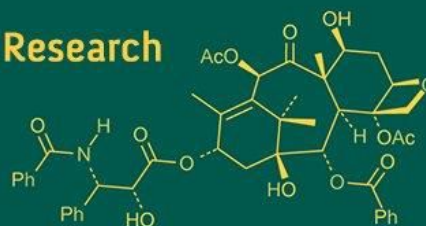
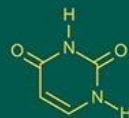


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Bovine milk hypothesis: A1 and A2 β casein, BCM-7 and its impact on human health

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Abstract

Genetic variation has been most raised interest in many research fields related to both disease diagnosis and health impacts. Bovine milk protein peptides is a growing discussion of whether on digestion of A1 milk, the release of opioid peptides like BCM-7 has any harmful or beneficial effect. A1 β casein milk has associated with type-1 diabetes, Coronary heart disease, sudden death syndrome in infants and atherosclerosis.

Keywords: Milk, a1/a2 β casein, beta-casomorphin-7, health impact

Introduction

Cow milk is a healthy food which is considered as excellent source of basic human needed minerals, which carries high nutritional value and also a great source of calcium and phosphorous. The composition of cattle milk is more protein in nature and an importance source of various nutrients including carbohydrates and selected micronutrients. (Abdulahdi *et al.*, 2018) [3]. Cow milk is majorly constituted of proteins like caseins and whey proteins. In India dairy sector has been significantly growing and consistently been top milk producer which contributes to 63.56%. Nutritional makeup of cow's milk varies depending upon the breed, health status and feed supplements which is provided to the cattle and other factors. The major components of milk are water, fat, protein, lactose, and ash. The minor components of milk are sterols, vitamins and minerals, milk pigments and enzymes. So as indigenous cattle is more adapted to climates and conditions like heat-resistance, which provides more nutritious milk compared to the western breeds (Rekha *et al.*, 2018) [5].

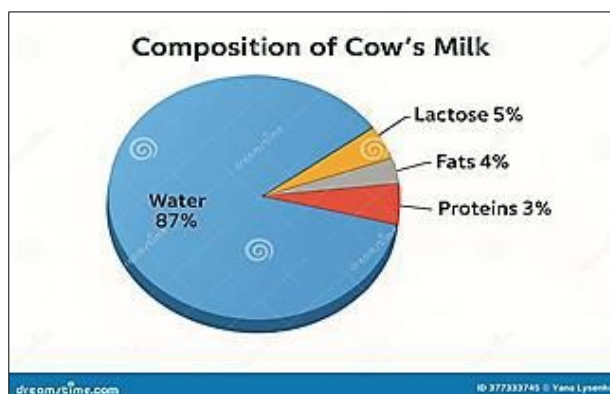


Table 1: Gross Composition of different milk animals

Name of the species	Water %	Fat %	Protein %	Lactose %	Ash %
Buffalo	84.2	6.6	3.9	5.2	0.8
Cow	86.6	4.6	3.4	4.9	0.6
Goat	86.5	4.5	3.5	4.7	0.8
Sheep	86.3%	7.2	5.5	4.8	0.9

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Genetic Variants of Bovine Milk

Milk protein is the primary macromolecule responsible for production of dairy products. Due to the genetic variations bovine milk proteins are encoded by polymorphic chromosomes where six major bovine milk proteins are seen. These protein variants are characterized by heat stability and coagulation properties of milk. The protein content of milk is majorly comprised of 80% of casein and 20% of whey proteins of which six major milk protein variants are casein (α S1, α S2, β , k-CN) and whey (α -La and β -LG) (Liam *et al.*, 2024) [6]. Among the milk protein casein is major source of all amino acids except sulphur containing amino acids. Casein protein constitutes of 35% of α -casein, 30% β variant and 9% of k-casein and remaining is peptides and amino acids. In that β -casein is second abundant and has more essential amino acids. Because of genetic variation bovine β -casein has been more focused area. In 1998 the complete sequence of β -casein was published by (Heck *et al.*, 2009) [15]. And until now 15 genetic variants of β -casein are been reported and named according to the order A1, A2, A3, B, C, D, E, F, G, H1, H2, I, J, K, L (Andrea *et al.*, 2020) [10]. In principle, each variant differed by one - three amino acids substitutions at different locations but generally β -casein classifies as A1 type (05 variants) and A2

type (10 variants) depending on the proline and histidine amino acid position at 67th position (Chitra 2022) [17].

A1 and A2 Milk β Casein

A1 milk is produced by the cows of western origin like Holstein Friesian and jersey cattle. A2 milk is produced by the indigenous native cows which are more beneficial compared to the A1 milk (Shreya *et al.*, 2022) [4]. The protein variation of A1 and A2 milk is with casein protein (i.e. mainly β -casein) is solely under the control of genetics. There are several types of casein proteins like α , β casein with sub variants like A1, A2, B, C and E (Tom 2020) [1]. The milk which contains A1- β casein is called A1 milk and the milk which contains A2 β casein is called A2 milk. A1 milk and A2 milk variant β -case in which differs at 67th amino acid where due to mutations A1 is linked to histidine A2 is codes for amino acid proline (Monika *et al.*, 2012) [2]. As many of the studies suggested that A1 milk is associated with several health issues like type -1 diabetes, coronary heart disorders and digestive disorders. Some research suggests that during digestion of A1 milk protein variant beta casein can breakdown to BCM-7 like biological peptides.

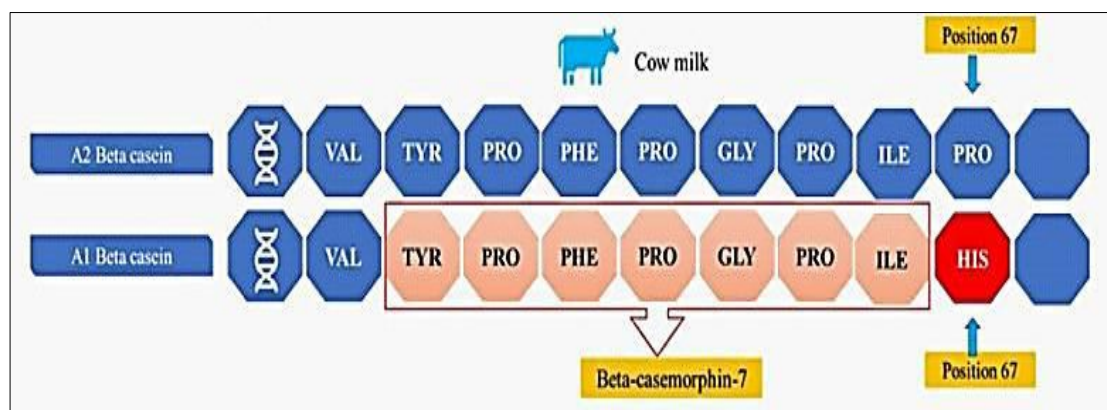


Fig 1: Difference between A1 and A2 beta-casein

The A1 and A2 β casein is single nucleotide polymorphism found in different breeds, therefore they are considered as potential genetic markers. A1 allele is linked to high milk yield, high fat and protein yield where A2 is linked to reduces serum cholesterol (Alan *et al.*, 2025) [8].

Digestive Effect of A1 and A2 Milk β Casein

When milk is consumed, proteins are degraded into peptides which help in growth of healthy gut microbe environment. These biological peptides are released in intestine further gets absorbed in main bloodstream which shows systemic effects.

On gastrointestinal digestion of β casein releases several bioactive peptides which vary from medium to large size peptides of size (750 - 1800kDa). Several studies showed that on intraluminal digestion of A1 β casein releases the

opioid peptide like beta- casomorphin-7 (β CM-7) (Alan *et al.*, 2025) [8] whereas digestion of A2 milk releases BCM-9 and a less amount of BCM-7.

β CM-7 is a bioactive peptide of seven amino acid which is released on digestion with pepsin, leucine, aminopeptidase and elastase in small intestine which activates morphine like opioid receptors which are present in gastrointestinal tract and immune system while many of the hypothesis suggest that on digestion of A2 β casein does not release the β CM-7. Epidemiological works suggested that A1 β casein has association with type 1 diabetes (insulin dependent diabetes) is due to β CM-7 is opioid in nature has shown inhibitory effect on human lymphocyte infiltration and also influences gut tolerated lactose intolerance (Elliott *et al.*, 1999) [9]. The β CM-7 has increased effect of pro inflammatory markers, interleukin (IL-4) and histamine in the rat intestinal fluid.

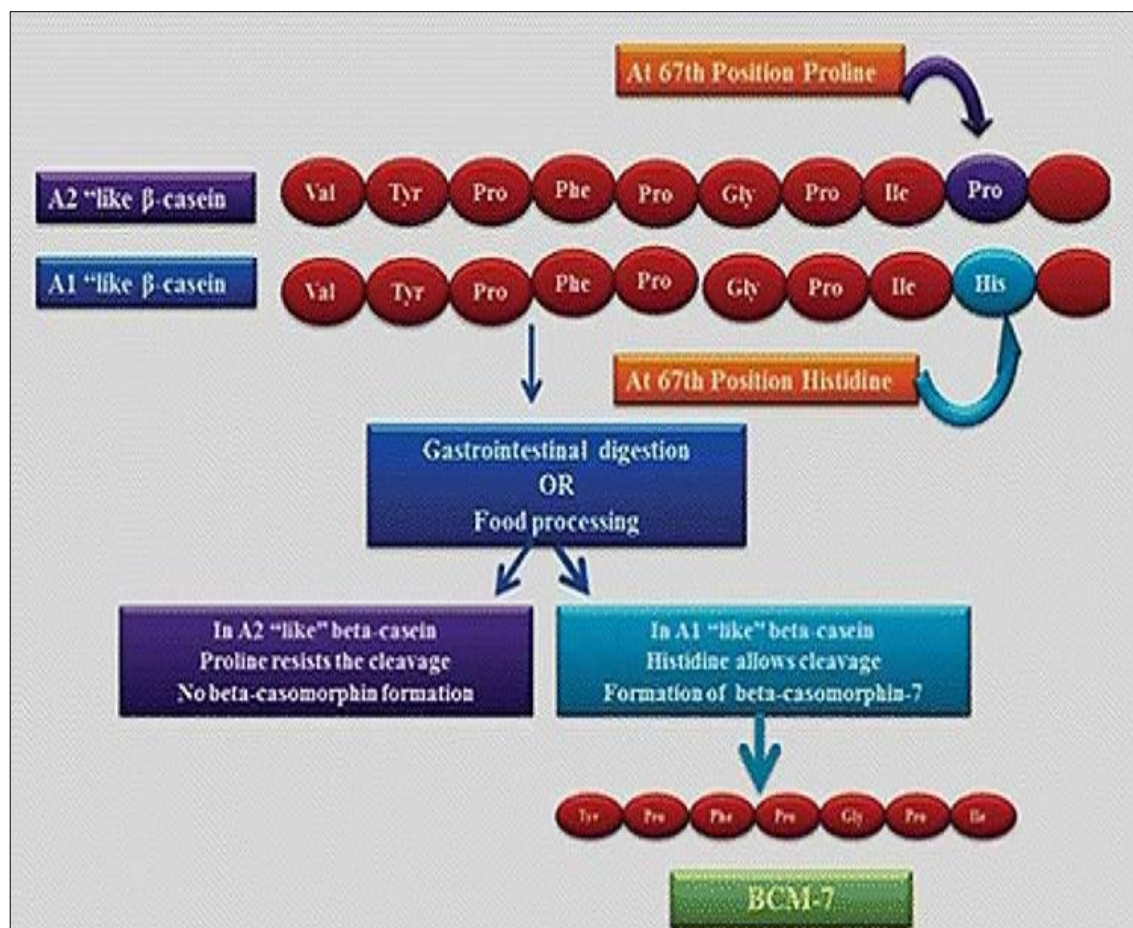


Fig 2: Release of BCM-7 from A1 variant of B-casein

Bovine β -Casomorphins and Health Impacts

Casomorphins are bovine and human milk peptides which are released on digestion of protein casein. Among casomorphins, β -Casomorphins are the most abundant group of peptides having morphine like activity which act by binding to opioid receptors that are normally present in central nervous system and the gastrointestinal tract. There are different β -Casomorphins are present in bovine milk which vary by sequence of amino acids and source of milk. The commonly seen variants of casomorphin are BCM 4,5,6,7,8,9 and neocasomorphins-6 and human BCM-4,5,7,8 and α -casomorphin. But BCM-7 is most common part of discussion due to their health impacts (Ecem *et al.*, 2024) [14]. Many types of research has shown that BCM-7 is not easily digestible in body, and has pro-inflammatory properties which leads various problems like coronary heart diseases, arteriosclerosis, sudden infant death syndrome and type 1 diabetes (Elliott *et al.*, 1999) [9].

BCM-7 can penetrate the gastrointestinal wall and get into blood circulation. causes inflammation high in the duodenum which may decrease absorption of lactose in ileum which manifest as Lactose intolerance. They also reported that BCM-7 induces the inflammatory responses in the gastrointestinal tract by activating the Th2 pathway and increases the myeloperoxidases, monocyte chemo attractant protein-1, antibodies (IgE, IgG, IgG1, IgG2a) and Toll-like receptors 1 and 2 into the intestine which causes intolerance. (Sun Jianqin *et al.*, 2016) [11].

BCM-7 participates in immune related event, which might trigger metabolic disorder like type-1 diabetes. BCM-7 stimulates the production autoantibodies against the GLUT-2 transporters and these autoantibodies inhibit the activity of

GLUT-2 which prevents the uptake glucose by the cell. BCM-7 can also disrupts the insulin hormone transmission regulation and impact on insulin action (Ecem *et al.*, 2024) [14].

On consumption of cow milk, β casomorphin 7 released by pancreatic elastase by degrading the peptide bond between Ile⁶⁶ and His⁶⁷ of A1 β casein (Tailford *et al.*, 2003) [13]. rabbit model showed that β casein of both A1 and A2 produced fatty streaks but A1 produced more extensive lesions and thickened fatty streaks in the aortic arch are more. So, such type of caseins ingested by children is more prone for atherosclerosis. (Torreilles and Guerin 1995) [12]. BCM-7 can also trigger the oxidative state within system. Glutathione act as major antioxidant, directly neutralizes the free radicles and reactive oxygen species (ROS). Due to it opioid effect BCM-7 inhibit the uptake of cysteine amino acid into the cell which affects the production of GSH (glutathione). This decreases the GSH levels in blood which could potentially lead to neurodegenerative disease (Ecem *et al.*, 2024) [14].

Conclusion

India stands for world's largest milk producer, achieved by strategic selection of high yield breeds, improvements in fodder quality and efficient implementation of cattle cross breeding programs. Milk is globally consumed as a rich source of protein and calcium. This A1/ A2 hypothesis plays an important role on public health. The protein variation of A1 and A2 milk is with casein protein (i.e. mainly β -casein) is solely under the control of genetics. The hypothesis A1 milk is associated with several health issues like type -1 diabetes, coronary heart disorders and digestive disorders.

Most of the *in vitro* studies showed that A1milk derived BCM-7 has most potential health impacts compared to A2 milk BCM-7. Though there is no scientific evidence of health impacts on human consumption and its part of controversial topic which needs more research and consideration for gaining better information.

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