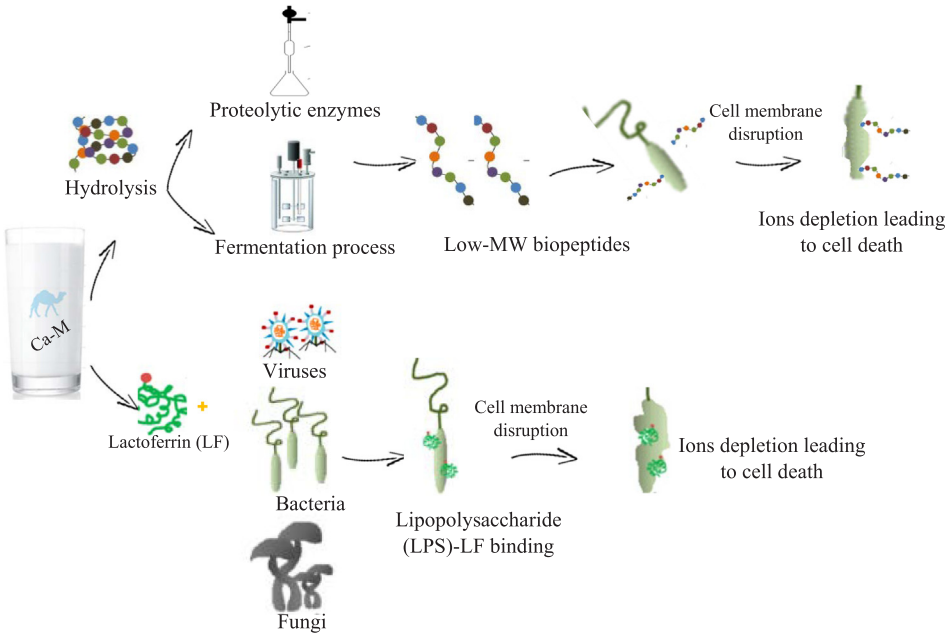

Fig. 1. The antimicrobial mechanism of Ca-M' proteins (e.g., LF) and its hydrolysates.

components in Ca-M are protective proteins of Igs, LF, and LZ. In contrast to LF and LZ, the content of Igs in Ca-M is much more than human milk (1.54 *vs.* 1.14 mg/mL) (Shamsia, 2009; Tavakolizadeh, Izadi, Seirafi, Khedmat, & Mojtahedi, 2018). The LZ level of Ca-M was higher than that of the milk of other ruminant animals (e.g., cow, sheep, goat, and buffalo), whereas this value was lower than the LZ content of human, donkey and mare milks. Although Ca-M had a lower LF level compared to human milk, more content of this protective protein in Ca-M than in cow, sheep, goat, and buffalo milks was recorded (El-Agamy, Nawar, Shamsia, Awad, & Haenlein, 2009). Conesa

et al. (2008) evaluated the antimicrobial potential of LFs isolated from alpaca, elephant, grey seal, goat, sheep, camel, and human milks against *Escherichia coli* O157:H7. Results showed that the isolated LF from Ca-M through the disruption of cell membrane had the maximum antibacterial activity against this food-borne pathogen (Fig. 1), while the minimum antimicrobial activity was determined for LFs of alpaca and human milks. Benkerroum, Mekkaoui, Bennani, and Hidane (2004) earlier reported that *Listeria monocytogenes* and *E. coli* could be inhibited by incubating these pathogen strains with Ca-M and camel's colostrum for two days at storage temperatures of 4 and 20 °C. This inhibitory effect against *L. monocytogenes* and *E. coli* was related to the activity of the LP/thiocyanate/hydrogen peroxide system and LZ, respectively. They concluded that heat treatment (70 °C for 0.5 h) could significantly destroy the protective effect against microorganisms through the inactivation of natural inhibitory systems (Benkerroum et al., 2004). El-Agamy (2000) assessed the effect of the heating process (65 °C for 0.5 h) on the activity of antimicrobial proteins (LZ, LF, and IgG) of Co-M, Ca-M, and buffalo milk samples. Although LZ and LF were not affected by the heat treatment, there was a significant reduction in the IgG activity. The heat resistance of IgG present in Co-M and buffalo milk at a temperature of 75 °C for 0.5 h was entirely lost, whereas the activity loss of Ca-M's IgG was 68.7% (El-Agamy, 2000). Therefore, the antimicrobial potential of heat-treated Ca-M can be highly attributed to the presence of LZ and LF proteins. The antibacterial effect of Ca-M against *Staphylococcus aureus* and *E. coli* in Wistar rats was also demonstrated. Besides, there was a synergistic effect between Ca-M rich of protective proteins and ciprofloxacin to decrease microbial resistance and even the used antibiotic dose (Rahbarimanesh et al., 2019; Yassin, Soliman, Mostafa, & Ali, 2015).

Jrad et al. (2015) also explored that the cell growth of *E. coli* XL1 blue could be reduced by 19.3% in the presence of 20 g/L Ca-M casein. Recently, Alhaj et al. (2018) have realized that the Ca-M fermented with *Lactobacillus acidophilus* or *helveticus* and *Streptococcus thermophilus* compared to the unfermented Ca-Ms could significantly inhibit the cell growth of *B. cereus*, *Salmonella typhimurium* and *S. aureus* for a 15 day-storage.

On the other hands, the hydrolysis of Ca-M caseins by GI proteolytic enzymes leads to the release of their fragments for inhibiting the bacterial cells. The growth rate of the Gram-negative strain of *Pseudomonas aeruginosa* ATCC 15742, and Gram-positive strains of *Bacillus cereus* ATCC 11778, *L. innocua* LRGIA 01, and *S. aureus* nosoco 3011 in the presence of casein hydrolysates of Ca-M was significantly reduced compared to the native caseins (Jrad et al., 2015). These researchers earlier had found that the cell growth of *E. coli* XL1 blue and *L. innocua* LRGIA01 can be stopped by the undigested and digested Ca-M and colostrum. The primary mechanism probably is due to the release of bioactive peptides and antibacterial fragments or the high resistance of antimicrobial proteins against pepsin and pancreatin (Jrad, El Hatmi et al., 2014). Salami et al. (2010) showed that the limited proteolysis of camel whey proteins results in a more significant improvement in the antimicrobial activity. Kumar et al. (2016a) also reported that proteases such as alcalase and α-chymotrypsin could develop casein peptides with higher antimicrobial potential. The antimicrobial activity of fragments obtained after the hydrolysis is profoundly affected by the size of generated fragments because a smaller peptide can easily penetrate the lipid membrane of microbial cells, and increase leakage of ions and other cell content, disrupting cell functions (Fig. 1) (Gharibzahedi & Mohammadnabi, 2016; Gharibzahedi, 2018). It was mentioned that the size of a protein sequence with 2–20 amino acids would be suitable for antimicrobial aims (Salami et al., 2010). Moreover, the antimicrobial activity of Ca-M protein hydrolysates is depended on a number of other physicochemical factors such as hydrophobicity, and load or concentration of peptides, as well as the presence of some amino acids (e.g., arginine, cysteines, glycine, histidine, and proline) in their structure (Kumar et al., 2016a).

3.2. Antioxidant properties

The high ascorbic acid content in Ca-M and colostrum can notably improve its antioxidant and antiradical activities, contributing to the control of tissue damage (Stahl et al., 2006). Habib, Ibrahim, Schneider-Stock, and Hassan (2013) also highlighted that the LF present in Ca-M could potentially improve the antioxidant ability by the scavenging free radicals of $DPPH^{\cdot}$ (2,2′ diphenyl-1-picrylhydrazyl), and nitric oxide ($NO^{\cdot}$), as well as ferric reducing antioxidant power (FRAP). Nonetheless, bioactive peptides derived from Ca-M proteins (mainly αs1-, αs2-, and β-caseins) play the highest role in the antioxidant potential. As well, a high number of studies have recently focused on the fermentation role in Ca-M digestion to increase the antioxidant activity. Some of these probiotic bacteria include *L. rhamnosus* PTCC 1637 (Moslehishad et al., 2013), *L. plantarum*, *L. paraplantarum*, *L. paracasei*, *L. gasseri*, *L. kefiri*, *Enterococcus faecium*, *Weissella cibaria*, and *Leuconostoc lactis* (Soleymanzadeh, Mirdamadi, & Kianirad, 2016), *L. acidophilus* or *L. helveticus* and *St. thermophilus* (Alhaj et al., 2018). Most of the studies showed that the fermented Ca-Ms have more antioxidant peptides compared to the fermented types based on Co-M. This discrepancy can be due to the difference in the class of proteins present in these milks. This fact may be owing to the structural divergence of proteins present in Ca-M. β-casein of Ca-M compared to Co-M is more, shorter, more abundant in proline, and different in the N-terminal fragment (Beg, Bahr-Lindström, Zaidi, & Jörnvall, 1986).

A significant improvement in antioxidant properties of whey proteins of Ca-M and Co-M after enzymatic treatment was reported (Salami et al., 2010). Generally, a high number of proteins intrinsically have amino acid residues with a high capacity to donate protons to free radicals (cysteine, histidine, phenylalanine, tyrosine, and tryptophan), and to chelate metal ions (arginine, aspartic and glutamic acids, histidine, and lysine) (Elias, McClements, & Decker, 2005). It seems that the partial hydrolysis of whey proteins results in the generation of bioactive peptides with lower molecular weights (MWs) containing antioxidant amino acid residues with more bioaccessibility to quench free radicals and/or to chelate oxidizing metals. Higher antioxidant activity for hydrolysates obtained from whey proteins of Ca-M compared Co-M was also found (Salami et al., 2010). This fact is owing to the presence of higher amounts (four times) of α-lactalbumin rich of antioxidant amino acid residues in Ca-M than Co-M (Salami et al., 2009). Kumar et al. (2016b) evaluated the antioxidant activities of Ca-M's casein hydrolysates produced by alcalase, α-chymotrypsin, and papain based on $DPPH^{\cdot}$, $ABTS^{\cdot+}$ (2,2′-azino-bis-(3-ethylbensothiazoline-6-sulfonic acid) and FRAP assays. An increase in hydrolysis degree and time led to the enhancement in antioxidant activities. Even though all the produced hydrolysates showed the acceptable antioxidant potential, α-chymotrypsin was introduced as the best proteolytic enzyme to develop casein hydrolyzates with the highest antioxidant activity. Jrad, Girardet et al. (2014) found that the FRAP antioxidant activity of casein peptides produced after the GI digestion with pepsin and pancreatin was significantly higher than that of digestive hydrolysates of Ca-M, colostrum and whey proteins. In general, β-casein is composed of 65% of total caseins present in Ca-M. The hydrolysis of Ca-M's β-casein with proteolytic enzymes like chymotrypsin considerably increased the hydrophobicity of bioactive peptides and the release rate of antioxidant amino acids such as phenylalanine, tryptophan, and proline (Jrad, Girardet et al., 2014; Salami et al., 2011). Al-Shamsi, Mudgil, Hassan, and Maqsood (2018) reported an increase in $ABTS^{\cdot+}$ and $DPPH^{\cdot}$ scavenging activities of Ca-M protein hydrolysates generated by proteolytic enzymes of papain, alcalase, and bromelain. However, the FRAP antioxidant activity of Ca-M proteins after the proteolytic digestion was decreased. For the first time, they found applied these hydrolysates to hinder lipid peroxidation in a food model system (minced fish (*Nile perch*) muscle) and realized that the samples covered by papain-induced hydrolysates had the minimum lipid peroxidation rate (Al-Shamsi et al., 2018). Overall, the difference in antioxidant activity

of different hydrolysates is because of the discrepancy in protein conformation, hydrolysis degree, and release rate of antioxidant peptides.

3.3. Antidiabetic properties

The results of epidemiological investigations show that the Ca-M consumption in different societies not only can significantly decrease the prevalence diabetes but also can contribute to the reduction of insulin doses in 92% of diabetic patients (Agrawal et al., 2007; Dubey et al., 2016). A recent review reported that the Ca-M consumption as a bio-remedy in arid rural areas of Asia and Africa could be effective in treating diabetes, asthma, and edema (Khalesi, Salami, Moslehishad, Winterburn, & Moosavi-Movahedi, 2017). The intake of Ca-M could also reduce the levels of glycosylated hemoglobin (HbA1c) and fasting blood sugar due to the presence of insulin and insulin-like protein (Agarwal et al., 2003; Ereifej et al., 2011). In a recent review, Ayoub, Palakkott, Ashraf, and Iratni (2018) reported a high content of insulin (52 U/L) and insulin-like protein (three-fold of Co-M) in Ca-M, which is significantly depended on the camel species, lactation period, and storage time and temperature (Abdulrahman et al., 2016; Wernery, Johnson et al., 2006; Wernery, Nagy et al., 2006). Moreover, the presence of high amounts of antioxidant enzymes and non-enzymatic antioxidants (e.g., glutathione, and vitamins E and C) in Ca-Ms through quenching free radicals in the body may reduce/prevent the damage of metabolic pathways and the risk of diabetes diseases (Chauhan, Chauhan, Brown, & Cohen, 2004; Shori, 2015). El-Said, El-Sayed, and Tantawy (2010) assessed the impact of Ca-M oral administration on levels of oxidative stresses in experimentally-induced diabetic rabbits. The Ca-M consumption could highly reduce the lipid peroxidation (malondialdehyde levels), and the catalase activity and improved the glutathione concentration. The activity increase of superoxide dismutase (SOD) enzyme with Ca-M was also reported by Al-Hashem (2009) in diabetic rabbits and Badr (2013) in streptozotocin-induced diabetic mice.

In general, this excellent dairy product directly affects the insulin receptor function and glucose transport in the body's insulin-sensitive tissues (e.g., liver, and pancreas) to regulate glucose homeostasis (Fig. 2). Ca-M not only facilitates the synthesis and secretion of insulin via the pancreatic β-cells but also has a positive role in the growth, viability, and activity improvement of pancreatic cells (Alavi, Salami, Emam-Djomeh, & Mohammadian, 2017; Ayoub et al., 2018; Malik, Al-Senaidy, Skrzypczak-Jankun, & Jankun, 2012). Meanwhile, the synthesis and secretion of insulin from the pancreas are controlled by a large group of hormones and their receptors, including gastric inhibitory polypeptide (GIP), glucagon-like peptide-1 (GLP-1), and dipeptidyl peptidase IV (DPP-IV) (McIntosh, Widenmaier, & Kim, 2009; Seino & Yabe, 2013). King (2008) pointed out that Ca-M consumption because of anti-inflammatory, anti-apoptotic, and antioxidant effects can notably potentiate the secretory activity of insulin from the pancreatic β-cells. Recently, the effect of Ca-M on the expression of carnitine palmitoyl transferase type I (CPT-I), insulin receptor substrate type 2 (IRS-2), and fatty acid synthases (FASN) has been reported. This activity through the insulin synthesis and regulation contributes to the improvement of levels of blood glucose, total cholesterol and glycerides, and high-density lipoprotein (HDL) in diabetic patients (Aqib et al., 2019)

Ayyash, Al-Dhaheri et al. (2018) have recently evaluated the antidiabetic effects of Ca-M, and Co-M fermented with two probiotic bacteria (i.e., *Lactococcus lactis* KX881782 and *L. acidophilus* DSM9126) based on the results of the inhibition activities of α-amylase and α-glucosidase enzymes. Donkor, Stojanovska, Ginn, Ashton, and Vasiljevic (2012) explained that the activity inhibition of these enzymes substantially decreases the carbohydrate hydrolysis, and the possibility of the intestine absorption of sugars. Ayyash, Al-Dhaheri et al. (2018) found that the inhibition of α-amylase by Ca-M fermented by both probiotic strains remarkably enhanced by increasing the storage time, while a non-significant change was recorded for the α-amylase inhibition by fermented Co-Ms. Although a higher inhibition of α-glucosidase in milks fermented by *Lc. lactis* KX881782 was resulted compared to that of in milks fermented by *L. acidophilus* DSM9126, this enzyme was only inhibited by 30–40% by fermented milks. Overall, the high enzyme inhibitory potential of Ca-M may be owing to the release of small bioactive peptides as a result of the secretion of proteolytic enzymes by two probiotic strains, especially *Lc. lactis* KX881782 (Kumar et al., 2016a). It was mentioned that the peptide fractions obtained from Ca-M and Co-M fermented by *L. rhamnosus* PTCC 1637 with an MW lower than 3 kDa showed higher bioactivity than those of 3–5 kDa (Moslehishad et al., 2013).

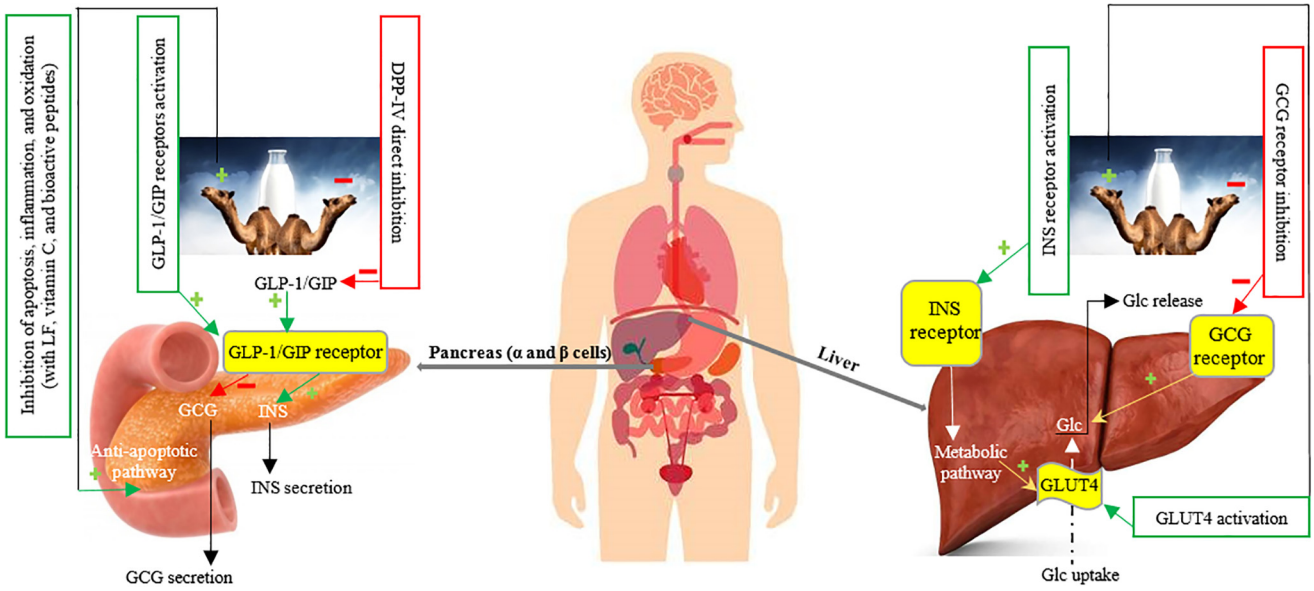

Fig. 2. A schematic representation of different action mechanisms of Ca-M to induce antidiabetic effects in liver and pancreas tissues (*abbreviations*: Glc, glucose; GCG, glucagon; INS, insulin; GLUT4, glucose transporter 4; LF, lactoferrin; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1; DPP-IV, dipeptidyl peptidase IV).

3.4. Angiotensin-converting enzyme inhibitory properties

The digestion of Ca-M proteins through proteolytic enzymes (Jrad, El Hatmi et al., 2014; Rahimi et al., 2016; Tagliazucchi, Shamsia, & Conte, 2016) or lactic fermentation process (Alhaj et al., 2018; Alhaj, 2017; Moslehishad et al., 2013; Quan, Tsuda, & Miyamoto, 2008; Solanki & Hati, 2018; Solanki, Hati, & Sakure, 2017) would result in the development of bioactive peptides with a remarkable ACE inhibitory activity. In these studies, the most common proteolytic enzymes used to generate Ca-M peptides with an ACE inhibitory activity were pepsin and pancreatin (Jrad, El Hatmi et al., 2014; Tagliazucchi et al., 2016), proteinase K (Rahimi et al., 2016), and α-amylase (Tagliazucchi et al., 2016), whereas the used probiotics were *L. helveticus* 130B4 (Quan et al., 2008), *L. rhamnosus* PTCC 1637 (Moslehishad et al., 2013), *L. acidophilus* LMG11430 and *L. helveticus* LMG11445 (Alhaj, 2017), *St. thermophilus* with *L. acidophilus* or *L. helveticus* (Alhaj et al., 2018), and *L. bulgaricus* NCDC and *L. fermentum* TDS030603 (Solanki & Hati, 2018).

Dziuba and Dziuba (2014) mentioned the formation of tripeptides of valine-proline-proline and isoleucine-proline-proline after the enzymatic hydrolysis can strongly inhibit ACE to normalize the level of blood pressure. The efficiency analysis of fermented Ca-Ms with lactobacilli compared to the same fermented Co-Ms has recently shown that the fermented source based on Ca-M has higher ability to show antihypertensive activity (Ayyash, Al-Nuaimi et al., 2018; Ayyash, Al-Dhaheri et al., 2018). Short- and long-term blood pressure lowering effects of free-fat Ca-M camel milk fermented by probiotic strains of *L. helveticus* LMG11445 and *St. thermophilus* ATCC 19,258 on spontaneously hypertensive rats was also demonstrated (Yahya, Alhaj, & Al-Khalifah, 2017). Quan et al. (2008) explored a new hypotensive peptide through the hydrolysis of κ-casein (amino acid nos. 107–115: alanine-isoleucine-proline-proline-lysine-lysine-asparagine-glutamine-aspartic acid) during fermentation. 3–10 kDa peptide sequences of isoleucine-proline-proline and valine-proline-proline with antihypertensive potential in fermented Ca-M were also identified (Solanki et al., 2017). In addition, the hypotensive effect of isoleucine-proline-proline tripeptide liberated during the GI digestion of Ca-M's κ-casein was previously reported (Tagliazucchi et al., 2016). Another bioactive low-MW peptide rich of proline residues exhibited high ACE-inhibitory activity with Ca-M fermentation by *L. rhamnosus* PTCC 1637 (Moslehishad et al., 2013). It seems that the existence of proline amino acid in the structure of formed peptides has a significant role in their blood pressure lowering ability (Hosseini et al., 2017). Alhaj et al. (2018) also emphasized that the ACE-inhibitory peptides from dromedary Ca-M not only are rich in proline but also have tyrosine and arginine at their final, C-terminal position.

3.5. Anti-inflammatory and hepatoprotective properties

Badkook (2013) reported the six week-consumption of fermented Ca-Ms with *L. acidophilus* and a probiotic mixture of *Bifidobacterium bifidum* and *St. thermophilus* could significantly decrease inflammatory biomarkers C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-α) in obese rats fed with a high-fat diet. Fallah, Feizi, Hashemipour, and Kelishadi (2018) evaluated the effect of fermented Ca-M on inflammatory factors related to metabolic syndrome. Compared to the consumption of Co-M based-diluted yogurt, a non-significant decrease levels of interleukin 6 (IL6) and TNF-α with the use of fermented Ca-M was found. Korish and Arafah (2013) inferred that the presence of minerals (e.g., Zn, and Mg), vitamins (e.g., C, and E), Igs and insulin-like protein in Ca-M substantially contributes the glycemic control and the preservation of normal lipid profile, reducing non-alcoholic fatty liver disease in rats fed with a high-fat and HDL-cholesterol diet (Ereifej et al., 2011; Gharibzahedi & Jafari, 2017). Moreover, Ca-M fermented by probiotics contains bioactive peptides with ACE inhibitory and antioxidant activities which can remarkably prevent the lipid peroxidation and oxidative stress. Arab et al. (2014) also mentioned that Ca-M through the suppression of inflammatory cytokines and colon apoptosis and also the decrease of oxidative stresses induced by the main reactive oxygen (ROS) and nitrogen (RNS) species can act as a high-efficient supplement to attenuate inflammatory bowel diseases. It also showed anti-inflammatory and antioxidant effects on lipopolysaccharide-induced acute respiratory distress syndrome in rats (Zhu et al., 2016). Besides, the concentration of serum TNF-α, IL-10, and IL-1β as proinflammatory cytokines as well as amounts of malondialdehyde, myeloperoxidase, and total antioxidant capacity in the lung as biomarkers of oxidative stress after the consumption of Ca-M were significantly reduced (Zhu et al., 2016). Similar results related to the role of Ca-M in inhibiting the key constituents involved in inflammatory angiogenesis were obtained (Alhaider, Abdel Gader, Almeshaal, & Saraswati, 2014). In general, the anti-inflammatory effects of unfermented and fermented Ca-Ms are mainly due to the high content of antioxidant components such as LF, vitamin C, and bioactive peptides (Habib et al., 2013).

Redwan and Tabll (2007) proved that the LF of Ca-M compared to human and bovine LFs has a stronger antiviral capacity to inhibit hepatitis C virus entry into human white blood cells. El–Fakharany et al. (2017) also verified that whole Ca-M has a high *in vivo* efficiency against hepatitis C virus through decreasing the serum viral load of infected individuals and switching the IgG isotype profile to T helper type 1 (Th1) cell immunity. Anti-hepatic effects of unfermented Ca-M (El-Bahr, 2014), as well as the mixture of Ca-M fermented by *Lc. lactis* subsp. *cremoris* FCM-LLC and aqueous extract of rosemary leaves (AERLs) (Hamed, El Feki, & Gargouri, 2019) against carbon tetrachloride (CCl4)-induced hepatotoxicity with a significant reduction in the incidence of liver lesions in rats were confirmed. Ibrahim, Wani, and Rahiman (2017) found that the combined feeding based on Ca-M and extra virgin olive oil markedly in mice improves the toxicity induced by paracetamol painkiller in the liver. Similarly, Yahya, Alhaj, Al-Khalifah, and Almnaizel (2018) have recently reported that the consumption of skim Ca-M fermented with *L. helveticus* and *St. thermophilus* could play an important role in reducing the hypocholesterolemic effect in rats fed with a high LDL cholesterol-full diet. The presence of ascorbic acid and antioxidant peptides in Ca-M samples and phytochemicals (mainly, flavonoids) in AERLs can considerably quench CCl4-induced free radicals causing the cellular oxidative damage in liver tissue. It was evidenced that the above-mentioned antioxidant defense systems along with the enzymatic antioxidants (e.g., catalase, glutathione (GTH) peroxidase (GPx), and SOD) via scavenging the free radicals (e.g., ROS), improving the GTH level and keeping the standard membrane integrity and function meaningfully potentiate the hepatoprotective activity such as alleviating the non-alcoholic steatohepatitis (Eskandarifar, Fotoohi, & Mojtahedi, 2017; Hamed et al., 2019; Korish & Arafah, 2013).

3.6. Anti-cancer properties

In recent years, there has been tremendous growth in the number of studies on the anticancer effects of unfermented and fermented Ca-Ms. Badawy, El-Magd, and AlSadrah (2018) reported the *in vitro* and *in vivo* anticancer effects of fresh Ca-M and its exosomes on MCF-7 breast cancer cells via the apoptosis pathway and the prevention of oxidative/inflammation stress, angiogenesis, and metastasis in the tumor models. Yang et al. (2018) isolated an antitumor fraction (namely TR-35) from whey proteins of Ca-M which was able to eradicate the epithelial cell lines of human esophageal carcinoma (Eca 109) in both *in-vitro* and *in-vivo* conditions. Krishnankutty et al. (2018) also explained that the Ca-M's LF has a strong antiproliferative effect on human colorectal (HCT-116) and breast (MCF-7) cancer cells through the induction of autophagic death. The mechanism of the autophagy induction by LF is graphically illustrated in Fig. 3. The autophagic adaptor p62 protein (sequestosome 1, SQSTM1) as a selective substrate for autophagy is co-

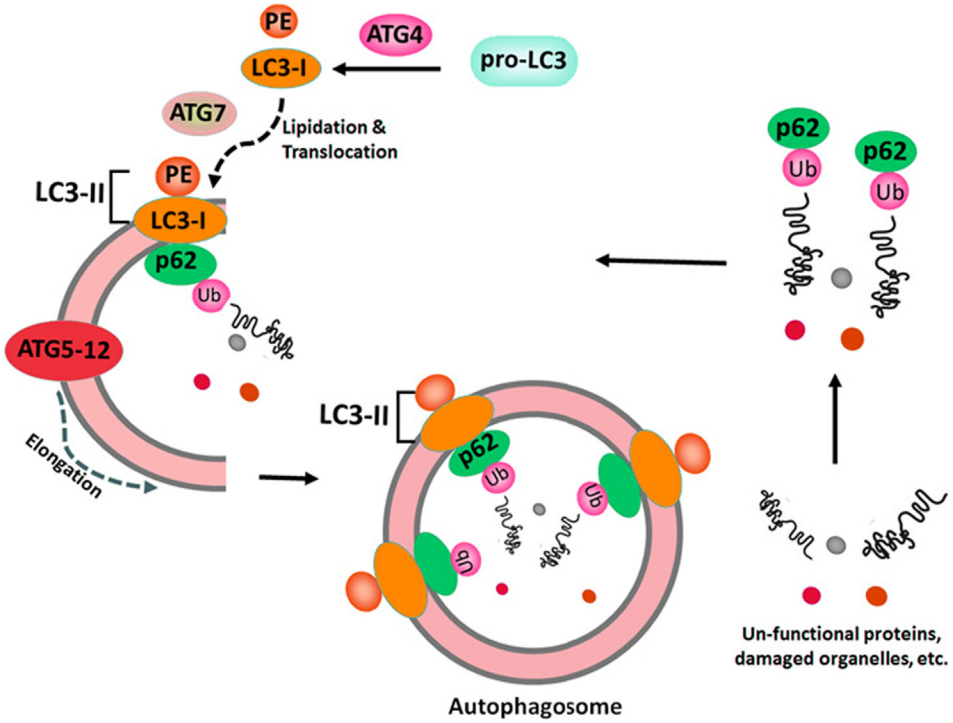

Fig. 3. A schematic illustration of the critical role of different proteins involved in anti-cancer activity against human colorectal and breast cancer cells through induction of autophagic death (*definitions and abbreviations*: LC3, a microtubule-associated protein 1 light chain 3 (LC3-I precursor); PE, phosphatidylethanolamine; ATG4 and ATG7, autophagy proteins; ATG5-12, a complex of autophagy proteins; p62, sequestosome 1 (SQSTM1); ubiquitin (Ub)-proteasome). Retrieved from Krishnankutty et al. (2018).

aggregated with the ubiquitinated proteins in forming cytoplasmic inclusion bodies. This protein is able to bind both ubiquitin and microtubule-associated protein 1A/1B-light chain 3 (LC3) with different isoforms. The LC3 precursor is processed to develop LC3-I and then lipidated by phosphatidylethanolamine (PE) to create the LC3-PE conjugate (LC3-II). This active isoform (LC3-II) localized onto the double-layered spherical structure to form the nascent autophagosomes. Expression of autophagy-related gene 5–12 complex (ATG5-12) in the membrane vesicles facilitates the elongation process required to create the autophagosome. The cytoplasmic surface LC3-II is considered as the autophagosome marker, while the LC3-II/LC3-I ratio indicates the autophagic flux. There is a dose-dependent increase in the conversion level of LC3-I to LC3-II in cancer cells of colorectal HCT 116 and breast MCF-7 treated with Ca-M, showing the cytotoxicity effects in terms of the formation of the autophagosomes with a positive autophagic flux (Krishnankutty et al., 2018). It had earlier realized that the LF of Ca-M is in charge of the activity inhibition of colon (HCT-116) and breast (MCF-7) cancer cells, respectively (Habib et al., 2013). Shariatikia, Behbahani, and Mohabatkar (2017) compared the anticancer efficiency of milks milked from different ruminants (e.g., camel, cow, sheep, goat, mare, and donkey) and their constituent proteins. According to the antiproliferation effect against MCF-7 cell line, they inferred that Ca-M along with mare and donkey milks are promising anticancer products for treating breast cancer cells. The *in vitro* proliferation effects of liquid and freeze-dried Ca-Ms on the human hepatoma (HepG2) and breast (MCF-7 and BT-474) cancer cell lines were investigated (Hasson et al., 2015; Korashy, Maayah, Abd-Allah, El-Kadi, & Alhaider, 2012). Results revealed that Ca-M by the increased gene expression activity of caspase-3 mRNA, and also the expression of death receptors in cancer cells meaningfully could prevent the proliferation of HepG2, MCF-7, and BT-474 cells. Ayyash, Al-Dhaheri et al. (2018) scrutinized the *in vitro* anticancer activity of Ca-M and Co-M fermented by the single inoculant of probiotic strains of *Lc. lactis* KX881782 and *L. acidophilus* DSM9126. Results showed that the Ca-M fermented by *Lc. lactis* KX881782 had the maximum antiproliferative potential against Caco-2 (colon cancer cells), HELA (cervical cell line), and MCF-7 cells. A strong association between the anticancer activity and $DPPH^{\cdot}$ scavenging capacity in this study showed that bioactive peptides derived from Ca-M fermented by *L. acidophilus* DSM9126 are responsible for the antiproliferative activity. Uversky, El-Fakharany, Abu-Serie, Almehdar, and Redwan (2017) studied the effect of Ca-M's α-lactalbumin in combination with oleic acid on the inhibition of four human cancer cell lines of Caco-2, HepG-2, MCF-7, and PC-3 (prostate cancer cells). They found that this molecular complex at lower IC_{50}-concentrations could significantly inhibit the growth of cancer cells through the induction of selective apoptosis and the cell-cycle arresting effect as a result of the inhibition activity of tyrosine kinase by oleic acid (Uversky et al., 2017). In the stomach of breast-fed infants, human α-lactalbumin made lethal to tumor cells (HAMLET) is synthesized to protect them against the development of tumors (Mok, Pettersson, Orrenius, & Svanborg, 2007). It was also mentioned that oleic acid through interacting with a loosely-organized hydrophobic core of α-lactalbumin in a molten globule state could significantly improve the apoptotic activity to eradicate selective tumor cells (Nakamura et al., 2013). Spolaore et al. (2010) hypothesized that the protein portion in the structure of HAMLET, and the other HAMLET-like protein-oleic acid complexes possibly acts as a delivery carrier to transfer the hydrophobic molecules of cytotoxic oleic acid into tumor cells across the cell membrane bilayers. Biofunctional properties of both structures of the rigid native and the flexible molten globule in transferring oleic acid into tumor cells have been demonstrated (Nakamura et al., 2013; Zherelova et al., 2009). El-Fakharany et al. (2018) also proved the selective antitumor behavior for the formed complex between oleic acid and α-lactalbumin of Ca-M against similar cell lines was much more than that of the complex of oleic acid with albumins present in human milk and Co-M. Increasing the gene expression of albumin receptors on the cells membrane facilitates the binding between the molecular complex and the cancer cells and increases the permeability and diffusion rate of oleic acid from the structurally modified membrane to the cell cytoplasm, inducing the nuclear damage in cancer cells (Uversky et al., 2017).

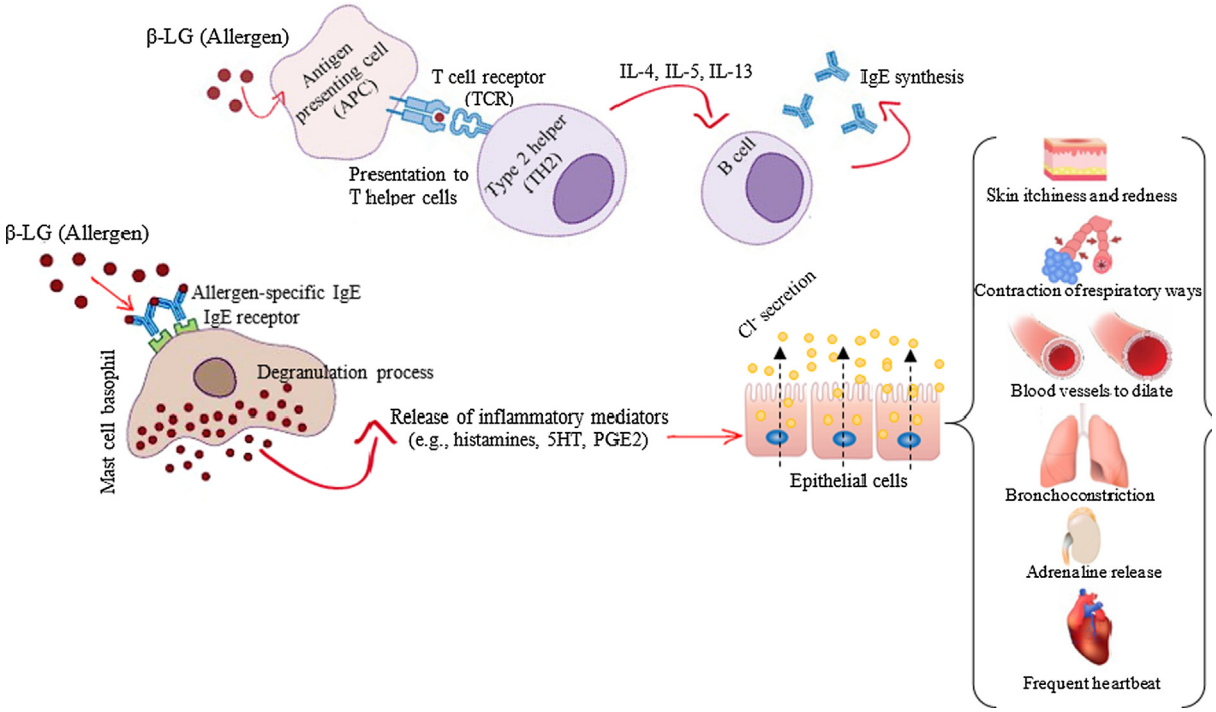

Fig. 4. A schematic image of allergenicity mechanism of bovine milk in the body (*abbreviations*: β-LG, β-lactoglobulin; IL-4, IL-5 and IL-13, inflammatory cytokines; IgE, immunoglobulin E; 5HT, 5-hydroxytryptamine; PGE2, prostaglandin E2).

4. Bio-functionality of camel milk as a dietary supplement in children

4.1. Antiallergic effects

In general, food allergy as a growing nutritional disorder is an immunologically-mediated abnormal response to food materials (Kaskous, 2016). This common allergy can seriously make mild to life-threatening anaphylactic reactions in children and adults. The anaphylaxis symptoms often are more severe in people with asthma, eczema, and hay fever (Shabo et al., 2005). Cow's milk protein allergy (CMPA) as the most dominant food allergy among infants and children induces IgE-mediated type I hypersensitivity reactions and enhances the degranulation process of mast cells. This phenomenon results in the release of inflammatory mediators such as histamine, 5-hydroxytryptamine (5HT), and prostaglandin E2 (PGE2), which can significantly intensify epithelial cell Cl^- secretion within the intestine (Fig. 4) (Swar, 2011). Many efforts to find solutions or alternatives to overcome this problem have been recently made. Replacing the Co-M with milks formulated with soy proteins or fully-hydrolyzed milk proteins in addition to feeding children with other kinds of milk such as sheep, goat, buffalo, donkey and mare milks were initial steps to eliminate this nutritional problem. However, the existence of secondary allergies with the absorption of soy proteins (Zeiger, Sampson, & Bock, 1999), and also the immunological cross-reactions between proteins present in Co-M and other milk types have caused researchers to look for safer and better alternatives (El-Agamy et al., 2009).

In recent two decades, a large group of scientists have introduced Ca-M as an ideal substitute to treat children patients with CMPA (Abderrahmane, Mezmaze, Chekroun, Saidi, & Kheroua, 2015; Al-Hammadi, El-Hassan, & Al-Reyami, 2010; Boughellout et al., 2016; Ehlayel, Bener et al., 2011; Ehlayel, Hazeima et al., 2011; El-Agamy, 2007; Katz, Goldberg, Zadik-Mnuhin, Leshno, & Heyman, 2008; Merin et al., 2001; Navarrete-Rodríguez et al., 2018; Shabo et al., 2005). They reported that there is no immunological similarity between proteins present in Co-M and Ca-M so that IgE of more sensitive children to Co-M proteins did not react with Ca-M. There is no β-lactoglobulin in Ca-M, which is considered a major allergen in Co-M (Merin et al., 2001). Moreover, the presence of similar Igs in human milk and Ca-M can potentially decrease children's allergic reactions (Boughellout et al., 2016; Shabo et al., 2005). Abderrahmane et al. (2015) evaluated the *in vitro* GI digestion of whey proteins of Ca-M and Co-M. It was confirmed that Ca-M's whey proteins had a better digestibility based on the higher hydrolysis degree and the shorter peptide chains length. Therefore, Ca-M in an original and modified form can be fed to infants and children sensitive to Co-M.

A simple trial study with the participation of eight children (4-month to 10-year old) with severe allergic reactions was conducted to evaluate the consumption effect of Ca-M to treat their illness. Lower allergy symptoms in pediatric patients were recorded after a day of treatment, while all the symptoms were entirely missed by feeding Ca-M for four days (Shabo et al., 2005). Katz et al. (2008) using a standard diagnostic method (skin prick test (SPT)) detected type I hypersensitivity reactions in CMPA patients fed with Ca-M. They observed only 25% positive SPT in subjects were consuming Ca-M during the treatment. In a cohort clinical study, Ehlayel, Bener et al. (2011) recruited children aged 6–126 months with allergy symptoms to Co-M proteins and assessed the consumption of Ca-M as a food treatment. Results showed that the allergy symptoms in 28 out of 35 patients (80%) were disappeared. Navarrete-Rodríguez et al. (2018) have currently implemented a cross-over clinical trial to determine the safety and tolerability of Ca-M intake in 1–18 y aged Mexican children with CMPA. They reported that Ca-M with a good taste and flavor in dairy formulas can be used to decrease allergic signs and symptoms in children. This result was verified by Boughellout et al. (2016), who found the improving effect of Ca-M's caseins and whey proteins on 10 patients with CMPA. Cardoso, Santos, Cardoso, and Carvalho (2010) also confirmed that the pasteurized and fresh Ca-M is suitable for Caucasian patients (children and adults, 2–65 years) with lactose intolerance.

4.2. Anti-autism effects

Nowadays, it is revealed that the use of healthy-functional, balanced diets enables children with ASD to the extent acceptable in their better

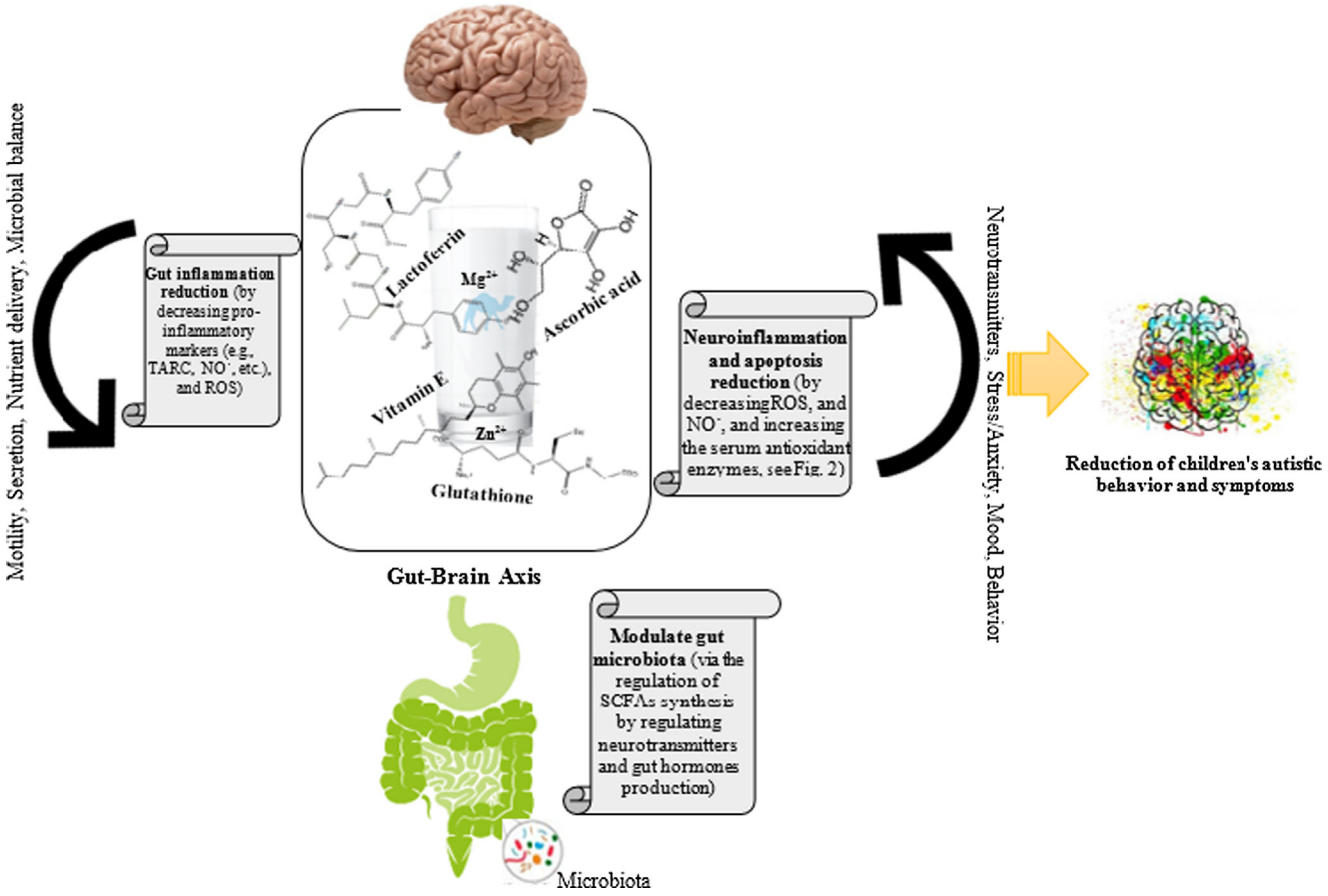

Fig. 5. Some improving mechanisms of Ca-M in autistic behavior of children with ASD after the Ca-M consumption (*abbreviations*: ROS, reactive oxygen species; NO, nitric oxide; TARC, thymus and activation-regulated chemokine; SCFAs, short-chain fatty acids).

self-understanding and life quality. Therefore, finding the appropriate nutritional strategies to prepare the best foods with attractive sensory attributes such as taste, smell, color, and texture may play a key role in promoting communicative and cognitive-social abilities of autistic children. Fig. 5 shows some mechanisms involved in alleviating autistic symptoms in children with ASD. According to the obtained data of baseline psychology scales including childhood autism rating scale (CARS), social responsiveness scale (SRS), autism treatment evaluation checklist (ATEC), and thymus and activation-regulated chemokine (TARC), recent studies have shown that the daily consumption of Ca-M has an emerging therapeutic effect in improving autistic behavior in children with ASD (Adams, 2013; Al-Ayadhi & Elamin, 2013; Al-Ayadhi, Halepoto, Al-Dress, Mitwali, & Zainah, 2015; Bashir & Al-Ayadhi, 2014; Hamzawy, El-Ghandour, Abdel-Aziem, & Ali, 2018; Shabo & Yagil, 2005; Wernery et al., 2012). Results of treating the ASD with Ca-M were promising and exciting. Overall, the health status of the children with ASD after Ca-M consumption was significantly improved. In some cases, the complete disappearance of autistic behavior was detected, and in other cases, there was a significant partial reduction in the illness symptoms so that autistic children behaved less destructive, more productive, and quieter with better a communicative, emotional and social manner.

Adams (2013) reported the regular consumption of raw Ca-M for six consecutive years could remarkably improve autism symptoms in an American 9-year-old boy with ASD. Al-Ayadhi et al. (2015) based on the comparison of CARS, SRS, and ATEC data before and after 14 days of raw Ca-M therapy in 65 children aged 2–12 years with ASD found that the nutrition intervention with Ca-M has a substantial effect on some autistic behaviors. In a randomized, double-blind, placebo-controlled trial, Bashir and Al-Ayadhi (2014) evaluated the 14 d-therapy effects of consumption of raw fresh and boiled Ca-M (0.5 L/d), and Co-M in 45 children with ASD based on the TARC serum concentration and CARS score. The TARC works on the chemokine receptor type 4 (CCR4) to increase the activation of asthmatic T helper 2 (TH2) inflammation cells. Results showed that the consumption of fresh and boiled Ca-Ms could significantly reduce the serum TARC level with an improvement in CARS scores. However, the fresh Co-M had not any positive effect on the studied responses. Wernery et al. (2012) earlier had found the improving effect of regular 14 d-consumption of pasteurized Ca-M (0.5 L/d) on the decrease of ASD symptoms or related neurological pathogenesis in children aged 5–14 years. The treatment of autistic behavior with the daily consumption of Ca-M for six days in valproic acid-induced autistic rats has been recently evaluated (Hamzawy et al., 2018). They proved that the regular consumption of Ca-M could potentially improve ASD symptoms through the adjustment of inflammatory and apoptotic pathways. This fact revealed that the therapeutic effects of Ca-M in reducing ASD symptoms is highly related to antioxidant components and protective proteins such as LF in Ca-M structure.

Different investigations showed that children with ASD compared to healthy developing ones had more oxidative stress (Al-Ayadhi, 2012) in terms of decreased concentrations of GTH (James et al., 2004; McGinnis, 2004) and serum antioxidant enzymes such as SOD and GPx (McGinnis, 2004), and also increased levels of toxic prooxidants of NO˙ (Söğüt et al., 2003). James et al. (2004) explained that the use of antioxidants could notably increase the serum GTH level in children with ASD. Al-Ayadhi and Elamin (2013) pointed out the use of Ca-M can significantly raise the levels of GTH, SOD, and myeloperoxidase. It can be concluded that the presence of high amounts of antioxidant enzymes (e.g., LF) and non-enzymatic antioxidants (e.g., vitamins C and E, and GTH) in Ca-M has a significant role in the behavioral improvement of

children with ASD. Moreover, the presence of some minerals such as Zn and Mg in Ca-M in improving the antioxidant power are well known. High concentrations of Mg can decrease the oxidative stress by increasing the absorption rate of antioxidant vitamins of C and E, while Zn enhances the total concentration of GTH, SOD, GPx in biological systems (Al-Ayadhi & Elamin, 2013; Ashwood et al., 2011). As a result, there is a necessity to evaluate the consumption of fermented Ca-M and Ca-M based food products in promoting the health and life quality of children with ASD because the role of anti-inflammatory and antioxidant peptides obtained during enzymatic hydrolysis and fermentation process of Ca-M in increasing the antioxidant capacity has been documented.

5. Conclusion and future trends

The present overview highlighted the composition, physicochemical, and functional properties of native and enzymatic hydrolysates of Ca-M proteins to understand their health effects on the behavioral control of children with ASD. Ca-M is considered an invaluable alternative source to Co-M. It has much less allergic effects than Co-M due to the lack of β-lactoglobulin. The high amounts of protective proteins, minerals, and vitamin C accompanied by a balanced ratio of saturated and unsaturated fatty acids in Ca-M make it an excellent candidate to improve the growth performance of infants and children. Recent therapeutic effects of Ca-M about its bio-functional characteristics, including antimicrobial, antioxidant, ACE-inhibitory, anticancer, antitumor, anti-hepatic, and anti-inflammatory activities were discussed. Above all, this nutritious dairy source by suppressing oxidative stresses through changing the ratios of antioxidant enzymes and nonenzymatic antioxidants reduces children's autistic behavior.

Although protective proteins present in Ca-M compared to Co-M have higher thermal stability, the use of non-thermal processing such as high-pressure, pulsed electric field, ultrasonication, etc. can remarkable contribute the milk pasteurization to keep the structure and functionality of proteins. As the synergistic function of Ca-M with antibiotics in several studies has been well known, this milk due to its strong antimicrobial activity can significantly diminish antibiotic resistance of bacteria. Therefore, the supplementation of Ca-M powders can substantially reduce the required antibiotic dose to cure patients. Despite the identification of the positive role of Ca-M hydrolysates in designing nutraceuticals and fortified functional foods, there is a research gap to optimize the operating conditions involved in hydrolyzing Ca-M proteins. It is necessary to implement the practical strategies to optimize the concentration of selected proteolytic enzyme, the enzyme/substrate ratio, hydrolysis time and temperature, and the reaction pH. In general, economical and quality organoleptic issues should be taken into account to hydrolyze Ca-M proteins at an industrial scale. A shorter hydrolysis time would be suitable because longer enzymatic hydrolysis times not only increase the cost of unit operation but also produce an amino acid mixture with a bitter taste, restricting their application in final bio and food formulations. It is strongly recommended to follow dietary patterns favoring the consumption of fermented probiotic Ca-Ms because lactic proteolytic strains are able to hydrolyze bioactive peptides with antioxidant and ACE-inhibitory potentials from Ca-M proteins. The Ca-M-based dietary pattern is a promising and safe preventive therapy for behavioral disorders in pediatric patients with ASD. Based on the known structure-activity relationship of bioactive peptides, further clinical studies should be directed towards the ASD reduction as a result of the consumption of Ca-Ms fermented by probiotic bacteria and pasteurized with innovative non-thermal methods. Also, further wide-scale studies aiming at understanding the main molecular and physiological mechanisms about the positive effect of Ca-M in the therapy of this behavioral disorder should be conducted.

6. Ethics statement

Our research did not include any human subjects and animal experiments

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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