Quality Assurance and Safety of Crops & Foods, 2026; 18(1): 167–194

Protein conjugates and probiotic interactions of dairy products for innovative and future functional foods

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Academic Editor: Rana Muhammad Aadil, PhD: National Institute of Food Science & Technology, University of Agriculture, Faisalabad, Pakistan

Received: 2 September 2025; Accepted: 7 December 2025; Published: 11 March 2026

REVIEW ARTICLE

Abstract

This review critically assesses the strategies and mechanisms underlying interactions between protein conjugates and probiotics in dairy foods, aiming to detail how these conjugates stabilize probiotics, facilitate gut colonization, and stimulate immunomodulation. Protein–based carriers and complexes play key roles in improving probiotic protection, adhesion, and metabolic activity. Notable strategies include developing milk proteins (e.g., casein and whey proteins), plant–derived protein conjugates, and advanced encapsulation techniques for polysaccharide–protein complexes. The protein shell in conjugates protects probiotics from harsh conditions, enables targeted intestinal release, enhances mucosal adhesion, and contributes to enhanced antioxidant and anti–inflammatory effects. Such strategies also can improve probiotic survival and colonization and reduce inflammation (with increased IL–10 and decreased tumor necrosis factor–alpha), enhance mucus secretion (with a rise in mucin 2 [MUC2]), and elevate beneficial gut microbes. Advancements in probiotic research have enabled more precise and targeted applications using protein conjugates and encapsulation systems. These approaches form part of integrative nutrition strategies that deliver precision, protection, and personalization in the design of functional foods, contributing to food nutrition improvement. Moreover, protein conjugates are increasingly recognized as active modulators of probiotic function and immune signaling, rather than passive carriers, thereby offering new avenues for food production.

Keywords: protein conjugates; probiotics; dairy foods; functional foods; encapsulation; Maillard reaction

Introduction

Probiotics are widely used in functional dairy products because of their health benefits and consumer acceptance (Hasnain *et al.*, 2024; Jang *et al.*, 2024). However, their viability is often compromised during processing, storage, and gastrointestinal (GI) transit, limiting product efficacy (D'Amico *et al.*, 2025). Protein conjugation has emerged as a promising strategy to enhance probiotic stability and functionality, primarily through the Maillard reactions and emerging technology–assisted or chemical approaches. Such conjugates protect probiotics from environmental stress, improve intestinal adhesion, and enhance dairy product quality (Vivek *et al.*, 2023), positioning protein–probiotic interactions as a key innovation in functional food design.

The escalating demand for functional dairy products has stimulated growing interest in integrating probiotics with protein–based technologies to enhance nutritional and health benefits. Emerging processing approaches, such as ultrasound, ohmic heating, and high–pressure treatment, have been investigated for their effects on probiotic viability and metabolic performance (Gavahian *et al.*, 2021). In this context, dairy–derived proteins have become key functional ingredients in food, clinical, and pharmaceutical formulations owing to their exceptional reconstitution, emulsifying, and foaming properties, which surpass those of lipids and carbohydrates (Wu *et al.*, 2021). Beyond their physicochemical roles, protein hydrolysates have demonstrated prebiotic potential by supporting probiotic proliferation (Guo *et al.*, 2022), while hydrogel–based protein–polysaccharide complexes have been developed for targeted probiotic delivery in therapeutic applications (Zheng *et al.*, 2023). Complementary investigations conducted by Wu *et al.* (2024) have provided molecular insights into plant protein–probiotic interactions and underscored the structural and compositional constraints of plant–based matrices. Despite substantial progress in probiotic delivery and functional dairy research, few studies have systematically elucidated how the chemical nature and formation parameters of protein conjugates influence the survival, metabolic activity, adhesion, and host interactions of probiotics within dairy systems. Current reviews often address these aspects in isolation; for instance, Xiang *et al.* (2021) examined the effects of the Maillard reaction on milk proteins without linking these effects to probiotic functionality, underscoring the need for integrative perspectives on protein conjugate–probiotic interactions.

Recent research has demonstrated that under unfavorable conditions, Maillard–type conjugates formed from milk proteins, such as whey or casein, combined with carbohydrates, such as dextran or glucose, can enhance the viability of probiotics. For instance, Guo *et al.* (2022) demonstrated that whey protein (WP)–dextran encapsulated conjugates enhanced the heat and acid resistance of *Lactiplantibacillus plantarum* 21805 in yogurt formulations. Similarly, Wu *et al.* (2021a) demonstrated that glycosylation of whey protein via controlled dry heating of skim milk powder significantly enhanced protein thermal stability under clean–label conditions, enabling recombined evaporated milk emulsions to withstand heating at 120°C for 30 min without loss of stability. A'yun *et al.* (2020) reported a great improvement in the heat stability of whey protein isolate (WPI)–lactose conjugates, which could successfully stabilize oil–in–water (O/W) emulsions against heating (80°C for 20 min). In addition, the Maillard conjugates of whey protein hydrolysates (WPH) and linear dextrins (LD; degree of polymerization [DP] 23.78–64.96) were prepared by Pan *et al.* (2020) by dry heating, with glycation degree increasing with LD content. Glycation altered WPH secondary structure, reduced α–helix content, and enhanced antioxidant activity. Additionally, conjugation of casein–derived hydrophobic peptides with *Acacia seyal* polysaccharides markedly enhanced the stability of O/W emulsions (Hou *et al.,* 2017). Thus, the Maillard–type protein–carbohydrate conjugates, such as those formed from whey, casein, or serum albumin with sugars such as dextran or glucose, hold strong potential to enhance probiotic stability and functionality in dairy products, even under heat, acid, and GI stress.

This review summarizes recent advances in protein conjugation strategies, evaluates their effects on probiotic functionality in dairy products, and highlights their potential for developing next–generation dairy products with improved health benefits and nutritional value. The review discusses key health impacts, including modulation of the gut microbiota, enhancement of the immune system, increased bioavailability of bioactive peptides, and antioxidant properties. Finally, current technological and regulatory challenges are considered along with future perspectives for the commercial application and continued development of protein–conjugation techniques in probiotic dairy products.

Overview of Probiotics and Protein Conjugation

Probiotics in dairy foods

Probiotics, defined as live microorganisms that confer health benefits when consumed in adequate amounts, remain a key focus of modern health food research (Zavišić *et al.*, 2023; Gao *et al.*, 2021; Hill *et al.*, 2014). Probiotic food sources have their historical roots in fermented dairy products, including cheese and yogurt, which were traditionally produced through spontaneous fermentation by lactic acid bacteria (LAB)

(Kaur *et al.*, 2022), and are valued for their taste, shelf life, and promotion of intestinal health (Jang *et al.*, 2024). Élie Metchnikoff, "father of innate immunity," linked regular consumption of fermented dairy products to improved immunity, longevity, and many biochemical processes (Lee *et al.*, 2025). Over time, scientific knowledge about probiotics has evolved to the point that the concept has expanded beyond microorganisms derived from food to include bacteria isolated from the human gastrointestinal tract (GIT), particularly those capable of promoting health and maintaining intestinal homeostasis (Zommiti *et al.*, 2020).

Today, probiotics are widely available in various forms, including functional foods, nutritional supplements, and pharmaceutical preparations. Owing to their advantageous physicochemical characteristics, including buffering capacity, nutritional richness, and compatibility with microbial growth and survival, dairy products remain the most widely used and effective carriers of probiotics (Latif *et al.*, 2023). This also reflects the worldwide acceptance of dairy–based probiotics as promoting overall health, lifespan, and disease prevention (Kaur *et al.*, 2022).

Applications derived from dairy products benefit from a wide range of probiotic species. Among these, the most commonly employed genera include *Lactobacillus*, *Bifidobacterium*, *Streptococcus*, *Lactococcus*, *Enterococcus*, *Leuconostoc*, and *Propionibacterium* (Vivek *et al.*, 2023). A broad spectrum of strains, such as *Lactobacillus acidophilus*, *Lacticaseibacillus rhamnosus*, *Lacticaseibacillus casei*, *L. plantarum*, *Limosilactobacillus reuteri*, *B. bifidum*, *Bifidobacterium longum, and Bifidobacterium lactis*, are regularly included in yogurt, fermented milk, cheese, and milk powders (Vivek *et al.*, 2023). Importantly, there is no consensus on the lowest effective dose of probiotics; however, a reasonable daily intake of approximately 10^9 colony–forming units (CFU), taken consistently, is usually considered sufficient to confer health benefits (Latif *et al.*, 2023).

In addition to probiotics, nondigestible food ingredients, known as prebiotics, are sometimes added to enhance the effectiveness of most fermented dairy products. Probiotic species, including *Bifidobacterium* and *Lactobacillus*, break down prebiotics, such as inulin, fructooligosaccharides (FOS), and galactooligosaccharides (GOS), thereby improving gut microbiota composition and mucosal immunity (Wang *et al.*, 2020). Consequently, in synbiotic formulations, probiotics and prebiotics exhibit synergistic effects that promote colonization, enhance microbial survival, and yield more physiological outcomes in the host (Parhi *et al.*, 2024). A comprehensive overview of probiotic microorganisms used in various dairy products and their applications are presented in Table 1.

Dairy products are among the most established and successful vehicles for probiotics in the food industry because of their inherent nutrient content, favorable physicochemical properties, and consumer acceptance (Jang *et al.*, 2024). In particular, LAB play a vital role in ensuring microbiological safety, shelf life, and sensory quality of fermented dairy products by synthesizing organic acids and antimicrobial peptides and competing with pathogens through competitive inhibition (Ibrahim *et al.*, 2021). Milk provides an ideal medium for delivering viable probiotic cultures because of its buffering capacity, nutritional density, and protein structure, which protect probiotics during GI transit (Gao *et al.*, 2022). Among fermented dairy products, yogurt is the most commonly consumed and investigated vehicle for probiotic bacteria. Moreover, the sector has recently expanded to include probiotic–enriched fermented dairy products, such as pasteurized milk, ice cream, and infant formula, which use microencapsulation or post–fermentation addition techniques to ensure probiotic viability during storage (Sbehat *et al.*, 2022).

Various studies have demonstrated that probiotic dairy products can regulate gut bacteria, improve lactose digestion, enhance the immune system, and alleviate manifestations of GI diseases (Mudgil *et al.* 2024a). The combinations of probiotics in both fermented and nonfermented dairy matrices reflect growing innovation in the design of functional dairy foods. These products are developed for their nutritional value and targeted health benefits, including relief from lactose intolerance, immune modulation, and gut microbiota balance. However, maintaining probiotic viability throughout processing, distribution, and storage remains a key challenge, particularly for nonfermented products, such as ice cream and infant formula. Therefore, to fully harness the health benefits of probiotic dairy products, especially nonfermented types, it is essential to enhance the stability of probiotics across processing and storage.

Protein–probiotic conjugation mechanisms

Protein conjugates interact with probiotics at the molecular level to enhance gastrointestinal stability, adhesion, and colonization via multiple biochemical and structural mechanisms. These strategies enable targeted delivery (Liu *et al.,* 2025), enhance stress tolerance (Zhang *et al.,* 2023a), and improve therapeutic efficacy in the gut environment (Peled *et al.,* 2024; Yin *et al.,* 2025). Table 2 presents key protein–probiotic conjugation mechanisms.

The initial improvements in probiotic survival, adhesion, and localization are primarily driven by direct protein–probiotic interactions, whereas the major therapeutic outcomes, such as production of short–chain

Table 1. Probiotic microorganisms used in dairy products and their applications.

Probiotic strains/species	Product type	Dose	References
Lactococcus lactis subsp. *cremoris*, *Propionibacterium freudenreichii* spp. *Shermanii*	Cheese	10^6–10^8 CFU/g	Kondrotiene *et al.*, 2023; Rabah *et al.*, 2017
L. acidophilus, Bifidobacterium spp., *Streptococcus thermophilus* (ABT culture)	Cream cottage cheese (fortified with bovine colostrum)	10^7–10^8 CFU/g	Abdeen *et al*., 2024
L. acidophilus	Probiotic cream cheese (with *Opuntia ficus*–indica mucilage)	10^7–10^8 CFU/g	Rodrigues *et al*., 2024
Pichia cerevisiae, *Pediococcus acidilactici, Pediococcus pentosaceus*	Swiss cheese	10^6–10^7 CFU/g	Doğan and Ay, 2021
L. plantarum L33	White–brined cheese (co–cultured with probiotic)	10^7 CFU/g	Zareie *et al*., 2025
Limosilactobacillus fermentum (probiotic)	Infant formula with dairy lipids + probiotic	1.9 × 10^8 CFU/mL	Lemaire *et al*., 2021
L. rhamnosus GG	Fermented beverage kefir (from grains or starter culture)	10^6–10^8 CFU/mL	Yousefvand *et al*., 2022
Lactobacillus helveticus, *B. longum*, *L. rhamnosus* GG	Probiotic–fortified kefir	10^7–10^8 CFU/mL	Noori *et al*., 2025
Saccharomyces cerevisiae, *Candida utilis (Candida torulopsis)*	Fermented milk	10^7–10^8 CFU/mL	Benedetti *et al*., 2024
Lacticaseibacillus paracasei JY025	Probiotic–fortified milk powder	10^6–10^7 CFU/mL	Shen *et al*., 2024
L. casei 431, *L. acidophilus* LA–5, *L. paracasei* L–26, *L. rhamnosus*, *Bifidobacterium animalis subsp. lactis* BB–12	Sheep–milk symbiotic probiotic ice cream	10^8 CFU/g	Kowalczyk *et al*., 2022
L. paracasei (Shirota), *L. lactis subsp. lactis* YIT 2027	Shirota–style fermented milk drink	10^7–10^8 CFU/g	Oana *et al*., 2023
L. acidophilus, *L. plantarum*, *B. lactis*	Buffalo milk yogurt	10^6–10^8 CFU/g	Akbal *et al*., 2025
L. plantarum, *L. casei, L. rhamnosus*, *S. thermophilus*, *Lactobacillus delbrueckii* spp. *Lactis*	Cashew/camel milk labneh (concentrated yogurt)	10^7–10^9 CFU/mL	Al–Sulbi and Shori, 2022
B. bifidum, *B. longum*, *Bifidobacterium breve*, *B. lactis*, *Bifidobacterium adolescentis*	Yogurt	10^7 CFU/mL	Sibanda *et al*., 2024; Talearngkul *et al*., 2023
L. paracasei	Yogurt with added probiotic strains	10^7–10^8 CFU/g	Moiseenko *et al*., 2023
S. thermophilus,	Yogurt, cheese		Huang *et al*., 2024
L. acidophilus, *L. casei, L. rhamnosus*, *L. delbrueckii*, *L. plantarum*, *L. fermentum*, *Streptococcus intermedius*, *Lactobacillus salivarius*, and *Lactobacillus brevis*	Yogurt, fermented milk	10^7–10^9 CFU/mL	Dimitrellou *et al*., 2025

Notes: ABT: a mixed starter culture for fermented foods, combining *Lactobacillus acidophilus*, *Bifidobacterium* spp., and *Streptococcus thermophilus* culture; CFU: colony–forming unit.

fatty acids (SCFA), immune modulation, and disease relief, are largely mediated by secondary microbiome–driven effects (Liu *et al.*, 2025; Peled *et al.*, 2024). In practice, full efficacy results from synergistic coupling of both mechanisms, rather than from either pathway alone. Furthermore, despite the potentiality of these mechanisms in the protein–probiotic interactions, they approach challenges related to strain specificity, environmental variability within the gut, and long–term microbiome interactions (Song *et al.,* 2022; Zhang *et al.*, 2023a), thus paving the way for further study, such as validation through *in vivo* to show feasibility for clinical translation.

Protein conjugation techniques used in dairy systems

Protein conjugates refer to covalently bonded complexes formed between proteins and other biomolecules, such as carbohydrates, polyphenols, or similar compounds, through various chemical or enzymatic processes, enhancing the functional properties of the resulting complexes. Structurally and functionally, protein–sugar conjugates can shield probiotics from environmental stresses, increase their adherence to the intestinal epithelium, and even improve the sensory quality of the final dairy product (Vivek *et al.*, 2023; Zhang *et al.*, 2023b). Conjugation

Table 2. Important mechanisms for protein–probiotic conjugation.

Strategy	Mechanism	Functional outcome	Trial application	References
Bioorthogonal reactions	DBCO–modified probiotics react with azido–decorated D–alanine in gut bacteria	Enhanced adhesion, prolonged gut retention	Improved colonization, colitis relief	Song *et al.*, 2022
Maillard–conjugates	Core–shell conjugates of 2′–fucosyllactose and lactoferrin hydrolysates	Increased probiotic growth, SCFA production, and reduced inflammation	Enhanced gut health	Peled *et al.*, 2024
Surface protein interactions	LPxTG motif proteins bind phenols and oligosaccharides	Improved stress resistance and GI tolerance	Stronger gut colonization	Zhang *et al.*, 2022a
Probiotic–drug conjugates	Surface–modified probiotics deliver drugs site–specifically	Synchronized colonization and localized therapy	Ulcerative colitis treatment	Yin *et al.*, 2025
Multicellular microcolonies	Encapsulation into acid–resistant, stress–relaxing colonies	Significantly enhanced gut survival and colonization	Clinical probiotic delivery	Liu *et al.*, 2025

Notes: SCFA: short–chain fatty acids; DBCO: dibenzocyclooctyne; LPxTG: Leu–Pro–any–Thr–Gly.

can alter the physicochemical and biological characteristics of milk proteins. The growing demand for functional dairy products has therefore driven substantial advances in protein modification technologies. Among the various techniques available, studies have identified three main approaches: the Maillard–type conjugation, enzymatic cross–linking, and physical activation, which currently hold the greatest potential. The methods and parameters used in recent studies on protein–carbohydrate conjugates in dairy products are presented in Table 3.

The Maillard, enzymatic, and chemical conjugation each provides distinct mechanistic avenues for improving probiotic functionality in dairy systems, although their benefits and limitations diverge. The Maillard conjugation, driven by the covalent attachment of reducing sugars to lysine residues, reinforces protein matrix stability while simultaneously enhancing the protective barrier against acid and bile stress (Gao *et al.*, 2021; Zhang *et al.*, 2023b). By contrast, enzymatic conjugation, most notably via microbial transglutaminase (MTGase), exhibits greater substrate specificity, producing ε–(γ–glutamyl)–lysine cross–links that not only stabilize probiotic encapsulation but also enhance mucosal adhesion and promote the controlled release of bioactive peptides during digestion (Milczek, 2018). Chemical conjugation expands versatility by enabling the covalent grafting of proteins with polyphenols or polysaccharides to form complexes that provide strong shielding against environmental stressors; however, concerns over off–flavors, altered digestibility, and regulatory approval limitations restrict their translational potential (Zhang *et al.*, 2023a).

Polysaccharide–protein complexes (PPCs) offer significant advantages over single–protein carriers in dairy systems, serving as biocompatible alternatives to synthetic emulsifiers (Sun *et al.,* 2022). They enhance colloidal stability during processing and storage, improve the encapsulation and bioaccessibility of bioactive compounds, and positively modify textural and sensory attributes, collectively leading to greater consumer acceptance of dairy products (Liu *et al.,* 2025). Despite these functional benefits, the industrial application of PPCs is constrained by scalability and reproducibility challenges. Protein–polysaccharide interactions are highly sensitive to processing conditions, such as pH and ionic strength, often resulting in variability in complex formation and performance (Goh *et al.,* 2020). Furthermore, maintaining consistent quality during large–scale production and meeting clean–label and regulatory requirements remain critical hurdles that must be addressed to enable broader adoption of PPCs in commercial dairy systems (Liu *et al.,* 2025).

Maillard–protein conjugation

The Maillard reaction is a nonenzymatic glycation process in which reducing sugars react with protein amino groups to form Schiff bases, ultimately leading to stable ketoamine linkages (Figure 1) (Liu *et al.*, 2020). In dairy systems, this reaction is typically performed under dry or semi–dry conditions at moderate temperatures (50–80°C) and approximately 70% relative humidity (RH) for 24–72 h (da Silva *et al.*, 2019). The reaction alters protein structures by exposing hydrophilic groups and increasing surface activity, thereby enhancing their functional and protective roles. It has been widely applied to milk proteins, including WPI (Xu *et al.*, 2019), casein (Yuan *et al.*, 2024), and milk protein concentrate (Wu *et al.*, 2021b), with saccharides, such as inulin, dextran, Arabic gum, and xylooligosaccharides (XOS)/GOS. While this processing can improve the nutritional quality and quality of foods, it requires precise control. Excessive heating may cause undesirable browning, nutritional losses of essential amino acids, and the formation of advanced glycation end products (AGEs), which are increasingly concerning for health–conscious

Table 3. **Methods of protein–carbohydrate conjugations in dairy–based probiotics.**

Conjugation	Method	Dairy products	Probiotic strains	Properties	References
WPI–Dextran	Dry heating at 80°C for 5 h, 79% RH	Milk beverage	*L. plantarum*	• Storage at 4°C for 90 days with a reduction of 0.33 log CFU/mL • GI survival improved, and heat resistance demonstrated at 65–85°C	Guo *et al*., 2022
WPI–XOS	Dry heating 65°C, 79% RH, 24–48 h	Yogurt	*L. rhamnosus*	• Spray drying survival 99.83 ± 8.44% • Storage reduction is less than 1 log CFU/g over 10 weeks at 4°C • GI digestion reduction 0.20 log CFU/g after 4 h • Final count 4.09 × 109 CFU/g	Liao *et al*., 2021
Gelatin–XOS	Dry heating 65°C, 79% RH	Spray–dried capsule	*L. fermentum*	• Increased GI survival and heat resistance • Maximum survivability of 13.91% observed at 60–min MRP	Li *et al*., 2023
SPI–Xylose	Maillard 70°C, 65% RH, 24 h	Spray–dried powder	*L. acidophilus*	• Spray drying survival 21.36–25.31% for MRP–based samples, compared to 20.17% for the mixture	Du *et al*., 2023
Milk exosome–protein conjugates	Low–temp exosome adsorption (4°C), pH 6.8	Functional milk	*Akkermansia muciniphila*	• Initial viable count 1 × 108 CFU/mL • Encapsulation efficiency 90.37 ± 0.45% • *In vitro* GI survival rate 94.53 ± 0.26% • Nontoxic to cells and promoted cell health	Hao *et al*., 2025
Protein–oligosaccharide	Shell–cross–linked conjugation	Functional delivery system	Mixed LAB strains	• Targeted colon delivery and improved bioactive delivery • Growth of *L. casei* increased two–fold • Peptide fraction above 5 kDa 64.4–82.9% compared to 12% for native	Peled and Livney, 2021
WP–carboxymethylated dextran + sugar (trehalose/lactose/sucrose)	50–60°C, RH–controlled oven, 24–48 h	Yogurt matrix	*L. plantarum* LP90	• Freeze–drying survival trehalose 97.8% and lactose 98.5% • GI tolerance greater than 5 h	Li *et al*., 2025

Note: WPI: whey protein isolate; XOS: xylooligosaccharide; SPI: soy protein isolate; GI: gastrointestinal; LAB: lactic acid bacteria; CFU: colony forming unit; MRP: Maillard reaction products.

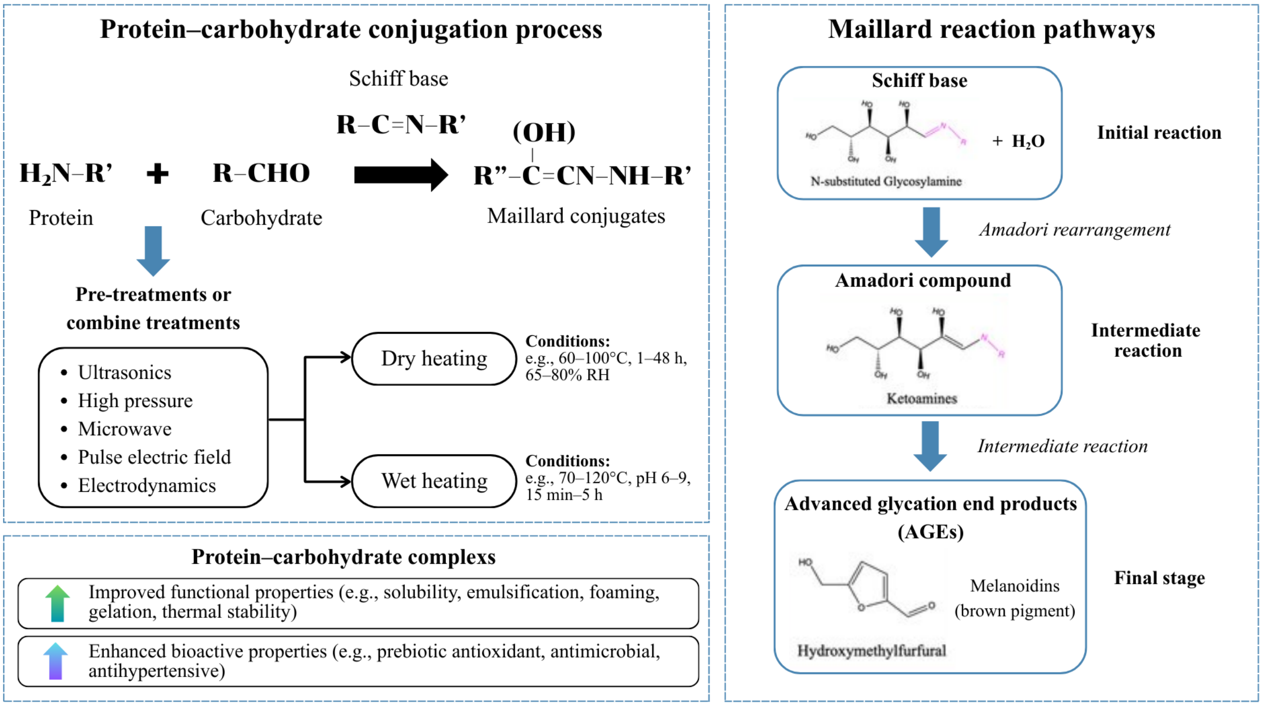

Figure 1. Schematic illustration of protein–carbohydrate conjugation pathways. Physical pretreatments followed by dry or wet heating promote Maillard conjugation, enhancing the functional and bioactive properties of the resulting protein–carbohydrate complexes.

consumers. For the same reason, Bi *et al.* (2023) recommended exposure at 70°C for 15 s as optimal conditions to preserve both quality and nutritional value in a study on the effect of pasteurization on the Maillard reaction in lactose–free milk.

The Maillard conjugation substantially improves the functional properties of milk proteins, including solubility, heat stability, emulsifying ability, and antioxidant activity (Xu *et al.,* 2019). These enhancements directly translate into improved probiotic survival during GI stress and thermal processing, making this approach particularly valuable for yogurt and fermented milk products. In such matrices, Maillard–modified proteins not only protect probiotic cells but also enhance texture and provide prebiotic benefits, supporting synbiotic formulations. Consistently, higher counts of *Lactobacillus* and *Bifidobacterium* have been reported in conjugate–fortified dairy, compared with nonconjugated carriers (Chaiwong *et al.,* 2025; Liao *et al.,* 2021).

Extending this strategy to plant–based proteins presents challenges because of structural heterogeneity, reduced solubility, and lower lysine availability, all of which can hinder conjugation efficiency. For example, pea protein–polydextrose conjugates produced by wet heating have been shown to improve solubility, emulsifying, and foaming properties, with the protein–to–polydextrose ratio, temperature, and time as key factors (Khan *et al.,* 2024). Similarly, soy protein isolate–oligosaccharide Maillard conjugates enhanced the antioxidant activity of the carrier and improved *Lactobacillus casei* survival under simulated digestion, maintaining 7.4 log CFU/mL, compared to 1.6 log CFU/mL in free cells (Zhong *et al.,* 2021). Moreover, Nghiep (2024) found that optimized energy–nitrogen combinations enhance nutrient value and protein efficiency, affecting feed intake and nutrient digestibility in Saanen crossbred goats, suggesting that the conjugation effect of protein–polysaccharides is of great importance in dairy systems. Despite such progress, plant–based Maillard reaction products (MRPs) still fall short of the probiotic protection typically achieved with dairy carriers, underscoring the need for further optimization of conditions and formulations.

Importantly, the Maillard conjugation utilizes food–safe materials and provides multifaceted functionality without relying on synthetic additives. It improves solubility, emulsification, antioxidant activity, and probiotic stability (Chaiwong *et al.,* 2025). Nonetheless, uncontrolled reactions may induce browning, off–flavors, and the formation of AGEs, which pose nutritional and health concerns. When carefully managed, however, the Maillard–protein conjugation remains a powerful strategy for probiotic delivery, particularly in dairy applications (Dong *et al.,* 2023; Kathuria *et al.,* 2023). Moreover, recent work has highlighted the potential of two–stage complexation–covalent conjugation followed by complex coacervation as a promising route to engineer more stable protein–carbohydrate systems (Zhang *et al.,* 2023b).

Enzymatic protein–conjugation

Enzymatic protein conjugation involves specific biocatalysts that form covalent bonds between proteins or between proteins and other biopolymers, thereby tailoring their functional and structural properties. Among these, MTGase is the most widely used enzymatic conjugation method in dairy systems. Other enzymes, such as laccases, tyrosinases, and peroxidases, catalyze protein–polyphenol or protein–protein cross–linking, potentially conferring functional benefits in plant–based systems due to their broader substrate ranges (Gouseti *et al.,* 2023). MTGase catalyzes the formation of ε–(γ–glutamyl) lysine bonds via acyl transfer between glutamine and lysine residues (Milczek, 2018), thereby generating larger, more stable protein networks. Reactions usually occur under mild conditions (30–50°C, near–neutral pH) and are completed within 1–4 h (da Silva *et al.*, 2019), making the process compatible with probiotic viability. In dairy matrices, MTGase is effective at low doses, is safe, and enhances the texture of yogurt and cheese by strengthening casein gels, thereby improving viscosity and gel strength, and enabling physical entrapment of probiotic cells (da Silva *et al.,* 2019; Milczek, 2018). Furthermore, Halavach (2024) demonstrated that enzymatic hydrolysis of whey and colostrum proteins using alcalase and protozyme (5%, 50–60°C) generated low–molecular–weight peptides (<10 kDa) with high immunoglobulin hydrolysis (82.4%). These hydrolysates are potentially hypoallergenic and suitable for functional foods and nutraceutical applications. Compared to chemical cross–linking, enzymatic conjugation offers advantages in precision, safety, and the avoidance of unwanted by–products, such as AGEs (Kathuria *et al.,* 2023).

Despite the advantages of enzymatic conjugation in dairy systems, the cost of enzymes, batch–to–batch variability in activity, and inhibition by food components (e.g., metal ions, phenolics, or extreme pH levels) may limit scalability (Kathuria *et al.,* 2023). Additionally, although MTGase efficiently cross–links caseins owing to their flexible, open structures, plant proteins (e.g., soy, pea, and oats) pose greater challenges. Their globular conformation and reduced lysine/glutamine accessibility reduce conjugation efficiency (Chen *et al.*, 2020), often necessitating pretreatment (e.g., denaturation, hydrolysis, or high–pressure processing) to expose reactive sites. This distinction highlights a crucial difference: applying the same approach to plant–based matrices often compromises sensory quality by producing excessive gel rigidity and off–flavors, or necessitates higher enzyme inputs, thereby increasing regulatory concerns (Sim *et al.*, 2021). However, such effects may be more tolerable in plant–based alternatives (Santoso *et al.*, 2024; Yi *et al.*, 2024). Therefore, a critical balance must be achieved between functionality and sensory acceptance. Furthermore, future research should critically compare enzyme systems across both domains, tailoring approaches to optimize reactivity while preserving desirable sensory attributes.

Chemicals–protein conjugation

Chemical conjugation, which has limited applications in commercial dairy products due to regulatory constraints, employs external cross–linking agents to form covalent bonds between protein molecules or to graft functional groups, such as polyphenols, oligosaccharides, or polysaccharides (Figure 2), onto proteins (Zanjani *et al.*, 2018). These reactions target nucleophilic functional groups on protein surfaces, including amines, carboxyls, thiols, and phenolic residues. Among these, common food–compatible cross–linkers include genipin (from *Gardenia jasminoides*), EDC (1–ethyl–3–(3–dimethylaminopropyl) carbodiimide), and oxidized polysaccharides with reactive aldehyde groups (Wei and Huang, 2019; Zanjani *et al.*, 2018).

Chemical conjugation approaches in dairy applications are primarily limited to food–grade, safe cross–linking agents. For example, genipin–cross–linked protein matrices have been utilized to encapsulate probiotic strains, such as *L. reuteri*, thereby enhancing their viability during spray drying and exposure to simulated GI fluids (Laurujisawat *et al*., 2025). Additionally, chemical grafting of proteins to dietary fibers (e.g., pectin or alginate derivatives) or polyphenolic compounds (e.g., tannic acid and catechins) can create protein–polyphenol or protein–fiber complexes with protective, antioxidant, and antimicrobial properties within the constraints of food safety regulations (Wei and Huang, 2019).

Protein conjugation via chemical methods offers high versatility and stability, enabling the design of multifunctional delivery systems resistant to acid, heat, and mechanical stress. However, potential limitations include off–flavors, discoloration (especially with genipin), and reduced digestibility of excessively cross–linked proteins. Additionally, the regulatory status of some cross–linkers may pose challenges, as only specific agents, such as genipin, are approved for food use, and any unreacted chemicals must be removed or proven unsafe (Laurujisawat *et al*., 2025; Wei and Huang, 2019; Zanjani *et al*., 2018). Thus, chemical–protein conjugation offers strong functional benefits but is limited by regulatory restrictions, sensory changes, and the need for safe, food–grade cross–linkers.

Mechanism of interactions of protein conjugates in the dairy system

The description of the Maillard, enzymatic, and chemical conjugation techniques provides an overview of

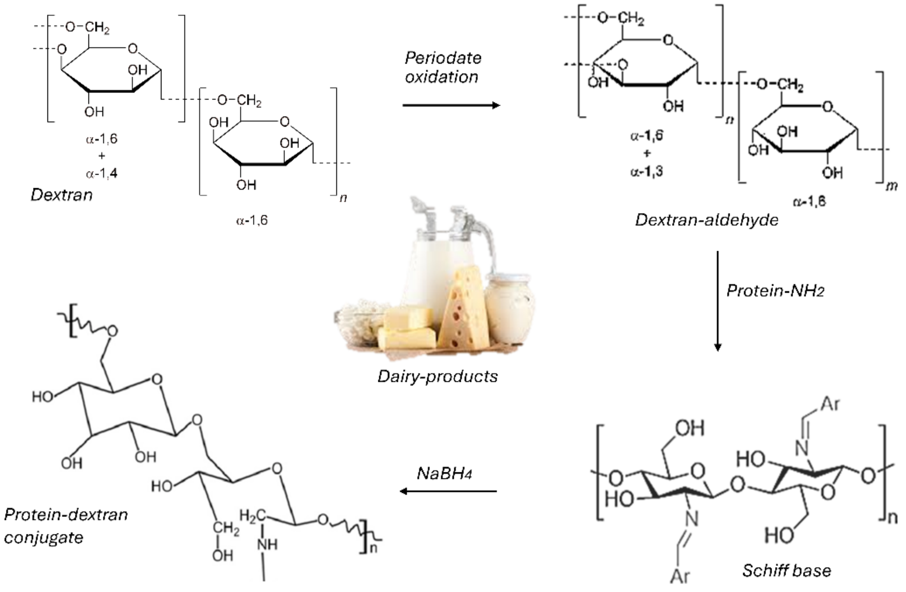

Figure 2. Schematic illustration of dextran–protein conjugate formation via periodate oxidation and reductive amination. Dextran is first oxidized by sodium periodate to produce aldehyde groups, which subsequently react with the amino groups of proteins to form Schiff bases. The imine linkages are then reduced by sodium borohydride ($NaBH_4$) to yield stable covalent dextran–protein conjugates.

their synthesis; however, a mechanistic understanding is essential to explain how these conjugates interact with probiotic cell surfaces. At the molecular level, electrostatic attraction, hydrophobic interactions, and hydrogen bonding are primarily responsible for binding between conjugated biopolymers and bacterial membranes (Liu *et al.*, 2023; Sun *et al.*, 2023). The cationic amino acid residues of proteins in the conjugates can interact with the negatively charged teichoic acids, peptidoglycan, and exopolysaccharides on the probiotic cell walls, whereas the hydrophobic regions anchor to the lipid components of the membrane (Sun *et al.*, 2022). In Maillard– and enzymatically derived conjugates, reactive carbonyl and amino groups can form weak covalent or hydrogen–bonding interactions with surface proteins or polysaccharides, thereby enhancing adhesion stability (Liu *et al.*, 2023). Additionally, surface–layer (S–layer) proteins, lipoteichoic acids, and extracellular polysaccharides of *Lactobacillus* and *Bifidobacterium* species act as specific binding sites that mediate these interactions (Bönisch *et al.*, 2018; Du *et al.*, 2023). The conjugate–cell–surface associations reinforce membrane integrity, reduce permeability to environmental stressors, and enhance probiotic resilience during processing and GI transit (Sun *et al.*, 2023).

This study confirms that the effectiveness of conjugation varies among probiotic strains because of differences in surface proteins and cell wall composition, making the response largely strain–dependent, as highlighted in Table 3. Furthermore, there is no universal ratio; most studies report effective conjugation between 1:1 and 1:3 (w/w), but the optimal proportion depends on the strain and the conjugation method used. The conjugation approaches in this review provide insight into a continuum between functional efficacy and practical applicability, suggesting that future innovation may dwell in hybrid systems that combine the biological precision of enzymatic strategies with the structural resilience of both Maillard and chemical pathways, as indicated by several studies in Table 3.

Role of Protein Conjugates on Probiotic Functionality of Dairy Products

Role of conjugation on the survival of probiotics in dairy products

Probiotics often experience viability loss under various processing conditions, including thermal treatments, spray drying, freeze drying, and prolonged storage (Manyatsi *et al.*, 2024). However, protein conjugation has proven highly effective in addressing these challenges. Several studies have demonstrated that conjugating proteins, such as WPI, sodium caseinate, soy protein isolates, and plant–derived proteins such as peas and rice, with carbohydrates or polyphenolic compounds via various encapsulation processes enhances the proportion of probiotic survival (Xu *et al.*, 2019). Pumpkin carotenoids complexed with casein and soy proteins showed improved stability and functionality after spray drying

(Werasakulchai *et al.*, 2025). Protein–carotenoid powders are suitable for use in food. This is consistent with protein conjugation strategies in dairy foods to enhance bioactive delivery.

For example, Liao *et al.* (2021) prepared the Maillard reaction conjugates of WPI and XOS to encapsulate *L. rhamnosus* by spray drying. Results showed that WPI–XOS conjugates improved the survival of *L. rhamnosus* during spray drying with enhanced storage stability (at 4°C) for up to 8 weeks. Similarly, Song *et al.* (2024) investigated WPI–soybean hull polysaccharide conjugates that encapsulated *L. casei* by freeze–drying at −80°C. The result showed that probiotics encapsulated with conjugates can survive during processing and storage. This results in higher viability during freeze–drying (87.35% vs. 24.95% for unencapsulated) and better thermal resistance during pasteurization at 60°C and 80°C. Furthermore, ultrasound–assisted multilayer Pickering emulsions prepared from WPI conjugated with (−)–epigallocatechin–3–gallate (EGCG) protected *L. plantarum* well during pasteurization at 63°C for 30 min. The probiotic survival proportion after pasteurization for the unconjugated sample was 48.5%, compared to 74.25% for the WPI–EGCG conjugated multilayer emulsion. This indicates that the conjugated system improved thermal protection by approximately 25.75% (He *et al.*, 2023).

Additionally, Mudgil *et al.* (2024b) investigated the stability of *L. reuteri* DSM 17938 encapsulated within pea and rice protein conjugates with inulin. The results showed that conjugating plant proteins with prebiotic inulin and rice protein achieved the highest percentage of efficiency (96.99%), compared to pea protein conjugates (92.87%). Protein conjugates form dense protective layers around probiotics, shielding them from environmental stresses, including heat, moisture, oxygen, and acidic conditions (Li *et al.*, 2025). Specifically, the Maillard reaction enhances barrier properties by forming stable covalent bonds between proteins and carbohydrates, resulting in robust microcapsules that prevent probiotic degradation during processing and storage (Gao *et al.*, 2021; Liao *et al.*, 2021; Minj and Anand, 2022).

Protection of probiotics against gastrointestinal stressors

During digestion, probiotics encounter several stressors: in the stomach, the environment is highly acidic (pH 1.5–3.0) and contains digestive enzymes, such as pepsin; in the small intestine, exposure to bile salts and pancreatin at near–neutral pH (6.5–7.5) further threatens cell viability; and in the colon, anaerobic conditions and microbial competition present additional survival hurdles (Li *et al.*, 2025; Minj and Anand, 2022; Werasakulchai *et al.*, 2025). To improve probiotic viability, recent research has focused on the use of protein–carbohydrate Maillard conjugates formed by covalent bonding between proteins (e.g., WPI, soy protein isolate, and caseinate) and carbohydrates (e.g., oligosaccharides and polysaccharides) as effective protective encapsulating agents (Du *et al.*, 2023; Liao *et al.*, 2021; Mudgil *et al.*, 2024b). Similarly, Liao *et al.* (2021) reported enhanced resistance of *L. rhamnosus* encapsulated in WPI–XOS Maillard conjugates under simulated gastric conditions. When exposed to simulated gastric fluid (pH 2.0, for 2 h at 37°C), free cells exhibited a drastic reduction in viability, dropping to below 4.0 log CFU/g, while encapsulated cells maintained over 7.5 log CFU/g, indicating strong acid resistance and potential for delivery to the intestines.

Moreover, probiotics encapsulated within WPH–maltodextrin conjugates demonstrated improved survival under simulated gastric acid conditions (pH 2.5 for 2 h at 37°C). *L. acidophilus* encapsulated maintained a viability of 7.4 log CFU/g, compared with a sharp decline to 3.2 log CFU/g in the control. Furthermore, upon exposure to bile salts (0.3% for 3 h at 37°C), the encapsulated cells remained above 7.0 log CFU/g, demonstrating the conjugate's effectiveness in maintaining probiotic viability across GI conditions (Minj and Anand, 2022). Furthermore, the hydrophilic–hydrophobic balance and viscoelastic gel structure of protein conjugates delay digestive penetration and modulate controlled release, enabling colon–targeted delivery (Gao *et al.*, 2021; Minj and Anand, 2022). The challenge in moving forward exists in optimizing conjugate formulations for large–scale food applications while ensuring safety by avoiding the overproduction of AGEs.

Protein conjugates enhance probiotic survival under GI stress by creating a multi–layered protective matrix that reduces direct exposure of cells to gastric acid, bile salts, and digestive enzymes (Li *et al.*, 2025; Werasakulchai *et al.*, 2025). Mechanistically, conjugated proteins reduce proton permeability and bind bile salts, thereby mitigating membrane disruption in probiotic cells. Studies in simulated GI models demonstrate that whey protein–oligosaccharide conjugates increase survival proportions of *Lactobacillus rhamnosus* and *Bifidobacterium longum*, compared to unconjugated carriers (da Silva *et al.,* 2019; Liao *et al.,* 2021; Rolim *et al.,* 2021). Preliminary human intervention studies further suggest that probiotic delivery with whey protein conjugates results in higher recovery of viable *Lactobacillus* in the small intestine, supporting improved colonization and persistence (Rolim *et al.,* 2021). These findings suggest that protein conjugation strategies not only serve as physical shields but also modulate the digestive microenvironment, thereby creating translational opportunities for next–generation probiotic formulations in functional dairy systems.

Role of Protein Conjugates on the Quality of Dairy Products

Functional quality of dairy products with protein–carbohydrate conjugation

Researchers have demonstrated that conjugated proteins with carbohydrates, formed through the Maillard reaction, can seriously impact the technological and functional properties of the final conjugates, particularly in areas such as solubility, heat stability, emulsification, foaming properties, gelation, and texture (Deng *et al*., 2025; Urango *et al*., 2024; Zhang *et al*., 2023b). Primarily, conjugates made through the Maillard–type glycation or enzymatic cross–linking exhibit amphiphilic characteristics that enable them to serve as protective matrices and functional stabilizers in dairy–based systems. The key function of protein–carbohydrate conjugates in probiotic dairy systems is their ability to act as encapsulating agents. Protein conjugates can form protective matrices around probiotics through microencapsulation processes (Loyeau *et al*., 2021; Werasakulchai *et al*., 2025).

Additionally, several studies have demonstrated diverse applications of protein conjugates in dairy products. Mudgil *et al*. (2025) showed that camel milk protein complexed with polyphenols from dates' seeds achieved substantially improved emulsification stability and nearly three–fold increase in foaming capacity compared to nonconjugated protein powders. Chaiwong *et al.* (2025) reported that whey protein–GOS conjugates (1:2 ratio, heated for 6 h at 90°C) exhibited superior solubility and emulsion stability compared to whey protein alone, demonstrating better technological properties than other conjugate ratios tested. Additionally, Akalan *et al.* (2024) added 1% protein conjugate prepared from brown rice protein and microcrystalline cellulose, or 1% brown rice protein, to set yogurt. The protein conjugate and brown rice protein considerably improved dry matter, water–holding capacity, firmness, consistency, viscosity index, and cohesiveness while decreasing syneresis in yogurt samples compared to plain yogurt. The application of protein conjugates also extends to plant–based dairy alternatives. Soy protein isolate–maltodextrin conjugates can be effectively used as substitutes for conventional proteins in various applications, including enhancing foaming stability and improving solubility (Choi *et al*., 2025). Similarly, microalgal proteins have emerged as promising ingredients for dairy alternatives, often outperforming terrestrial plant proteins because of their balanced amino acid profile and superior techno–functional properties (Samarathunga *et al*., 2025). In another investigation on ice cream incorporating WPI and rare sugars (D–allose and D–psicose) for glycation, it was reported that ice cream with WPI glycated with rare sugars had a higher overrun than ice cream with untreated WPI (Puangmanee *et al*., 2008).

In addition to protecting probiotics, protein conjugates markedly influence the flavor and physicochemical properties of dairy products. Key quality characteristics of yogurt, cheese, and milk–based beverages include enhanced emulsification capacity, gel–forming ability, and water–holding capacity, which define texture, viscosity, and mouthfeel (Mudgil *et al*., 2025). For instance, conjugates generated by the Maillard reaction between WPI and inulin have been shown in yogurt systems to reduce whey separation and increase product creaminess (Żbikowska *et al*., 2020). For dried milk, a conjugated WPH with maltodextrin was used as a carrier to protect *B. animalis* spp. *lactis* ATCC 27536 and *L. acidophilus* ATCC 4356 (Minj and Anand, 2022). The protein conjugate provided better probiotic protection during spray drying, resulting in a final probiotic count of 8.98 log CFU/g, compared to an initial count of 10.58 log CFU/mL before drying.

Gut microbiome analysis can be more effectively integrated into protein–probiotic conjugate design by using microbial composition and functional outputs to guide the selection of compatible prebiotics and probiotic strains for targeted outcomes. For instance, nondigestible dextrin, α–cyclodextrin, and dextran selectively enhance acetate and propionate production in human fecal fermentation models, highlighting how microbiome–driven SCFA profiles can inform conjugate design aimed at gut and metabolic health (Sasaki *et al*., 2018). Clinical evidence further demonstrates the value of microbiome–informed selection, as *Lactobacillus*–, *Bifidobacterium*–, and multi–strain formulations, such as a multi–strain formulation comprising four *Lactobacillus* strains, three *Bifidobacterium* strains, and one *Streptococcus salivarius* subsp. *Thermophilus strain modulates inflammatory pathways, enhances mucosal barrier function, and reduces* systemic markers of inflammation in inflammatory bowel disease and ulcerative colitis (Ganji–Arjenaki and Rafieian-Kopaei, 2018; Groeger *et al*., 2013). Together, these findings support a targeted design strategy in which microbiome profiling and host biomarkers directly inform the development of protein–probiotic conjugates with predictable anti–inflammatory and gut–protective effects.

Sensory attributes of protein conjugate containing dairy products

Gharibzahedi and Altintas (2024) further reported the sensory properties of set yogurt added with a protein conjugate, showing a slight difference with an optimum condition of 4.65% (w/w) transglutaminase–cross–linked protein isolate and 10.1 log CFU/mL *L. acidophilus* LA–5® producing yogurt with maximum lightness, firmness, apparent viscosity, and probiotic survivability, combined with minimum syneresis. Moreover, the yogurt with transglutaminase–cross–linked protein isolate exhibited less sensory deterioration than other yogurt samples during refrigerated storage over 2 weeks.

Nevertheless, the issue of product color after adding the protein conjugate was reported by researchers who supplemented the conjugate in ice cream and cream products. Seo and Yoo (2022b) used milk protein isolate–κ–carrageenan conjugates as part of the whipping cream ingredients and noted that excessively high levels of the conjugates affected the color of the whipping creams, making them appear more yellow A similar drawback was discovered if imitation Mozzarella cheese was supplemented with conjugates of cricket protein and FOS (Chailangka *et al.*, 2023). The findings revealed that imitation Mozzarella cheese with 30% or higher conjugates received lower sensory scores for its appearance, color, odor, texture, flavor, and overall acceptability.

Protein sources in protein–probiotic conjugation

Protein conjugates from both milk and plant sources play important roles in stabilizing probiotics, enhancing their adhesion, and modulating host immunity. However, they function through distinct mechanisms and with varying effectiveness. Milk proteins, such as whey and casein, are particularly effective for microencapsulation, protecting probiotics during processing and GI transit, and their surface properties enhance adhesion to the intestinal mucosa (Abd El–Salam and El–Shibiny, 2015). They also influence gut immunity by promoting beneficial microbiota and SCFA production, thus reducing inflammation (Peled *et al.,* 2024). In contrast, plant proteins primarily interact with exopolysaccharides in fermented products to maintain probiotic structural integrity and support functional effects, including antioxidative and anti–inflammatory activities. However, their encapsulation and immune–modulatory capacities are less well characterized (Zang *et al.,* 2025). These findings suggest that milk–derived proteins offer robust and predictable benefits for probiotic stabilization and immune modulation. In contrast, plant proteins provide complementary advantages in specific applications, such as fermented foods, making the choice of protein system dependent on health goals, product type, and dietary considerations.

Role of Protein Conjugates in Delivering Nutritional and Health Advantages of Probiotics in Dairy Products

Probiotics can take the form of live cultures, inactivated cultures, postbiotics, and prebiotics, and are regarded as integral to functional dairy products. Owing to the presence of probiotics in dairy products, these products functionally improve overall digestive performance by influencing the intestinal microbiota, particularly when combined with protein conjugates. It has been found to confer various health benefits, including alleviating lactose intolerance, modulating the immune system, and controlling cholesterol levels (Mokhtari *et al.*, 2019). Furthermore, it is asserted that probiotics, when combined or encapsulated in protein–conjugated products within a dairy product matrix, could enhance their benefits through the stabilization and delivery of probiotics, thereby increasing their bioavailability and modulating immune responses and gut flora (El Jeni *et al.*, 2024).

Recent studies also suggest that protein–carbohydrate conjugates may enhance the biofunctional activity of probiotic systems. After digestion, these conjugates release bioactive peptides that exhibit antioxidant, antibacterial, and antihypertensive properties (Minj and Anand, 2022). Additionally, oxygen–sensitive bacteria (*A. muciniphila*) have been encapsulated using emerging delivery methods, including those employing milk exosomes coupled to bioactive proteins. A recent *in vitro* study in mice has shown that such systems can enhance mucosal immunity and metabolic balance compared with unencapsulated systems (Hao *et al.*, 2025). Protein conjugates also aid in regulating immune responses, thereby enhancing probiotics' ability to support immune function (Hao *et al.*, 2025). Moreover, they enhance the bioavailability of probiotics and bioactive peptides, thereby maximizing their health benefits (Hadjimbei *et al.*, 2022; Li *et al.*, 2023), as illustrated in Figure 3. Most evidence supporting the benefits of protein–probiotic conjugates remains largely confined to *in vitro* studies and animal models.

Evidence studies on the nutritional and health roles of protein conjugates in probiotic–based dairy products

Recent studies have explored the potential of protein conjugates to enhance the nutritional and health–promoting effects of probiotics in food systems. For instance, in a study conducted by Massounga Bora *et al.* (2021), WPI and (−)–epigallocatechin–3–gallate conjugates were evaluated as carriers for *L. acidophilus*, demonstrating enhanced *in vitro* antioxidant (78%) and antidiabetic (52%) activities as well as improved probiotic survival ability and surface hydrophobicity. Similarly, Yu *et al.* (2021) examined the effects of casein and chicken–protein diets on recovery from dextran sulfate sodium (DSS)–induced colitis in mice. While DSS caused no physiological differences between the diet groups, the casein diet increased the beneficial gut bacteria. These findings collectively highlight the role of protein–based

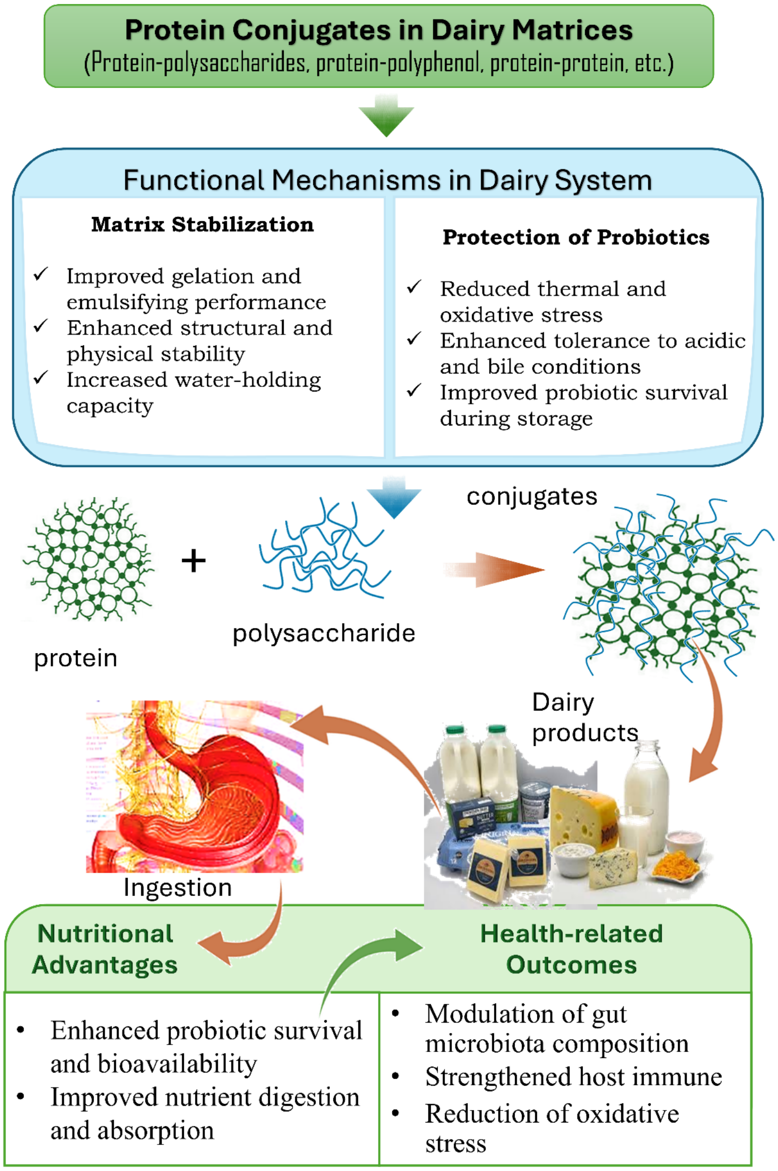

Figure 3. Overview of the functional roles of protein conjugates in probiotic dairy systems, highlighting their contribution to probiotic bioavailability, nutrient absorption, and host health protection. Source: Hadjimbei *et al.* (2022); Hao *et al.* (2025); Li *et al.* (2023); Lim *et al.* (2024); Rashidi *et al.* (2021).

conjugates and dietary proteins in improving probiotic delivery, physiological functioning, and GI health.

Evidence suggests that protein conjugates enhance the survival, adhesion, and colonization of probiotics by forming protective matrices and promoting the targeted release of bioactive peptides and prebiotic–like sugars (Li *et al.,* 2023; Mudgil *et al.,* 2024a). Mechanistically, MTGase–mediated cross–linking strengthens hydrophobic and electrostatic interactions with intestinal epithelium, while the Maillard–derived reductones and melanoidins provide antioxidant protection to both probiotics and the host. Rashidi *et al.* (2021) reported that human clinical trials have demonstrated that dairy products containing protein–modified matrices increase *Lactobacillus* and *Bifidobacterium* abundance, improve cytokine profiles (e.g., elevated interleukin–10 [IL–10] and reduced tumor necrosis factor–alpha [TNF–α]) (Santiago–López *et al.*, 2018), and enhance systemic antioxidant markers, confirming the translational potential of these functional dairy systems.

Microbiota modulation

The human gut microbiota, often referred to as a "forgotten organ," comprises approximately 95% of all the cells in the human body and contains an estimated 10^{11}–10^{12}

CFU/g of intestinal content (Fucarino *et al.*, 2022; Yao *et al.*, 2021). The gut microbiota plays a vital role in maintaining epithelial barrier function and supporting metabolic and biochemical activities. Probiotics have been shown to promote intestinal eubiotics through various processes, including the synthesis of SCFAs, enhancing gut barrier integrity, competitive exclusion of pathogens, and modulation of immunological responses (Gao *et al.*, 2022).

Protein conjugates modulate gut microbiota by enhancing probiotic adhesion and supplying selective metabolic substrates. MTGase–mediated casein conjugates strengthen hydrophobic and electrostatic interactions with intestinal epithelial cells, improving colonization and persistence (Gao *et al.*, 2022; Wang *et al.*, 2020). In parallel, the gradual hydrolysis of protein–carbohydrate conjugates releases short peptides and reducing sugars that act as prebiotic–like substrates, promoting the growth of *Bifidobacterium* and *Lactobacillus* while suppressing less favorable taxa through nutrient competition (Abdeen *et al.,* 2024). Human studies support these mechanisms, showing an increased fecal abundance of beneficial genera and a favorable Firmicutes–Bacteroidetes ratio in subjects consuming protein–modified dairy matrices (Vivek *et al.*, 2023). Thus, protein conjugates serve as both protective carriers and active modulators of microbiota composition.

Freeze–drying *L. plantarum* with whey protein and sodium alginate enhanced the survival of probiotics compared to spray drying (Liu *et al.*, 2019). This treatment process is crucial for maintaining the viability of probiotics during processing conditions. Further supporting this, studies on probiotic cheese highlight the positive effects of probiotics on gut microbiota. For example, supplementation with goat cheese containing *L. rhamnosus* EM1107 in mice challenged with *S. enteritidis* decreased *Salmonella* colonization while promoting the development of beneficial bacteria (Rolim *et al.*, 2021). Thus, the combination of protective carriers, such as whey protein and sodium alginate, during freeze–drying effectively enhances probiotic viability, which, as evidenced in probiotic–enriched cheese studies, translates into improved gut microbiota balance and pathogen suppression.

Studies have also investigated the various benefits of probiotics in ice cream, apart from the encapsulation process. Chaikham and Rattanasena (2017) studied ice cream complemented with *L. acidophilus* LA–5 and *L. casei* 01 probiotic flora, providing the update about the modulation effect of the product against colon microbiome, which led to an increase in helpful secondary metabolites (e.g., butyrate, acetate, lactic acid, and propionate) because of the supplementation. This demonstrates how probiotics in dairy products can contribute to the production of metabolites that enhance digestive health.

Immune response and regulation in dairy foods

The effectiveness of *Lactobacillus* and *Bifidobacterium* probiotics in dairy products supports their role in enhancing the immune system, thereby reducing the risk of inflammatory diseases. When incorporated into dairy products with protein conjugates, these probiotics often exhibit improved stability in dairy products; they are better protected during digestion when combined with protein conjugates, such as whey protein, which enhances and regulates gut homeostasis and immune functioning (Liu *et al.*, 2019).

Protein conjugates enhance probiotic–host immune interactions by stabilizing cell–surface proteins and facilitating mucosal adhesion, which amplifies recognition by dendritic cells and epithelial receptors (e.g., toll–like receptors 2 and 4 (TLR2 and TLR4) (Gao *et al.*, 2022). This interaction modulates cytokine profiles, increasing anti–inflammatory mediators (IL–10) while reducing pro–inflammatory markers (TNF–α and interleukins–6 [IL–6]) (Kariyawasam *et al.*, 2021). Some conjugates also release bioactive peptides with direct immunomodulatory activity, such as opioid–like or angiotensin–converting enzyme (ACE) inhibitory peptides (Han *et al.*, 2020). Human intervention studies with dairy–based protein conjugates have reported reductions in systemic inflammation and enhanced mucosal immunity, supporting their translational relevance.

A study conducted on fermented milk samples produced from a blend of *Lactobacillus* and *Bifidobacterium* strains demonstrated immune–enhancing effects. Consuming fermented milk containing the mentioned probiotics has been linked to increased immune markers, such as immunoglobulin A (IgA), IL–6, and IL–10, which are crucial for enhancing animal mucosal immunity (Santiago–López *et al.*, 2018). The findings of this study provided information on how probiotic fermentation can more favorably modulate immune responses and contribute to the overall health benefits. Additionally, Mai *et al.* (2021) found that probiotic fermented milk has shown potential in alleviating digestive– and respiratory–related problems in young children. The findings indicated that *L. casei* Shirota in probiotic milk drastically reduced constipation, diarrhea, and respiratory infections in children aged 3–5 years.

These findings suggest that adding protein conjugates to dairy–based probiotics enhances their capacity to modulate the immune system. As shown in Figure 4, protein conjugation enhances probiotic function, including improved gastric survival, targeted intestinal delivery, enhanced mucosal adhesion, and synergistic bioactivities (e.g., antioxidant and anti–inflammatory effects). Compared to free probiotics, conjugated probiotics more effectively modulate gut microbiota, strengthen the intestinal barrier, and support immune regulation.

Furthermore, fermented milk with probiotic strains provides health benefits by producing bioactive peptides, including ACE inhibitors and antioxidative peptides. Production of high gamma–aminobutyric acid has been observed, with up to 5.5 g/L when *S. thermophilus* is present and up to 8.3 g/L when co–cultured with *L. rhamnosus* in casein hydrolysate–enriched milk (Han *et al.*, 2020). *Bifidobacterium* and *Lactobacillus* probiotics are essential components of the human gut microbiota, playing a crucial role in restoring intestinal barrier function and enhancing immune function (El Jeni *et al.*, 2024).

Although probiotic–protein immunomodulatory interactions remain underexplored, available evidence suggests that they are strain– and matrix–dependent. Recent studies have demonstrated that *Lactobacillus* strains can stimulate regulatory T cells to produce IL–10 and transforming growth factor–beta (TGF–β), increase IL–6 secretion in a TLR–2–dependent manner, and induce clonal expansion of IgA–producing B cells. Muhammad *et al.* (2026) showed that multi–species synbiotic supplementation, containing six probiotic species with inulin and FOS, significantly increased serum IL–10 levels and fecal SCFAs in adult men with dyslipidemia after 12 weeks. This highlights the need for systematic comparisons across probiotic strains and protein or prebiotic matrices to identify formulations with targeted immunomodulatory effects.

Bioavailability enhancement of probiotics and bioactive peptides

Protein conjugates play a crucial role in enhancing the bioavailability of probiotics in dairy products. They are commonly referred to as wall materials, including carbohydrates (e.g., starch and maltodextrin) and proteins (e.g., casein and whey protein). The absence of these wall materials can highlight the viability of probiotics during spray drying, resulting in a complete loss of viability of probiotics (Liu *et al.*, 2019). Binary systems, which utilize proteins and polysaccharides to form conjugates, provide better protection for probiotic systems (Deng *et al.*, 2025).

Protein conjugates enhance bioavailability by forming protective matrices that delay gastric degradation and facilitate targeted intestinal release (Mao *et al.*, 2022; Wu *et al.*, 2021b). Cross–linked proteins maintain probiotic viability until the colon while simultaneously enhancing

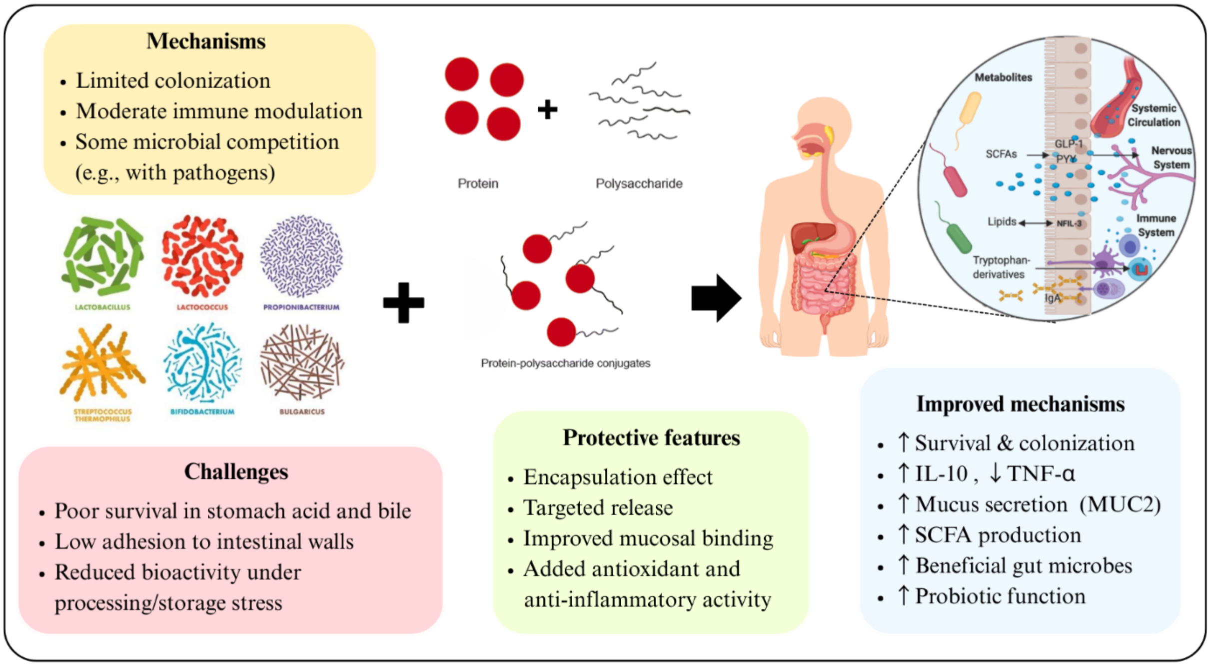

Figure 4. Schematic illustration of the protective role of protein–polysaccharide conjugates in improving probiotic functionality. Native probiotics face challenges, such as poor survival in gastric and bile conditions, low intestinal adhesion, and reduced bioactivity during processing and storage. Source: Hao *et al.* (2025); Jang *et al.* (2024); Latif *et al.* (2023); Lim *et al.* (2024).

solubility and uptake of associated bioactive peptides (Sbehat *et al.*, 2022). Once released, peptides can cross epithelial barriers more efficiently because of improved resistance against proteolysis (Lemaire *et al.,* 2021). Clinical studies using conjugated whey proteins in fermented dairy products have shown higher plasma levels of bioactive peptides and improved metabolic outcomes, underscoring the connection between structural protection and functional absorption (Gu *et al.,* 2024; Huang *et al.,* 2024).

Research has demonstrated that spray drying *L. zeae* LB1 with a combination of Arabic gum and sodium caseinate results in higher survival proportions at pH 2.0, compared to using sodium caseinate alone (Liu *et al.*, 2016). Probiotics face stress in handling processes, storage, and digestive conditions, but their survival is critical for efficacy. The most common international standards on fermented products require a minimum of 10^7 CFU/g for *L. acidophilus* and 10^6 CFU/g for *B. bifidum* in fermented milk, with some specific variations in some countries (Stuivenberg *et al.*, 2022). Ensuring probiotic viability through protein conjugate encapsulation helps to meet these regulatory requirements.

Protein–probiotic conjugates enhance probiotic stability during food processing, storage, and GI transit, although their effectiveness depends strongly on the protein matrix and conjugation strategy used. Plant– and dairy–based proteins, including rice, pea, whey, and soy protein isolates combined with inulin, have shown improved conjugation efficiency and protection of *Lactobacillus reuteri* against thermal and storage stresses, with rice and whey protein systems often providing superior stability (Mudgil *et al.*, 2024b). Emerging technologies, such as 3D printing coupled with freeze–drying, further increase survival, achieving up to 96–98% viability of *Lactiplantibacillus plantarum* during extended storage and digestion (Yoha *et al.*, 2021). In addition, highly resilient strains, such as *bacillus* coagulans, maintain over 99% viability under severe processing conditions, while alternative proteins, such as Spirulina isolates, show promising lyoprotective effects, outperforming whey protein under certain conditions (Maity *et al.*, 2021). Consquently, selecting appropriate protein carriers and conjugation methods is critical for enhancing probiotic stability in functional food applications.

Antioxidant properties

Conjugation of milk carbohydrates with proteins through the Maillard reaction enhances protein functional properties, resulting in more heat–stable, soluble, and emulsified products (Zhang *et al.*, 2020). Additionally, this conjugation enhances antioxidant activity by forming melanoidin and heterocyclic compounds, as well as reducing ketones, thereby improving the health–promoting properties of dairy products (Wu *et al.*, 2021b). Specifically, when WPI is heated with reducing sugars, the Maillard reaction enhances its reducing power and scavenging capacity, improving its antioxidant properties (Zhang *et al.*, 2020). Additionally, a study has shown that the synergistic effect of ascorbic acid enhances the survival of *L. acidophilus* in yogurt. At the same time, enzyme–based scavengers, such as glucose oxidase, have been found to increase *B. longum* counts by up to 40% (Gupta, 2024).

Accordingly, protein conjugation stabilizes the food matrix while introducing antioxidant–active groups, particularly reductones and melanoidins, which scavenge reactive oxygen species (ROS) and chelate pro–oxidant metal ions (Wu *et al.,* 2021b). This dual action mitigates oxidative stress in the gut, protecting encapsulated probiotics while simultaneously delivering systemic antioxidant benefits to the host (Noori *et al.,* 2025). Clinical investigations corroborate these effects, demonstrating that dairy products enriched with protein conjugates improve redox balance, as evidenced by increased total antioxidant capacity and decreased lipid peroxidation in human subjects (Lemaire *et al.,* 2021; Mudgil *et al.,* 2024a).

Moreover, synbiotic yogurts have gained popularity because of their antioxidant, anti–inflammatory, and antihypertensive properties, which have a positive impact on the overall health. For example, synbiotic formulations containing *L. brevis* KU200019 and FOS have exhibited antioxidant, ACE–inhibitory, and immune–modulating effects in dairy products (Kariyawasam *et al.*, 2021). Yogurt containing *L. rhamnosus* and *B. lactis* improves gut motility and relieves irritable bowel syndrome (IBS) (Olson and Aryana, 2022). Similarly, cheese fortified with *L. casei* and *L. plantarum* has been linked to reduced blood pressure and body mass index (BMI) (Shah *et al.*, 2024). Additionally, ice cream enriched with *L. acidophilus* LA–5 and *L. casei* 01 increased the modulation of SCFAs production and promoted beneficial gut microbiota (Chaikham and Rattanasena, 2017). Another probiotic ice cream containing *L. lactis* NZ1330 has been shown to reduce Immunoglobulin E (IgE) levels and allergic responses in mice (Vasiee *et al.*, 2020). Therefore, the antioxidant properties of dairy probiotic products suggest that their presence supports the health–promoting features of these products, as probiotics in them have been observed to remain qualitatively intact during GI transit. Beyond direct food applications, protein conjugates have found innovative uses in active packaging systems. For instance, whey protein–polyphenol conjugates incorporated into carboxymethyl cellulose films demonstrate enhanced vapor barrier properties, tensile strength, and intelligent pH–sensing capabilities for monitoring of freshness (Zhao *et al.*, 2023). This innovative approach offers potential for extending the shelf life of dairy products while preserving probiotic viability.

Challenges Associated with Protein Conjugates in Dairy Foods

Hussain *et al.* (2021) postulated that the use of protein conjugation in dairy probiotics presents both problems and opportunities that must be addressed carefully prior to its application in any domain. Among the discrepancies are the technological challenges that have become most common. The issues of stability and the need for efficient delivery systems add to the complexity of conjugation methods, making it more challenging to incorporate them into protein conjugates containing probiotic dairy products. Another significant barrier to the market's widespread acceptance of protein–conjugated probiotics is the complex regulations governing the clearance process and safety investigations for novel compounds (Cerk and Aguilera-Gómez, 2022). Consumer acceptance and market perception also predispose the success of protein–conjugated probiotics. Purchase decisions are influenced by a product's efficacy, safety, and health benefits, as evidenced by a study on the development of the Maillard reaction in UHT milk under varying storage temperatures and thermal cycles (Sunds *et al.*, 2018).

Technological challenges

Probiotics face significant challenges in maintaining viability and functionality throughout the manufacturing, processing, and storage of dairy products. The main factors affecting the survival and stability of probiotics in dairy foods are low temperatures, pH levels, and the composition of the probiotics (Deng *et al.*, 2025; Mazhar *et al.*, 2024). Thermal destabilization and low microbial growth present crucial challenges in dairy product manufacturing, as high–protein dairy matrices, such as evaporated milk, undergo structural changes under heat stress that compromise stability and probiotic viability. Wu *et al.* (2021a) investigated the modification of milk proteins via glycation via the Maillard reaction to enhance functionality by improving heat stability, eliminating the need for harmful catalysts, and optimizing the performance of dairy proteins during thermal processing.

Furthermore, whey proteins have relatively weak emulsifying properties, leading to instability, turbidity, and phase separation in acidic dairy products, especially during storage and heat exposure (Dıblan *et al.*, 2024). Co–encapsulation with prebiotics serves as a potential strategy to enhance probiotic survival by protecting the cells from environmental stress during processing, storage, and digestion (Rashidinejad *et al.*, 2022). Therefore, addressing these technological challenges through advanced protein conjugation and co–encapsulation strategies is a key to improving the stability and functionality of probiotics in dairy applications.

Regulatory barriers and safety concerns of protein conjugation

The practical applicability of protein–conjugation in dairy probiotics is linked to specific regulatory challenges. The US Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA) are regulatory agencies that require comprehensive safety data, including toxicity and allergen tests, before these products are permitted for human consumption, as reported by Cerk and Aguilera–Gómez (2022) and Zavišić *et al.* (2023). Strict rules must be backed by solid scientific research when labeling products to make health claims, such as those that boost immunity. Although both EFSA and FDA have established regulations for probiotics and food additives, a gray area remains regarding protein–probiotic conjugates with exception of the study reported by Awaluddin *et al.* (2025), in which the study confirmed that synbiotic systems exhibit superior biological functionality, compared with probiotic or prebiotic alone, reflecting coordinated regulation of gut structure, nutrient bioavailability, and host performance. Manufacturing these conjugates at a larger scale while maintaining consistent quality and stability can be challenging, and additional steps may be required if the ingredient is considered novel (Spacova *et al.*, 2023).

Moreover, while protein conjugation can enhance probiotic stability and functionality, one critical safety concern is the unintended formation of AGEs, which have been implicated in various metabolic and chronic diseases. The accumulation of AGEs in serum induces oxidative stress and activates the chromogranin A–uncoupling protein 2–glucose transporter 1 pathway, contributing to diabetes–related complications (Sun *et al.*, 2023). Beyond diabetes, dietary AGEs exacerbate inflammation and oxidative stress, representing risk factors for chronic liver diseases. Another study confirmed that higher intake of AGEs, particularly Nε–(carboxymethyl) lysine and methylglyoxal–derived hydroimidazolone–1, were positively correlated with the incidence of fatty liver disease (Xie *et al.*, 2023). To counteract these risks, several strategies are explored to inhibit the formation of AGEs. Approaches include blocking early glycation intermediates, preventing protein cross–linking, chelating metal ions, and suppressing AGE to their receptor (AGE–RAGE) signaling through antioxidant and anti–inflammatory pathways. Potential interventions involve glycation inhibitors (e.g., aminoguanidine and pyridoxamine), AGE breakers (e.g., alagebrium chloride), metal chelators, and natural phytochemical antioxidants (Gu *et al.,* 2024). Excessive heating causes browning, loss of amino acid, and formation of AGE; thus, Bi *et al.* (2023) recommended 70°C for 15 s to preserve quality and nutrition in dairy systems.

Protein conjugation, while promising for improving stability and functionality, raises critical concerns regarding allergenicity Spacova *et al.* (2023). Structural modifications can mask epitopes and sometimes reduce IgE–binding, but uncontrolled conjugation reactions may expose new epitopes or generate neoallergens, increasing sensitization risks (Vasiee *et al.*, 2020). Enzymatic methods, such as MTGase, further complicate this issue by altering the conformational epitopes of caseins and whey proteins, which can unpredictably affect immune recognition (Chen *et al.,* 2020). Evidence to date is dominated by *in vitro* IgE–binding assays and rodent models, both of which have limited predictive value for human allergic responses (Cerk and Aguilera-Gómez, 2022). This lack of translational data creates uncertainty for regulatory assessment, as agencies, such as EFSA and FDA, mandate rigorous evaluation of allergenicity for novel protein modifications, including structural, digestibility, and clinical immunogenicity data. Without systematic human studies, the allergenic safety of conjugated milk proteins remains unresolved, highlighting the urgent need for targeted allergenicity assessments before such technologies can be safely applied in probiotic dairy foods.

Future perspectives and research needs in protein conjugation–based dairy products

The advent of protein conjugates in dairy products presents both opportunities and challenges from consumer and technological perspectives, as summarized in Table 4. They enhance probiotic survival, emulsification, and solubility, but also introduce off–flavors and bitterness if the Maillard reaction is not carefully controlled (Sunds *et al.*, 2018). Consumer resistance to genetically modified organisms (GMOs), particularly in regions such as the European Union (EU), supports the use of non–GMO approaches, such as protein conjugation, to enhance acceptance (Börner *et al.*, 2019; Hussain *et al.*, 2021). As gut health remains a primary interest in probiotic consumption, improving formulations to show that clear health benefits can enhance consumer appeal (Gao *et al.*, 2021; Rashidinejad *et al.*, 2022). Therefore, optimization of the Maillard reaction is also crucial to avoid negative impacts on the appearance and flavor of products (Wu *et al.*, 2021b).

Protein conjugates offer functional benefits, such as enhanced probiotic delivery; however, they may negatively affect color and flavor (Deng *et al.*, 2025; Wu *et al.*, 2021b). Incorporating postbiotics, including those derived from *L. acidophilus*, further enhances immune responses. Using strains such as *L. reuteri* and other fermented probiotic derivatives can strengthen these effects (Garnier *et al.*, 2019). Additionally, probiotic–based exopolysaccharides enhance the rheological properties of dairy products, improving their texture, flavor, and consumer appeal while contributing to health benefits (Ali *et al.*, 2023; Zhao and Liang, 2023). Thus, future studies are expected to provide information on how these upcoming industrial processes may affect probiotic dairy foods in a practical setting.

Future research should combine detailed mechanistic investigations, such as molecular signaling, microbial adhesion, and bioactive peptide release, with well–designed human clinical trials to validate the effects of protein conjugates on probiotic functionality, gut microbiota modulation, and immune responses within real–world dairy matrices. Further cost–benefit analysis of protein conjugation is required to assess its economic feasibility and guide industrial–scale implementation while balancing functional efficacy and product quality.

Study Limitations

Although this review provides an integrated overview of protein conjugation strategies and their impact on probiotic functionality in dairy systems, several limitations must be considered. First, most of the available evidence is derived from *in vitro* experiments and animal models, which do not fully capture the complexity of human digestive and immune responses. For example, allergenicity assessments rely heavily on rodent models and IgE–binding assays, both of which exhibit limited predictive value for human outcomes (Cerk and Aguilera–Gómez, 2022; Vasiee *et al.*, 2020). Similarly, most studies evaluating thermal stability, GI tolerance, or encapsulation performance examine individual probiotic strains, despite clear strain–dependent variability in conjugation efficiency and functional response (Li *et al.*, 2025; Liao *et al.*, 2021; Mudgil *et al.*, 2024b). Second, variations in processing conditions, such as temperature, RH, pH, and ionic strength, that affect reproducibility and hinder cross–study comparison. Lack of standardized protocols for the Maillard reaction, enzymatic, or chemical conjugation leads to difficulties in identifying optimal conditions and determining scalability for industrial applications (Gao *et al.*, 2021; Wu *et al.*, 2021b). Additionally, most current reports focus on small–scale laboratory processes, with limited evaluation of pilot– or industrial–scale production, limiting insights into cost, energy demand, and process robustness (Parhi *et al.*, 2024). Moreover, the potential formation of AGEs during

Table 4. Constraints and the way forward on applying protein conjugates in probiotic dairy products.

Category	Description	Possible solutions	References
Technological barriers			
Thermal destabilization	Heat treatments impact the viability of probiotics and the conjugate fatty acid content. Conjugated fatty acid degradation	Microencapsulation or co–encapsulation with prebiotics to protect probiotics. Improving fermentation conditions to preserve fatty acids. Also, use of moderate temperatures (60–70°C), RH: 65–75%, for 24–48 h depending on protein–sugar system; monitor browning index or absorbance at 420 nm; for lactose–free milk, 70°C for 15 s preserves nutrition conjugates.	Bi *et al*., 2023; Mao *et al*., 2022; Wu *et al*., 2021a
Low microbial growth in dairy matrices	Environmental stresses in high–protein dairy products can inhibit the growth of probiotics.	Selecting probiotic strains that can withstand stress with oxygen scavengers, such as tocopherols. Use strains like *L. rhamnosus* GG, *L. plantarum* WCFS1, *B. longum* BB536; choose strains with EPS production, thick cell walls, and robust membrane fatty acids to enhance thermal and acid tolerance.	Guo *et al*., 2022; He *et al*., 2025; Liao *et al*., 2021
Phase separation, poor solubility, and emulsification	Because whey protein concentrates are poorly soluble, they become turbid and unstable in acidic drinks.	Glycation enhances the solubility and functional qualities of whey proteins. Conjugated polysaccharides improve stability and emulsifying qualities.	Dıblan *et al*., 2024
Encapsulation efficiency	Probiotic survival can be enhanced by utilizing optimized co–encapsulation methods that incorporate prebiotics.	By enhancing probiotic protection with the use of multi–layer microencapsulation.	Rashidinejad *et al*., 2022
Raw milk availability (input procurement)	Environmental disruptions (e.g., volcanic eruption) reduce dairy cattle populations and milk yield, threatening stable raw material supply for functional dairy production.	Diversifying milk sourcing, integration of milk powder or alternative protein sources, and developing shelf–stable protein conjugates to buffer supply volatility.	Guntoro *et al*., 2025
Technology adoption	Modern technologies (financial, communication, and product) can enhance dairy cooperative efficiency and financial performance.	Capacity building, tax incentives, supportive policies, and training programs.	Nyakio Ireri *et al*., 2025
Regulatory hurdles			
Novel food approval and GRAS certification	Protein conjugation in probiotics is a novel approach, thus requiring extensive approval and meeting GRAS criteria for market acceptance.	Communicate safety studies, including toxicity and allergenicity assessments, to regulatory agencies for approval and submission.	Cerk and Aguilera-Gómez, 2022; Spacova *et al*., 2023
Labeling and health claims	Strict regulations on health claims related to probiotics and protein conjugates.	By ensuring clinical trial–backed claims that are scientifically validated. Moreover, uniform standards for labeling protein–conjugated probiotics should be established. EU: EFSA Novel Food Regulation 2015/2283; US: FDA GRAS new dietary ingredient notifications provide compositional, toxicological, and allergenicity data; document safe processing and residual cross–linkers.	Aduah *et al*., 2024
Consumer expectations and market perception			
Consumer expectations	Protein conjugates can enhance the survival of probiotics but may also lead to off–flavors and bitterness.	The Maillard reaction is carefully controlled to prevent the development of unwanted flavors. Protein conjugates enhance emulsification and solubility while reducing bitterness. Use approved food–grade cross–linkers (e.g., genipin) at the minimal effective concentrations; remove any unreacted chemicals; and evaluate sensory properties in pilot formulations.	Laurujisawat *et al*., 2025; Sunds *et al*., 2018; Wei and Huang, 2019
Consumer perception of GMO	GMO products face consumer resistance in regions such as the EU.	Non–GMO methods (e.g., protein conjugation) may improve consumer acceptance of dairy probiotics.	Börner *et al*., 2019; Hussain *et al*., 2021

Notes: GRAS: generally recognized as safe; EPS: extracellular polymeric substances; GMO: Genetically modified organisms.

the Maillard conjugation presents unresolved safety concerns. Although the existing research highlights correlations between dietary AGEs and inflammatory or metabolic disorders (Sun *et al.*, 2023; Xie *et al.*, 2023), there is still limited research that measures AGE formation in conjugated dairy systems or examines the potential long–term exposure risks in humans. Finally, the regulatory landscape for protein–probiotic conjugates remains underdeveloped. Limited human clinical trials, insufficient allergenicity data, and unclear classification frameworks restrict the translation of these technologies into commercial dairy products (Cerk and Aguilera–Gómez, 2022; Spacova *et al.*, 2023). Addressing these limitations requires coordinated efforts to develop standardized methodologies, conduct well–designed human studies, and establish regulatory guidance specific to conjugated protein systems.

Conclusions

Protein conjugation, through processes such as the Maillard–type and enzymatic cross–linking, has demonstrated considerable potential in enhancing the functionality and viability of probiotics in dairy systems. These conjugates act as dual–function systems, providing a protective barrier for probiotic cells under adverse conditions, such as heat, acidity, and bile salts, while simultaneously improving texture, emulsifying properties, and the overall stability within dairy matrices. Consistent findings across various applications continue to show improvements in encapsulation efficiency, thermal tolerance, and water–holding capacity, which together support the broader integration of conjugated systems in both fermented and nonfermented dairy products.

Despite these advantages, broader application remains limited by several factors, including the need for tighter control of the Maillard reaction conditions to prevent excessive browning and the formation of undesirable compounds, along with the continued challenge of managing potential sensory changes and navigating complex regulatory frameworks related to food safety and functional claims. Consequently, future research on protein conjugation should prioritize the refinement of reaction conditions, particularly through optimization of the Maillard reaction and enzymatic pathways to improve reproducibility, minimize undesirable end products, and enhance safety. In addition, exploring novel protein and carbohydrate sources with promising functional and nutritional attributes may further expand the applicability of conjugates across diverse food systems.

Personalized functional dairy foods represent a promising direction, emerging from the integration of gut microbiome profiles, metabolic and immune biomarkers, and indicators of gut–barrier function. When combined with predictive modeling approaches, including machine–learning (ML)–based diet–microbiome response tools, these developments open the possibility for designing protein–probiotic conjugates that align more closely with individual health objectives, such as metabolic regulation, GI tolerance, and immune modulation. Within this framework, protein conjugation offers opportunities to improve nutrient interactions, modulate allergenicity, and selectively influence host–microbiota dynamics.

However, translating these advances into practical applications require comprehensive cost–benefit evaluations and well–designed human clinical studies to verify efficacy and safety beyond laboratory and animal evidence. At the same time, successful commercialization depends on achieving industrial scalability through environmentally responsible and economically viable processing strategies, supported by artificial intelligence (AI)–driven and omics–based formulation tools that strengthen process robustness and accelerate innovation. Ultimately, long–term progress depends on adherence to international regulatory frameworks to ensure that functional claims are scientifically substantiated and that consumer safety is maintained consistently.

Data Availability

The data are available upon request.

Mandatory Disclosure on Use of Artificial Intelligence

The authors declare that no AI-assisted tools were used in the preparation of this manuscript. All references have been manually verified for accuracy and relevance.

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Conflicts of Interest

The authors declared no conflict of interest.

Funding

This research was funded by the “Reinventing University Program” and “International Research Fellowship at Chiang Mai University (Visiting Professor),” Chiang Mai University, Thailand. In addition, thanks to the Center of Excellence at Agro Bio–Circular–Green Industry, Chiang Mai University.

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