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Decoding A1 and A2 Milk: A thorough exploration

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Abstract

Milk from dairy cows has long been celebrated as one of nature's most complete foods, providing a comprehensive array of essential nutrients. It is a vital source of high-quality proteins, easily digestible carbohydrates, and an array of micronutrients that are crucial for human health. This nutritional richness makes milk an indispensable part of the global diet, valued for its ability to support growth, development, and overall well-being. Among the various components of milk, β-casein has recently garnered significant attention, especially within health-conscious communities. β-casein, a major milk protein, exists in different genetic variants, the most notable being A1 and A2. The distinction between these two variants has become increasingly important due to emerging research linking the A1 variant of β-casein to a range of health concerns. Studies have suggested that consumption of milk containing the A1 β-casein variant may be associated with an increased risk of certain diseases, including cardiovascular issues, type 1 diabetes, and digestive discomfort. In contrast, the A2 variant of β-casein, which is more prevalent in certain breeds of cattle, has not been associated with these health risks and is considered safer for consumption. This has led to a growing demand for A2 milk, particularly among those seeking to minimize potential health risks associated with dairy consumption. The genetic makeup of dairy herds varies significantly across different regions. In many European countries, the prevalence of the A1 variant in cattle has raised public health concerns, prompting further investigation into the long-term effects of A1 milk consumption. Meanwhile, India, known for its indigenous cattle breeds such as the Gir, Sahiwal, and Red Sindhi, has been traditionally rich in A2 β-casein-producing animals. Historically, the predominance of A2 milk in India's dairy sector has provided a natural safeguard against the potential adverse effects linked to A1 milk. However, the landscape of Indian dairy farming is changing. The introduction of cross-breeding programs aimed at increasing milk production has inadvertently led to a decline in the availability of pure A2 milk. This shift poses a significant public health concern, as the increasing presence of A1 β-casein in the national milk supply could undermine the traditional health benefits associated with desi breeds.

To address this issue, there is an urgent need to reassess and refine India's breeding policies. Preserving the genetic purity of indigenous cattle breeds is not just about maintaining biodiversity; it is about protecting the health of future generations. By prioritizing the conservation of A2-rich dairy animals and promoting the production of A2 milk, India can continue to offer its population the health benefits that have been safeguarded by its dairy traditions for centuries.

Keywords: A1 Milk, A2 milk, βCM-7, Casein, Health

Introduction

Milk is a staple in many diets worldwide, celebrated for its nutritional benefits and versatility. Milk has been a fundamental part of human diets for thousands of years, providing essential nutrients like calcium, protein, and vitamins. Since ancient times, milk has been considered a nearly perfect food due to its rich supply of nutrients and micronutrients. Comprising approximately 87 percent water and 13 percent milk solids, milk contains essential components such as fat, lactose, minerals, and proteins. The primary protein in milk is casein, with beta-casein making up around 30-35 percent of this protein. The genetic background of dairy animals determines the type of beta-casein present, with the two major variants being A1 and A2 (Swinburn, 2004) [46]. Beta-casein is composed of 229 amino acids, and the difference between A1 and A2 milk lies in the amino acid at the 67th position in the chain: A2 milk has proline, while A1 milk has histidine (Woodford, 2007) [56]. Cows producing A2 milk are referred to as A2 cows, whereas those producing A1 milk are called A1 cows. Breeds such as Jerseys, Guernsey, and most Asian and African cows typically produce A2 milk, whereas Holstein and Ayrshire breeds mainly produce A1 milk (Woodford, 2007) [56]. Additionally, animals like sheep, goats, yaks, buffalo, camels, donkeys, and most Asian cows naturally have a higher content of A2 beta-casein protein (Briden, 2013) [4].

In 2007, the publication of the book "Devil in the Milk" had a significant impact by suggesting a link between the consumption of A1 β-casein and the development of Type 1 diabetes (Woodford, 2009) [59]. This association alarmed many milk consumers, leading to a surge in demand for A2 milk in Australia and New Zealand. The book's argument was based on an extensive review of over 100 scientific reports, which examined the potentially harmful effects of A1 milk. It explored how beta-casomorphin-7 (BCM-7), a bioactive peptide released during the digestion of A1 milk, could enter the bloodstream, particularly in individuals with

leaky gut syndrome. The book suggested that this peptide could pass through a compromised gut barrier, raising health concerns.

Furthermore, the book claimed that BCM-7 could also enter the bloodstream of infants, raising additional concerns about the health effects of A1 milk on young children. It even linked BCM-7 to conditions like autism and schizophrenia. These assertions sparked considerable debate and further research. Despite the controversy, the book increased interest in A2 milk as a safer alternative. However, the exact relationship between A1 milk, BCM-7, and various health conditions remained a topic of ongoing scientific investigation and discussion.

In response to consumer concerns, the New Zealand Food Safety Authority (NWFSA) enlisted the help of the European Food Safety Authority (EFSA) in 2008. The EFSA conducted a comprehensive scientific review and, in 2009, concluded that there was no clear cause-and-effect relationship between the dietary intake of BCM-7 and several health issues. They found no link between the oral consumption of BCM-7 or related peptides and the development of non-communicable diseases, contradicting some earlier studies (EFSA, 2009). Consequently, the EFSA did not recommend a formal risk assessment for food-derived peptides. These findings were widely accepted by food safety authorities in Australia, New Zealand, and other countries, reassuring regular milk consumers. However, since the report acknowledged that some individuals might experience gastrointestinal changes, research shifted towards understanding digestive issues associated with A1 milk, especially among those with milk intolerance.

In India, crossbreeding programs aimed at creating high-yield milk-producing cows involved breeding Indian cattle with European breeds, which resulted in cows that produced A1 milk. Despite this, the majority of milk in India comes from buffaloes, which produce A2 milk. The controversy surrounding A1 milk remains an urgent issue, but its harmful effects have yet to be definitively proven. This review aims to gather and investigate the available information on the A1 and A2 milk debate to provide a comprehensive understanding of the topic.

Understanding Milk Proteins

Milk proteins are a heterogeneous group of polymeric compounds that have a wide range of different molecular structures and properties. They occur as Caseins, whey proteins, proteins of the fat globule membrane, enzymes, minor proteins and nitrogen compounds (Frister H,2007; Kaminski et al.,2007; Stanton et al., 2013) [17, 44]. In recent years, a new type of cow's milk, named "A2 milk", has been introduced in the market. This type of milk was first commercialized in New Zealand and has since been gaining a presence in the markets of several countries (Alfonso et al., 2019) [2]. A2 milk is characterized by being free of the A1 variant of β-casein: a protein that represents approximately 30% of the caseins in cow's milk (Miranda et al.,2015) [36]. At its core, the difference between A1 and A2 milk lies in the type of casein proteins present in the milk. Casein proteins are the primary proteins found in milk, making up about 80% of its total protein content. They are crucial for the milk's structure and play a significant role in its nutritional profile. The variation between A1 and A2 milk is determined by a genetic difference in the dairy cattle that produce them. Milk is composed of various proteins, but the most abundant are caseins, which are categorized into different types. The two primary types of casein are A1 and A2, and they differ in their amino acid sequences due to genetic variations in dairy cattle. In type A1 β-casein, there is an amino acid histidine at this position, whereas in type A2 protein, this histidine is replaced by a proline (Brooke-Taylor et al.,2017) [5]. Thus, the original codon cytosine-cytosine-thymine (CCT), which forms the amino acid proline in the A2 variant, is modified to cytosine-adenine-thymine (CAT), which encodes the formation of histidine at position 67 of the β-casein polypeptide chain in A1 variants (Kay et al., 2020) [24].

Composition and Significance of Casein Protein in Bovine Milk

Milk is a complex fluid that primarily consists of about 85% water. The remaining 15% includes essential components such as lactose (milk sugar), protein (comprising approximately 3.5 to 3.9% of milk's composition), fat, and minerals. Bovine milk is an abundant source of amino acids, proteins, lipids, vitamins, minerals, growth factors, hormones, immunoglobulins, and various bioactive compounds. The composition of milk varies due to factors like the age and breed of the animal, the stage of lactation, dietary factors, and the overall health of the udder tissue.

One of the key constituents of milk is beta-casein, which constitutes about 30% of the total protein content (Fig-1). Besides beta-casein, milk contains other proteins and lipids, with proteins making up approximately 3-3.5% of milk's composition. Casein is the predominant protein fraction in milk, accounting for 76-86% of the total milk proteins, while whey proteins make up the remaining 14-24%. In bovine milk, there are various casein fractions, including β-Lactoglobulin (making up approximately 50% of whey protein), α-Lactalbumin (comprising around 20%), Proteose/Pantones (approximately 20%), immunoglobulins (about 8%), and certain fractions of blood albumins. The intricate balance of water, proteins, fats, and minerals in milk plays a critical role in nutrition and is influenced by numerous factors that are crucial in understanding its biological significance.

The colloidal complexes of casein micelles are formed through interactions between proteins and calcium, while milk lipids are emulsified in globules within membranes, and most minerals are present in lactose solution. Understanding the detailed composition of milk and the factors influencing it is essential for appreciating its nutritional and biological importance.

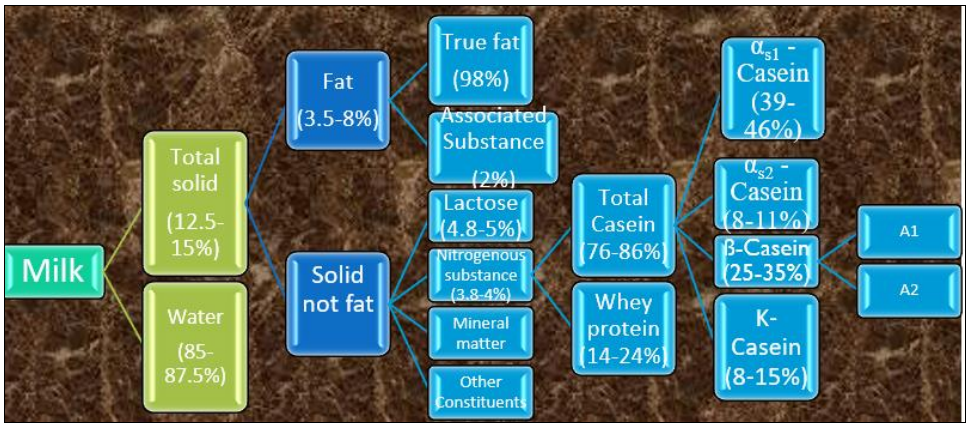

Fig 1: Milk composition and Proportion of A1/A2 milk

Cow breeds and type of milk

All Indian domesticated cow recognized as Bos Indicus or zebu cow which are humped, produces milk with high concentration of A2 beta-casein. Zebu type cow is also found in many places in Africa also. India has 53 pure indigenous cattle breeds. They are Sahiwal, Gir, Red sindhi, Tharparkar, Rathi, kankrej, Ongole and Hariana to name a few. The milk delivered by all the desi cow was of A2 variety. Foreign breed like Holestin Friesian, Jersey milk which gets its name from A1 beta-casein protein present in it. However, India went on to hybrid its native desi cow with the European species of jersey and Holstein Friesian which delivered A1milk. Originally, all milk was A2, but due to a genetic mutation at some point, the A1 form appeared (Ng-Kwai-Hang et al.,2002) [37]. That means the genetic mutation changed the amino acids from proline to histidine based and gradually became the prevalent form of beta casein. This shift has had significant implications for dairy farming and consumer health. The majority of cow's milk consumed in Europe (with the exception of France), the United States, Australia, and New Zealand contains the A1 beta-casein type. The frequency of the A2 allele appears to be around 60% in Holsteins. This means that about 35% of Holstein Friesian produce A2-milk, 48% produce a mix of A1-and A2- milk, and 16% produce A1-milk . Therefore, Holstein Friesian has the lowest proportion of A2-milk in relation to other breeds. Brown Swiss and Fleckvieh have the proportion at around 65%, which produce A2-milk (Inhofer C,2019) [19]. The Guernsey has the highest proportion of the A2-milk gene at over 90% among exotic breed. All the other main exotic dairy breeds have about 50%. Thus, most cows of exotic breed produce a combination of these two proteins A1-and A2-milk. However, A1-milk is absent in purebred Asian and African cattle . All indigenous breeds of cattle and buffalo are thought to have the A2 gene, making all indigenous cattle and buffalo milk A2. By looking at indigenous breeds, NBAGR has analyzed the frequency of A-A2 alleles in Indian breeds and discovered that the A2 allele is 100% present in the five high-yielding milch breeds Red Sindhi, Gir, Rathi, Sahiwal, and Tharparkar. The avoidance of A1-milk is feasible within dairy based diets through the consumption of sheep, buffalo and goat milk or through the consumption of bovine milk from the native Asian and African bovine breeds (Brooke-Taylor et al.,2017) [5]. However, the consumption of milk from European-type cattle is possible, which is free of the A1-milk. Such herds are being developed in many countries (Inhofer C,2019) [19].

Venerated A2 Cows: The Indian Perspective

According to Hindu mythology and saying of sages the Kamdhenu is the mother of all cow. since thousands of years, we worship cow as Kamdhenu the god who fulfil our desires. We worship cow as the mother of all entities which give all pleasures to everyone. Native cow are the only species in this world whose product and by product are created for the economics, social and spiritual betterment of human beings in many ways since ages. However, since the sixties, in a bid to increase the production of cow milk the Indian Government has resorted to "cross-breeding" by using foreign bull and semen. This causes gradual extinction of our low-maintenance superior and enduring variety of native breed of cows. For the past period we have neglected the caring for the sacred Indian cows due to various factor and dynamics. Now the time has come to enlist ourselves in the mission to preserve the Native Breed of our Indian cattle from the spiritual perspective cow play a vital role in providing core ingredients for worship.

The Indian native cow will have hump at the shoulder, long ear and the skin is hanging on the neck. They have suryaketu nerve on the back and it is believed that suryaketu nerve absorbs medicinal essences from atmosphere and makes milk urine and cow dung more nourishing. The ability to shake only a particular part of the body, for example it can shake only the skin the stomach area without shaking the other part of the body. It can withstand the tough climatic condition of this country either hot, rain or cold. It delivered around 15-20 calves in her life span. India possesses 53 acknowledged indigenous breeds of cattle. Desi cattle have been a part of Indian life styles since ages unknown. It has helped mankind in farm of plough on road, to carry load of home with milk and with urine and cow dung for several other uses in day-to-day life. Desi cow is not only looks upon as a source of benefit but also considered as a family member and revered with a motherly state and often called Gaumata.

Indigenous cow has a distinct hump curved back and a flap (dewlap) on the neck, long and pendulous ears, convex forehead, round hind legs posture while HF, Jersey other exotic cow no hump, small ears, smaller flat forehead, small neck, table top hind legs posture. This is the easiest way to identify an indigenous cow.

Actually, this problem has been occurred due to the mutation in the cow before thousands of years ago and cattle has been taken to western countries where the proline is replaced with histidine at position 67, spreading widely throughout the herds of the western world through breeding till now (Swinburn.B,2004) [46]. Whereas the Asian especially in subcontinental countries like India are with A2 milk producing breeds till 18th century only a few amounts of cows in India used to produce A1,but this has been changed in this century it may be due to increase the demand for milk in India, many of the herdsmen has shown interest in A1 milk producing breed cows like jersey, Karan swiss, Holstein breed cows especially this breed cows do produce more amount of milk when compare with that of A2 breed cows which happened with the help of White Revolution it introduced foreign cow breeds to India which are capable of producing bulk amount of milk and replaced the Indian cow. In New Zealand and Australia now, they started finding a solution to these problems by pushing the people to drink the A2 milk which may be a high cost for them.

The Evolutionary Origins of A1 and A2 Milk

A2 beta-casein, a protein present in cows bred for over 10,000 years before domestication, is associated with no known adverse effects on human health. The timeline illustrating the evolution of A1 and A2 milk is depicted in Figure 2. However, a significant transformation occurred over the past few millennia due to a natural mutation within the cattle population, particularly among European breeds. This mutation introduced a casein variant known as A1 beta-casein, which gradually became more prevalent in milk production. The genetic change that led to this shift involved a modification in the beta-casein gene, specifically at the 67th amino acid position out of 209 amino acids, where proline was replaced by histidine (see Figures 3). As a result, A1 beta-casein emerged, becoming dominant in the milk of crossbred cows such as Jersey and Holstein Friesian (HF).

The debate over A1 versus A2 milk gained considerable attention starting in September 2007 with the publication of Keith Woodford's book in New Zealand. This narrative is rooted in compelling epidemiological evidence that highlights a strong correlation between countries with high A1 milk consumption and increased rates of type 1 diabetes and heart disease. A2 milk, which contains the A2 beta-casein protein, contrasts with A1 milk, which is defined by the presence of A1 beta-casein or the A1A2 type variant. The A1 protein variant is mainly found in milk from crossbred and European cattle breeds, while A2 milk primarily comes from indigenous cows and buffaloes in regions like India and across Asia. This historical background emphasizes the complex relationship between genetics, milk composition, and its potential impact on human health.

Fig 2: A1 and A2 Milk: An Evolutionary Journey and the Debate That Follows

Difference between A1 and A2 milk

Milk proteins are a diverse group of polymorphic compounds with varying molecular structures and properties. They include caseins, whey proteins, enzymes, minor proteins, and other non-protein nitrogen compounds. Caseins make up the majority, comprising about 80% of the total milk protein. Among the different types of caseins, β-caseins are particularly significant, being the second most abundant and existing in 13 different variants. Of these, the A1 and A2 β-caseins are the most prevalent and have garnered considerable attention. The type of β-casein a cow produces Is determined by Its genetic makeup. A cow can be homozygous for A1 or A2, or heterozygous, expressing both forms due to co-dominance. As a result, milk containing A1 β-casein is referred to as A1 milk, while milk with A2 β-casein is called A2 milk. Historically, all milk was of the A2 type, but a genetic mutation in the A2 beta-casein gene occurred approximately 3,000 years ago in Europe, leading to the emergence of the A1 variant (Kaskous, 2020) [23]. The distinguishing structure between these 2 forms of Beta casein is the presence of either histidine (His 67) in A1 or proline(pro67) in at position 67 of these 209 amino acid proteins with A1 being consequential to a point mutation from pro67 to His67 occurring in ancestors to modern European type cattle (Kaminiski et al., 2007). The His67 mutation is absent in pure breed Asian and African cattle (De Noni et al. 2009) [12]. A1 protein variant is commonly found in milk from cross breed and European breed of cattle. A2 milk is found basically in indigenous cows and buffaloes of India (Asia as whole). When consumed, A1 and A2 casein proteins undergo different biochemical processes. A1 casein, when digested, releases a peptide known as β-casomorphin-7 (BCM-7). BCM-7 has been the focus of research due to its potential effects on gut health and its interaction with opioid receptors in the human body. In contrast, A2 casein does not produce BCM-7, leading some researchers to suggest that A2 milk may be less likely to cause digestive discomfort.

What is BCM-7

The term ‘casomorphin’ derives from the words ‘caso,’ referring to casein, and ‘morphine,’ linked to Morphus, the Greek God of sleep, as explained by Meisel et al. (1999). These peptides are produced through the breakdown of β-casein in milk and possess opioid-like properties with pharmacological effects. They specifically bind to μ-receptors, which are located in various parts of the body, including the central nervous system, gastrointestinal tract, and certain immune cells, as noted by Teschemacher et al. (2003) [48].

BCMs, or beta-casomorphins, are a group of peptides that range from 4 to 11 amino acids and are initially present in an inactive form within the structure of β-casein. These peptides are released during digestion, either in-vivo or in-vitro. Among this group, the most potent peptides are BCM-7 and BCM-5, corresponding to fragments f60–66 and f60–64 of β-casein, respectively, as discussed by Kostyra et al. (2004) [28].

BCM-7 is an opioid peptide. It is a small protein that does not digest in our body. This can lead to indigestion and many researches have shown that it may lead to various other diseases like diabetes etc., so we can say that proline amino acid in A2 prevent BCM-7 from going into our body (Woodford, 2008) [55]. But A1 cow does not make proline, so BCM-7 goes into our body and later it dissolves in the blood. It is believed that generation of BCM-7 is the major causative factor associated with A1milk related health disorder. However, A2 casein not been linked to any of such health issues. The absorption of BCM-7 in to the blood stream lead to the high incidences autism, schizophrenia and other neurological disorder (Birgisdottir et al., 2006) [3]. Many diseases such as autism, schizophrenia (Laugesen *et al*., 2003 and Tailford *et al*.,2003) [30, 46] have been shown to have associated with consumption of β-casein A1 milk. This protein is also linked to milk intolerance in some protein. Genetic polymorphism of bovine milk protein has great in trust in animal breeding due to its relationship with milk production traits, milk composition and milk quality (Roginski et.al., 2003 and Jaiswal et.al., 2014) [21]. BCM-7 has been the focus of research due to its potential effects on gut health and its interaction with opioid receptors in the human body. In contrast, A2 casein does not produce BCM-7, leading some researchers to suggest that A2 milk may be less likely to cause digestive discomfort.

Although active BCMs are of 5–7 amino acids long, their absorption and transport across the intestinal epithelial cells in the intestine in the form of amino acids and small peptides, i.e., up to tripeptides (Webb et al.,1992) [53]. Umbach et al., (1985) [49] identified the presence of irBCM-7 (a precursor of BCM-7) in the plasma of newborn calves following milk consumption. In a comparative study, Singh et al., (1989) [41] examined the levels of irBCM-7 in the plasma of 2- and 4-week-old pups and adult dogs after they were fed a bovine casein-based formula. The researchers suggested that the immature tight junctions in the intestinal mucosa of newborns may allow relatively large peptides to pass through, thereby escaping hydrolysis. While both human and bovine irBCM have been detected in the blood of human infants (Kost *et al*.,2009) [27], a more recent study by Wasilewska *et al.,* (2011) [52] identified the presence of BCM-5 in the blood of human infants. However, the detection of irBCM-7 antibodies in plasma has raised concerns about potential cross-reactivity with other antigen epitopes in plasma, an aspect not explored by the researchers. Mahé *et al*. (1989) proposed that the brush border peptidases, particularly the dipeptidyl peptidase IV (DPP IV) enzyme, may be crucial in limiting the transfer of morphiceptin. The transepithelial transport of BCM-5 and BCM-7 across human intestinal Caco-2 cells has been demonstrated (Shimizu *et al*.,1997; Iwan *et al*.,2008; Sienkiewicz-Szlapka *et al*.,2009) [39, 20, 40], with findings showing that the relative flux of BCM-5 increased when the cell layer was treated with a DPP IV inhibitor, an enzyme known to be involved in the hydrolysis of the peptide.

Health Complications Linked with BCMs

There is substantial evidence linking β-casomorphins (BCMs) to a range of adverse biological responses. These include an association with type 1 diabetes mellitus (Elliott,et al.,1999) [14], heart diseases (Laugesen et al.,2003) [30] and neurological disorders such as autism and schizophrenia (Cade et al.,2000) [7]. Additionally, BCMs have been implicated in conditions like sudden infant death syndrome (SIDS).

Cardiovascular diseases

Ecological studies have established a connection between the intake of BCM-7 and mortality from cardiovascular diseases (Elliott *et al.*,1999) [14]. Research by Chin-Dusting *et al* (2006) [10], has shown a correlation between the consumption of A1 β-casein and an increased risk of cardiovascular diseases in humans. A1 β-casein has been linked to hypercholesterolemia and atherosclerosis, which are associated with a higher incidence of heart disease, as demonstrated in animal studies. Additionally, a relationship was observed between ischemic heart disease mortality rates and the consumption of milk proteins and components (McLachlan *et al*., 2001) [33]. In one study, rabbits fed A1 β-casein milk exhibited higher cholesterol levels and a greater percentage of aortic surface area covered by fatty streaks compared to those fed A2 β-casein (Tailford, *et al*.,2003) [46].

Type 1 Diabetes

There are claims suggesting a positive correlation between the consumption of A1 milk and the incidence of Type-1 diabetes, with several theories proposed to explain this relationship. One theory posits that β-casomorphin-7 (βCM-7), a peptide derived from A1 β-casein, may suppress the immune system and enhance the vitality of enteroviruses, endogenous retroviruses, or pathogenic bacteria such as Mycobacterium avium. These pathogens, in turn, could damage pancreatic β-cells, leading to the onset of Type-1 diabetes (Kaminski et al., 2007; Parashar & Saini, 2015; Chia et al., 2018) [37, 9]. Another theory suggests that certain peptides, which are hydrolysates of β-casein, resemble the structure of the GLUT-2 protein, responsible for glucose transportation. The immune system, mistakenly identifying these peptides as harmful antigens, prompts T-cells to activate beta cells, leading to the production of antibodies. These antibodies not only target the β-casein peptides but also inadvertently destroy the insulin-producing beta cells, potentially resulting in Type-1 diabetes (Parashar & Saini, 2015) [37]. Supporting evidence includes a study conducted in Finland, which observed that children under 15 years of age who consumed cow milk proteins before two months old had double the risk of developing Type-1 diabetes (Virtanen et al., 1993) [50]. Some researchers have further indicated that cow milk proteins may increase the risk of Type-1 diabetes in genetically predisposed children (Knip et al., 2010b; Chia et al., 2017) [25, 8], while others have suggested that cow milk could be a risk factor for Type-1 diabetes regardless of genetic predisposition (Lamb et al., 2015) [29].

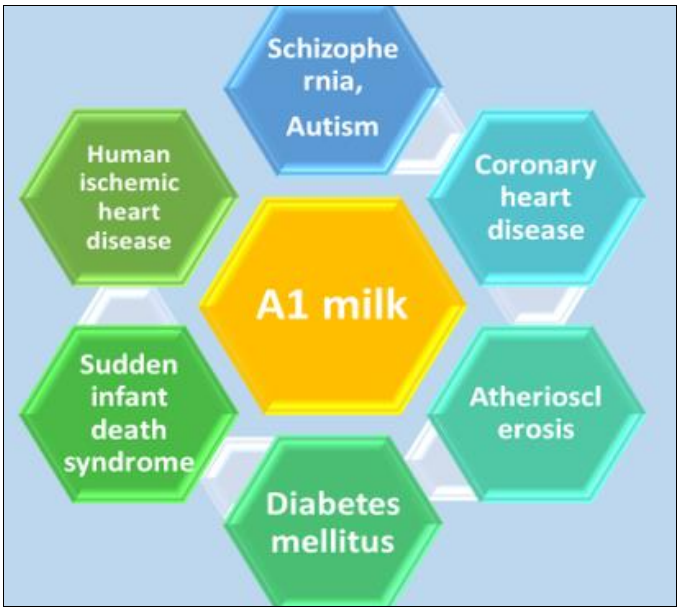

Fig 3: Health Complications Linked with BCMs (A1 milk)

Ischemic Heart Disease

In a study encompassing 17 countries, a strong correlation was identified between the consumption of A1 milk in 1980 and the incidence of cardiovascular disease-related deaths in 1985 and 1990. Another investigation into the relationship between cow's milk consumption and ischemic heart disease revealed a notably high correlation (r=0.76) between the intake of A1 β-casein per individual and the occurrence of ischemic heart disease, considering a five-year lag in disease manifestation (Laugesen and Elliott, 2003) [30]. Similarly, the WHO MONICA project reported a strong correlation (r=0.86) between the intake of A1 β-casein from milk proteins (excluding cheeses) and deaths caused by ischemic heart disease (McLachlan, 2001) [33].

Autism and Schizophrenia

Autism is a lifelong neurodevelopmental disorder that often impacts social interactions, cognitive functions, and creative abilities (Shattock and Whiteley, 2002; Crane et al., 2016) [38, 11]. Although certain genes associated with autism have been identified, it is suggested that both genetic and environmental factors may contribute to the development of this disorder (Shattock and Whiteley, 2002; Abrahams and Geschwind, 2008; Sokolov et al., 2014) [1, 38, 42]. The observation that specific milk protein-derived peptides exhibit opioid-like effects has led to the hypothesis of a possible link between autism and excessive opioids. According to this hypothesis, genetic predisposition and/or environmental stress during early development can alter

intestinal function, increase intestinal mucosa permeability, and reduce proteolytic activity. These factors, along with decreased peptidase activity and increased blood-brain barrier permeability, may lead to the accumulation of opioid peptides, such as casomorphin, in the brain and bloodstream, resulting in hyperpeptidemia. Ultimately, chronically elevated levels of exorphins in the brain may disrupt opioid and neurotransmitter systems, potentially contributing to the development of disorders like autism (Shattock and Whiteley, 2002; Sokolov et al., 2014) [38, 42].

Schizophrenia and autism have been linked to conditions like hyperpeptidemia and hyperpeptiduria. It has been observed that removing low molecular weight peptides from the bloodstream through hemodialysis or following a diet free of milk and gluten may lead to a reduction in schizophrenic symptoms. Additionally, studies have found that 90% of schizophrenic patients and 86% of autistic patients had elevated levels of βCM-7 IgG antibodies (Cade et al., 1990) [6].

Sudden Infant Death Syndrome (SIDS)

Sudden Infant Death Syndrome (SIDS) refers to the unexpected death of infants under 12 months old, typically occurring during sleep. Potential causes of SIDS include brain abnormalities, low birth weight, respiratory infections, and environmental factors that impair the baby's ability to breathe. Some studies have suggested that βCM-7 might also be a contributing factor (Mallepalli *et al.*, 2017; Sun *et al*., 2003) [32, 44]. βCM-7 is notably resistant to enzymatic degradation, though it is a substrate for Dipeptidyl-peptidase IV (DPPIV). Research has shown that infants who experienced apnoea had higher levels of βCM-7 and lower levels of DPPIV in their serum compared to healthy infants. This imbalance may lead to respiratory depression, as the high concentration of βCM-7 due to reduced DPPIV activity could depress breathing (Wasilewska *et al.*, 2011). βCM-7, when ingested through diet, can be absorbed through the digestive tract and cross the blood-brain barrier, especially in infants whose central nervous system is not yet fully developed. In infants with impaired breath control or vagal nerve development disorders, βCM-7 may depress the brain's respiratory center, leading to death (Sun *et al*., 2003) [44].

Atherosclerosis

The effects of A1 and A2 milk on human health have been studied, with an experiment conducted on rabbits as a model. In this study, one group of rabbits was fed A1 milk, while another group was given A2 milk. The results showed that the rabbits consuming A1 milk developed fatty deposits on the walls of their blood vessels, which could potentially lead to severe cardiac issues such as angina. In contrast, the rabbits that were fed A2 milk did not exhibit these effects. Additionally, A1 milk was found to increase the levels of low-density lipoproteins (LDL), often referred to as "bad cholesterol," while decreasing the levels of high-density lipoproteins (HDL), known as "good cholesterol." The fatty deposits observed were composed of foam cells, which differ from the typical atherosclerotic plaques that form when macrophages ingest oxidized LDL in damaged blood vessels (Torreilles and Guérin, 1995) [48].

Unlocking the Business Potential of A2 Milk

The global market for A2 milk presents a significant opportunity for commercialization, driven by a growing demand for this type of milk, which is considered safer and more easily digestible by many consumers. A2 milk, which contains only the A2 variant of beta-casein protein, is believed to be a healthier alternative to regular milk that typically contains both A1 and A2 proteins. The perceived health benefits of A2 milk have sparked interest worldwide, leading to a rapid expansion in its production and marketing.

One of the pioneers in the commercialization of A2 milk is the New Zealand-based company, originally known as A2 Corporation Ltd., which has since rebranded as the a2 Milk Company Ltd. This company has successfully established a substantial market presence, not only in New Zealand but also in Australia, the United States, and various Asian markets. Their product line, branded as A2™, includes a range of milk and milk-based products specifically marketed for their A2 protein content. This strategic marketing approach has positioned the company as a leading force in the A2 milk industry globally.

In addition to its operations in the Southern Hemisphere and the Americas, the a2 Milk Company has also expanded into Europe through its subsidiary, A2 Milk UK Ltd. This branch focuses on producing and marketing A2 protein-containing milk in the United Kingdom and Ireland (www.a2milk.co.uk). The success of these ventures underscores the increasing consumer demand for A2 milk in developed markets, where consumers are willing to pay a premium for perceived health benefits.

The global interest in A2 milk is also creating opportunities for countries like India, which has a large population of cattle naturally producing A2 milk. Indian breeds, known for their A2 milk, are seeing rising demand in regions such as Australia, South America, Africa, Brazil, and Southeast Asia (De et al., 2015). This demand presents an excellent opportunity for the selective breeding and genotyping of herds to enhance A2 milk production. By segregating A2 milk from A2-genotyped herds and marketing it at a premium, India can tap into the global market and command higher prices for this niche product (www.suruchiconsultants.com).

Moreover, the unique properties of A2 milk make it particularly suitable for producing specialized products such as baby food. As consumers become increasingly aware of the health implications of the food they consume, there is a growing market for infant formulas made from A2 milk, which could position India as a leading global supplier of A2-based infant nutrition products. Given the potential for growth in this segment, India has the opportunity to become a world leader in the supply of A2 milk and related products, capitalizing on its existing dairy resources and the global demand for healthier alternatives.

The ongoing demand for A2 milk and its derivative products indicates that there is considerable potential for the expansion of the A2 milk market. By focusing on strategic breeding, product diversification, and targeted marketing, countries and companies involved in A2 milk production can achieve substantial commercial success in this burgeoning sector.

A1 and A2 Milk: An Unsettled Scientific Debate

The debate surrounding the health impacts of A1 and A2 milk remains unresolved, with research yielding mixed results. While some studies have highlighted potential negative health effects associated with A1 milk, suggesting links to conditions like diabetes and coronary heart disease, the evidence is not definitive. The European Food Safety Authority (EFSA) reviewed the available data and concluded that there is no clear connection between the consumption of A1 milk, particularly the peptide beta-casomorphin-7 (BCM-7), and the development of these diseases (Hills, 2009) [18]. Similarly, food safety authorities in Australia and New Zealand have conducted thorough investigations and reported that there is no significant evidence to suggest a relationship between A1 or A2 milk and the incidence of diabetes or coronary heart disease.

Given the current state of research, it is evident that the scientific community has not reached a consensus on whether A1 milk poses a higher risk for these health issues. The existing studies present conflicting outcomes, and as a result, no definitive conclusion can be drawn at this time. This lack of clarity underscores the importance of continued research to explore the potential associations between A1 and A2 milk consumption and the development of diabetes, coronary heart disease, and other related conditions. More robust and comprehensive studies are necessary to better understand the role of these milk types in human health and to provide clearer guidance to consumers and healthcare professionals alike (Indian Dairymen, 2017).

Conclusion

India is fortunate to have a rich heritage of dairy cattle and buffalo breeds that predominantly produce A2 milk, which is often considered healthier than A1 milk. The abundance of these indigenous breeds is a valuable asset that has been cultivated over generations. As global interest in the potential health benefits of A2 milk grows, it is becoming increasingly important to focus on the improvement and conservation of our native dairy germplasm. Preserving these breeds not only safeguards a vital part of our agricultural heritage but also ensures the continued availability of A2 milk for future generations.

However, despite the widespread belief in the superiority of A2 milk, the scientific community has yet to reach a definitive conclusion on its health benefits compared to A1 milk. To truly understand the potential advantages and disadvantages of A1 versus A2 milk, it is essential to conduct more comprehensive and rigorous research. Such studies would provide the necessary evidence to support or refute the claims surrounding A2 milk and offer clearer guidance for consumers, policymakers, and dairy farmers. By investing in research and conservation efforts, India can lead the way in validating the benefits of A2 milk while protecting the genetic diversity of its dairy livestock.

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