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REVIEW ARTICLE

Is A2 milk a healthier choice than A1 milk?: A review

Karandeep Singh Sodhi, Rishabh Chaudhary, BhavnitaDhillon*
Department of Food Science and Technology,
Guru Nanak Dev University, Amritsar, Punjab, India.
*Corresponding author: bhavnita.food@gndu.ac.in

ABSTRACT
Over the years milk has become an important part of our diets and is consumed by people of all ages ranging from infants to elderly. Numerous studies have been carried out to determine the benefits as well as the detrimental aspects of milk on human health. However, from the past few decades the focus of research has shifted towards the effect of consuming A1 milk. A1 milk is an allele of milk which is obtained from certain high yielding varieties of cows namely Holstein, Jersey and their hybrids. The amino acid sequencing of A1 milk established proline on the 67th position of amino acid while histidine at this position for the A2 milk. They further differ in the mode of digestion as A1 milk produces a μ-opioid BCM-7(betacasomorphin-7). In many studies, this BCM-7 production has been linked with various health problems such as ischemic heart disease, diabetes type-1, sudden infant death syndrome, and certain mental disorders i.e. autism, schizophrenia, etc. On the other hand, A2 milk has been suggested as an apt substitute to A1 milk. However, A2 milk has certain limitations as it is much more expensive in comparison to A1 milk owing to its lesser yield and production by some indigenous breeds only. Also, due to no reliable quick detection methods being currently available it leaves room for adulteration.
Keywords: *A1 Milk, A2 Milk, Beta-casein, BCM-7, Health concerns*

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INTRODUCTION

Milk is a highly evolved secretion of mammary glands of mammals [1].It serves as a complete nourishment as it contains nutrients such as proteins, fat and other essential micronutrients such as calcium, vitamin D, potassium, phosphorus which are required by the neonate animals and humans for their optimum growth and immunological protection [2, 3].It contains 85% moisture and rest 15% is fat, protein, solid-not-fat(SNF), lactose and ash.

The milk production in India has increased by three folds over the past 3 decades. The milk production in 1991-92 was 55.6 million tonnes which rose to 187.7 million tonnes in 2018-2019, increasing by about 4 percent annually [4]. There is a worldwide surge in the milk production as well from 391.95million tonnes in 1970 to 827.88 million tonnes in 2017 [5].As the markets expand the researchers and consumers have become increasingly skeptical about its health benefits as it is surrounded by numerous facts as well as myths.

One of these is related with the protein alleles A1 and A2 of milk which differ by a pair of genes on their sixth chromosome [6]. Milk on an average contains 3.6% protein[4, 7]out of which 80% is casein. There are four different variants of casein namely α-S1-(CSN1-S1, 39–46%), α-S2-(CSN1-S2, 8–11%), β-(CSN2, 25–35%) and κ-casein (CSN3, 9–15%), that occur in the approximate proportions of 4:1:4:1, respectively [8, 9],and the rest 20% being serum or whey protein. There are further twelve different genetic variants of beta-casein namely A1, A2, A3, B, C, D, E, F, H1, H2, I and G[10]. The A1 and A2 among these are being ubiquitous [11]. The beta casein have an amino acid chain length of 229 units. The A1 and A2 alleles could be differentiated on the basis of 67thamino acid position. If the milk contains histidine at 67thposition, it is termed as A1-like milk and the one containing proline has been coined as A2-like milk [12]. Cows like Holstein, Ayrshire cattle and Swedish red and white cattle breeds predominantly produce A1 milk while

Jerseys, Guernsey, Asian and African cows along with most of the buffalo breeds such as Murrah, Mehsana, Marathwada, Nilli Ravi are known to produce A2 milk[13, 14].

Origin of A1 milk

About 10,000 year ago, prior to the domestication of cows, they produced A2 milk but 8,000 years ago due to a single mutation in the genes in Holstein cows resulted in production of A1 β-casein. As these cows belonged to the higher yielding breeds and were used to improve the milk yield of additional breeds/herds, so the A1 gene got incorporated in other breeds/herds as well [15]. This A1-like milk has been associated with numerous diseases. When A1 milk is ingested, during its digestion the hydrolysing bio-active peptides are released due to the presence of histidine on the 67th position and allows the cleavage of the bond and results in the formation of a bio-active compound called β-casomorphinor (BCM-7) in the small intestine (Fig. 1). It has structural similarity to endogenous opioid peptides and therefore, is deemed to be linked with various non-communicable diseases such as diabetes [16],cardiovascular disease [17], and gut inflammation [18].Whereas, this opioid is not produced in case of A2 milk as it contains proline on the same position and it prevents the proteolytic release of BCM-7 [19].

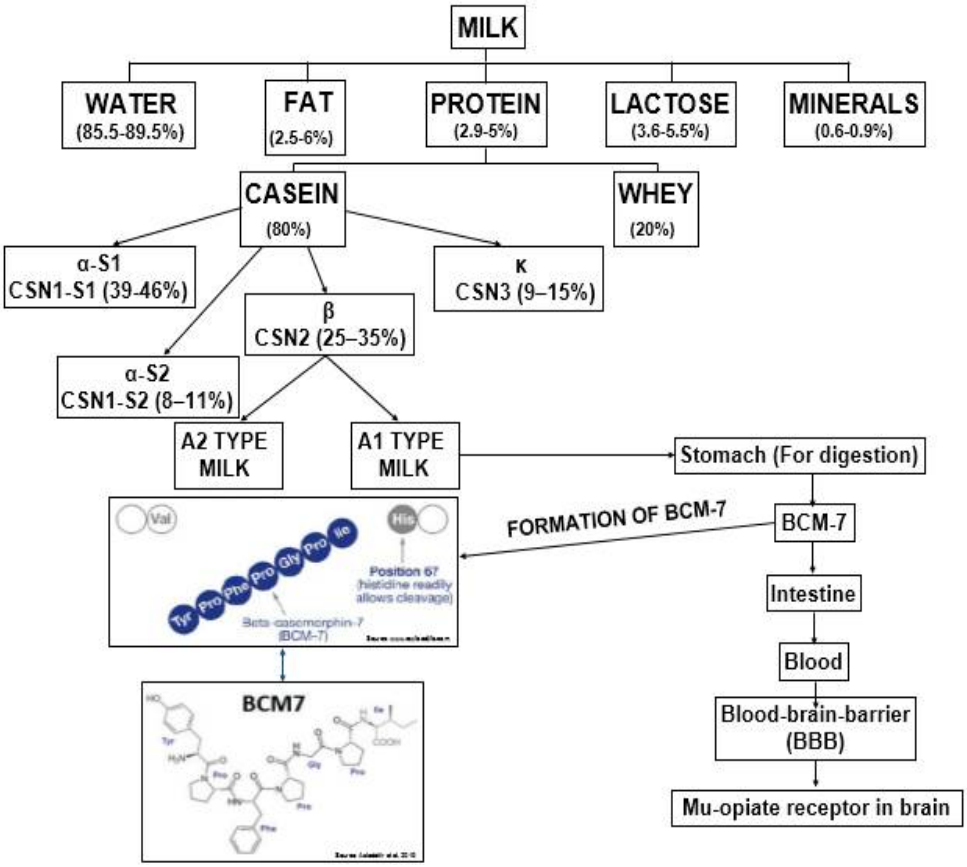

Fig. 1: An overview of milk depicting beta-casomorphin-7 (BCM-7) production.

Sensory aspects of A1 and A2 milk

A sensory analysis was carried out by Mendes et al. [20] on 100 consumers and then on a focus group of 15 members, with 12 females and 3 male subjects. The products were made from A1A1 and A2A2 milk. The test was carried out for two types of cheese namely Petit Suisse and Minas Frescal.

1. In case of Petit Suisse cheese the results showed that there was no significant difference ($p > 0.05$) between the products while comparing the data for sensory flavor and texture responses.
2. Where in case of Minas Frescal cheese, 85 out of 100 consumers were able to identify A2A2 cheese samples with significant difference ($p \leq 0.05$) between the cheeses produced by different milks. The consumers were able to differentiate by attributing A2 milk with an acidic taste and only a few by its flavor. A2 Minas Frescal cheese was described as a softer (macio) and creamier (cremoso) sample, whereas A1 cheese was considered more consistent, rubbery (borrachento) and drier (seco).

BCM-7 and its potential for causing diseases

A research was carried to investigate BCM-7's stability or degradation by gastrointestinal juices and porcine jejunal brush border membrane peptidases during the in vivo digestion with real human volunteers and was monitored by HPLC-electrospray ionization mass spectrometry (ESI/MS). It was observed that BCM-7 degrades into 3 proteolytic fragments [21].It revealed that 79% BCM-7 was degraded in 4 hours with supplementation of brush border membrane (BBM) peptidases and most of it degrades with gastro intestinal juices [21]. The opioid effects of BCM-7 have been proved in vivo, upon intraperitoneal or intracerebellaradministration [22, 23].

Whereas, to interact with the central nervous system after the ingestion, this peptide must be able to survive the breakage of the BCM's after they are broken from beta-casein. They must be absorbed through the intestines and lastly, they must be able to penetrate through the blood-brain barrier. It has been observed that the BCM's act locally at gastrointestinal level weakening the gastrointestinal functions and increasing the delivering time [24, 25].

A detailed discussion regarding the role of BCM-7 in causing some significant diseases has been given below.

Diabetes type-1

BCM-7 is a μ-opioid receptor agonist [26] and it is quite similar to the opioid released by gluten (which is a type of protein found in cereal), both of them have been linked with the type-1 diabetes [27]. It is one of the major chronic illness affecting children, it is caused by loss of pancreatic β-cells responsible for production of insulin in numerous individuals, but a trigger from the environment is generally needed[28]. A1 β-casein acts as a trigger for type-1 diabetes.It is lucid from various researches that human milk is of A2 type as it contains proline at the corresponding position with the cow's A2 beta-casein[29]. Thereby breastfeeding the neonate will eliminate the exposure to A1 beta-casein at an early stage of life. But it does not eliminate the transfer of BCM-7 as it can be transferred through human milk if A1 milk has been ingested by the milk producing individual [30]. A study was conducted across 12 countries to determine the correlation between diabetes mellitustype-1 (DM-1) and the consumption of milk by children of Finland and Iceland. It was rendered inconclusive as the amount of milk consumed had no detrimental effect[31] but rather an interesting conclusion was derived that children of Iceland with higher consumption in comparison to Finnish children were at a lower risk of DM-1 [32]. When the same scientific research was carried out upon predisposed non-obese diabetic (NOS) mice, they developed DM-1 if they were fed with milk from A1 cows, but when fed with milk from A2 cow's milk, cow's milk whey, soya protein or even with (fully) hydrolyzed A1 β-casein they did not develop DM-1 [33]. Finally, when fed with naloxone (morphine antagonist) that gives an antithetical effect as β-casomorphin-7, that A1 β-casein proved to have no effect when ingested with naloxone. Also, A1 β-casein had no effect when given with naloxone, a morphine antagonist that opposes the opioid effect of β-casomorphin-7 [34].

It has also been observed that nearly all studies conducted on humans fed with A1 milk have concluded that no amount of BCM-7 was detected in human adults, whereas BCM-7 has been found in the blood of infants [35]. But these studies were unable to link BCM-7 as a cause of diabetes, but the health of patients who already suffer from diabetes decline even further. But no conclusive evidences are present as no clinical trials were carried upon any human subjects with DM-1.

Sudden infant death syndrome

Sudden infant death syndrome(SIDS) is observed in a healthy child below the age of 1 year, which remains unexplained. It affects the children of the age above 1 month and below 1 year [36]. There have been many proposed causes to this problem i.e. narcoticusage, young age, poor nutrition, and smoking during pregnancy and some other abnormalities in parents. But one common factor arises in all such cases, it is their source of nutrition i.e. milk. It is alleged that when the casein brakes down it results in the release of β-casomorphin. These BCMs, prominently BCM-7 is fairly resistant to breakage due to the presence of proline and hence a significant quantity of these get accumulated in the stomach. Following absorption from the gastrointestinal (GI) tract, BCMs can easily cross the blood-brain barrier (BBB) because of the infant's immature central nervous system leading to death [37].

Other problems associated with the BCM-7 production

A study conducted by Svedberg et al. [38], involving the in vitro digestion of cow's milk found a considerable amounts of BCM-7 in adult human beings. Although another study conducted on immunoreactive BCM in blood was unable to detect any such opioid in humans. However, in newborn calves a precusor of BCM-7 i.e. plasma-CM(1-7) were detected after ingesting the first milk [39].Therefore, it is concluded that BCMs are much more likely to be observed in newborns rather than

adults a result of highly developed circulation system in adults. Along with this BCMs' were also isolated from the urine [40]as well as blood [41]of patients suffering from autism, schizophreniaand postpartum psychosis.It is of utter most importance to know thatthe level of circulating BCM-7 may be elevated due to the deficiency of metabolizing enzymes and/or intestinal disorders and can easily be correlated with the fact that the enzyme required for proteolysis are non-existent in pre-weanlings, allowing the absorption of peptides and proteins from milk [42].

It is a well-known fact that human babies have an immature BBB and hence it is easier for BCMs to enter the central nervous system and reach the brain of the neonate. It has also been implied that these BCMs (1-7) are equipotenttomorphine and causes severe effect on respiratory frequency. As it is equipotent to morphine, it can also be linked with Hering-Breuer reflex[43]. Hering-Breuer reflex has been successfully identified as a risk factor for SIDS.

Cardiovascular diseases

Cardiovascular diseases such as stroke and ischemic heart disease (IHD) are a result of many combined factors that occur over time in the human body. It occurs not because of a single component rather there are several risk factors associated with it, such as increased blood pressure, high cholesterol levels in the body, smoking and high amount of alcohol consumption, etc. At the same time due to several researches carried out on milk and its impact on the human health it has become somewhat evident that the A1 allele has an adverse effect on our cardiovascular health[33]. The report submitted by Professor Boyd Swinburn to New Zealand Food Safety Authority indicates that high intake of A1-casein also acts as a risk factor in IHD. Although it is based upon the same ecological data as in the case of DM-1 but during the analysis there have been some significant correlation, though it's not as high as in the case of DM-1, yet it's still impressive for a multifactorial disease. Although some studies have been conducted on animals but it's difficult to translate animal studies to human health and therefore there is need for more human based trails[11].

Autism and Schizophrenia

Autism and schizophrenia are mental disorders which originate in the brain. They have also been linked with the consumption of A1 milk and the post-consumption, production of BCM-7 opioid. Patients who are suffering from schizophrenia (leaky gut syndrome) and autism have shown significant amount of BCM-7 in their urine[44]. Which links these mental diseases with the consumption of A1 milk. It is believed that these could be cured by changing the diet. These patients have shown great improvements in their symptoms after ingesting diets free from milk casein and gluten diets[45].

There are several other diseases associated by ingestion of A1 milk. Summarized information regarding the role of milk types in triggering or causing various diseases has been summed up in Table 1.

CONCLUSION

Many research studies have been conducted worldwide to highlight the potential health risks associated with consumption of A1 milk. The alternate being offered is the A2 milk, however, no studies so far have noticeably shown any health benefits of A2 milk. Yet, it continues to be sold at elevated prices. At the same time the production of A2 milk is considerably low worldwide owing to this extremely low production and high costs of A2 milk as well as lack of instant (platform) detection methods, it poses a challenge as whether the consumer paying extra price for it is justified. When, the world is already struggling with food scarcity and sustainability issues and consumer is already trapped in tags like "organic", "pesticide free", "Non-GMO". The need of the hour is to conduct more research to completely understand the pathway of A1/A2 milk digestion process and its association with triggering/causing diseases in different age groups, regions and races as well as to develop quick detection methods. So as the consumer gets the complete knowledge before making the choice about switching to A2 milk and judiciously using their money. Therefore, further efforts assert with certainty that A2 milk is a better choice than A1 milk for human health.

Table 1: Role of milk type in triggering/causing diseases

DISEASES CAUSED	A1 MILK	A2 MILK	REFERENCE
TYPE 1 DIABETES	Yes	No	33
ARTERIOSCLEROSIS	Yes	No	17
BRAIN FUNCTION	Yes	No	33, 46
INFLAMMATION	Yes	No	18
SUDDEN INFANT DEATH	Yes	No	37
AUTISM	Yes	No	46, 17
GASTROINTESTINAL DISEASES	Yes	No	25
ABDOMINAL PAIN	Yes	No	47
CARDIOVASCULAR DISEASES	Yes	No	17
CALCIUM DEFICIENCY	Yes	No	48
ACNE	Yes	No	49
UPPER RESPIRATORY TRACT INFECTIONS	Yes	No	2
METABOLIC SUPPRESSION	Yes	No	2
LYMPHATIC OBSTRUCTION	Yes	No	49
SCHIZOPHRENIA	Yes	No	17, 33
EAR INFECTIONS	Yes	No	50
CANCER	Yes	No	51
CONSTIPATION	Yes	No	52
BRUCELLOSIS	Yes	Yes	53
TONSILLITIS	Yes	No	54
IMMUNE DESTRUCTIVE EFFECT	Yes	No	2
CAMPYLOBACTER JEJUNI INFECTIONS	Yes	Yes	55
STAPHYLOCOCCUS AUREUS INFECTIONS	Yes	Yes	56
MYCOBACTERIUM BOUIS INFECTIONS	Yes	Yes	57
YERSINIA ENTERCOLITIS INFECTIONS	Yes	Yes	58
SALMONELLA INFECTIONS	Yes	Yes	59
BOVINE SPONGIFORM	Yes	Yes	60
ASTHMA	Yes	No	61
ISCHEAMIC HEART DISEASES	Yes	No	33, 62

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