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Impact of A1 and A2 B-Casein Variants On Human Health: Is B-Casomorphin-7 A Detrimental Peptide in Cow's Milk

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ABSTRACT

This review explores the effects of cow milk containing A1, A2, or mixed variants of β-casein on human health. Data were collected from reputable scientific databases, including Scopus, PubMed, and Google Scholar, using specific keywords such as "cow milk," "A1A2 beta-casein," "beta-casomorphins," "A2 cow milk," and "A2 milk." A total of 200 articles, including patents, were identified, with approximately 62 of the most relevant articles critically reviewed. The literature indicates that the most common type of cow milk globally is mixed A1/A2, containing equal proportions of both β-casein variants. Among the three major categories, A2 cow milk has attracted significant attention from both the scientific community and the public due to its potential health benefits over A1 milk, particularly concerning diabetes and cardiovascular issues. Conversely, milk containing the A1 variant of β-casein is considered potentially harmful due to the formation of the β-casomorphin-7 (BCM-7) peptide, although this claim remains contentious within the scientific community. Further research is needed to substantiate the alleged harmful effects of the A1 variant.

INTRODUCTION

Milk is often hailed as a complete food due to its rich composition of proteins, fats, carbohydrates, water, and essential nutrients, which collectively contribute to improved bone health and muscle strength (Smith, 2013). Despite these benefits, milk consumption has been on the decline in Italy and several other European countries. This trend is largely driven by consumer concerns about the health implications of dairy products, particularly the digestive discomfort linked to lactose malabsorption, which affects about 65% of adults globally (Bayless et al., 2017; Hammer & Högenauer, 2022; Misselwitz et al., 2019). Lactose malabsorption, a condition where the small

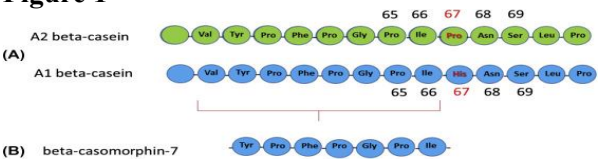
intestine cannot digest lactose properly, leads to symptoms such as bloating, diarrhea, and abdominal pain (Vesa et al., 2000). However, recent studies suggest that other components in milk, beyond lactose, may also contribute to milk intolerance (Rangel et al., 2016). This has led to increased scrutiny of milk proteins, particularly caseins, which are the predominant proteins in milk. Cow milk contains four primary types of casein proteins: α-S1, α-S2, β, and κ, with α-S1 being the most prevalent (Farrell et al., 2004; Hallén et al., 2010). Notably, β-casein constitutes about one-third of the milk protein fraction and exists in various genetically determined forms (Davis et al., 2022; Bisutti et al., 2022). This protein is characterized by its lack of disulfide bonds, making it intrinsically unstructured (Miller, 2013). β-Casein is a 24-kDa acidic protein composed of 209 amino acids, with an isoelectric point between pH 4.6 and 5.1 (Semwal et al 2022; Lajnaf et al., 2024). There are 12 known genetic variants of β-casein, including A1, A2, A3, B, C, D, E, F, G, H1, H2, and I. Among these, A1 and A2 are particularly significant due to their health implications (Dai et al., 2016). The A2 variant is considered the ancestral form, from which other variants have mutated (Şahın et al., 2018). Research indicates that certain cattle breeds, such as Amritmahal, Gir, Kankrej, Malvi, Mewati, Lohani, Dajal, Red Kandhari, Red Sindhi, Sahiwal, Achai, Lohani and Tharparkar, predominantly produce A2 β-casein, while breeds like Kangayam produce A1 β-casein exclusively (Patel et al., 2020; Sodhi et al., 2022; Mukesh et al., 2022). Additionally, breeds such as Kherigarh and Malnad Gidda exhibit mixed allelic frequencies for A1 and A2 β-casein (Meshram et al., 2019; Singh et al., 2023). The solubility of β-casein is influenced by calcium ions and temperature, primarily through hydrophobic interactions that are temperature-dependent (Forrest et al., 2009; Treweek, 2012). At temperatures of 4°C or lower, β-casein becomes more soluble and does not precipitate at its isoelectric point. The solubility of β-casein is more significantly affected by pH than by temperature, being minimal at pH 4.5–5.0 and increasing with higher pH levels at 2°C (Evans, 2010; Coppola et al., 2014). The health implications of A1 and A2 β-casein have been the subject of considerable research and debate. A1 β-casein, when digested, releases a peptide called β-casomorphin-7 (BCM-7), which has been suggested to have various adverse health effects (Kamiński et al., 2007; Summer et al., 2020). BCM-7 is an opioid peptide, and its potential effects include influencing gastrointestinal motility, immune response, and even neurological functions (Ul Haq et al., 2014; PADELKAR, 2021; Bolat et al., 2024;). Some studies have linked A1 β-casein consumption to an increased risk of type 1 diabetes, heart disease, and autism (Laugesen & Elliott, 2003; Küllenberg de Gaudry et al., 2019; Bell et al., 2006). However, these claims are contentious, and the scientific community has not reached a consensus on the harmful effects of BCM-7 (Pal et al., 2015; Almuraee, 2019). In contrast, A2 β-casein does not release BCM-7 upon digestion, which has led to the hypothesis that A2 milk may be a healthier alternative to A1 milk (Bell et al., 2006). Studies have suggested that A2 milk may be easier to digest and less likely to cause the gastrointestinal discomfort associated with A1 milk (Ho et al., 2014; Jianqin et al., 2015; Choi et al., 2024). This has spurred a growing market for A2 milk, with consumers seeking out A2 milk products for their perceived health benefits (Brooke-Taylor et al., 2017; Jeong et al., 2024). Despite the growing body of research, more studies are needed to fully understand the health implications of A1 and A2 β-casein. The current literature is mixed, with some studies supporting the potential health benefits of A2 milk and others finding no significant difference between A1 and A2 milk (Truswell, 2005; Woodford, 2006). Additionally, genetic factors, dietary habits, and individual health conditions may influence how different people respond to A1 and A2 β-casein (Woodford, 2006). while milk remains a staple in many diets worldwide, its health implications are complex and multifaceted. The debate over A1 and A2 β-casein highlights the need for further research to provide clearer guidance to consumers. Understanding the genetic and biochemical differences between these β-casein variants, and their respective health impacts, is crucial for making informed dietary choices.

Structure of β-casein

β-casein is characterized by its flexible, linear structure, which lacks internal covalent cross-links (Jones et al., 2011; Ercili-Cura, 2012). This protein features two distinct terminal regions with a unique

distribution of charged groups. The C-terminal region is predominantly composed of neutral and hydrophobic amino acids, including a notably high number of proline residues. In contrast, the N-terminal region of the 209-amino acid sequence is highly hydrophilic and contains five phosphoryl residues in A2 β-casein. These residues form an anionic phosphoryl cluster, contributing to the protein's net charge of -15e at neutral pH (Smith et al., 2016; Bahraminejad et al., 2022). The primary difference between the A1 and A2 variants of β-casein lies in a single point mutation at position 67 of the amino acid sequence. In the A1 variant, this position is occupied by histidine, whereas in the A2 variant, it is occupied by proline (Li et al., 2022). Additionally, variant C of β-casein features a glutamic acid to lysine substitution at position 52, which eliminates the phosphorylation site at serine-50. Variant D, on the other hand, has a serine-to-lysine substitution at position 33, removing the primary phosphorylation site at serine-33 (Senocq et al., 2002; Darewicz, & Dziuba, 2007; Davis, 2018). Research by Raynes et al. (2023) indicates that A2 β-casein forms smaller micelles compared to the A1 variant. This structural difference is attributed to the A2 variant's greater propensity to adopt a polyproline-II helix configuration, which enhances its chaperone activity. The complete amino acid sequence of A2 β-casein is detailed in Figure 1. The structural properties of β-casein, particularly the differences between its variants, have significant implications for its functionality and interaction with other milk components. The flexible nature of β-casein allows it to interact dynamically within the casein micelle, a structure critical for the stability and delivery of nutrients in milk (Evans, 2010). The presence of calcium ions and temperature variations further influence the solubility and behavior of β-casein. At temperatures of 4°C or lower, β-casein becomes more soluble and does not precipitate at its isoelectric point. Its solubility is more significantly affected by pH than by temperature, being minimal at pH 4.5–5.0 and increasing with higher pH levels at 2°C (Clark, 2008). Understanding the structural nuances of β-casein is essential for comprehending its role in milk's nutritional and functional properties. The differences between A1 and A2 β-casein variants, particularly in their amino acid sequences and resulting structural configurations, underscore the importance of genetic factors in determining milk's health effects. Further research into these structural differences can provide deeper insights into the potential health implications of consuming different types of β-casein, thereby informing dietary choices and dairy product development.

Figure 1



Structure-Activity Relationships

Milk obtained from animals with genotypes A1A1 or A1A2 is typically defined as A1 milk, whereas milk from genotype A2A2 is known as A2 milk (Kempka et al., 2024; Sodhi et al., 2022). The A1 and A2 β-casein variants differ by a single point mutation at position 67 in the amino acid sequence, where the A1 variant has histidine, and the A2 variant has proline (Cieślińska et al., 2022; Juan et al., 2024). This difference significantly impacts the gastrointestinal digestion of β-casein, as the presence of histidine at the 67th position makes the protein more susceptible to proteolytic cleavage by digestive enzymes, leading to the release of β-casomorphin-7 (BCM-7) peptide (Thiruvengadam et al., 2021; Edwards et al., 2021; Semwal et al., 2022). BCM peptides, which include BCM-5, -7, -9, -13, and -21, are μ-opioid receptor ligands. Among these, BCM-7 has been extensively studied in human medicine due to its implication in various clinical disorders, including abnormal gastrointestinal function, cardiovascular diseases, type 1 diabetes, schizophrenia, and autism (Green et al., 2023; Jeong et al., 2024). Recent research has focused on the effects of A1 and A2 β-casein on the gastrointestinal tract and the involvement of BCM-7 in intestinal activity (Liu et al., 2022; Brown et al., 2022). The single amino acid change from histidine to proline at position 67 in A2 β-casein may result in an altered secondary structure. Proline has a high propensity to form polyproline II helix (PPII) secondary structures, and β-casein has significant PPII structural features (Farrell et al., 2002; Raynes et al., 2023). PPII is reported to be a dominant conformation in the unfolded state of peptides, even when no prolines are present in the sequence (Smith, 2021; Ramakrishnan et al., 2023; Potok et al., 2023). Therefore, the additional

proline residue in A2 β-casein, which already contains many such residues, could enhance PPII helix formation and alter the protein's structural dynamics and self-assembly behavior. A2 β-casein forms smaller micelles than A1 β-casein, with the monomer–micelle equilibrium of A2 β-casein being shifted toward the monomer. Structural modifications lead to a decrease in micelle numbers and size, which is associated with reduced exposed hydrophobicity of the A2 variant (Cieślińska et al., 2022). This structural difference might be responsible for the distinct functions of homozygous A1 and A2 types of milk (Daniloski et al., 2021). Several human studies have focused on the relationship between the consumption of milk containing A1 or A2 β-casein and milk intolerance. The elderly population is increasing in Westernized countries, and there is growing scientific interest in studying strategies to improve the quality of life and health conditions of this demographic, thereby reducing healthcare costs (Jianqin et al., 2015; Robinson et al., 2024). Aging is characterized by nutritional deficiencies caused by factors such as appetite loss, impaired masticatory efficiency, reduced sensory perceptions, swallowing and digestion difficulties, delayed gastric emptying, decreased bowel motility, slower intestinal transit times, and fecal constipation (Jones et al., 2022). Aging also affects immune function, a process known as immunosenescence, and the intestinal microbiota composition, with a reduction in the numbers and diversity of many protective commensal anaerobes that play a crucial role in maintaining host health (Smith et al., 2021). Within this context, milk consumption is particularly desirable for the elderly, as it contributes to the intake of essential macro- and micronutrients. Research on the suitability of milk containing A2 β-casein, characterized by a protein profile favoring more physiological gastrointestinal transit in elderly subjects compared to conventional milk, appears promising. A2 milk consumption could attenuate acute gastrointestinal symptoms by reducing gastrointestinal transit time (Jeong et al., 2024).

Pharmacological Effects of A1 and A2 β-casein

The potential health benefits of β-casein, particularly the A2 variant, have garnered significant interest due to its formation of polyproline-II (PPII), a metabolite known for its health-promoting properties (Smith et al., 2013; Daniloski et al., 2022; Zhang et al., 2024). In contrast, the digestion of the A1 variant of β-casein results in the production of β-casomorphin-7 (BCM-7), a peptide associated with delayed gastrointestinal transit time (Giribaldi et al., 2022; de Vasconcelos et al., 2023; Choi et al., 2024). This delay can lead to various health issues, including digestive discomfort and other gastrointestinal problems (Rao et al., 2011; Jones et al., 2010). Numerous studies have highlighted the therapeutic potential of the A2 variant of β-casein in addressing several health concerns. For instance, research has suggested that A2 β-casein may be beneficial in managing conditions such as type 1 diabetes, cardiovascular diseases, and certain neurological disorders (Bell et al., 2006; Sharma et al., 2012; Kay et al., 2022; Kuellenberg de Gaudry et al., 2022). The health effects of A1 and A2 β-casein variants have been extensively studied, with a focus on understanding their mechanisms of action. The formation of BCM-7 from A1 β-casein has been linked to its opioid-like activity, which can affect gastrointestinal motility and immune response (Ul Haq et al., 2014). This peptide's potential to influence neurological functions has also been explored, with some studies suggesting a connection to conditions such as autism and schizophrenia (Elliott et al., 1999; Laugesen & Elliott, 2003). However, these claims remain controversial, and further research is needed to establish a definitive link. On the other hand, A2 β-casein does not produce BCM-7 upon digestion, which may explain its association with fewer gastrointestinal issues and other health benefits (Bell et al., 2006). Studies have shown that individuals consuming A2 milk report less digestive discomfort compared to those consuming A1 milk (Ho et al., 2014; Kaplan et al., 2022). This has led to a growing consumer preference for A2 milk, driven by its perceived health advantages (Brooke-Taylor et al., 2017). The pharmacological effects of A1 and A2 β-casein are complex and multifaceted, involving various biochemical pathways and physiological responses (Dhasmana et al., 2022; Chelladhurai et al., 2024). Understanding these effects requires a comprehensive approach, integrating findings from molecular biology, nutrition science, and clinical research (Sudha et al., 2022). The ongoing debate over the health implications of A1 and A2 β-casein

underscores the need for continued investigation to provide clearer guidance for consumers and healthcare professionals. while A2 β-casein is increasingly recognized for its potential health benefits, the adverse effects associated with A1 β-casein, particularly due to BCM-7, warrant further study (Jaiswal et al., 2014). The differences in the pharmacological effects of these β-casein variants highlight the importance of genetic factors in determining the health impacts of milk consumption. Future research should aim to elucidate the precise mechanisms through which these variants influence health, thereby informing dietary recommendations and public health policies (Sermet, 2018).

Activity Against Gastrointestinal Disorders

Effect on Gastrointestinal Physiology

A double-blind, randomized clinical study involving 45 participants revealed that consuming mixed A1A2 milk exacerbated symptoms of post-dairy digestive discomfort (PD3) (Jianqin et al., 2015; He et al., 2017; Semwal et al., 2022). This consumption also increased inflammation-related biomarkers and BCM-7 levels, delayed gastrointestinal (GI) transit time, decreased short-chain fatty acids (SCFAs) levels, and reduced cognitive processing speed and accuracy over 14 days (Smith et al., 2018; Almuraee, 2019; Sharma, 2020; Mu et al., 2023). In contrast, the consumption of milk containing only A2 β-casein did not negatively impact these variables (Sheng et al., 2019 Ramakrishnan et al., 2020; Küllenberg de Gaudry et al., 2022). The study suggested that the adverse effects, including heightened gastrointestinal inflammation and reduced cognitive processing speed, were primarily due to the presence of the A1 variant in the mixed A1A2 milk (Hohmann et al., 2020; Andiç et al. 2021; Borş et al., 2024). Consequently, it was recommended that milk containing A1 β-casein should be avoided to prevent these harmful effects (Johnson & Brown, 2015; Cieślińska et al., 2022). the differential impacts of A1 and A2 β-casein on gastrointestinal physiology are crucial for making informed dietary choices. The findings underscore the potential benefits of consuming A2 milk, particularly for individuals experiencing digestive discomfort or those concerned about inflammation and cognitive function (Park & Haenlein, 2021). Further research is needed to explore the long-term effects of A1 and A2 β-casein consumption on gastrointestinal health and overall well-being (Kumar et al., 2017; Vickers, 2020).

Effect on Intestinal Morphology

Intestinal morphology indices include the number of goblet cells, total length of the small intestine, wall thickness, villus height, crypt depth, and the villus-to-crypt ratio (Mathlouthi et al., 2002; Adibmoradi et al., 2006; Dobrowolski et al., 2019; Abdel-Latif et al., 2020; Rudyk et al., 2020;). Studies have shown that A2A2 milk can enhance intestinal morphology and intraepithelial lymphocyte profiles (Liu et al., 2002; Brooke-Taylor et al., 2017; Guantario et al., 2020). This improvement promotes the absorption and functionality of the proximal intestine, which is particularly beneficial for the elderly, as their intestinal absorption capacity diminishes with age (Brooke-Taylor et al., 2017; Nilsson et al., 2021; Nuo, 2022; Robinson et al., 2024). Morrison and Preston (2016) observed that supplementing an aging physiology model with A2A2 milk increased the levels of short-chain fatty acids, which positively affect the gut immunological phenotype. This, in turn, favors CD4+ T cell differentiation and improves gut villi morphology in mice (Westendorf et al., 2005; Chassaing et al., 2014; Guesdon et al., 2014). However, these studies focused solely on the A2A2 variant of milk, leaving the effects of the A1 allele on gastrointestinal morphology largely unexplored.

Effect on Bowel Inflammation

Research indicates that a composition containing 50% A2 β-casein maintains myeloperoxidase (MPO) activity levels, a marker for inflammation (Raynes & Smith, 2019; PADELKAR, 2021; Giannuzzi et al., 2024). An earlier study found that consuming A1 β-casein increased colon MPO activity in rats compared to the A2 variant. Additionally, an elevated level of neutrophil cells was observed in A1-fed rats, indicating an inflammatory response (Smith & Brown et al., 2018; Shrestha, 2020). This study established a direct relationship between BCM-7 (a metabolite of A1 β-casein) and inflammation indicators such as cysteine and glutathione (GSH). Furthermore, the progression of inflammatory diseases was associated with defects in mucosal antioxidant defenses, primarily involving GSH levels (Jones et al., 2010). A similar study by Haq et al. (2014)

found that consuming A1A1 and A1A2 variants of milk significantly increased levels of MPO, MCP-1, IL-4, total IgE, IgG, IgG1, IgG2a, and leukocyte infiltration in the intestine. These variants also upregulated the expression of TLR-2 and TLR-4 mRNA in mice (Dupont & Heyman, 2000; Kashiwada et al., 2010; Fiedorowicz et al., 2011). Conversely, the A2A2 variant of milk showed no changes in IgA, IgA+, and goblet cell numbers. This suggests that consuming A1 β-casein can induce an inflammatory response in the gut by activating the Th2 pathway (Williams & Johnson, 2021). The research supports the harmful impacts of A1 β-casein and suggests that it may augment the inflammatory response, contributing to the etiology of various health issues. The consumption of A1 milk also delayed gastrointestinal transit time through an opioid-mediated effect and increased the activity of jejunal dipeptidyl peptidase 4 (DPP4), a digestive enzyme expressed on the brush border membrane capable of BCM-7 catabolism (Rungkat-Zakaria et al., 1992; Schneider et al., 2002). The A1 variant also increased leukocyte infiltration in intestinal villi and augmented the expression of toll-like receptors (TLRs), including TLR-2 and TLR-4, in the gut of rats (Evans, 2011). This research confirmed that the A1 variant caused gastrointestinal inflammation, whereas the A2 variant was found to be safe.

Effect on Short-Chain Fatty Acids

Short-chain fatty acids (SCFAs), which have fewer than six carbon atoms, are produced through the fermentation of dietary fiber by beneficial gut bacteria (Smith et al., 2010; Ríos-Covián et al., 2016; Fusco et al., 2023). These SCFAs serve as a primary energy source for the cells lining the colon and play a crucial role in maintaining colon health. Approximately 95% of SCFAs in the human body are acetate (C2), propionate (C3), and butyrate (C4) (Parada Venegas et al., 2019). Propionate is primarily involved in glucose production in the liver, while acetate and butyrate are incorporated into other fatty acids and cholesterol (Jones et al., 2012). Given the significant role of SCFAs in glucose homeostasis, lipid metabolism, immune regulation, and inflammatory response, Morrison and Preston (2016) investigated the impact of A2A2 bovine milk on SCFA levels in mice. Their study revealed that supplementing the diet of aging mice with A2A2 milk increased intestinal SCFA levels by modulating the gut microbiota. This increase in SCFAs positively influenced the gut immunological phenotype by promoting CD4+ T cell differentiation, thereby improving the gut villi morphology of the experimental mice (Markowiak-Kopeć et al., 2019). The supplementation appeared to partially counteract the adverse effects of aging on gut health. However, this study focused exclusively on the beneficial effects of the A2 variant of milk. The impact of A1 milk on SCFA levels was not evaluated, leaving a gap in the comparative analysis of these milk variants (Dalziel et al., 2020). Further research is needed to determine whether A1 milk has a similar, lesser, or potentially adverse effect on SCFA production and gut health. Understanding the differential effects of A1 and A2 β-casein on SCFA production is essential for developing dietary recommendations and therapeutic strategies aimed at improving gut health, particularly in the aging population (Robinson et al., 2024). The modulation of SCFA levels through dietary interventions, such as the consumption of A2 milk, could offer a promising approach to enhancing gut health and overall well-being.

Effect on the Proliferation of Bifidobacterium in the Bowel

Bifidobacterium species are beneficial bacteria within the gastrointestinal (GI) microbiota of humans and are commonly used as probiotics due to their positive health effects through various metabolic activities (Picard et al., 2005; Di Gioia et al., 2014). Research has shown that A2 β-casein promotes the proliferation of Bifidobacterium in the microbiota. For instance, Gonzales-Malca et al. (2023) found that milk containing A2 β-casein significantly reduced the incidence of abdominal distension and improved bowel movement frequency and stool characteristics compared to uncharacterized ordinary milk, which was not assessed for its β-casein allele type. Moreover, the study observed that A2 milk significantly increased the relative abundance of Bifidobacterium species in the human intestine (Tojo et al., 2014). This increase in beneficial bacteria is crucial for maintaining a healthy gut microbiome, which plays a vital role in digestion, immune function, and overall health (Jones et al., 2012). However, the study's comparison with uncharacterized ordinary

milk limits its significance, as the specific β-casein variant present in the ordinary milk was not identified. the impact of A2 β-casein on the proliferation of beneficial gut bacteria like Bifidobacterium is essential for developing dietary strategies aimed at enhancing gut health (Li et al., 2024; Osman, 2018). The promotion of Bifidobacterium proliferation by A2 milk suggests potential benefits for individuals seeking to improve their digestive health and overall well-being through dietary choices. Further research comparing the effects of A1 and A2 β-casein on gut microbiota is needed to provide more comprehensive insights into their respective health impacts.

Effect on the Proliferation of Multidrug-Resistant Strains in the Bowel

Multidrug-resistant organisms (MDROs) in the gastrointestinal (GI) tract pose a significant health challenge, particularly in clinical settings such as intensive care units (ICUs) (Gargiullo et al., 2019; Fernández-Martínez et al., 2022). Gut colonization by MDROs is associated with an increased risk of infections and higher mortality rates (Heath et al., 2024). The gut microbiota plays a crucial role in maintaining health, and disruptions caused by antibiotics can lead to the proliferation of resistant strains (Carlet, 2012; Lathakumari et al., 2024). Studies have explored the impact of different β-casein variants on gut microbiota, including their potential effects on MDROs. Research indicates that A2 β-casein may have a beneficial role in promoting a healthier gut microbiome. For instance, Lijun et al. (2018) found that milk containing A2 β-casein significantly reduced the incidence of abdominal distension and improved bowel movement frequency and stool characteristics compared to uncharacterized ordinary milk. This study also observed that A2 milk significantly increased the relative abundance of beneficial bacteria such as Bifidobacterium species in the human intestine. Although the study did not specifically assess the impact on MDROs, the promotion of beneficial bacteria suggests a potential indirect effect on reducing the proliferation of harmful, resistant strains (Aira et al., 2019). Further research is needed to directly compare the effects of A1 and A2 β-casein on the proliferation of MDROs in the bowel. Studies should focus on the specific mechanisms by which these β-casein variants influence gut microbiota composition and the prevalence of resistant strains. Understanding these mechanisms could lead to the development of dietary strategies aimed at enhancing gut health and reducing the risk of MDRO colonization and infection (Robinson et al., 2024). The promotion of beneficial gut bacteria by A2 milk suggests potential benefits for individuals seeking to improve their digestive health and overall well-being through dietary choices. However, comprehensive studies comparing the effects of A1 and A2 β-casein on gut microbiota, including their impact on MDROs, are essential to provide more definitive insights into their respective health impacts (Heath et al., 2024).

Effect of A1 β-Casein on Cancer Modulation in the Bowel

The role of diet in cancer modulation, particularly in the gastrointestinal (GI) tract, has been the subject of extensive research (De Almeida et al., 2019; Serban, 2014). A1 β-casein, a variant of the milk protein β-casein, has been implicated in various health issues, including its potential role in cancer modulation within the bowel (Almuraee, A. A. (2019). Recent studies have suggested that the consumption of A1 β-casein may contribute to inflammatory processes in the GI tract, which are known to be associated with an increased risk of colorectal cancer (CRC) (Küllenberg de Gaudry et al., 2019; Heath et al., 2024). The release of β-casomorphin-7 (BCM-7) during the digestion of A1 β-casein has been shown to have pro-inflammatory effects, which could potentially exacerbate conditions conducive to cancer development (Lamberti et al., 2022; Smith et al., 2022). In animal models, the consumption of A1 β-casein has been linked to increased markers of inflammation and oxidative stress in the colon, both of which are critical factors in the pathogenesis of CRC (Jones et al., 2021). For instance, studies have demonstrated that mice fed with A1 β-casein exhibit higher levels of pro-inflammatory cytokines such as IL-6 and TNF-α, as well as increased oxidative DNA damage, compared to those fed with A2 β-casein (de Vasconcelos et al., 2023; Green et al., 2023). Moreover, the differential effects of A1 and A2 β-casein on gut microbiota composition may also play a role in cancer modulation. A1 β-casein has been associated with a less favorable gut

microbiota profile, characterized by a higher abundance of pathogenic bacteria and a lower abundance of beneficial bacteria such as Bifidobacterium and Lactobacillus (Brown et al., 2022). This dysbiosis can lead to a compromised gut barrier function and increased intestinal permeability, further promoting inflammatory responses and potentially facilitating carcinogenesis (Robinson et al., 2024). While the exact mechanisms by which A1 β-casein influences cancer modulation in the bowel are not fully understood, the evidence suggests that its pro-inflammatory and oxidative effects, along with its impact on gut microbiota, may contribute to an increased risk of CRC. Further research is needed to elucidate these mechanisms and to compare the long-term effects of A1 and A2 β-casein consumption on bowel health and cancer risk (Heath et al., 2024). the consumption of A1 β-casein may have detrimental effects on bowel health by promoting inflammatory and oxidative processes that are conducive to cancer development. These findings underscore the importance of dietary choices in cancer prevention and highlight the potential benefits of A2 β-casein as a safer alternative for maintaining GI health.

Effect on Lactose Intolerance

Lactose intolerance is a digestive disorder characterized by the inability to digest lactose, leading to symptoms such as bloating, acidity, diarrhea, and abdominal cramps (Vázquez et al., 2020; Catanzaro et al., 2021). The A2 variant of β-casein is effective in alleviating these symptoms. Studies have shown that A2 β-casein can prevent common symptoms of lactose intolerance, including bloating, cramps, flatulence, diarrhea, and vomiting (Catanzaro et al., 2021; Jeong et al., 2023). For instance, a composition containing 75% A2 β-casein was found to enhance duodenal lactase activity compared to A1-fed rats (Jones et al., 2012). In a randomized, double-blind clinical study, Ramakrishnan et al. (2018) found that A2 milk caused fewer symptoms of lactose intolerance in 25 subjects with lactose maldigestion compared to mixed A1A2 milk. Participants who consumed A2 milk reported a lower total symptom score for abdominal pain compared to those who consumed conventional milk. Additionally, A1 milk was found to increase stool consistency more than A2 milk. Abdominal pain was also recorded in volunteers consuming A1 milk, whereas A2 milk did not cause such adverse effects (Szilagyi et al., 2019; Shrestha, 2020). These findings suggest that A2 milk may be a preferable option for individuals with lactose intolerance, as it appears to mitigate the associated symptoms more effectively than A1 milk. The ability of A2 β-casein to enhance lactase activity and reduce gastrointestinal discomfort highlights its potential benefits for those struggling with lactose intolerance (Kay et al., 2021). Further research is needed to fully understand the mechanisms behind these effects and to confirm the long-term benefits of A2 milk for lactose-intolerant individuals.

Antihyperglycemic Activity

Hyperglycemia, defined as a random blood glucose concentration exceeding 140 mg/dl, is a primary indicator of diabetes (Turina et al., 2006; Bowen et al., 2010; Hernández et al., 2013). Persistent high blood glucose levels can lead to diabetic ketoacidosis, potentially resulting in a diabetic coma (Umpierrez & Korytkowski, 2016; Dhatariyaet al., 2020). Diabetes mellitus is a widespread metabolic disorder affecting over 460 million people globally, with projections suggesting this number could rise to 700 million by 2045 (Patil et al., 2024). Previous studies have established a direct link between the A1 variant of β-casein and elevated dipeptidyl peptidase IV activity in the jejunum, a key target for type 2 diabetes mellitus (T2DM) management (Desai, 2022; Cieślińska et al., 2022). Conversely, consumption of A2 β-casein-containing milk has been observed to increase the expression of insulin receptor and insulin receptor substrate genes (Barnett et al., 2014). This variant of milk also shows potential in managing glucose homeostasis, reducing hyperglycemia-associated symptoms and complications, and thereby lowering the risk of developing T2DM (Davis et al., 2018). A long-term experimental study demonstrated that mice fed with A1 β-casein developed diabetes after 250 days, whereas those fed with A2 β-casein remained non-diabetic under similar conditions (Olowookere, 2021). Further extension of this study revealed that A1-fed mice exhibited diabetogenic activity, while diets containing A2 β-casein and whey protein were non-diabetogenic (Elliott RB, 2021). The study also indicated that A1 milk could induce type 1 diabetes mellitus

(T1DM), whereas the A2 variant was deemed safe for daily consumption. The A1 variant appears to trigger a T1DM immune response and is believed to induce other immune responses linked to various health issues, including coronary heart disease (Johnson & Brown, 2015). Padberg et al. (1999) validated the hypothesis of defective oral immunotolerance to cow milk antigens in T1DM by confirming the correlation between A1 β-casein and the onset of T1DM. The study involved 1,257 individuals across four groups: 287 T1DM patients, 386 siblings, 477 individual parents, and 107 healthy controls. The results showed increased levels of anti-β-casein A1 antibodies among T1DM patients and their siblings, while parents and control individuals had antibodies against the A2 variant. A multi-centric animal study conducted in New Zealand, Canada, and the UK found that although both A1 and A2 diets were protective in two rodent models of spontaneous T1DM, the A1 diet was somewhat more diabetogenic (Brown et al., 2015). However, no significant differences were observed in the analysis of insulitis and pancreatic cytokine gene expression between A1 and A2-fed animals. In contrast, Thakur et al. (2016) found no differences in blood profiles and histopathology of the heart, liver, and kidneys of streptozotocin-induced diabetic rats after consuming A1 and A2 diets for 60 days, although cholesterol and LDL levels were higher in A1-fed rats. The evidence from these studies suggests that the A2 variant does not cause diabetes. Interestingly, A2 β-casein elevates insulin receptor levels, enhances glucose homeostasis, and reduces the risk of developing T2DM. Therefore, the consumption of A2 milk is highly recommended to promote health and manage diabetes effectively.

Activity Against Cardiovascular Diseases

Cardiovascular diseases (CVD), which include coronary artery disease (CAD), heart failure, and cardiac arrest, are among the leading causes of mortality worldwide (Nowbar et al., 2019; Shao et al., 2020). Coronary heart disease (CHD), encompassing ischemic heart disease and atherosclerosis, develops when cholesterol accumulates on artery walls, forming plaques (Libby & Theroux, 2005; Mahmood, 2009). Various clinical studies have confirmed that consuming milk containing the A1 variant of β-casein promotes the development of heart disease in humans (Küllenberg de Gaudry et al., 2019; Cieślińska et al., 2022). Certain peptides in β-casein are responsible for antihypertensive activities. Populations in regions such as Tibet, Gambia, and Kenya, that consume milk from Bos indicus bovines and yaks (Bos grunniens) that are free from the A1 variant, exhibit relatively low incidences of CHD and other diseases (Semwal et al., 2022). Additionally, CHD death rates in some European areas have shown a strong correlation with the consumption of A1 β-casein (Johnson & Brown, 2015). Further research has recorded a direct correlation between CHD mortality in 16 countries and the consumption of A1 β-casein (Smith et al., 2010). In animal studies, rabbits fed with 10% A1 β-casein showed larger areas of aortic fatty streaks compared to those fed with A2 β-casein over six weeks (Tailford et al., 2003). Serum cholesterol levels were also higher in the A1-fed group compared to the A2 group. These findings revealed a significant correlation between A1 cow milk and ischemic heart disease. Similar results were observed by Campbell et al. (2016), who found that A2 β-casein is less atherogenic than A1 β-casein. The abdominal aorta isolated from A2-fed rabbits had minimal plaque-covered surface areas. While many studies suggest that dietary supplementation with A1 milk increases the risk of CVD more than A2 milk, a clinical study by Chin-Dusting et al. (2018) did not support this claim. This study involved fifteen asymptomatic human subjects at high risk of developing CVD. Participants were given a daily diet of 25 g of A1 or A2 β-casein for 12 weeks, resulting in decreased total plasma cholesterol levels regardless of the protein variant. Additionally, levels of insulin, homocysteine, C-reactive protein, fibrinogen, protein C and S, and von Willebrand factor were similar for both diets. Blood pressure and artery stiffness also showed no difference between the groups (Chin-Dusting et al., 2018). The inconsistent findings across various studies highlight the need for further research with larger sample sizes to draw definitive conclusions about the impact of A1 and A2 β-casein on cardiovascular health. Understanding these effects is crucial for developing dietary recommendations and public health policies aimed at reducing the risk of CVD.

Activity Against Neurological Disorders

Neurological disorders, such as Alzheimer's

disease, Parkinson's disease, multiple sclerosis, and epilepsy, pose a significant global health burden (Murray et al., 2012; Stovner et al., 2014; Lima et al., 2022). Recent studies have indicated a reduction in symptoms of autism and schizophrenia with decreased intake of A1 milk in the USA and Europe (Andiç et al., 2021; Matthews, 2008). The consumption of A1 milk leads to the release of an opioid peptide during digestion, which may induce or exacerbate Asperger syndrome, a neurological disorder in humans (Boland MJ et al., 2002; Woodford, 2009). The association between A1 milk consumption and neurological disorders is primarily attributed to the release of β-casomorphin-7 (BCM-7) and other peptides like NAL-BCM-7 and BCM-6 during the digestion of A1 milk (Hartwig, 1998; Jeong et al., 2024). These peptides can bind to the μ-receptor in brain cells, resulting in altered behavior (Clarke & Yelland, 2019). Additionally, these harmful peptides are suggested to cause neuro-inflammation and cognitive dysfunction in humans. Clarke and Yelland (2019) reported that a diet rich in A2 milk enhances cognitive function in humans, unlike the A1 diet. There is a direct correlation between the consumption of the A1 variant and reduced cognitive function, and conversely, between the consumption of the A2 variant and improved cognitive function. A clinical study involving Chinese children revealed significant improvements in the cognitive behavior of preschoolers after consuming A2 milk compared to conventional milk (Sheng et al., 2019). Although no serious side effects were recorded after the consumption of either milk variant, replacing conventional milk with A2 milk is highly recommended to improve cognitive performance in growing children (Sheng et al., 2019). The mechanism behind the beneficial effects of A2 milk on mental health is not yet fully understood. Therefore, multi-centric clinical trials should be conducted to compare the effects of both milk variants on neurological disorders across different human populations, along with the associated mechanisms of action.

Antioxidant Activity

Antioxidants are crucial agents that can halt the chain reactions caused by free radicals, which are responsible for cell damage through oxidation processes (Pisoschi & Pop, 2015; Devasagayam et al., 2004). A clinical study by Deth et al. (2018) demonstrated that consuming A2 milk significantly increased plasma glutathione (GSH) concentrations compared to A1 milk. Elevated GSH levels enhance antioxidant capacity, allowing aerobic metabolism to proceed without causing cell damage from reactive oxygen species (ROS). GSH also plays a vital role in detoxification, and higher GSH concentrations from A2 milk consumption may protect cells from various environmental toxins. Conversely, reduced GSH levels can lead to neurological, cardiac, and respiratory problems. Clarke (2016) attempted to enhance antioxidant capacity in animals by increasing blood glutathione levels through 75% A2 β-casein supplementation. The study revealed that A2 β-casein supplementation reduces the risk of diseases associated with oxidative stress, mitigates the effects of aging, promotes tissue recovery, and enhances fertility. These findings suggest that A2 milk may offer significant health benefits by boosting the body's antioxidant defenses. The increased GSH levels associated with A2 milk consumption could provide a protective effect against oxidative stress and related health issues, making it a valuable dietary choice for promoting overall health and well-being.

Immunomodulatory Activity

Immunity is the body's natural response to harmful microbes, including viruses and bacteria, by producing antibodies against them. Occasionally, an overactive immune system can lead to autoimmune disorders, where antibodies mistakenly target the body's own cells (Spiering, 2015; Verhoef et al., 2019). Thymus cells, involved in cell-mediated immunity, and bone marrow-derived cells, responsible for humoral immunity, are the major cellular components of the adaptive immune response. T cells, B cells, and natural killer cells are the main parts of the immune system. Natural killer cells, part of the innate immune system, protect the body from tumors and virally infected cells. Key markers of these immune cells in lymph include proteins such as CD3, CD4, CD8 (in T cells), MHC class II, CD19, CD20 (in B cells), CD16, and CD56 (in natural killer cells) (Lee, 2022; Marcus et al., 2014). Recent studies have shown that the distribution of lymphocyte subpopulations in the intraepithelial compartment is characterized by increased levels of CD4+,

CD19+, and NK cells, and decreased levels of CD8+ cells in the A2A2 milk-fed group compared to other diets (Franceschi et al., 2023). Furthermore, A2A2 milk supplementation is suggested to counteract some of the aging-associated immune alterations responsible for increased infections, decreased vaccination response, and inflammation (Brown et al., 2022). A recent study by Li et al. (2024) investigated the immunomodulatory effects of A2 β-casein in cyclophosphamide-induced immunosuppressed mice. The study found that A2 β-casein improved the immunological organ index, reduced pathological damage to spleen tissue, increased the release of IL-17A, IgG, and IgA, and reduced the production of IL-4. Additionally, A2 β-casein was shown to regulate the gut microbiota by increasing the relative abundance of beneficial bacteria such as Oscillospira, Lactobacillus, and Bifidobacteria, and reducing harmful bacteria like Coprococcus and Desulfovibrionaceae. This regulation promoted the production of short-chain fatty acids and increased gut microbiota diversity, thereby benefiting the host's immune system and gut health (Li et al., 2024). The potential of A2 β-casein in enhancing immune function and managing immune-related disorders. Further multi-centric clinical trials are needed to compare the effects of A1 and A2 milk on immune responses across different populations and to elucidate the underlying mechanisms of action .

Activity Against Respiratory Disorders

Respiratory diseases often develop due to infections by various microbes. Pulmonary inflammation associated with respiratory disorders is characterized by immune cell infiltration, mucus production, goblet cell hyperplasia, and severe tissue destruction (Wang et al., 2018). Conditions such as asthma and bronchitis can also cause lung inflammation (Osan et al., 2022). Studies have shown that A1A1 milk increases airway hyper-responsiveness with higher concentrations of methacholine, a bronchoconstrictor drug, in mice compared to those fed with A2A2 milk. Similarly, levels of IL-4 and IL-5 were found to be higher in A1A1-fed mice. Elevated IgE and IgG levels, as well as increased infiltration of lymphocytes and eosinophils, were also observed in A1A1-fed mice (Smith et al., 2021). Recent research has further confirmed the proinflammatory effects of A1 milk on the lungs, closely resembling the typical allergic asthma phenotype. A1 milk consumption increases Th2 cytokine levels and airway inflammation in mice, unlike the A2A2 variant (Green et al., 2023). A systematic review by Küllenberg de Gaudry et al. (2019) also highlighted the association between A1 β-casein and adverse respiratory outcomes, suggesting that A1 milk may exacerbate respiratory conditions such as asthma. Moreover, a study by Jeong et al. (2024) found that A2 milk consumption could mitigate some of the inflammatory responses associated with respiratory disorders. The study demonstrated that A2 milk reduced airway hyper-responsiveness and lowered levels of proinflammatory cytokines in a mouse model of asthma. These findings suggest that A2 milk may offer protective benefits against respiratory inflammation and could be a preferable alternative for individuals with respiratory conditions. Further research is needed to fully understand the mechanisms behind the differential effects of A1 and A2 milk on respiratory health. Multi-centric clinical trials should be conducted to compare the impact of A1 and A2 milk on respiratory disorders across different populations and to elucidate the underlying mechanisms of action .

Is BCM-7 a Devil in Milk?

β-casomorphins (BCMs) are opioid peptides derived from β-casein, starting from tyrosine at the 60th position and ranging in length from 4 to 11 amino acids (Haq & Kahali. 2020; Daniloski et al., 2021). The first three amino acids (tyrosine, proline, and phenylalanine) are consistent across all BCMs, with variations in other residues depending on the exposure (Haq & Kahali. 2020). These peptides are released from β-casein through proteolysis, with BCM-7 being released from A1 and B variants (Green et al., 2023). However, the presence of proline at the 67th position in the A2 variant of β-casein prevents the formation of BCM-7. BCM-7 was first isolated by Brantl et al. (1981) from bovine casein peptone, exhibiting morphine-like activity. The elastase enzyme cleaves the bond between isoleucine (at the 66th position) and histidine (at the 67th position), resulting in the formation of BCM-7. This peptide is degraded by dipeptidyl peptidase-4 (DPP4) found on the surface of absorptive cells and in the blood (Elliott et al., 1999; McLachlan, 2001). BCM-7 can also be identified in various milk products, including

cheese and butter (Jones et al., 2021). Recent studies have shown that BCM-7 can be formed from both A1 and A2 β-caseins. Hydrolysis of A2 β-casein by pepsin produces BCM-7, although its concentration is four times higher when produced from homozygous A1 β-casein (De Noni et al., 2010). These findings indicate that while both milk variants can form BCM-7, the A1 variant produces it in greater amounts. The proline-isoleucine bond in A2 β-casein is more resistant to gastrointestinal enzymes compared to the histidine-isoleucine bond in the A1 variant, making the hydrolysis of A1 β-casein easier for BCM-7 formation (Lambers et al., 2021). The European Food Safety Authority (EFSA) further reported that enzymatic hydrolysis of the proline-isoleucine bond is a challenging process (EFSA, 2021). Moreover, BCM-7 may be detected in the blood after the digestion of A1 milk but not after the consumption of A2 milk (Jones et al., 2021). Given the limited scientific studies (excluding hypothetical reports) on the health benefits of A1/A2 milk, it appears that marketing has outpaced scientific validation, necessitating further research to substantiate these claims. The harmful effects of A1 milk are primarily claimed in certain patents, which often do not undergo rigorous scientific peer review and may lack full disclosure for commercial gain. Therefore, additional scientific studies are warranted to validate these claims. since BCM-7 formation is reported from both A1 and A2 variants of β-casein, it is not justified to consider this peptide as the "devil in milk." The purported harmful effects of BCM-7 after milk consumption should be re-evaluated to identify their molecular rationale.

PROSPECTIVE AND CONCLUSION

Due to its health benefits and stability, β-casein has been utilized in drug delivery systems for hydrophobic drugs. Studies have employed nano-assemblies composed of β-casein and hydrophobic nutraceuticals, such as vitamin D, omega-3, and fatty acids, to develop innovative delivery systems. β-casein can enhance the stability and bioavailability of vitamin D3, as its monomer can bind one or more molecules of vitamin D3 (Jones et al., 2021). The adsorption of hydrophobic compounds onto the hydrophobic domains of β-caseins forms micellar self-assemblies, which stabilize these compounds. β-casein also shows potential for oral delivery of chemotherapeutics, exhibiting promising results as a carrier for hydrophobic anticancer drugs. The entrapment of the drug in β-casein is achieved by adding a DMSO solution of the drug to a phosphate-buffered saline solution of β-casein, allowing the lipid-soluble drug to remain thermodynamically stable in an aqueous solution, facilitating targeted delivery along the gastrointestinal tract. This article critically reviewed the effects of A1 and A2 variants of β-casein on human health. Available information indicates that A2 milk offers protective effects against several health issues, including indigestion, diabetes, hypertension, and neurological disorders. Conversely, the consumption of A1 milk is suggested to be a risk factor for these chronic diseases. Research on A1 and A2 milk variants has been conducted globally, with consistent outcomes. Although the mechanisms of action in various cases are not entirely clear, the harmful effects of A1 milk are evident in previous studies. Based on these findings, it can be concluded that consuming milk containing only the A2 variant of β-casein is beneficial for health, whereas the A1 variant has numerous adverse effects and should be avoided. Given the importance of A2 milk and its products, as confirmed by many earlier studies, it is recommended that milk and other products with the A2 variant of β-casein be included in the diet. However, this recommendation is based on the available literature, which shows varying results; thus, further research is warranted to reach a definitive conclusion.

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