International Journal of Food Science and Nutrition
ISSN: 2455-4898
Impact Factor: RJIF 5.14
www.foodsciencejournal.com
Volume 3; Issue 6; November 2018; Page No. 84-89

A review on milk and its biological effects on human health: Neurological conditions, cardiovascular diseases and cancer

Shirley Huan Fang Lee[1], Ihsan N Zulkipli[2], Sheba R David[3], Siti Rohaiza Ahmad[4], Fairuzeta Ja'afar[5], Ya Chee Lim[6], Rajan Rajabalaya[7*]

[1-4, 6-7] PAPRSB Institute of Health Sciences, Universiti Brunei Darussalam, Jalan Tungku Link Bandar Seri Begawan BE 1410, Brunei Darussalam

[5] Department of Chemical Sciences, Faculty of Sciences, Universiti Brunei Darussalam, Bandar Seri Begawan BE 1410, Brunei Darussalam

Abstract
The components of milk are a complex ingredient and its processing should be the combination of a thermal and non-thermal method to retain its health benefits. High intensity pulsed electric fields with thermal exposure are beneficial for milk stability. The biological benefits of different milk such as cow, camel and human milk were discussed in this review paper. Camel milk significantly increased anti-oxidant biomarkers in autistic children and hence reduces oxidative stress to improve autistic behaviour. The fermented dairy products, such as camembert cheese generates anti-inflammatory compounds which may exert therapeutic benefits in Alzheimer disease. This paper also discusses the relation between whole milk and blood lipid concentrations with respect to cardiovascular risk; the milk did not lead to significant changes in blood cholesterol. The moderate intake of whole milk may be ideal for optimal health; hence it has less triggers mechanistic target of rapamycin complex 1 activity which is responsible for cancer cellular growth. This review paper also discussed infectious diseases, microbial resistance, and allergic disease.

Keywords: high intensity pulsed electric fields, neurological disorder, cardiovascular disease, cancer, infectious disease, caseins

1. Introduction

Worldwide consumption of milk from livestock products were expected to projects up to 89.5 Kg per year/person in 2030 from only 78.1 Kg per year in between the year 1997-1999 (FAO 2013) [38]. It is well documented and known that, milk possess valuable nutrients and contributes to our body requirements such as calcium, magnesium, selenium, riboflavin, vitamin B12 and vitamin B5 (FAO 2013) [38]. Breast milk has been recommended as the gold standard by the World Health Organization (WHO) for growing young children (FAO 2013) [38]. For full term new born baby, the consumption of human milk of up to six months and above has led to fewer cases of diarrhoea, vomiting and infections. Apart from that it also helps to reduce the predisposition of obesity and non-communicable diseases such as diabetes and cardiovascular diseases in their adult life (Lönnerdal 2014) [71].

Particularly for pre-term babies, breast milk is the best option to support their survival. Pre-term babies (very low birth weight) benefits from the intake of human milk because it promotes good neurodevelopmental outcome, protection again infections, low rates of metabolic syndrome in the long-term and during adolescent years, associated with low blood pressure and lower risks of insulin resistance. Milk glycan components in breast milk has prebiotic effects that helps with the prevention of diseases such as necrotizing enterocolitis, a common and devastating diseases of preterm infants (Pacheco *et al*. 2015) [90].

However, in some cases, due to some health issues of the mother or the children, animal milk is considered for consumption to support growth. Different types of animal milk with varying level of nutrients are available and consumed in different parts of the world. Five of the most common milk producing animals worldwide are from cows, buffaloes, camel, goat and sheep (Lönnerdal 2014) [71]. Nowadays, milk from yak, donkey, camel, reindeer, horses and moose are also consumed but depends on the regional locations and availability. (FAO 2013) [38]. It was found that some of these varying sources of milk have therapeutic effects such as the treatment of metabolic disorder, prevention of cardiovascular diseases and by arthritis (Uniacke-Lowe *et al*. 2010; Uniacke-Lowe and Fox 2012) [119, 118]. In particular, gaining its popularity nowadays is camel's milk which has been believed to have therapeutic effects towards the treatment of disorders such as jaundice, tuberculosis and asthma (Kumar *et al*. 2016) [25].

Cow's milk is the most commonly consumed animal milk, thus largely commercialized globally to make up about 85% of milk global production (Claeys *et al*. 2014) [35]. However, animal milk contains low iron, which makes it not suitable for infants/ growing children under twelve years old (FAO 2013) [38]. It is very well documented, that infants and young children that consumes cow's milk has detrimental effects on their body iron stores (Ziegler 2011) [127]. Several mechanisms has been identified contributing to this factor including low iron levels presence in cow's milk, intestinal blood loss as a

results from cow's milk consumption during young age (40% of occurrence) and the inhibition of iron absorption by calcium and casein which are found to high in amount in cow's milk (Ziegler 2011) [127]. Apart from low iron levels found in animal milk sources, consumption of animal milk has also been associated with the increased risk of being overweight or obese in the adult years when consuming more number serving than daily consumption milk as part of a healthy and balanced diet. (Ziegler 2011; FAO 2013) [38, 127]. Over breast milk, animal milk such as cow's milk has been recommended to be taken at the modest level as much as possible (Ziegler 2011) [127].

For formula milk, there has been an attempt to add supplementation to improve its quality similar to breast milk, for better health benefits. One attempt was to add milk fat globule membranes containing bioactive compounds as found in breast milk (Hernell *et al*. 2016) [54]. Oligosaccharides found in milk possess important functions related to the newborn's development and health, prebiotic pro bifidogenic effects, anti-adherence of pathogenic bacteria, and immunomodulation (Goehring *et al*. 2014; Hsieh *et al*. 2015) [47, 56]. The inclusion of Milk Fat Globule Membrane (MFGM) supplementation in milk has also helped to reduce the incidence and duration of illness, improved nutrients status and cognitive development during the first year of life in children (Hernell *et al*. 2016) [54]. The consumption of milk by the children (1-12 years) that contains MFGM supplementation was found have higher hand, eye coordination and higher skill performance (Hernell *et al*. 2016) [54]. Studies have also shown that camel milk have promising therapeutic treatment of autism after 2 weeks consumption (Al-Ayadhi *et al*. 2015; Kumar *et al*. 2016) [6, 25]. The consumption of milk is also beneficial for adults. Studies has shown that the intake of fermented milk containing probiotic bifidobacterium bifidum has led to reduced gastric symptoms such as stomach pain, bloating or constipation (Gomi *et al*. 2015) [48]. The intake of cow's milk has also been beneficial in the prevention of several chronic diseases such as heart diseases, some form of cancer and diabetes (Pereira 2014a) [94]. Milk-derived proteins and peptides have the potential to act as co-adjuvants in conventional therapies, addressing cardiovascular diseases, metabolic disorders, intestinal health, and also chemopreventive (Hsieh *et al*. 2015) [56]. Consumption of milk has also been found to be beneficial for the elderly age group as it have positive impact on cardiovascular health, bone health and weight management (Wolfe 2015) [121]. This review discusses and analysis the breast milk, processed milk and camel milk with their nutritional values as well as advanced milk processing technique.

2. Materials and Methods

This review article that obliged as a base for the current update of milk processing and its effect of major diseases was compiled by using Google Scholar and Science Direct databases, and the search was directed by using terms such as: milk and its biological effects on human health: neurological conditions, cardiovascular diseases and cancer including novel processing methods of milk and it shelf life periods. This review also will be useful to update their knowledge of health-care professionals such as pharmacist, nutritionist and biomedical scientist about effect of milk on various chronic diseases.

3. Milk Composition

3.1 Percentage composition of the main constituents in milk

The main constituents in cow milk are water, fats, proteins, lactose and minerals. Milk also contain trace amounts of pigments, enzymes, vitamins, lipids and gases. (Bylund 2015) [27]. The percentage quantities of the constituents can vary considerably between individual cow breeds and processing methods. Thus, the reported values in Table 1 are an example of a percentage composition of the main constituents in milk.

Table 1: Percentage composition of main constituents in cow's milk (Adapted from (Bylund 2015) [27]

Constituents	Percentage composition*
Water	87%
Fats	3.9%
Proteins	3.4%
Lactose	4.8%
Minerals	0.8%

*may vary between different breed and processing methods

3.2 Milk Fat

Milk fat is composed of 99% neutral lipids. triglycerides (triacyl glycerols) being the predominant group, accounts for 95% of the lipid fraction and are composed of fatty acids of different lengths and saturation.(Jensen 1996) [58] Diglycerides make up 1-2% of this fraction, followed by very small amounts of monoglycerides, some sterols and free fatty acids. More than half of milk fatty acids are saturated and while there could be more than 200 types of fatty acids in milk, only fatty acids that are available in significant amounts are listed in Table 2.

Table 2: Fatty acid content (saturated and unsaturated) of milk fat (Adapted from (Jost 2000; Fox and Kelly 2012) [61, 43]

Saturated fatty acid	Chemical symbol	Weight% of total fatty acid content	Unsaturated Fatty acid	Chemical symbol	Weight% of total fatty acid content
Butyric acid	C4:0	3.3	Oleic acid	C18:1	29.8
Caproic acid	C6:0	1.6	Linoleic acid	C18:2	2.4
Caprylic acid	C8:0	1.3	Linolenic acid	C18:3	0.8
Capric acid	C10:0	3.0	Linoleic acid	C18:2	2.4
Lauric acid	C12:0	3.6	Linolenic acid	C18:3	0.8
Myristic acid	C14:0	9.5	Total		**33**
Palmitic acid	C16:0	26.3			
Stearic acid	C18:0	14.6			
Total		63.2			

3.3 Proteins

Milk contains hundreds of types of proteins and conventionally have been classified into caseins, whey proteins (also milk serum proteins) and other miscellaneous membrane proteins (Farrell *et al*. 2004) [39]. Table 3 lists the concentration of these proteins. For the sake of simplicity, only main classifications of proteins were listed.

Table 3: Concentration of proteins in milk (Adapted from (Jost 2000; Farrell *et al*. 2004; Bylund 2015) [27, 39, 61]

Protein - Caseins	Mean concentration in milk (g/kg)	Percentage (%) of total protein content (w/w)	Whey (serum) proteins	Mean concentration in milk (g/kg)	Percentage (%) of total protein content (w/w)
αs1-casein	10.7	32	α-lactalbumin	1.2	3.7
αs2-casein	2.8	8.4	β-lactoglobulin	3.2	9.8
β-casein	8.6	26	Serum albumin	0.4	1.2
κ-casein	3.1	9.3	Immunoglobulins	0.8	2.4
γ-casein	0.8	2.4	Proteose peptone	1.7	5.1
Total	26	78.3	Total	6.4	21.7

3.4 Caseins, Whey proteins and Lactose

Caseins is the dominant class of proteins in milk, subdivided into four major groups: α-s1 casein, α-s2 casein, β-casein and γ-casein. Caseins are present in the form of micelles and self-assemble to make large clusters, with spherical diameters of 50 - 500 nm. These colloidal spheres scatter light, giving milk its white colour. In contrast, whey proteins (also known as milk serum proteins) are soluble, heat-sensitive proteins. Whey proteins readily denature above 70°C, stopping coagulation and gelling, thus holding implications in stability and shelf-lives. However, this has a negative impact when curding is needed for example in cheese production. In terms of nutrition, α-lactalbumin in particular, has high nutritional value and is found in the milk of all mammals. Their amino acid composition is very close to what is regarded a biological optimum. Lactose is a sugar found only in milk. It is about 30 times less sweet than cane sugar. The lactose content represents roughly 50% of the total dry solids of skimmed cow's milk. Lactose, when heated at a high temperature could turn brown and caramelise. Lactose could also be attacked by enzymes producing lactic acid, which is one reason why milk turns sour (Jost 2000; Fox and Kelly 2012) [61, 43].

3.5 Vitamins and Minerals

Milk is a good source for vitamins. Some vitamins are water soluble, while others are fat soluble (refer to Table 4). Milk contains a number of minerals. The most abundant mineral in milk is potassium, followed by calcium (refer to Table 4). Calcium is required to build up bone mass, however, the low solubility of this mineral hampers its availability to the body for bone growth. In milk, 70% of calcium exists in a complex of phosphate and citrate ions, which is easy for our body to digest (Mc Sweeney and Fox 2009) [89].

Table 4: Vitamin content in 100 g of whole milk (Adapted from (Jost 2000) [61]

Vitamins	Amount (mg) per 100 g of whole milk
Water-soluble vitamins, mg/100 g	(mg/100 g)
Vitamin C	1.7
Panthothenic acid	0.35
Biotin	0.004
Folic acid	0.006
Thiamine (vitamin B1)	0.04
Riboflavin (vitamin B2)	0.18
Pyridoxine (vitamin B6)	0.05
Cobalamin (vitamin B12)	0.0004
Fat-soluble vitamins, mg/100 g	(mg/100 g)
Retinol (vitamin A)	0.03
Calciferol (vitamin D)	0.00006
Tocopherol (vitamin E)	0.09

Table 5: Mineral content of milk (Adapted from (Jost 2000) [61]

Microminerals (g/mg) per kg of whole milk		Trace elements (g/mg) per kg of whole milk	
Potassium	1.57	Zinc	3.80
Calcium	1.20	Iron	0.46
Phosphorus	0.92	Aluminium	0.46
Sodium	0.48	Fluorine	0.17
Magnesium	0.12	Iodine	0.11
-	-	Copper	0.10
-	-	Selenium	0.09
-	-	Manganese	0.02

4. Novel milk processing

4.1 High-Pressure Milk Processing (HPP) Technology

This section discusses about advanced milk processing methods compare to conventional milk processing methods. Consumers nowadays prefer fresh, healthy, high quality and micro-biologically safe milk products. A High-Pressure Processing (HPP) technology for the milk processing has proven to be very beneficial. Temperature during this process may be maintained subzero to more than 100°C and exposure times can be few seconds to over 20 mins. The HPP ranges from 300 and 600 MPa are effective to inactivate milk -borne pathogens and also it improves rennet or acid coagulation of milk without damaging the quality of characteristics, such as taste, flavour, vitamins, and nutrients. (CHOPDE *et al*. 2014) [33].

4.2 High Intensity Pulsed Electric Fields (HIPEF)

Non-thermal treatments, the application of high intensity pulsed electric fields (HIPEF) has been gaining interest over the last decade for the milk processing. HIPEF is a method to inducing the electric field on the liquid media flow (milk) in a continuous system. The electrical charges applied on the milk, fat content, pH and temperature are altered due to interference in the conductivity of the ions such as the chlorides, phosphates, citrates, carbonates, sodium, calcium and magnesium. And also this application of HIPEF, leads to reduction of globule size of the milk fat significantly (Lindgren *et al*. 2002; Zulueta *et al*. 2007) [70, 128]. In contrary another researcher reported that the application of HIPEF on milk media may leads to form a complex composition of high milk protein and this complex milk protein content may prevent the microorganisms growth during storage or transportation (Mabrook and Petty 2003) [74].

This method also decreases the pH of the milk, that leads to solubilisation of casein micelles thereby, an increase in the final conductivity of milk media considered lethal to microbial survival (Lindgren *et al*. 2002) [70]. However with lower frequency of HIPEF-treated milk (35 kV/cm, 188ls without exceeding the outlet temperature of 52°C) reported that there is no significant changes in physicochemical and nutritional properties of the cow milk (MARTÍN *et al*. 1997; Bendicho *et al*. 2002) [21, 77]. A pasteurized milk bulk-shipped to long distant place is generally again pasteurized for a second time after arrival for the safe consumption. This kind of double thermal treatment that leads to reduction of sensual and nutritional quality of milk; therefore, the use of a non-thermal preservation is most suitable for milk industry. This double thermal treatment issue was overcome by the researcher by developing combination of thermal (High-temperature short-time) with five pulsed electric fields treatments were applied immediately after pasteurization. This kind of treatment has been produced an extended-shelf life of the milk. This is type of treatment were economically viable to bulk shipping of milk products in different parts of the world without stability issues (FERNANDEZ-MOLINA *et al*. 2005; Sepulveda *et al*. 2005) [40, 105]. The high-pressure treatment with thermal approach, may improve the antigenicity of β-lactoglobulin (β-LG) significantly due to increases its affinity to β- LG specific to IgG as well as IgE (Chicón *et al*. 2008; Zhong *et al*. 2012) [31, 126]. The *in vivo* study conducted in rats and reported that under high-pressure conditions, the treated milk protein β-LG hydrolysates lost its allergenicity. This may be due to disorientation of hydrolysates of its peptides and leads to lost their capability to cross-link human IgE antibodies to induce mast cell degranulation hence it lost its allergenicity (López-Expósito *et al*. 2012) [73]. This high pressure method not only improves the protein digestion and also enhances the surface sterilization by irradiation due to formation of aggregates (Borad *et al*. 2016; Gallier *et al*. 2016) [25, 44]. The pulsed electric fields (PEF) applications makes the pores of the bacterial lipid cell membrane during the milk treatment and therefore the bacteria lost is integrity of cell wall membrane and died (Pothakamury *et al*. 1997; Bendicho *et al*. 2002; Barrea *et al*. 2015) [18, 21, 98].

The other research also reported that the combination of milk processing and treatment such as PEF and mild thermal treatment which leads to increase milk shelf life (Toepfl *et al*. 2007) [113]. The production of full-cream milk powder by high pressure homogenization is save energy for the milk industry compare with that of pasteurization process (Gallier *et al*. 2016) [44]. This has been recently proposed that the citrate cream fraction first homogenized and then followed by usual pasteurization and concentration of the dry milk powder production (Augustin *et al*. 2014) [13].

5. Pharmacological effect of milk on human health: Neurological Disorder

5.1 Alzheimer's Disease (AD)

Interestingly, it has been shown that women who breastfeed had lower risk of developing AD compared with non-breastfeeding women. It was postulated that breastfeeding modulates hormonal exposure in mothers and improves insulin sensitivity to reduce AD risk (Fox *et al*. 2013) [42]. Milk contains fatty acids including linoleic acid, linolenic acid, conjugated linoleic acid, stearic acid and oleic acid. During the fermentation of dairy products, oleamide is synthesized from the milk fatty acid, oleic acid. Alzheimer's disease (AD) is a progressive neurodegenerative disease with two key pathological features in the brain including inter-cellular amyloid-β (Aβ) plaques, and intra-cellular neurofibrillary tangles. In addition, post-mortem brain studies of individuals with AD have also shown increased expression of inflammatory mediators. Coupled with data from epidemiological studies which reported the role of anti-inflammatory drugs in reducing risk for AD (Wyss-Coray 2006) [126]. These suggest that inflammation within the brain is one of the key mediators of AD. A recent study utilizing mouse model of Alzheimer's disease has shown that the intake of dairy product fermented with *Penicillium candidum* reduces the accumulation of amyloid-β (Aβ) and hippocampal inflammation, and enhances hippocampal neurotrophic factors. The concentration of oleamide (100 – 1000 nM) stimulates microglial phagocytosis of $A\beta_{1-42}$ in a concentration-dependent manner *in vitro*, whereas oleic acid did not exert any effect (Ano *et al*. 2015) [9]. This study therefore shows that fermentation of a dairy product (camembert cheese) generates anti-inflammatory compounds which may exert therapeutic benefits in AD.

5.2 Docosahexaenoic acid (DHA) and other omega fatty acids

Red wine and fish are abundant in resveratrol and omega-3 fatty acids respectively, which confer protection against AD (Ano *et al*. 2015) [9]. The process of synapse formation within brain neurons is initiated by neuronal depolarization, and three key nutrients determine the numbers of synapses formed, namely uridine, the omega-3 fatty acid docosahexaenoic acid (DHA), and choline (Wurtman 2014) [123]. In Alzheimer's disease (AD) there is a decrease in basal plasma levels of these three nutrients due to impaired hepatic synthesis. Therefore high brain levels of uridine, DHA and choline are required to correct disease-associated synaptic membrane or synaptic conditions (Wurtman 2014) [123].

Studies have linked lower DHA content with weaker cognitive development, as well as visual function (Calder 2016) [28]. The enrichment of breast milk with DHA suggests that research into human milk constituents may aid development of synthetic DHA analogues, which may be therapeutic for AD.

5.3 Parkinson's disease

Oxidative stress occurs when there is an excess of free radicals or a decrease in antioxidant levels. Increase in markers of oxidative stress have been observed in AD, Huntington's disease and in both familial Amyotropic Lateral Sclerosis (ALS) and sporadic ALS. The nervous system is enriched with unsaturated fatty acids as well as iron. The high lipid content of the nervous tissue leads to higher metabolic activity therefore increases its susceptibility to oxidative damage (Ano *et al*. 2015) [9]. A key pathological feature in Parkinson's disease (PD) is the loss of neurons within a brain region called the substantia nigra. Tissue degeneration in the substantia nigra is frequently associated with antioxidant depletion (Perry *et al*. 2002) [96]. Indeed, patients with Parkinson's show reduced antioxidant levels and raised oxidative stress levels. Milk products contain Vitamin D and casein which may help to reduce oxidative stress in the nervous system (Singh *et al*. 2004) [105], and therefore may elicit neuroprotective roles through restoring anti-oxidant levels. Meanwhile, a recent study has shown that dairy food intake is related with higher risk of PD, particularly for men. The meta-analysis of prospective cohort studies from three populations (USA, Finland and Greece) on dairy food intake and risk of PD involved 1,083 PD cases among 304,193 subjects. PD risk increased by 17% for every 200g per day increment in milk intake and 13% for every 10g per day of cheese intake (Jiang *et al*. 2014) [59]. As this is the first study linking PD with dairy food intake, the relationship between milk intake and neurodegenerative diseases therefore awaits further validation in various population cohorts.

5.4 Autism spectrum disorders

Autism spectrum disorders (ASDs) are a group of disorders characterized by traits such as impairment in social interaction, communication deficits, and restricted repetitive interests and behaviours. ASDs are attributable to multiple genetic and environmental risk factors (Levy *et al*. 2009) [69]. The prevalence of autism is increasing at an alarming rate, and the current prevalence rate within various population cohort is about 1% (Baron-Cohen *et al*. 2014) [17]. The link between autism and gut microflora was first reported in 2005. Faecal flora analysis utilizing *Fluorescent In Situ Hybridization* (FISH) technique have shown a significant difference in the composition of human gut microflora of individuals with ASD compared to the healthy population. The predominant bacterial population in samples from ASD patients was *Clostridium histolyticum (C. histolyticum),* suggesting an association between *Clostridium* and the development of certain autistic traits (Parracho *et al*. 2005) [95]. As mentioned earlier, oxidative stress leads to numerous neurological disorders, including ASD. It has been reported that the consumption of camel milk for two weeks significantly increased anti-oxidant biomarkers in autistic children (by assessing levels of glutathione, superoxide dismutase, and myeloperoxidase). It is therefore suggested that camel milk increases anti-oxidant biomarkers, to reduce oxidative stress in children with autism. Improvements in behaviour of children with autism, as assessed through Childhood Autism Rating Scale (CARS) was thought to be due to the consumption of camel milk which increases anti-oxidant markers to counteract oxidative stress (Al-Ayadhi *et al*. 2015) [6].

The unique composition of camel milk has been postulated to benefit autism symptoms; as it contains lower levels of fat, cholesterol and lactose compared to cow milk. In addition, camel milk contains higher minerals contents (calcium, iron, magnesium, copper, zinc, and potassium) and vitamins A, B_2, C and E compared to cow milk. The absence of β-lactoglobulin and β-*casein* which are the main causative allergens in cow milk makes it suitable for children. Camel milk also comprises various protective proteins, predominantly antibacterial, antiviral and immunological enzymes such as immunoglobulins, lysozymes, lactoferrin, lactoperoxidase, N-acetyl-§-glucosaminidase (NAGase), and peptidoglycan recognition protein (PGRP). These enzymes are vital in preventing food allergy and additionally, enhance the immune system (Al-Ayadhi and Elamin, 2013) [4].

Severe dietary or gastrointestinal (GI) problems are commonly reported in autistic individuals including abdominal pain, constipation, bloating and diarrhoea (Parracho *et al*. 2005) [93]. Gluten-free and/or casein-free (GF/CF) diets have been related with reduced GI illnesses and enhanced the conduct of individuals *with* ASD (Knivsberg *et al*. 2002) [63]. As camel milk is free from gluten and casein, the improvement in symptoms in ASD individuals may be due to absence of these two common allergens as well as the additional bioactive compounds. As mentioned earlier, results from faecal flora assessments have reported a significant difference in the composition of human gut microflora of individuals with ASD compared to the healthy population, primarily in *Clostridium* bacterial population. It remains to be elucidated if camel milk influences gut microbiota to improve autism behaviour. Therefore, future studies may involve investigating the gut microflora in ASD children prior to and after camel milk consumption. Profiling, characterizing and isolating effective camel milk compound which enhances growth of beneficial gut bacteria makes it an attractive therapeutic avenue to explore for ASD treatment. The gut-brain axis uses neural, hormonal and immunological routes to provide bidirectional homeostatic communication routes. Impairment of this axis

may result in pathophysiological consequences (Mayer *et al*. 2014). Therefore, understanding the communication pathways between gut microbiota and gut-brain axis will pave the way towards development of microbiota-based therapeutic strategies for disorders of the central nervous system.

Various independent groups have reported the involvement of altered immune system in individuals with autism whereby immune dysfunction is associated with impaired behavioural outcomes (Ashwood *et al*. 2011; Bashir and Al-Ayadhi 2014) [11, 19]. A recent study has shown that consuming 500 ml of raw and boiled camel milk per day *decreases* thymus and activation-regulated chemokine (TARC) serum levels and CARS score in individuals with autism compared to placebo group (consumption of cow milk) (Bashir and Al-Ayadhi 2014) [19]. However, this finding awaits validation due to the small sample size of the study. Taken together, the data suggests that camel milk contains bioactive constituents with anti-oxidant and anti-inflammatory properties to improve behavioural symptoms in individuals with ASD.

5.5 Other brain related disorders

Cerebral hypoxia-ischemia (HI) is a type of brain injury frequently reported in premature infants that subsequently experience neurodevelopmental disabilities. Human milk contains lactoferrin, which has antioxidant, anti-inflammatory and antimicrobial properties. Supplementation of lactoferrin in maternal food during lactation has shown to elicit neuroprotective effect and is a subject of intense research for neuroprotection in the pre-term brain (van de Looij *et al*. 2014) [72]. As chronic immune activation of the microglia (resident macrophages of the central nervous system) is commonly observed in neurodegeneration including AD, diets rich in anti-inflammatory and anti-oxidants may be beneficial in preventing neurodegenerative disease (Amor *et al*. 2010) [8]. Since human milk contains lactoferrin which has anti-inflammatory roles, it remains to be investigated if breastfeeding decreases risk of neurodegenerative diseases (chronic immune activation) in offspring of breastfeeding mothers in later life. The association between duration of breastfeeding and risk of neurodegenerative diseases may also open up potential novel research avenues.

5.6 Child growth

Milk contains fat-soluble vitamins such as Vitamins A, D and E, and the amount of these vitamins are lower in low fat and skimmed milk (Pereira 2014b) [95]. Vitamin A is crucial for growth, development, immunity, and eye health. A retrospective study in African-American adolescents showed that high maternal intake of dairy products significantly increased femur length of foetus (Chang *et al*. 2003) [30]. A later study also reported an association between high maternal milk and protein intake with increased head circumference, biparietal diameter and abdomen circumference, in addition to increased femur length in the child. This is thought to be due to macronutrients, micronutrients and minerals enriched in milk (Borazjani *et al*. 2013) [26]. Milk comprises all essential nutrients required for the development and growth of the newborn. Human colostrum, which is milk produced up to eight days post-partum, or milk produced at the beginning of casein production during the third day of lactation is an essential source of hormones, nutrition and antibodies during the first days of lactation (Casado *et al*. 2009) [29]. Milk is also a good source of Vitamin D, which is important for calcium absorption and bone mass formation and therefore prevention of osteoporosis (reviewed in Pereira, 2014) [94]. The key components of cow, camel and breast milk and their functions in modulating neurological disorders were summarised in Table 5.

Table 5: The key components of cow, camel and breast milk and their functions in modulating neurological disorders.

Sources of milk	Component	Function
Cow	Oleamide (fermented product of oleic acid, a milk fatty acid) Vitamin D and casein Vitamins A, D and E	Enhances microglial phagocytosis and reduces Aβ-induced microglial inflammation in a mouse model of Alzheimer's Disease (AD)(Ano *et al*. 2015) [9] Reduce oxidative stress in the nervous system(Singh *et al*. 2004) [105] General growth, development, immunity and eye health(Chang *et al*. 2003 [30]; Borazjani *et al*. 2013 [26]; Pereira 2014b) [95]
Camel	Unknown (gluten and casein-free)	Reduced GI illnesses(Knivsberg *et al*. 2002 [63]; Parracho *et al*. 2005) [93]; anti-oxidant and anti-inflammatory properties to improve behavioural symptoms in individuals with ASD (Knivsberg *et al*. 2002 [63]; Al-Ayadhi and Elamin 2013a [5]; Al-Ayadhi *et al*. 2015) [6]
Breast	Omega-3 fatty acid docosahexaenoic acid (DHA) Lactoferrin	Studies have linked lower DHA content with weaker cognitive development, as well as visual function (Calder 2016) [28]; in AD, there is a decrease in basal plasma levels of DHA; therefore restoring levels of DHA may be required to correct disease-associated synaptic membrane or synaptic conditions (Wurtman 2014) [123] Neuroprotective effect through its antioxidant, anti-inflammatory and antimicrobial properties(van de Looij *et al*. 2014) [72]

6. Cardiovascular disorder

6.1 Effect of milk on cardiovascular disorder

Cardiovascular diseases (CVD) are conditions that involve narrowed or blocked blood vessels, and include diseases such as coronary heart disease (CHD) and ischaemic stroke. CVD is currently the highest cause of mortality in the world, as reported by WHO (2011) [13]. The risk factors for CVD have been well-studied and identified, and include both inherent factors, such as age and genetics, as well as external environmental factors (Balakumar *et al*. 2016) [25]. The authors identified control of diet as the safest strategy to prevent development of CVD. In particular, the consumption of large amounts of trans fats is one of the biggest dietary risk factors for the development and progression of CVD. Additionally, replacing saturated fats with polyunsaturated fats in the di*et al*so reduces CVD risk ((de Souza *et al*. 2015) [108]. Whole milk contains large amounts of saturated fats and so, dietary advice for CVD, advise reducing the consumption of high fat

dairy products and instead use low-fat alternatives. However, the evidence for the reasoning behind this is conflicted, and will be discussed below.

One of the original studies investigating the link between CVDs and milk intake was the Honolulu Heart Program, where over 8000 men of Japanese ancestry were followed up for 22 years to study the relationship between milk intake, calcium intake and risk of stroke (Abbott *et al*. 1996) [1]. The study found that risk of stroke decreased as the men increased their milk intake, where men who were non-drinkers of milk had twice the risk of stroke compared to men who did. It was hypothesized that high levels of calcium in milk was responsible for the decrease; however, the study found that calcium intake from non-dairy sources did not affect risk of stroke. Additionally, some limited evidence suggests that calcium, albeit non-dairy calcium, may in fact lead to higher incidences of myocardial infarction (van der Velde *et al*. 2014) [120]. The study did not differentiate between drinkers of whole-fat and reduced fat milk. Various studies have connected increased intake of milk and milk products with lowered blood pressure and this is thought to be attributable to the minerals present in milk as well as peptides which arise from digestion of milk proteins (Groziak and Miller 2000) [50].

A population-based cohort study report also revealed that lesser risk of coronary heart disease and stroke with high intakes of either high or low milk consumption, however the fermented milk even prevent or reduced the risk factors (Dalmeijer *et al*. 2013) [37]. A cross-sectional observational study carried out by Luigi Barrea *et al*. (Barrea *et al*. 2015) [18] on moderate-severe obesity subjects showed that after collection of seven day milk consumption record, the anthropometric measurements and lipid profile were better compare with that of no milk consumers (Barrea *et al*. 2015) [18]. Subjects who consume skim milk also have higher peak growth hormone response and insulin-like growth factor IGF) than non-milk consuming subjects.

This topic had been comprehensively analysed by Ian Givens in 2015, with the same conclusion. He found that the majority of prospective studies and meta-analyses looking at the link between milk intake and CVD also showed an inverse association between milk intake and total CVD risk; however, a handful of studies also showed no association between milk intake and occurrence of CVD (Givens 2015) [46]. One question that arises is whether drinking a reasonable amount of milk every day can be beneficial in terms of CVD risk. There are contradictory reports of associations of mortality rates such as fractures, ischemic heart disease and certain cancers with high milk consumption (Segall 1980; Song *et al*. 2013a) [103, 106]. This difference may be due to the D-galactose content in different types of dairy products, which is related with oxidative stress, chronic inflammation and the progress of these diseases (Cui *et al*. 2006; Jumbo-Lucioni *et al*. 2013) [36, 62]. The possible mechanisms as to how milk is able to attenuate CVD risk, with respect to blood pressure and concentration of blood lipids will be discussed below. Another interesting report from Korean researchers found less cardiovascular risk in males over 60 years old by consuming milk regularly compare to fermented dairy products (Joo *et al*. 2016) [60]

6.2 Effect of milk on Blood pressure

High blood pressure or hypertension, defined as blood pressures higher than 120/80 mmHg, is one of the most important risk factors for CHD and ischaemic stroke (Gorelick *et al*. 1999; Chobanian *et al*. 2003; Meschia *et al*. 2014) [32, 49, 83]. Evidence from epidemiological studies suggests that an increase in milk consumption may reduce blood pressure in hypertensive individuals. One of the main lines of evidence for this comes from the Dietary Approaches to Stop Hypertension (DASH) study (Appel *et al*. 1997) [10]. Participants were randomly assigned to a control diet rich in fruits and vegetables or to a combination diet rich in fruits, vegetables and low-fat dairy products for eight weeks. Results of the study show that participants in the combination diet had greater decreases in blood pressure. The DASH study indicates that the intake of low-fat dairy products can improve high blood pressure in hypertensive patients, admittedly in the short term. In addressing the question of what constituents in milk is able to alleviate high blood pressure; scientists have considered the different nutrients found in milk. Many *in vitro* studies reported that the lactic acid bacteria produce angiotensin converting enzyme (ACI) like antihypertensive peptides in the presence of proteolysis by endogenous milk enzymes. These bacterial enzymes are responsible in breaking down the milk protein into oligopeptides either through a fermentation process or in the gastrointestinal gut. This suggests that milk may be useful for treating hypertension (Hernández-Ledesma *et al*. 2011; Udenigwe and Mohan 2014; Beltrán-Barrientos *et al*. 2016) [20, 53].

Calcium is again proposed as being beneficial in the regulation of blood pressure, despite conflicts in scientific evidence. Toxqui *et al*. (2013) [113] argue that calcium contained in milk did not exert a significant effect on blood pressure in their small, short-term cohort study. However, the authors may have underestimated the role of Vitamin D in calcium absorption in their study, as their test group had additional Vitamin D supplementation which may affect the rate of calcium absorption (Stokes and Lammert 2016) [110]. On the other hand, Alonso *et al*. (2005) [7] carried out a prospective study of almost 29,000 middle-aged US women and showed that intake of low-fat milk and yogurt decreases risk of hypertension, where adjusting for dietary calcium attenuated the association. The authors claim that this confirms calcium's role in the regulation of blood pressure. However, the risk of hypertension was not changed with calcium supplements which echoes the results from the Honolulu Heart Study and the Women's Health Initiative Randomized Trial (Abbott *et al*. 1996; Margolis *et al*. 2008) [1]. These conflicting findings call into question as to whether dietary calcium truly plays a role in the regulation of blood pressure.

The presence of other minerals in milk has been suggested to be advantageous in the regulation of blood pressure. Studies involving potassium supplementation have indicated that this mineral has the highest effect on blood pressure (Massey 2001; Nguyen *et al*. 2013) [78, 86]. However, a possible explanation for the lack of effect of calcium supplementation compared to dairy-sourced calcium on blood pressure is that calcium may be working in tandem with other nutrients in

milk to exert its effects on blood pressure, giving rise to the conflicts in results obtained. Therefore, it is not clear whether the conclusion that potassium regulates blood pressure also applies to dairy-sourced potassium.

An alternative explanation for the benefits of milk in the regulation of blood pressure is the presence of milk-specific proteins. About 3% of whole milk is made up of proteins ([CSL STYLE ERROR: reference with no printed form.]). A recent meta-analysis carried out by Hidayat *et al*. (2016) [55] report that supplementation of milk-derived proteins has a small, but significant effect in the lowering of blood pressure. The finding that bioactive milk peptides may also have a role in the lowering or preventing high blood pressure supports the conclusions of Hidayat *et al* (Jauhiainen and Korpela 2007; Bhat *et al*. 2015) [24, 57]. It remains to be seen whether these findings can be generalized to the intake of these proteins and peptides not through supplementation, but through the intake of milk.

6.3 Effect of milk on Blood Lipid Concentration

Although it has been touted as a healthy foodstuff in the past, whole milk is at least 3% fatty acids, of which more than half is saturated fats ([CSL STYLE ERROR: reference with no printed form.]). Some evidence shows that high intake of saturated fats leads to higher serum cholesterol levels, which is another key risk factor for CVD (Gorelick *et al*. 1999; Meschia *et al*. 2014; Zhang *et al*. 2016) [49, 83]. Therefore, a general perception is that whole milk leads to higher risk CVD and it is currently recommended to drink low-fat milk instead to reduce the risk (Appel *et al*. 1997) [10]. However, the work of Ulven *et al*. [2016] [117] questions whether all fats can be treated equally, particularly since milk contains almost 400 different types of fatty acids (O'Donnell *et al*. 2010) [87]. Indeed, the inverse association of intake of milk with the risk of CVD, regardless of fat content, suggests that a closer look at the effect of milk lipids on blood lipid levels needs to be taken.

One of the first clues that milk may potentially be able to regulate blood cholesterol levels came from a study conducted on a group of men in the Kenyan Maasai tribe in 1974 (Mann 1974) [75]. Ohlsson (2010) [89] attempted to compare the effects of different dairy products on serum cholesterol. He compared low fat milk with high fat dairy products such as butter and cheeses, and concluded that low fat milk will diminish the risk of CVD. However, the question whether drinking whole milk will increase or decrease blood lipid concentrations have not been addressed. A few studies have attempted to study the association between intake of whole milk and blood lipid concentrations with respect to CVD risk (Hepner *et al*. 1979; Rossouw *et al*. 1981; Thompson *et al*. 1982) [102, 112]. The general consensus was that drinking milk did not lead to significant changes in blood cholesterol levels, as would be expected based on the saturated fat content. The studies available, however, are old and lacked detailed information about their respective studies.

Two studies have been published so far, which compare the effects of whole milk versus skim milk on serum cholesterol concentrations. Steinmetz *et al*. [1994] [109] carried out a 6-week crossover feeding study and reported that while total and LDL-cholesterol were lower on the skim milk diet compared to the whole milk diet, there were no differences in HDL-cholesterol levels. The authors claim that the reduction in total cholesterol supports the conclusion that skim milk is more beneficial than whole milk in attenuating CVD risk. However, they appear to have failed to take into account the fact that higher plasma HDL cholesterol levels are associated with lower CVD risk (Rader and Hovingh 2014) [101]. Additionally, a limitation of their study was that it was short-term and only involved 8 participants. Nestel *et al*. [2013] [85] also concluded that a low-fat dairy diet would lead to lower concentrations of both HDL and LDL cholesterol. However, as with Ohlsson [2010] [89], the study also compared low fat milk with high fat dairy products such as butter and cream. Whole milk is suggested to have a plethora of beneficial effects on human health (Astrup *et al*. 2016) [12], and therefore, more research is required to understand the effects of drinking whole milk on blood lipid profiles and CVD risk.

7. Effect of milk on cancer

The high calcium content in dairy products has been postulated to be responsible for the protective effect against cancer. Calcium binds proinflammatory secondary bile acids and ionised fatty acids and may reduce cell proliferation and promote cell differentiation (Lamprecht and Lipkin 2001) [66]. The recent study indicates that milk activates the nutrient-sensitive kinase, mechanistic target of rapamycin complex 1 (mTORC1). M TORC1 is the master regulator of protein and lipid synthesis that couples nutrient sensing to cell proliferation and cancer. Milk contains four important metabolic messengers, namely branched-chain amino acids (BCAAs), glutamine, palmitic acid and bioactive exosomal microRNAs which enhance mTORC1-dependent translation. Constitutive activation of mTORC1 is implicated with ageing and ageing-related disorders including obesity, type 2 diabetes mellitus, cancer and neurodegenerative diseases (Melnik 2015) [81].

Epidemiological data has shown that higher dairy protein intake is a main dietary risk factor for prostate cancer. As mentioned earlier, cow milk upregulates mTORC1 signalling to promote cell growth and proliferation. Regular intake of cow milk proteins provides highly branched-chain amino acids (BCAAs) due to fast hydrolysation of whey proteins, which increases plasma insulin levels post-prandially, and elevate hepatic insulin growth factor 1 (IGF-1) plasma concentrations through casein-derived amino acids. Constitutive activation of mTORC1 by BCAAs, insulin and IGF-1 coupled with oestrogens from milk of pregnant cow may explain the association between higher intake of dairy leads to higher risk of prostate cancer in the West (Melnik *et al*. 2012) [82]. A recent *in vitro* study has also shown that the milk protein, casein, promotes growth of prostate cancer cells such as PC3 and LNCaP (Park *et al*. 2014) [92]. Although milk triggers mTORC1 activity which enhances cellular growth, constitutive mTORC1 activation has been reported in various cancers and therefore a balanced diet comprising moderate milk intake may be the solution to optimal health.

The consumption of milk intake varies geographically, where consumption level is closely correlated to the distribution of lactase persistence (LP), which is a genetic trait that allows milk consumption beyond the weaning period without

unpleasant gastrointestinal side (Prentice 2014) [99]. The persistence of lactase activity in European population suggests that there is a strong selection for lactase persistence (LP) gene (Bersaglieri *et al*. 2004) [23]. Whether positive selection for the lactase persistence gene (Bersaglieri *et al*. 2004) [23] confers any evolutionary/survival advantages remains to be explored.

7.1 Colorectal Cancer

A meta-analysis by Aune *et al* (2012) [14] reported that there is an inverse association between milk consumption and colorectal cancer, with a relative risk of 0.91 with 95% confidence interval of 0.85 to 0.94 per 200g/day of milk intake. Total dairy products were also observed to have a negative association with colorectal cancer as consumption of 400g/day of total dairy products resulted in 0.83 relative risks with 95% confidence interval of 0.78 to 0.88. However, consumption of 50g/day of cheese did not show any significant negative association with colorectal cancer, giving a relative risk of 0.91 with 95% confidence interval of 0.83 to 1.12. This analysis included 19 cohort prospective studies from Pub MED database from 1997 to 2010. In short, there are nonlinear associations between milk and total dairy products and colorectal cancer risk ($P < 0.001$) with the inverse associations strongest at the higher range of intake (Aune *et al*. 2012) [14]. It is noted that the comparison of consumption between total dairy products, milk and cheese were 400g/day, 200g/day and 50g/day, respectively. The difference in quantity measured may result in different levels of calcium as well as fat contents that include conjugated linoleic acids, sphingomyelin, butyric acids and ether lipids (Molkentin 2000; Larsson *et al*. 2006) [68, 84]. However, despite the lack of evidence of negative association between cheese consumption and colorectal cancer, Larsson *et al* (2005) [67] reported that high consumption of cheese was associated with the lowest risk for colorectal cancer (Larsson *et al*. 2005) [67].

7.2 Ovarian cancer

Qin *et al* (2016) [100] assessed the associations between dairy products, lactose, calcium and vitamin D, and the risk of ovarian cancer in African-American women. African-American women have been known to suffer high mortality rate from ovarian cancer and are high risk for calcium and vitamin D deficiency. The study of 490 ovarian cancer cases and 656 age- and site-matched controls of African-American descent yielded in odds ratio of 1.97 (95% CI: 1.25 to 3.10) for the association of lactose and ovarian cancer, 0.51 (95% CI: 0.30 to 0.86) for the association between calcium intake and ovarian cancer and 0.71 (95% CI: 0.51 to 0.99) for the association between longer sun exposure and ovarian cancer. The study therefore suggests a high-calcium and low-lactose diet with increase vitamin D from sun exposure to lower the risk of ovarian cancer in these African-American ladies (Qin *et al*. 2016) [100].

7.3 Prostate cancer

In 2007, World Cancer Research Fund International reported a positive association between prostate cancer and milk consumption. However, as more evidence shed light on the matter, the 2014 World Cancer Research Fund International reported that there is currently limited evidence associating consumption of dairy products or calcium with prostate cancer (World Cancer Research Fund International: Continuous Update Project Report 2014). Systematic review and meta-analysis of thirty-two cohort studies by Aune *et al* (2014) reported a positive association between prostate cancer and high consumption of dairy products, milk, low-fat milk, cheese, total and dietary and dairy calcium (Aune *et al*. 2015) [15]. Epidemiological study involving a 28 years follow up cohort study in the Physicians' Health Study of 21,1660 subjects by Song *et al* (2013) [106] to investigate the association between intake of dairy products and the incidence and survival of prostate cancer concluded that skim/low-fat milk contributes to the risk of low-grade, early stage, and screen-detected cancers. Conversely, fatal prostate cancer was only associated with whole milk intake. Evidence from survival analysis of 2,806 incident cases of prostate cancers within the 21,1660 subjects and 305 deaths were during the 28 years follow up period yielded a high risk of 2.17 with 95% CI: 1.34 to 3.51 between whole milk intake and progression to fatal disease after diagnosis (Song *et al*. 2013b) [106]. From this study, as only whole milk was associated with progression to aggressive and higher prostate cancer specific mortality cases, whereas skim/low-fat milk only contributes to higher risk of nonaggressive prostate cancer, the fat contents in the whole milk are most likely the culprits that aid the progression and aggressiveness of prostate cancer.

The controversial results from epidemiological studies led Bernichtein *et al* (2015) [22] to study prostate tumour progression in mouse models. Both benign (probasin-Prl mice, Pb-Prl) and neoplastic lesion mice (KIMAP mice) were studied. Skimmed and whole milk were administered to the mice for duration of 15 to 27 weeks, after which the prostate tumour progressions in these mice were assessed via tissue histopathology examination, stromal inflammation, epithelial proliferation and fibrosis, tumor invasiveness potency. The results from these mouse models negate any association between milk consumption and prostate cancer. It was suggested that certain milk type may confer protective effect as there were reduction in the expression of tumour markers in the tumours (Bernichtein *et al*. 2015) [22].

7.4 Breast cancer

Kojima *et al* (2017) studied the consumption of three food types (plant-based, animal-based and dairy-based) and their associations to breast cancer in 23,172 women in Japan. This study did not show any significant association between dairy product diet and breast cancer risk (Kojima *et al*. 2017). However, a study of 97 breast cancer patients and 104 control individuals showed that high consumption of cow's milk increased breast cancer risk (Galván-Salazar *et al*. 2015) [45]. The controversial issues in both breast cancer and prostate cancer are from epidemiological studies that cannot rule out confounding factors such as source of milk, consumption of meat, ethnic, cultural, and economic differences. The consumption of cow's milk and its effects of breast, colorectal, ovarian and prostate cancers were depicted in figure 1.

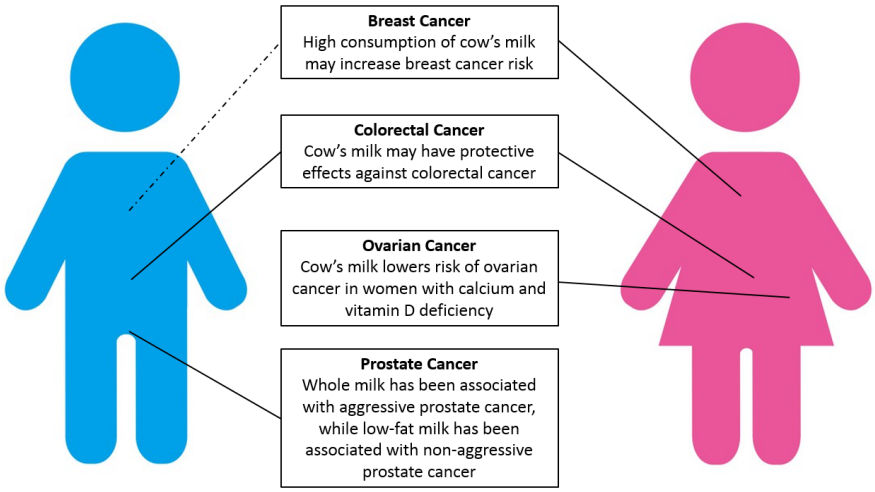

Fig 1: Association of consumption of cow's milk with breast, colorectal, ovarian and prostate cancers.

8. Miscellaneous

8.2 Effect of milk on infectious disease

The trend towards "natural" products has seen an increasing preference for raw milk consumption as it is perceived that heating may destroy health benefits of raw milk. However, raw cow milk is may carry various human pathogens. Foodborne infections in raw cow milk have been reported that the contamination with *Campylobacter*, *Salmonella spp*., verocytotoxin-producing *Escherichia coli*. These accounts for 2 to 6% of bacterial foodborne outbreaks in modern industrialized nations. It has thus been shown that raw milk consumption may pose health threats due to invasion by human pathogens. Consumption of ultra-high temperature treated milk (or similar treatments) is recommended as they do not alter the nutritional value of raw milk or other benefits associated with consuming raw milk (Claeys *et al*. 2013) [34].

Human milk is enriched in nutrients and components which are highly protective against a broad range of infective pathogens. Besides protective immunoglobulins, human milk also comprises free oligosaccharides, glycoproteins and glycolipids. Interestingly, the sugar epitopes present in human milk mimics the structure of glycan receptors that serve as pathogen adhesion sites in epithelial surfaces, including the human gastrointestinal (GI) tract. This therefore allows milk glycans to competitively adhere to disease-causing microorganisms before an infection can be triggered (Peterson *et al*. 2013) [97]. Lactoferrin (LF) is a milk protein which competently binds to receptors on the host cell's surface, and can also bind to both enveloped and non-enveloped viral particles to prevent viral infections (Pan *et al*. 2006) [91].

There is accumulating evidence on the role of glycoconjugates in disease prevention. Glycoproteins from human milk exhibit anti-pathogenic effects, and this is partly attributable to their glycan moieties such as secretory immunoglobulin a (sIgA), κ-casein, lactoferrin and proteins from the milk fat globular membrane (MFGM) such as lactadherin, mucins and bile salt-stimulated lipase (BSSL). For instance, some glycoconjugates such as secretory immunoglobulin A (sIgA) and lactoferrin exert anti-bacterial properties (Peterson *et al*. 2013) [97]. In addition, a systematic review involving 12 studies has revealed the importance of human milk cytokines like transforming growth factor-beta (TGF-beta) as they exert positive immunological outcomes in infants and young children (Oddy and Rosales 2010) [88].

It has been postulated that differences in levels of protection in human and bovine milk is attributable to the variation in concentration of glycoconjugates in human and bovine milk, as well as the types of attached glycans that can serve as sites for pathogen adhesion. In addition, bovine milk glycoconjugates may have progressed specifically to offer young calf protection against bovine pathogens, rather than protection against human pathogens in human infants. The impact of glycosylation changes in milk glycoconjugates throughout the lactation period on the protection against pathogen adhesion in breastfed infant remains unexplored (Peterson *et al*. 2013) [97].

Necrotozing enterocolitis is a disease common to premature infants that results in inflammation and death of intestinal tissues. In premature infants, human milk diet is associated with a significantly lower rate of necrotizing enterocolitis as well as enterocolitis requiring surgical intervention compared to a diet incorporating both human and bovine milk based products (Sullivan *et al*. 2010) [111]. This again may be reflected by the varying composition of nutrients present in human milk and bovine milk as well as differences in underlying genetic factors. Periodontal disease leads to damage the connective tissue which anchors teeth to alveolar bone, as a result of bacterial infection. A cross-sectional study has shown that intake of dairy calcium and fermented foods were considerably associated with lower risk of periodontitis. These findings propose that that calcium, mainly from milk and fermented products, may be protective against periodontitis (Adegboye *et al*. 2012) [2].

8.3 Milk and microbial drug resistance

Generally human milk is more useful for infant health and especially development muscles and protective against intestinal microbiota is due to glycans. It may show pleiotropic functions, that protection against infectious diseases and also acting as prebiotics (Pacheco *et al*. 2015) [90]. Another reason is that plenitude of xanthine oxidase (XO) in milk is responsible for antimicrobial properties. The XO is

positioned on the external surface of the milk fat globule, and pathogenic bacteria may bind to similar antigens on the milk fat globule membrane. Therefore, the higher concentrations of nitric oxide and peroxynitrite produced with near to the bacterial cell wall which leads to potentially very harmful.(Hancock *et al*. 2002) [51]. The recent research reported that antibiotic susceptibility of *Staphylococcus aureus* isolated from bulk and pasteurised milk were obtained randomly from supermarkets of the North-West Province, South Africa. They isolated *S. aureus* from contaminated milk samples and around 60 -100% of the isolates strains were resistant to wide variety of β- lactum antiobiotics and macrolides (Akindolire *et al*. 2015). This alarmed result of these bulk and pasteurised milk is contaminated with toxigenic and multi-drug resistant *S. aureus* strains. This kind of study needs to be conducted anywhere in the world if any microbial resistance problem occurs while consuming milk.

8.4 Effect of milk on allergy

Milk ingestion may result in two main adverse reactions-lactose intolerance and cow milk allergy. Lactose intolerance may be prevented by avoiding milk and/or consuming other dairy products with lower lactose content, such as yoghurt and cheese. Individuals with cow milk protein allergy may completely avoid cow milk products (Pereira 2014b) [95] or switch to other sources of animal milk, such as camel milk, which lacks beta-lactoglobulin and beta casein-the two main allergens in cow milk (Al-Ayadhi and Elamin 2013) [4]. Cow milk allergy is the most common food allergy observed in children with a prevalence varying from 2% to 7.5% (Turck 2013) [115]. The allergy arises due to an immunological adverse reaction towards cow milk protein which can occur during the neonatal period or during the first few years of life, and is rare in adults (Fiocchi *et al*. 2010) [41].

The main carbohydrate present in milk is lactose, which exists in two isomers-alpha (α) and beta (β) forms. Lactose is hydrolysed by β –galactosidase, which has a preference for beta-lactose. The enzymatic activity of β –galactosidase decreases in mammals from weaning, although the rate of enzymatic activity decline varies in humans. Classical lactose intolerance symptoms include abdominal cramps and bloating, flatulence, diarrhoea, nausea and vomiting due to lactose and sugar fermentation in the colon. In addition, β –galactosidase deficiency may also result in severe metabolic impairments (Pereira 2014b) [95]. A continuous ingestion of elevated doses of lactose may result in its conversion to galactitol which may result in blindness (when conversion occurs in lens tissue), or fatality (when conversion occurs in neural tissue) (Pereira 2014b) [95].

9. Conclusions

The non-thermal milk processing clearly having more advantageous in terms of increased shelf life and economically viable for long distance transportation. Milk and its products especially camel milk significantly increased anti-oxidant biomarkers in autistic children and therefore it reduces oxidative stress in children with autism, to improve autistic behaviour. The fermented dairy products, such as camembert cheese generates anti-inflammatory compounds which may exert therapeutic benefits in Alzheimer disease. All in all, most literature findings suggest protective benefits of dairy consumption with regards to weight control, stroke, coronary disease, hypertension, and most cancers. As there is an enormous diversity in global milk consumption, future studies may include investigating the association between geographic differences in levels of milk consumption and/or dairy consumption with diseases. Utilizing mass spectrometry to conduct proteomics, glycomics, glycoproteomics, and lipidomics analysis to profile and characterize bioactive compounds in milk from various animal sources and human milk, and understanding their mechanism of action may aid development of potential novel biomarkers (proteins/peptides, oligosaccharides and lipids) for disease prevention and treatment.

10. Acknowledgements

The invaluable sharing of knowledge from different field of experts in the BIND Team, Institute of Health Science, Universiti Brunei Darussalam and their support in developing this review paper is gratefully acknowledged.

Conflicts of Interest: The author declares no conflict of interest.

Author Contributions: SHFL described neurological effects on milk, INZ and SRD described cardiovascular effects, SRA described effect of milk on children growth, FJ described milk compositions, YCL described effects of milk on cancer and RR described novel processing milk products as well as corresponding author and SRD compiled all the review and edited whole article.

Funding: There is no funding for this article.

11. References

1. Abbott RD, Curb JD, Rodriguez BL, Sharp DS, Burchfiel CM, Yano K. Effect of dietary calcium and milk consumption on risk of thromboembolic stroke in older middle-aged men. The Honolulu Heart Program. Stroke; a journal of cerebral circulation. 1996; 27(5):813-8.
2. Adegboye ARA, Christensen LB, Holm-Pedersen P, Avlund K, Boucher BJ, Heitmann BL. Intake of dairy products in relation to periodontitis in older danish adults. Nutrients, 2012.
3. Akindolire MA, Babalola OO, Ateba CN. Detection of antibiotic resistant Staphylococcus aureus from milk: A public health implication. International Journal of Environmental Research and Public Health. 2015; 12(9):10254-75.
4. Al-Ayadhi LY, Elamin NE. Camel milk as a potential therapy as an antioxidant in autism spectrum disorder (ASD). Evidence-based Complementary and Alternative Medicine. 2013a, 2013.
5. Al-Ayadhi LY, Elamin NE. Camel milk as a potential therapy as an antioxidant in Autism Spectrum Disorder (ASD). Evidence-based complementary and alternative medicine : eCAM. 2013b; 2013:602834.
6. Al-Ayadhi LY, Halepoto DM, AL-Dress AM, Mitwali Y,

Zainah R. Behavioral benefits of camel milk in subjects with autism spectrum disorder. Journal of the College of Physicians and Surgeons Pakistan. 2015; 25(11):819–23.
7. Alonso A, Beunza JJ, Delgado-Rodríguez M, Martínez JA, Martínez-González MA. Low-fat dairy consumption and reduced risk of hypertension: the Seguimiento Universidad de Navarra (SUN) cohort. The American journal of clinical nutrition. 2005; 82(5):97-29.
8. Amor S, Puentes F, Baker D, Van Der Valk P. Inflammation in neurodegenerative diseases. Vol. 129, Immunology, 2010,1 54-69.
9. Ano Y, Ozawa M, Kutsukake T, Sugiyama S, Uchida K, Yoshida A, *et al*. Preventive effects of a fermented dairy product against Alzheimer's disease and identification of a novel oleamide with enhanced microglial phagocytosis and anti-inflammatory activity. PloS one. 2015; 10(3):e0118512.
10. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, *et al*. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. The New England journal of medicine. 1997; 336(16):1117–24.
11. Ashwood P, Krakowiak P, Hertz-Picciotto I, Hansen R, Pessah IN, Van de Water J. Altered T cell responses in children with autism. Brain, Behavior, and Immunity. 2011; 25(5):840-9.
12. Astrup A, Rice Bradley B, Brenna J, Delplanque B, Ferry M, Torres-Gonzalez M. Regular-Fat Dairy and Human Health: A Synopsis of Symposia Presented in Europe and North America (2014–2015). Nutrients. 2016; 8(8):463.
13. Augustin MA, Puvanenthiran A, Clarke PT, Sanguansri P. Energy use for alternative full-cream milk powder manufacturing processes. Journal of Food Engineering. 2014; 124:191-6.
14. Aune D, Lau R, Chan DSM, Vieira R, Greenwood DC, Kampman E, *et al*. Dairy products and colorectal cancer risk: A systematic review and meta-analysis of cohort studies. Annals of Oncology. 2012; 23(1):37-45.
15. Aune D, Rosenblatt DAN, Chan DSM, Vieira AR, Vieira R, Greenwood DC, *et al*. Dairy products, calcium, and prostate cancer risk : a systematic review and meta-analysis of cohort studies 1 – 4. American Journal of Clinical Nutrition. 2015; 101(1):87-117.
16. Balakumar P, Maung UK, Jagadeesh G. Prevalence and prevention of cardiovascular disease and diabetes mellitus. Pharmacological research. Elsevier Ltd. 2016; 113:600-9.
17. Baron-Cohen S, Auyeung B, Nørgaard-Pedersen B, Hougaard D, Abdallah M, Melgaard L, *et al*. Elevated fetal steroidogenic activity in autism. Molecular Psychiatry. 2014; 20:369-76.
18. Barrea L, Di Somma C, Macchia PE, Falco A, Savanelli MC, Orio F, *et al*. Influence of nutrition on somatotropic axis: Milk consumption in adult individuals with moderate-severe obesity. Clinical Nutrition, 2015,1-9.
19. Bashir S, Al-Ayadhi LY. Effect of camel milk on thymus and activation-regulated chemokine in autistic children: double-blind study. International Paediatric Research. 2014; 75(4).
20. Beltrán-Barrientos LM, Hernández-Mendoza A, Torres-Llanez MJ, González-Córdova AF, Vallejo-Córdoba B. Invited review: Fermented milk as antihypertensive functional food. Journal of Dairy Science. Elsevier.. 2016; 99(6):1-12.
21. Bendicho S, Barbosa-Cánovas G V., Martín O. Milk processing by high intensity pulsed electric fields. Trends in Food Science & Technology. 2002; 13(6-7):195-204.
22. Bernichtein S, Pigat N, Capiod T, Boutillon F, Verkarre V, Camparo P, *et al*. High milk consumption does not affect prostate tumor progression in two mouse models of benign and neoplastic lesions. PLoS ONE. 2015; 10(5):1-20.
23. Bersaglieri T, Sabeti PC, Patterson N, Vanderploeg T, Schaffner SF, Drake JA, *et al*. Genetic signatures of strong recent positive selection at the lactase gene. American journal of human genetics. 2004; 74(6):1111-20.
24. Bhat ZF, Kumar S, Bhat HF. Bioactive peptides of animal origin: a review. Journal of Food Science and Technology. 2015; 52(9):5377-92.
25. Borad SG, Kumar A, Singh AK. Effect of processing on nutritive values of milk protein. Critical Reviews in Food Science and Nutrition. 2016; 8398:00-00.
26. Borazjani F, Angali KA, Kulkarni SS. Milk and protein intake by pregnant women affects growth of foetus. Journal of Health, Population and Nutrition. 2013; 31(4):435-45.
27. Bylund G. Chapter 2 The Chemistry of Milk. Dairy Processing Handbook. Tetra Pak International S.A.; 2015.
28. Calder PC. Docosahexaenoic Acid. Annals of Nutrition and Metabolism. 2016; 69(1):8-21.
29. Casado B, Affolter M, Kussmann M. OMICS-rooted studies of milk proteins, oligosaccharides and lipids. Vol. 73, Journal of Proteomics, 2009, 196-208.
30. Chang SC, O'Brien KO, Nathanson MS, Caulfield LE, Mancini J, Witter FR. Fetal femur length is influenced by maternal dairy intake in pregnant African American adolescents. American Journal of Clinical Nutrition. 2003; 77(5):1248-54.
31. Chicón R, Belloque J, Alonso E, López-Fandiño R. Immunoreactivity and digestibility of high-pressure-treated whey proteins. International Dairy Journal. 2008; 18(4):367-76.
32. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, *et al*. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension (Dallas, Tex : 1979). 2003; 42(6):1206-52.
33. Chopde SS, Deshmukh MA, Kalyankar SD, Changade SP. Applications of high pressure technology for milk processing. Research Journal of Animal Husbandry and Dairy Science. 2014; 5(2):143-7.
34. Claeys WL, Cardoen S, Daube G, De Block J, Dewettinck K, Dierick K, *et al*. Raw or heated cow milk consumption: Review of risks and benefits. Food Control, 2013.
35. Claeys WL, Verraes C, Cardoen S, De Block J, Huyghebaert A, Raes K, *et al*. Consumption of raw or

heated milk from different species: An evaluation of the nutritional and potential health benefits. Vol. 42, Food Control, 2014, 188-201.
36. Cui X, Zuo P, Zhang Q, Li X, Hu Y, Long J, *et al*. Chronic systemic D-galactose exposure induces memory loss, neurodegeneration, and oxidative damage in mice: protective effects of R-alpha-lipoic acid. Journal of neuroscience research. 2006; 83(8):1584-90.
37. Dalmeijer GW, Struijk EA, van der Schouw YT, Soedamah-Muthu SS, Verschuren WMM, Boer JMA, *et al*. Dairy intake and coronary heart disease or stroke--a population-based cohort study. International journal of cardiology. Elsevier Ireland Ltd. 2013; 167(3):925-9.
38. FAO. Milk and dairy products in human nutrition. Milk and Dairy Products in Human nutrition, 2013.
39. Farrell HM, Jimenez-Flores R, Bleck GT, Brown EM, Butler JE, Creamer LK, *et al*. Nomenclature of the Proteins of Cows' Milk—Sixth Revision. Journal of Dairy Science. 2004; 87(6):1641-74.
40. Fernandez-Molina JJ, Fernandez-Gutierrez SA, Altunakar B, Bermudez-Aguirre D, Swanson BG. Barbosa-Canovas GV. The combined effect of pulsed electric fields and conventional heating on the microbial quality and shelf life of skim milk. Journal of Food Processing and Preservation. 2005; 29(5-6):390-406.
41. Fiocchi A, Schünemann HJ, Brozek J, Restani P, Beyer K, Troncone R, *et al*. Diagnosis and rationale for action against Cow's milk allergy (DRACMA): A summary report. Journal of Allergy and Clinical Immunology, 2010.
42. Fox M, Berzuini C, Knapp LA. Maternal breastfeeding history and alzheimer's disease risk. Journal of Alzheimer's Disease. 2013; 37(4):809-21.
43. Fox PF, Kelly AL. Chemistry and Biochemistry of Milk Constituents. Food Biochemistry and Food Processing: Second Edition, 2012, 442-64.
44. Gallier S, Acton D, Garg M, Singh H. Natural and processed milk and oil body emulsions: bioavailability, bioaccessibility and functionality. Food Structure, 2016.
45. Galván-Salazar HR, Arreola-Cruz A, Madrigal-Pérez D, Soriano-Hernández AD, Guzman-Esquivel J, Montes-Galindo DA. *et al*. Association of Milk and Meat Consumption with the Development of Breast Cancer in a Western Mexican Population. Breast Care. 2015; 10(6):393-6.
46. Givens DI. Dairy products: Good or bad for cardiometabolic disease? American Journal of Clinical Nutrition. 2015; 101(4):695-6.
47. Goehring KC, Kennedy AD, Prieto PA, Buck RH. Direct evidence for the presence of human milk oligosaccharides in the circulation of breastfed infants. PLoS One. 2014; 9(7):e101692.
48. Gomi A, Iino T, Nonaka C, Miyazaki K, Ishikawa F. Health benefits of fermented milk containing Bifidobacterium bifidum YIT 10347 on gastric symptoms in adults. Journal of dairy science. 2015; 98(4):2277-83.
49. Gorelick PB, Sacco RL, Smith DB, Alberts M, Mustone-alexander L, Rader D, *et al*. Prevention of a First Stroke. Journal of the American Medical Association. 1999; 281(12):1112-20.
50. Groziak SM, Miller GD. Natural bioactive substances in milk and colostrum: effects on the arterial blood pressure system. The British journal of nutrition. 2000; 84 Suppl 1:S119-25.
51. Hancock JT, Salisbury V, Ovejero-Boglione MC, Cherry R, Hoare C, Eisenthal R, *et al*. Antimicrobial Properties of Milk: Dependence on Presence of Xanthine Oxidase and Nitrite. Antimicrobial Agents and Chemotherapy. 2002; 46(10):3308-10.
52. Hepner G, Fried R, St Jeor S, Fusetti L, Morin R. Hypocholesterolemic effect of yogurt and milk. The American journal of clinical nutrition. 1979; 32(1):19-24.
53. Hernández-Ledesma B, del Mar Contreras M, Recio I. Antihypertensive peptides: production, bioavailability and incorporation into foods. Advances in colloid and interface science. 2011; 165(1):23-35.
54. Hernell O, Timby N, Domellöf M, Lönnerdal B. Clinical Benefits of Milk Fat Globule Membranes for Infants and Children. The Journal of Pediatrics. 2016; 173:S60-5.
55. Hidayat K, Du H-Z, Yang J, Chen G-C, Zhang Z, Li Z-N, *et al*. Effects of milk proteins on blood pressure: a meta-analysis of randomized control trials. Hypertension Research. Nature Publishing Grou, 2016, 1-7.
56. Hsieh CC, Hernández-Ledesma B, Fernández-Tomé S, Weinborn V, Barile D, De Moura Bell JMLN. Milk proteins, peptides, and oligosaccharides: Effects against the 21st century disorders, BioMed Research Internation, 2015.
57. Jauhiainen T, Korpela R. Milk Peptides and Blood Pressure. The Journal of nutrition. 2007; 137(12):825S-829S.
58. Jensen RG. Handbook of Milk Composition, edited by Robert G. Jensen. Academic Press, San Diego, 1995, 919 pp., 89.95. Journal of Food Composition and Analysis. 1996; 9(3):284.
59. Jiang W, Ju C, Jiang H, Zhang D. Dairy foods intake and risk of Parkinson's disease: a dose-response meta-analysis of prospective cohort studies. European journal of epidemiology. 2014; 29(9):613-9.
60. Joo NS, Yang SW, Park SJ, Choi SJ, Song BC, Yeum KJ. Milk Consumption and Framingham Risk Score: Analysis of the Korea National Health and Nutrition Examination Survey Data (2008-2011). Yonsei medical journal. 2016; 57(1):197-202.
61. Jost R. Milk and Dairy Products. Ullmann's Encyclopedia of Industrial Chemistry, 2000.
62. Jumbo-Lucioni PP, Hopson ML, Hang D, Liang Y, Jones DP, Fridovich-Keil JL. Oxidative stress contributes to outcome severity in a Drosophila melanogaster model of classic galactosemia. Disease models & mechanisms. 2013; 6(1):84-94.
63. Knivsberg M, Reichelt KL, Høien T, Nødland M. A randomised, controlled study of dietary intervention in autistic syndromes. Nutritional neuroscience. 2002; 5(4):251-61.
64. Kojima R, Okada E, Ukawa S, Mori M, Wakai K, Date C, *et al*. Dietary patterns and breast cancer risk in a prospective Japanese study. Breast Cancer, 2016.
65. Kumar D, Verma AK, Chatli MK, Singh R, Kumar P,

Mehta N, *et al*. Camel milk: alternative milk for human consumption and its health benefits. Nutrition and Food Science. 2016; 46(2):217-27.
66. Lamprecht SA, Lipkin M. Cellular mechanisms of calcium and vitamin D in the inhibition of colorectal carcinogenesis. Annals of the New York Academy of Sciences, 2001-952, 73-87.
67. Larsson SC, Bergkvist L, Rutegård J, Giovannucci E, Wolk A. Calcium and dairy food intakes are inversely associated with colorectal cancer risk in the Cohort of Swedish Men. American Journal of Clinical Nutrition. 2006; 83(3):667-73.
68. Larsson SC, Bergkvist L, Wolk A. High-fat dairy food and conjugated linoleic acid intakes in relation to colorectal cancer incidence in the Swedish Mammography Cohort. American Journal of Clinical Nutrition. 2005; 82(4):894-900.
69. Levy SE, Mandell DS, Schultz RT. Autism. The Lancet. 2009; 374(9701):1627-38.
70. Lindgren M, Aronsson K, Galt S, Ohlsson T. Simulation of the temperature increase in pulsed electric field (PEF) continuous flow treatment chambers. Innovative Food Science & Emerging Technologies. 2002; 3(3):233-45.
71. Lönnerdal B. Infant formula and infant nutrition: Bioactive proteins of human milk and implications for composition of infant formulas. American Journal of Clinical Nutrition. 2014; 99(3).
72. Van de Looij Y, Ginet V, Chatagner A, Toulotte A, Somm E, Huppi PS, *et al*. Lactoferrin during lactation protects the immature hypoxic-ischemic rat brain. Ann Clin Transl Neurol. 2014; 1(12):955-67.
73. López-Expósito I, Chicón R, Belloque J, López-Fandiño R, Berin MC. *In vivo* methods for testing allergenicity show that high hydrostatic pressure hydrolysates of β-lactoglobulin are immunologically inert. Journal of Dairy Science. 2012; 95(2):541-8.
74. Mabrook MF, Petty MC. Effect of composition on the electrical conductance of milk. Journal of Food Engineering. 2003; 60(3):321-5.
75. Mann GV. Studies of a surfactant and cholesteremia in the Maasai. The American journal of clinical nutrition. 1974; 27(5):464-9.
76. Margolis KL, Ray RM, Van Horn L, Manson JE, Allison MA, Black HR, *et al*. Effect of calcium and vitamin D supplementation on blood pressure: The women's health initiative randomized trial. Hypertension. 2008; 52(5):847-55.
77. Martín O, Qin BL, Chang FJ, Barbosa-Cánovas GV, Swanson BG. Inactivation of Escherichia coli in skim milk by high intensity pulsed electric fields. Journal of Food Process Engineering. 1997; 20(4):317-36.
78. Massey LK. Dairy food consumption, blood pressure and stroke. The Journal of nutrition. 2001; 131(7):1875-8.
79. Mayer EA, Knight R, Mazmanian SK, Cryan JF, Tillisch K. Gut microbes and the brain: paradigm shift in neuroscience. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2014; 34(46):15490-6.
80. Sweeney P, Fox PF. Advanced Dairy Chemistry Volume 3: Lactose, Water, Salts and Minor Constituents. Springer New York, 2009.
81. Melnik BC. Milk—a nutrient system of mammalian evolution promoting mTORC1-dependent translation. International Journal of Molecular Sciences. 2015; 16(8):17048-87.
82. Melnik BC, John SM, Carrera-Bastos P, Cordain L. The impact of cow's milk-mediated mTORC1- signaling in the initiation and progression of prostate cancer. Nutrition & Metabolism. 2012; 9(1):74.
83. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, *et al*. Guidelines for the primary prevention of stroke: A statement for healthcare professionals from the American heart association/ American stroke association. Vol. 45, Stroke, 2014.
84. Molkentin J. Occurrence and biochemical characteristics of natural bioactive substances in bovine milk lipids. The British journal of nutrition. 2000; 84(1):S47-53.
85. Nestel PJ, Mellett N, Pally S, Wong G, Barlow CK, Croft K, *et al*. Effects of low-fat or full-fat fermented and non-fermented dairy foods on selected cardiovascular biomarkers in overweight adults. The British journal of nutrition. 2013; 110(12):2242-9.
86. Nguyen H, Odelola O, Rangaswami J, Amanullah A. A review of nutritional factors in hypertension management. International Journal of Hypertension. 2013; 2013:1-12.
87. Donnell AM, Spatny KP, Vicini JL, Bauman DE. Survey of the fatty acid composition of retail milk differing in label claims based on production management practices. Journal of dairy science. Elsevier. 2010; 93(5):1918-25.
88. Oddy WH, Rosales F. A systematic review of the importance of milk TGF-beta on immunological outcomes in the infant and young child. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. 2010; 21(1 Pt 1):47-59.
89. Ohlsson L. Dairy products and plasma cholesterol levels. Food & nutrition research. 2010; 54:1-9.
90. Pacheco AR, Barile D, Underwood MA, Mills DA. The impact of the milk glycobiome on the neonate gut microbiota. Annual review of animal biosciences. 2015; 3:419-45.
91. Pan Y, Lee A, Wan J, Coventry MJ, Michalski WP, Shiell B, *et al*. Antiviral properties of milk proteins and peptides. Vol. 16, International Dairy Journal, 2006, 1252-61.
92. Park SW, Kim JY, Kim Y-S, Lee SJ, Lee SD, Chung MK. A milk protein, casein, as a proliferation promoting factor in prostate cancer cells. The world journal of men's health. 2014; 32(2):76-82.
93. Parracho HMRT, Bingham MO, Gibson GR, McCartney AL. Differences between the gut microflora of children with autistic spectrum disorders and that of healthy children. Journal of Medical Microbiology. 2005; 54(10):987-91.
94. Pereira PC. Milk nutritional composition and its role in human health. Vol. 30, Nutrition, 2014, 619-27.
95. Pereira PC. Milk nutritional composition and its role in human health. NUT. 2014b; 30:619-27.

96. Perry G, Sayre LM, Atwood CS, Castellani RJ, Cash AD, Rottkamp CA, *et al*. The role of iron and copper in the aetiology of neurodegenerative disorders: therapeutic implications. CNS drugs. 2002; 16(5):339-52.
97. Peterson R, Cheah WY, Grinyer J, Packer N. Glycoconjugates in human milk: Protecting infants from disease. Glycobiology. 2013; 23(12):1425-38.
98. Pothakamury UR, Barbosa-Canovas GV, Swanson BG, Spence KD. Ultrastructural changes in Staphylococcus aureus treated with pulsed electric fields / Cambios ultraestructurales en Staphylococcus aureus sometida a campos electricos pulsantes. Food Science and Technology International. 1997; 3(2):113-21.
99. Prentice AM. Dairy products in global public health. The American Journal of Clinical Nutrition. 2014; 99(5):1212S-1216S.
100. Qin B, Moorman PG, Alberg AJ, Barnholtz-Sloan JS, Bondy M, Cote ML, *et al*. Dairy, calcium, vitamin D and ovarian cancer risk in African–American women. British Journal of Cancer, 2016.
101. Rader DJ, Hovingh GK. HDL and cardiovascular disease. The Lancet. Elsevier Ltd. 2014; 384(9943):618-25.
102. Rossouw JE, Burger EM, Van der Vyver P, Ferreira JJ. The effect of skim milk, yoghurt, and full cream milk on human serum lipids. The American journal of clinical nutrition. 1981; 34(3):351-6.
103. Segall JJ. Hypothesis is lactose a dietary risk factor for ischaemic heart disease? International journal of epidemiology. 1980; 9(3):271-6.
104. Sepulveda DR, Góngora-Nieto MM, Guerrero JA, Barbosa-Cánovas GV. Production of extended-shelf life milk by processing pasteurized milk with pulsed electric fields. Journal of Food Engineering. 2005; 67(1-2):81-6.
105. Singh RP, Sharad S, Kapur S. Free Radicals and Oxidative Stress in Neurodegenerative Diseases: Relevance of Dietary Antioxidants. Journal, Indian Academy of Clinical Medicine. 2004; 5(3):218-25.
106. Song Y, Chavarro JE, Cao Y, Qiu W, Mucci L, Sesso HD, *et al*. Whole milk intake is associated with prostate cancer-specific mortality among U.S. male physicians. The Journal of nutrition. 2013a; 143(2):189-96.
107. Song Y, Chavarro JE, Cao Y, Qiu W, Mucci L, Sesso HD, *et al*. Whole Milk Intake Is Associated with Prostate Cancer-Specific Mortality among U. S. Male Physicians. The Journal of Nutrition. 2013b; 143(2):189-96.
108. De Souza RJ, Mente A, Maroleanu A, Cozma AI, Ha V, Kishibe T, *et al*. Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. Bmj. 2015; 351:1-16.
109. Steinmetz KA, Childs MT, Stimson C, Kushi LH, McGovern PG, Potter JD, *et al*. Effect of consumption of whole milk and skim milk on blood lipid profiles in healthy men. The American journal of clinical nutrition. 1994; 59(3):612-8.
110. Stokes CS, Lammert F. Vitamin D supplementation: less controversy, more guidance needed. F1000Research. 2016; 5(0):2017.
111. Sullivan S, Schanler RJ, Kim JH, Patel AL, Trawöger R, Kiechl-Kohlendorfer U, *et al*. An Exclusively Human Milk-Based Diet Is Associated with a Lower Rate of Necrotizing Enterocolitis than a Diet of Human Milk and Bovine Milk-Based Products. Journal of Pediatrics. 2010; 156(4).
112. Thompson LU, Jenkins DJ, Amer MA, Reichert R, Jenkins A, Kamulsky J. The effect of fermented and unfermented milks on serum cholesterol. The American journal of clinical nutrition. 1982; 36(6):1106-11.
113. Toepfl S, Heinz V, Knorr D. High intensity pulsed electric fields applied for food preservation. Chemical Engineering and Processing: Process Intensification. 2007; 46(6):537-46.
114. Toxqui L, Blanco-Rojo R, Wright I, Pérez-Granados AM, Pilar Vaquero M. Changes in blood pressure and lipid levels in young women consuming a vitamin D-fortified skimmed milk: A randomised controlled trial. Nutrients. 2013; 5(12):4966-77.
115. Turck D. Cow's milk and goat's milk. World review of nutrition and dietetics. 2013; 108:56-62.
116. Udenigwe CC, Mohan A. Mechanisms of food protein-derived antihypertensive peptides other than ACE inhibition. Journal of Functional Foods. 2014; 8:45-52.
117. Ulven SM, Leder L, Elind E, Ottestad I, Christensen JJ, Telle-Hansen VH, *et al*. Exchanging a few commercial, regularly consumed food items with improved fat quality reduces total cholesterol and LDL-cholesterol: a double-blind, randomised controlled trial. British Journal of Nutrition. 2016; 116(8):1383-93.
118. Uniacke-Lowe T, Fox PF. Equid Milk: Chemistry, Biochemistry and Processing. Food Biochemistry and Food Processing: Second Edition, 2012, 491-530.
119. Uniacke-Lowe T, Huppertz T, Fox PF. Equine milk proteins: Chemistry, structure and nutritional significance. Vol. 20, International Dairy Journal, 2010, 609-29.
120. Van Der Velde RY, Brouwers JRBJ, Geusens PP, Lems WF, van den Bergh JPW. Calcium and vitamin D supplementation: state of the art for daily practice. Food & nutrition research. 2014; 58:1-12.
121. Wolfe RR. Update on protein intake: importance of milk proteins for health status of the elderly. Nutrition Reviews. 2015; 73(suppl 1):41-7.
122. World Cancer Research Fund International: Continuous Update Project Report. Diet, Nutrition, Physical Activity and Prostate Cancer. 2014; 52.
123. Wurtman RJ. A nutrient combination that can affect synapse formation. Nutrients. 2014; 6(4):1701-10.
124. Wyss-Coray T. Inflammation in Alzheimer disease: driving force, bystander or beneficial response? Nature medicine. 2006; 12(9):1005-15.
125. Zhang J, Wang Z, Wang H, Du W, Su C, Zhang J, *et al*. Association between dietary patterns and blood lipid profiles among Chinese women. Public Health Nutrition. 2016; 12:1-8.
126. Zhong JZ, Liu W, Liu CM, Wang QH, Li T, Tu ZC, *et al*. Aggregation and conformational changes of bovine β-lactoglobulin subjected to dynamic high-pressure microfluidization in relation to antigenicity. Journal of Dairy Science. 2012; 95(8):4237-45.

127. Ziegler EE. Consumption of cow's milk as a cause of iron deficiency in infants and toddlers. Nutrition Reviews. 2011; 69(SUPPL. 1).
128. Zulueta A, Esteve MJ, Frasquet I, Frígola A. Vitamin C, vitamin A, phenolic compounds and total antioxidant capacity of new fruit juice and skim milk mixture beverages marketed in Spain. Food Chemistry. 2007; 103(4):1365-74.
129. United States Department of Agriculture Agricultural Research Service National Nutrient Database for Standard Reference Release 28.
130. WHO | About cardiovascular diseases. WHO. World Health Organization; 2011.