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Perspective

A Nutritional Perspective on the Role of Dairy-Derived Nutrients in the Stimulation of GLP-1 Secretion

Ratul Kalita*

South Dakota State University, Brookings, SD, USA

***Corresponding Author:** Ratul Kalita, South Dakota State University, Brookings, SD, USA.
ORCID ID: https://orcid.org/0009-0000-1310-3138.

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Abstract

Glucagon-like peptide-1 (GLP-1) is a key incretin hormone involved in glucose homeostasis, appetite regulation, and energy balance. Its therapeutic relevance in managing obesity and type 2 diabetes has increased interest in dietary strategies to enhance endogenous GLP-1 secretion. Dairy products, rich in bioactive proteins, peptides, lipids, and microbial metabolites, offer promising ways for modulating GLP-1 physiology. This review explores the literature on the role of dairy-derived nutrients, including whey and casein proteins, branched-chain and aromatic amino acids, milk fat globule membrane (MFGM) lipids, and fermented dairy metabolites in stimulating GLP-1 secretion via nutrient-sensing receptors and gut-brain axis pathways. Mechanistic insights reveal that these compounds activate G-protein coupled receptors (GPR40, GPR120, GPR93), calcium-sensing receptors (CaSR), and taste receptors (T1R1/T1R3), leading to enhanced GLP-1 release from intestinal L-cells. The review also explores the impact of dairy processing, matrix effects, and microbiota-mediated fermentation on GLP-1 modulation. By integrating molecular nutrition, nutrigenomics, and personalized dietary approaches, functional dairy formulations may emerge as non-pharmacological tools for metabolic disease prevention. Future research should focus on dose-response relationships, long-term outcomes, and validations of those compounds.

Keywords: *Glucagon-Like Peptide-1 (GLP-1); Milk Fat Globule Membrane (MFGM); G-Protein Coupled Receptors (GPR40, GPR120, GPR93); Calcium-Sensing Receptors (CaSR); Taste Receptors (T1R1/T1R3)*

Introduction

Incretin hormones, particularly glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), play vital roles in regulating postprandial insulin secretion, appetite, and energy metabolism. GLP-1, secreted by enteroendocrine L-cells in the distal intestine, enhances insulin release, inhibits glucagon secretion, delays gastric emptying, and promotes satiety. These physiological actions have placed GLP-1 as one of the main targets in the treatment of obesity and type 2 diabetes, with GLP-1 receptor agonists now widely used in clinical practice [5,10,17,63,67].

While pharmacological GLP-1 compounds have demonstrated efficacy, their cost and side effects have prompted exploration of nutritional strategies to stimulate GLP-1 secretion. Among dietary components, dairy products have emerged as promising alternatives

due to their rich content of proteins, peptides, lipids, and fermentation-derived metabolites that interact with nutrient-sensing receptors in the human gut [2,13,21,22,31,48]. Whey and casein proteins, branched-chain amino acids, milk fat globule membrane (MFGM) lipids, and short-chain fatty acids from fermented dairy have all been implicated in GLP-1 modulation [9,20,23]. Dairy-derived nutrients stimulate GLP-1 secretion via activation of G-protein coupled receptors (GPR40, GPR120, GPR93), calcium-sensing receptors (CaSR), and taste receptors (T1R1/T1R3) located on L-cells [37,55]. These pathways converge to increase intracellular calcium and cyclic AMP, triggering GLP-1 exocytosis. Additionally, the gut-brain axis plays a role in amplifying the satiety signals initiated by GLP-1, further supporting its role in energy balance [64].

Recent studies have also highlighted the role of fermented dairy products such as yogurt, kefir, and cheese in modulating GLP-1 secretion through microbiota-mediated mechanisms. These products contain probiotics and postbiotics that influence gut barrier integrity and produce metabolites like butyrate and acetate, which are known to stimulate GLP-1 release [13,61]. Furthermore, the milk fat globule membrane (MFGM), a bioactive component of dairy fat, has gained attention for its potential role in GLP-1 signalling. MFGM contains sphingolipids and phospholipids that may interact with intestinal receptors and influence metabolic pathways related to satiety and insulin sensitivity [43].

This review aims to provide a comprehensive analysis of the dairy-derived nutrients influencing GLP-1 secretion. It also examines the role of food processing, matrix effects, and gut microbiota in shaping the GLP-1 response to dairy intake. By integrating insights from nutritional biochemistry, dairy-derived product matrices, and their resultant effect on the GLP-1 secretion, the review seeks to summarise the focus area in the development of functional dairy products tailored for metabolic health.

Dairy derived proteins and peptides as GLP1 secretagogues

Dairy proteins, particularly whey and casein, have garnered significant attention for their ability to stimulate GLP1 secretion. Whey protein is rapidly digested and contains bioactive peptides such as βlactoglobulin and αlactalbumin, which have been shown to enhance GLP1 release through interaction with nutrient-sensing receptors on L-cells [31]. These peptides activate G-protein coupled receptors (GPR93) and calcium sensing receptors (CaSR), leading to increased intracellular calcium and cyclic AMP, which are key drivers of GLP1 exocytosis [54].

Casein, a slower-digesting protein, also contributes to GLP1 stimulation through its hydrolysates. Studies have identified specific casein-derived peptides, such as GPFPLPD and APDSGNFR, which exhibit dual functionality: inhibiting dipeptidyl peptidase IV (DPPIV) and stimulating GLP1 secretion [62]. These peptides demonstrate high oral bioavailability and potent activity *in vitro*, suggesting their potential as nutraceutical agents for metabolic regulation.

The digestion kinetics of whey and casein influence their secretagogue potential. Whey hydrolysates, due to their rapid absorption and peptide release, elicit a stronger GLP1 response compared to intact whey or casein proteins [30]. *In vitro* studies using STC1 enteroendocrine cells have shown that whey hydrolysates significantly increase GLP1 secretion and upregulate prepro-glucagon gene expression, which encodes GLP1 [53].

Human clinical trials further support the role of dairy proteins in modulating GLP1. A randomized crossover study demonstrated that a whey protein-based nutritional drink significantly increased postprandial GLP1 levels in individuals with type 2 diabetes compared to a standard breakfast [56]. Another trial using whey protein microgel showed enhanced GLP1 secretion and improved glycaemic control in overweight and obese subjects [34].

Amino acids from dairy and GLP-1 signalling

Amino acids derived from dairy proteins play a crucial role in modulating GLP-1 secretion through nutrient-sensing mechanisms in enteroendocrine L-cells. Among these, branched-chain amino acids (BCAAs), leucine, isoleucine, and valine are particularly potent in stimulating GLP-1 release. These amino acids activate G-protein coupled receptors such as GPRC6A and taste receptors T1R1/T1R3, leading to intracellular calcium influx and cAMP elevation, which are essential for GLP-1 exocytosis [27,49].

Leucine, in particular, stimulates GLP-1 secretion via the mTOR signalling pathway, which also influences insulin secretion and β-cell proliferation [1]. Clinical studies have demonstrated that dairy consumption increases plasma BCAA levels, with sheep milk producing higher postprandial BCAA concentrations than cow milk, suggesting a differential impact on GLP-1 secretion [32]. Aromatic amino acids such as tryptophan and phenylalanine also contribute to GLP-1 modulation. These amino acids interact with CaSR and are transported into L-cells via organic anion transporting polypeptides (OATP3A1), facilitating their role in GLP-1 release [57]. Tryptophan, a precursor to serotonin, has been implicated in gut-brain axis signalling, further enhancing satiety and GLP-1-mediated effects [44].

The metabolism of these amino acids influences GLP-1 gene expression. Amino acid availability regulates the transcription of the proglucagon gene, which encodes GLP-1, through nutrient-responsive transcription factors [50]. This regulation is particularly relevant in the context of high-protein diets, where increased amino acid flux enhances GLP-1 synthesis and secretion. Moreover, amino acids may exert indirect effects on GLP-1 through modulation of gut microbiota. Certain microbial species metabolize amino acids into short-chain fatty acids and other metabolites that stimulate GLP-1 release via free fatty acid receptors [3,66]. These interactions highlight the complex interplay between dietary amino acids, microbial metabolism, and enteroendocrine signalling.

Overall, amino acids from dairy not only serve as direct stimulants of GLP-1 secretion but also influence gene expression and gut-brain signalling pathways. Their multifaceted role underscores the potential of amino acid-rich dairy formulations in enhancing incretin responses and improving metabolic outcomes.

Dairy lipids and GLP-1 modulation

Dairy lipids, particularly those found in milk fat and the milk fat globule membrane (MFGM), play a significant role in modulating GLP-1 secretion through interactions with lipid-sensing receptors in the gut. Free fatty acids (FFAs), especially long-chain unsaturated fatty acids such as oleic and linoleic acid, activate G-protein coupled receptors GPR40 (FFAR1) and GPR120 (FFAR4), which are expressed on enteroendocrine L-cells and mediate GLP-1 release [16,52]. These receptors respond to dietary lipids by triggering intracellular calcium mobilization and cAMP signalling, leading to GLP-1 exocytosis. Recent studies have shown that microbial metabolites of long-chain fatty acids, such as hydroxy fatty acids, act as dual agonists of GPR40 and GPR120, enhancing GLP-1 secretion more effectively than their parent compounds [42].

The MFGM, a tri-layered structure surrounding milk fat globules, contains bioactive lipids including phospholipids, sphingolipids, and gangliosides. These components have been linked to improved metabolic outcomes, including enhanced insulin sensitivity and reduced inflammation [41,42]. Although direct evidence connecting MFGM to GLP-1 secretion is still emerging, its lipid constituents are known to interact with gut receptors and influence enteroendocrine signalling.

The chain length of fatty acids also affects GLP-1 modulation. Short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate produced during fermentation of dairy products stimulate GLP-1 secretion via FFAR2 and FFAR3 receptors [7,58]. Medium-chain fatty acids (MCFAs) and long-chain fatty acids (LCFAs) differ in their receptor affinities and metabolic fates, with LCFAs showing stronger GLP-1 secretagogue activity due to their interaction with GPR40 and GPR120.

Processing methods such as homogenization and heat treatment can alter the bioactivity of dairy lipids. Homogenization increases the surface area of fat globules, enhancing their digestibility and interaction with gut receptors. However, ultra-high temperature (UHT) processing may reduce bioactivity by degrading sensitive lipid components [25,40]. Vat pasteurization, in contrast, preserves more of the native bioactive properties of MFGM, including xanthine oxidase activity, which may indirectly support GLP-1 signalling [46].

Dairy lipids contribute to GLP-1 modulation through receptor-mediated mechanisms and microbial interactions. Their efficacy is influenced by fatty acid structure, processing conditions, and the presence of bioactive membrane components. These findings support the development of lipid-enriched dairy formulations aimed at enhancing incretin responses and improving metabolic health.

Fermented dairy products and microbial metabolites

Fermented dairy products, including yogurt, kefir, cheese, and cultured milk beverages, are increasingly recognized as functional foods capable of modulating GLP-1 secretion through microbiota-mediated mechanisms. These products contain live probiotic strains such as *Lactobacillus*, *Bifidobacterium*, and *Streptococcus thermophilus*, which survive gastric transit and colonize the gut, contributing to microbial diversity and metabolic activity [13]. During fermentation, these microbes produce postbiotic compounds, including short-chain fatty acids (SCFAs), bioactive peptides, exopolysaccharides, and bacteriocins. SCFAs, particularly acetate, propionate, and butyrate, are key microbial metabolites that stimulate GLP-1 secretion via activation of free fatty acid receptors FFAR2 (GPR43) and FFAR3 (GPR41) on L-cells [11,39,58]. These SCFAs also reinforce gut barrier integrity by upregulating tight-junction proteins such as ZO-1 and Occludin, thereby enhancing mucosal signalling and reducing inflammation [13]. Clinical studies have demonstrated that regular consumption of fermented dairy products improves metabolic biomarkers, including fasting glucose, lipid profiles, and systemic inflammatory markers such as C-reactive protein (CRP). These effects are influenced by strain specificity, fermentation conditions, and host genotype, particularly FUT2 polymorphisms that affect microbial engraftment [65].

Kefir, a fermented milk product rich in peptides and probiotics, has shown particular promise in enhancing GLP-1 secretion. Its unique microbial composition promotes butyrate production, which not only stimulates GLP-1 release but also serves as an energy source for colonocytes and supports epithelial health [45]. Similarly, yogurt enriched with postbiotics derived from *Lactobacillus delbrueckii* and *Streptococcus thermophilus* has demonstrated improved antioxidant activity and sensory attributes, suggesting its potential as a health-promoting food [51].

The gut-brain axis also plays a role in GLP-1 modulation by fermented dairy. SCFAs produced during fermentation influence brain function and appetite regulation through systemic circulation and interaction with the hypothalamic-pituitary-adrenal (HPA) axis [26,29]. These metabolites cross the blood-brain barrier and affect neuroendocrine signalling, further amplifying the satiety effects of GLP-1.

In summary, fermented dairy products offer a multifaceted approach to enhancing GLP-1 secretion through microbial and metabolic pathways. Their efficacy depends on microbial composition, fermentation parameters, and host factors, making them ideal candidates for personalized nutrition strategies aimed at improving metabolic health.

Processing and matrix effects on GLP-1 secretion

The processing of dairy products, including heat treatment, enzymatic hydrolysis, and fermentation, significantly influences their potential to stimulate glucagon-like peptide-1 (GLP-1) secretion. These processes alter the physicochemical properties of dairy proteins and lipids, affecting their bioactivity, digestibility, and interaction with nutrient-sensing receptors on enteroendocrine L-cells.

Heat treatment

Thermal processing methods such as pasteurization and ultra-high temperature (UHT) treatment can denature milk proteins, potentially reducing the bioavailability of sensitive peptides. However, moderate heat treatment may enhance peptide release during digestion, thereby improving GLP-1 stimulation [4,24,38]. For instance, denatured whey proteins like β-lactoglobulin may become more accessible to digestive enzymes, facilitating the release of bioactive peptides [47].

Enzymatic hydrolysis

Enzymatic hydrolysis using proteases such as Debitrase HYW20™ and Prolyve™ generates low-molecular-weight peptides (<1 kDa) that are more readily absorbed and have demonstrated increased GLP-1 secretagogue activity [14]. These hydrolysates exhibit enhanced bioactivity due to their ability to interact with G-protein-coupled receptors (GPCRs) on L-cells [31].

Fermentation

Fermentation further enhances the bioactivity of dairy by producing postbiotics and short-chain fatty acids (SCFAs), which stimulate GLP-1 via FFAR2 and FFAR3 receptors [7,58]. Precision fermentation techniques are now being used to produce targeted bioactive compounds that naturally enhance GLP-1 secretion, offering a promising avenue for functional food development [28].

Dairy matrix effects

The food matrix, the structural and compositional arrangement of nutrients within dairy products, plays a critical role in digestion kinetics and nutrient bioavailability. The dairy matrix includes proteins, lipids, minerals, and bioactive compounds embedded in a complex structure that influences how nutrients are released and absorbed during digestion [6,33]. For example, micellar caseins and milk fat globule membranes (MFGM) protect bioactive peptides during gastric transit, allowing them to reach the intestine intact and interact with L-cells [36,60].

Bioavailability of dairy-derived peptides

Peptides such as β-lactoglobulin and α-lactalbumin have demonstrated absorption into the bloodstream and interaction with metabolic pathways relevant to GLP-1 signalling [19,62]. However, bioavailability can be limited by peptide degradation, poor transport across the intestinal barrier, and competition with other nutrients [18].

Processing and matrix effects are critical determinants of the GLP-1 modulatory potential of dairy products. Optimizing these factors through controlled enzymatic hydrolysis, fermentation, and structural design can enhance the efficacy of dairy-based interventions for metabolic health.

Nutritional implications and future perspectives

The growing evidence from studies supporting dairy-derived modulation of glucagon-like peptide-1 (GLP-1) secretion has significant implications for nutritional science, public health, and food innovation. Functional dairy formulations designed to enhance GLP-1 responses are emerging as promising tools for managing metabolic disorders such as obesity, type 2 diabetes, and insulin resistance. These formulations may include combinations of whey peptides, milk fat globule membrane (MFGM) lipids, probiotics, and prebiotics tailored to stimulate GLP-1 secretion and improve satiety and glycaemic control [8,59].

The integration of nutrigenomics and personalized nutrition into dairy-based interventions represents a transformative shift in dietary therapy. Nutrigenomics explores how individual genetic variations influence responses to nutrients, enabling the development

of customized dietary strategies that optimize GLP-1 secretion and metabolic outcomes [12,15]. For example, genetic polymorphisms affecting taste receptors, insulin signalling, or gut microbiota composition may determine how effectively a person responds to dairy-derived GLP-1 secretagogues. Personalized nutrition platforms are increasingly incorporating omics technologies such as genomics, transcriptomics, proteomics, and metabolomics to identify biomarkers of GLP-1 responsiveness and tailor interventions accordingly [50,68]. These approaches allow for deep phenotyping and real-time monitoring of metabolic responses, paving the way for precision dairy formulations that align with individual health profiles.

Despite these advances, several research gaps remain. Long-term clinical trials are needed to evaluate the sustainability and safety of dairy-based GLP-1 interventions. Most existing studies focus on acute postprandial responses, leaving questions about chronic effects on weight management, insulin sensitivity, and cardiovascular health unanswered [35].

Moreover, variability in GLP-1 receptor expression and gut microbiota composition across populations necessitates stratified research designs. Future studies should explore how age, sex, ethnicity, and disease status influence the efficacy of dairy-derived GLP-1 modulators. Integration of real-world evidence and digital health tools such as biosensors and AI-driven dietary tracking may enhance the precision and scalability of these interventions [66].

Dairy-based strategies for GLP-1 modulation hold great promise for advancing metabolic health. By leveraging functional ingredients, personalized nutrition, and omics integration, the next generation of dairy products could serve as effective, non-pharmacological tools for disease prevention and health optimization.

Conclusion

The modulation of GLP1 secretion through dairy-derived nutrients represents a promising frontier in nutritional science and metabolic health. This review has synthesized evidence from molecular, cellular, and clinical studies to demonstrate how components such as whey and casein proteins, branched-chain and aromatic amino acids, milk fat globule membrane (MFGM) lipids, and fermented dairy metabolites interact with nutrient-sensing receptors on enteroendocrine L-cells to stimulate GLP1 release. These nutrients activate G protein-coupled receptors (GPR40, GPR120, GPR93), calcium-sensing receptors (CaSR), and taste receptors (T1R1/T1R3), triggering intracellular signalling cascades that culminate in GLP1 exocytosis. The resulting hormonal effects enhanced insulin secretion, suppressed glucagon release, delayed gastric emptying, and increased satiety, underscoring the therapeutic potential of dietary strategies for managing obesity and type 2 diabetes.

Processing and matrix effects further influence the bioactivity of dairy components. Techniques such as enzymatic hydrolysis and fermentation enhance peptide release and microbial metabolite production, while structural features of the dairy matrix affect digestion kinetics and nutrient absorption. These insights support the development of functional dairy formulations optimized for GLP1 stimulation. Despite these advances, several research gaps remain. Long-term studies are needed to assess the sustainability of GLP1 responses and their impact on weight management, insulin sensitivity, and cardiovascular health. Additionally, the integration of real-world evidence and digital health tools may facilitate the translation of laboratory findings into practical dietary solutions.

Dairy-derived strategies for GLP1 modulation offer a multifaceted, nonpharmacological approach to improving metabolic health. By combining molecular nutrition, personalized dietary planning, and innovative food processing, future dairy products may serve as effective tools in the prevention and management of metabolic diseases.

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