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Research Article

Synbiotics and Gut Microbiota Modulation in Type 2 Diabetes Mellitus: Mechanisms, Clinical Evidence, and Applications in Livestock-Derived Products

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ABSTRACT

This review evaluates the scientific evidence on synbiotic interventions for modulating the gut microbiota as an adjuvant strategy in type 2 diabetes mellitus (T2DM), with a focus on the roles of short-chain fatty acids (SCFAs), intestinal barrier integrity, and inflammation, as well as their relevance for applications in livestock-derived products. The literature was searched up to 30 November 2025 using PubMed, ScienceDirect, and Google Scholar (publication years 2010–2025) with keywords related to synbiotics, gut microbiota, T2DM, probiotics, prebiotics, and SCFAs. The references considered included controlled clinical trials, preclinical animal studies, and relevant English-language review articles available in full text, which were then synthesized narratively. Dysbiosis in T2DM is generally characterized by a reduction in SCFA-producing bacteria and an increase in pro-inflammatory taxa, which are associated with increased intestinal permeability, lipopolysaccharide (LPS) endotoxemia, and low-grade inflammation that exacerbates insulin resistance. The clinical and preclinical evidence reviewed suggests that synbiotics may shift the gut microbial composition toward commensal SCFA-producing taxa, increase SCFA production, improve intestinal barrier function, reduce inflammatory markers, and improve glycemic outcomes. However, heterogeneity in strains, substrates, doses, intervention durations, and the reporting of microbiota/metabolite endpoints limits comparability across studies. Overall, synbiotics show potential as an adjuvant approach for T2DM through modulation of the microbiota, SCFA, intestinal barrier axis, and suppression of inflammation. The development of functional foods based on livestock-derived products is promising, but requires formulation standardization, more robustly designed controlled clinical trials, and evaluation of stability/viability during processing and storage.

Keywords: synbiotic, gut microbiota, type 2 diabetes, short-chain fatty acids, fermented dairy

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia resulting from insulin resistance and impaired insulin secretion. Its prevalence is rising globally and it has become a leading cause of metabolic disease–related morbidity and mortality (Yang et al., 2022). In recent years, the role of the gut microbiota in the pathophysiology of T2DM has attracted considerable attention, as intestinal microorganisms influence not only glucose metabolism but also immune function and gastrointestinal mucosal integrity (Liu et al., 2022; Patra et al., 2023; Yarahmadi et al., 2024).

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Gut microbiota dysbiosis has been linked to a low-grade inflammatory state and insulin resistance in T2DM (Scheithauer et al., 2020; Chong et al., 2025). Individuals with T2DM commonly exhibit reduced abundance of beneficial short-chain fatty acid (SCFA)–producing bacteria such as *Faecalibacterium prausnitzii* and *Akkermansia muciniphila*, which play important roles in regulating energy metabolism and immune modulation (Jan et al., 2024), along with an increased abundance of opportunistic Gram-negative bacteria that produce pro-inflammatory lipopolysaccharide (LPS) (Zhao et al., 2019; Zhao et al., 2020).

A decline in SCFA-producing bacteria leads to lower intestinal SCFA levels, which may compromise intestinal barrier integrity and increase gut permeability (Cox et al., 2017; Fusco et al., 2023). Consequently, LPS endotoxins can more readily enter the circulation and activate TLR4 receptors, triggering systemic inflammatory responses that contribute to insulin resistance (Saleem et al., 2022). Conversely, a higher abundance of butyrate-producing bacteria (e.g., *Roseburia* and *Faecalibacterium*) is positively associated with better insulin sensitivity (Arora et al., 2021). These findings underscore the key role of the gut microbiota in T2DM pathophysiology through its effects on anti-inflammatory pathways, intestinal barrier function, and glucose homeostasis.

In this context, food-based approaches that target the gut microbiota, such as synbiotics, combinations of probiotics (beneficial live microorganisms) and prebiotics (fiber substrates that support beneficial microbes) have shown therapeutic potential. Synbiotics act through a synergistic mechanism: probiotics introduce beneficial microorganisms, while prebiotics provide substrates that promote their growth. This combination has been shown to increase SCFA production, improve intestinal barrier function, reduce inflammatory biomarkers, and enhance insulin sensitivity (Kim et al., 2015; Wang et al., 2016; Xiao et al., 2025; Mafe et al., 2025).

Synbiotic interventions may improve glycemic profiles in individuals with T2DM by reshaping the gut microbiota composition and increasing the production of health-promoting metabolites such as SCFAs. Early evidence suggests that gut microbiota modulation with synbiotics may represent a promising strategy for diabetes management (Setayesh et al., 2025). This review aims to evaluate the most recent scientific evidence on the effects of synbiotic interventions in modulating the gut microbiota as an adjuvant strategy in T2DM therapy. The review focuses on key biological mechanisms, SCFA production, intestinal barrier integrity, and immune responses as mediators of the antidiabetic effects of synbiotics.

MATERIAL AND METHODS

This article is a narrative review that synthesizes and discusses scientific findings on the role of synbiotics in modulating the gut microbiota in type 2 diabetes mellitus (T2DM), with an emphasis on mechanisms involving short-chain fatty acid (SCFA) production, intestinal barrier integrity, inflammatory responses, and implications for metabolic outcomes. The literature search was conducted up to 30 November 2025 using PubMed, ScienceDirect, and Google Scholar, covering publications from 2010 to 2025. The search terms included “synbiotic”, “gut microbiota”, “type 2 diabetes”, “probiotic”, “prebiotic”, and “short-chain fatty acids”, along with relevant combinations.

The literature considered comprised original studies (e.g., controlled clinical trials and preclinical animal studies) as well as scientific review articles relevant to the topic. Only English-language publications with accessible full text (preferably open access) were included. References were selected in a stepwise manner through title and abstract screening, followed by full-text review to confirm relevance to the scope of the review. The collected information was then

synthesized narratively to develop a structured discussion addressing: (1) the role of the gut microbiota in the pathogenesis of T2DM, (2) mechanisms of probiotics and prebiotics in the context of synbiotics, and (3) evidence on the effects of synbiotics on SCFAs, intestinal barrier function, inflammation, insulin sensitivity, and glucose metabolism based on both preclinical and clinical findings. The evidence from these sources was compiled and discussed in line with the objectives of this review.

RESULTS AND DISCUSSION

The Role of the Gut Microbiota in the Pathophysiology of T2DM

The gut microbiota plays an important role in maintaining metabolic homeostasis, and shifts in its composition can influence diabetes risk. In healthy individuals, commensal bacteria produce short-chain fatty acids (SCFAs) through fermentation of dietary fiber, which nourish the intestinal epithelium, regulate appetite, and suppress inflammation (Drucker, 2018; Yao et al., 2019). In contrast, people with T2DM commonly experience dysbiosis characterized by reduced microbial diversity and disrupted proportions of beneficial microbes. Studies have reported reduced abundance of beneficial genera such as *Akkermansia*, *Bifidobacterium*, *Faecalibacterium*, *Roseburia*, and *Prevotella* in T2DM, while pro-inflammatory opportunistic bacteria (e.g., *Escherichia-Shigella* from the *Enterobacteriaceae* family) increase (Ragupathi et al., 2018). *Escherichia coli* and related taxa produce lipopolysaccharide (LPS), which can damage the intestinal mucosa and trigger both local and systemic inflammation (Zhao et al., 2020).

LPS activates Toll-like receptor 4 (TLR4) signaling pathways, promoting the production of pro-inflammatory cytokines (e.g., TNF-α and IL-6). Accordingly, dysbiosis dominated by Gram-negative bacteria is associated with chronic inflammation in diabetes and insulin resistance (Larsen, 2017; Vallianou et al., 2018). Conversely, many taxa that are reduced in T2DM have protective roles. *Bifidobacterium* and *Lactobacillus* help maintain microbial balance and produce anti-inflammatory metabolites (e.g., lactic acid and acetic acid), and may reduce intestinal permeability by strengthening epithelial cell–cell junctions (Ling et al., 2016). *Faecalibacterium prausnitzii* and *Roseburia* produce butyrate, an SCFA that serves as an energy source for colonocytes and exerts anti-inflammatory immunomodulatory effects. Depletion of *Faecalibacterium* and other butyrate producers in T2DM has been confirmed across multiple studies and has been linked to heightened inflammation and poorer glycemic control (Zhu et al., 2019; Kallassy et al., 2023).

Microbiota-derived SCFAs support intestinal barrier integrity by lowering luminal pH (thereby limiting pathogen growth) and upregulating tight-junction protein expression, which helps prevent translocation of bacteria and LPS into the circulation (Xu et al., 2020). When SCFA-producing bacteria decline, intestinal butyrate and propionate levels decrease, potentially weakening the gut barrier and leading to a “leaky gut” state in which more LPS enters the bloodstream (Camargo et al., 2019). The consequence is persistent low-grade systemic inflammation, a recognized driver of insulin resistance and pancreatic β-cell dysfunction in T2DM (Kumawat et al., 2019).

Clinical findings further support these associations. Increased abundance of *Escherichia-Shigella* has been linked to higher HbA1c (Pushpanathan et al., 2016), higher fasting glucose (Gaike et al., 2020), and markers of insulin resistance in patients with diabetes (Tao et al., 2019). Conversely, interventions that increase butyrate-producing bacteria appear beneficial. A fecal microbiota transplantation study from lean healthy donors to recipients with metabolic syndrome

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reported increased *Roseburia* and fecal butyrate levels, which correlated with improved insulin sensitivity in transplant recipients (Zhu et al., 2019). Collectively, a balanced gut microbiota composition enriched in commensal SCFA-producing bacteria and low in pathogenic taxa may be protective against metabolic disorders, whereas dysbiosis contributes to T2DM pathogenesis through increased endotoxemia, inflammation, and disrupted metabolic signaling.

Probiotics, Prebiotics, and Synbiotics in T2DM

Metabolic disorders such as T2DM are increasingly understood as systemic conditions that are also influenced by gut microbiota dysbiosis and alterations in microbial metabolites. A recent review on cardiometabolic therapies emphasizes that the gut microbiota can exert endocrine or paracrine effects through its metabolites, and that various modulation strategies including probiotics, prebiotics, and synbiotics are considered to have potential to improve key metabolic outcomes in cardiometabolic diseases, including T2DM (Reddy, 2021).

At the mechanistic level, disruption of microbial balance (dysbiosis) may promote low-grade inflammation and metabolic dysfunction. Conversely, probiotics have been reported to help restore microbial balance and to generate metabolites such as SCFAs that support intestinal barrier function and suppress inflammation, making them relevant for preventing or improving metabolic disorders, including T2DM (Chaudary et al., 2024).

In the context of probiotics, fermented dairy matrices are often selected because they support bacterial viability and facilitate daily consumption. In patients with T2DM, probiotic yogurt fortified with *Lactobacillus acidophilus* La5 and *Bifidobacterium lactis* Bb12 has been reported to reduce fasting glucose and HbA1c (Ostadrahimi et al., 2015; Tonucci et al., 2017), and to enhance antioxidant responses while lowering markers of oxidative damage (Mirjalili et al., 2023). Another study using a similar formulation also showed improvements in atherogenic lipid ratios, such as the LDL-C to HDL-C ratio (Mohamadshahi et al., 2014). Mechanisms frequently proposed for these fermented products include increases in beneficial bacterial populations and shifts in metabolites such as SCFAs that may influence insulin sensitivity and glucose regulation.

Prebiotics are positioned as substrates that are selectively fermented by the microbiota and ultimately enrich metabolites such as SCFAs that are relevant to glucose metabolism. In a summary of interventions involving T2DM and obesity populations, one synbiotic approach used a combination of *Lacticaseibacillus paracasei* YIT 9029 and *Bifidobacterium breve* YIT 12272 with galactooligosaccharides up to 7.5 g per day for 24 weeks (Kanazawa et al., 2021). In addition, prebiotic fortification has also been incorporated into other functional foods, for example synbiotic bread combining *Bacillus* coagulans with inulin (10 g per serving/package) (Ghafouri et al., 2019). Conceptually, this supports the idea that prebiotics are not merely accompanying components, but can also steer microbial fermentation toward metabolite profiles that are more favorable for metabolic conditions.

By consensus, the International Scientific Association for Probiotics and Prebiotics (ISAPP) defines synbiotics as mixtures of live microorganisms and substrates that are selectively utilized by host microorganisms to confer a health benefit. This definition emphasizes that the substrate component should be biologically relevant to the microbiota or the targeted strain(s), rather than a generic addition of fiber. Within the ISAPP framework, synbiotics can be complementary (probiotic and prebiotic act in parallel) or synergistic (the substrate is specifically selected to enhance the survival, colonization, or metabolic activity of the administered strain). This classification supports more measurable formulation design and facilitates interpretation across studies (Swanson et al., 2020).

Clinically, synbiotics are being investigated across multiple contexts, including metabolic disorders. Several early studies suggest potential improvements in glycemic control in type 2 diabetes mellitus, along with immunometabolic effects such as reduced systemic inflammation. However, the clinical evidence base for synbiotics remains more limited than that for probiotics or prebiotics alone, and outcomes vary depending on strain combinations, substrate type, dose, intervention duration, and population characteristics. Therefore, standardized reporting of formulations and more rigorously designed clinical trials are needed to establish efficacy and clarify the contexts in which synbiotics may be used (Colica & Vecchio, 2025).

Mechanistically, synbiotics may increase SCFA production, which supports intestinal barrier integrity, for example by strengthening tight junctions thereby reducing the translocation of lipopolysaccharide (LPS) into the circulation. This reduction in metabolic endotoxemia is relevant to low-grade inflammation and insulin resistance, which are hallmarks of metabolic syndrome and T2DM (Dimeji & Ayodeji, 2025).

The choice of prebiotic substrate also influences the SCFA profile produced in the colon, the acetate:propionate:butyrate ratio is often reported to be approximately 60:25:15, and fermentation capacity varies across fiber types. Consequently, synbiotic design should align with metabolic goals (e.g., increasing butyrate) and participants' dietary patterns to maximize responsiveness (Malinowska et al., 2023). Beyond intervention trials, population-level evidence has also emerged from a cohort of older adults in the United States, where the use of non-food probiotic, prebiotic, or synbiotic supplements was associated with lower risks of all-cause and cardiovascular mortality. These findings are observational and therefore do not establish causality, but they are consistent with the hypothesis that microbiota modulation contributes to improved cardiometabolic risk (Shen et al., 2023).

For dairy-based food applications, synbiotic formulations in yogurt as well as traditional fermented dairy products can leverage the effects of the fermentation matrix. Beyond serving as a functional food matrix, probiotic microflora in local fermented dairy products such as dadiah have also been reported to exhibit antagonistic activity against foodborne pathogens, including Listeria monocytogenes (Melia et al., 2017), potentially adding value in terms of food safety and product quality. However, bacterial viability may decline during storage due to low pH and processing-related stress. Technological approaches such as encapsulation and the selection of appropriate prebiotic substrates have been reported to help maintain viability and functionality throughout product shelf life (Chakma et al., 2025).

Livestock-Derived Product–Based Interventions for T2DM Therapy

Table 1 Previous Studies on Livestock-Derived Product–Based Interventions for T2DM Therapy

Intervention	Synbiotic Components	Model/Subjects	Key Glucose-Related Findings	Microbiota and Metabolite Findings	Author(s) Year

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Synbiotic Yogurt Fortified with Monk Fruit Extract as a Sweetener	ABY-8 starter culture (a blend of *Streptococcus thermophilus* and *Lactobacillus delbrueckii* subsp. *bulgaricus*), with *Bifidobacterium* BB-12 and *Lactobacillus acidophilus* LA-5 as adjunct starters; supplemented with inulin and pectin (and polymerized whey protein in the formulation).	Male Wistar rats (5 weeks old) with a T2DM model induced by a high-fat diet and streptozotocin; seven groups including a diabetic control, a yogurt control, three doses of MFE-yogurt, and a metformin group (300 mg/kg).	On day 42, fasting blood glucose was 18.53 mmol/L in the diabetic control group and 15.01 mmol/L in the yogurt control group, while the monk fruit extract (MFE)–synbiotic yogurt groups recorded 11.14, 10.67, and 11.34 mmol/L for the low-, medium-, and high-dose treatments, respectively. Compared with the diabetic control, serum insulin and HbA1c decreased; in the MY-L, MY-M, and MY-H groups, insulin decreased by 17.6%, 20.6%, and 26.7%, and HbA1c decreased by 11.6%, 12.9%, and 18.3%, respectively.	Fecal SCFA levels (acetate, propionate, and butyrate) increased in the MFE-yogurt groups. At the genus level, Lactobacillus, Akkermansia, and Bifidobacterium were more abundant in the yogurt-treated groups than in the diabetic control. The authors concluded that the antidiabetic effects were associated with improved glycemic control, reduced insulin resistance, protection of pancreatic β-cell function, and beneficial modulation of the gut microbiota.	Ban et al., 2020

Synbiotic Fermented Yak Milk Based on *Lacticaseibacillus paracasei* YT805 and Inulin	Formulation F3 used 5% (v/v) mixed inoculum with a YT805-to-commercial starter ratio of 50:1 and was supplemented with 1.5% (w/v) inulin. Fermentation was carried out at 42°C until a titratable acidity of 70–90°T was reached, followed by storage at 4°C for up to 21 days. Functional evaluation was conducted using an in vitro colonic fermentation model with fecal samples.	A product development study with an in vitro colonic fermentation assay (not an animal or clinical T2DM study).	Not evaluated, because the study focused on the product's physicochemical characteristics, probiotic viability, and modulation of the gut microbiota and SCFA production via in vitro colonic fermentation.	In the in vitro colonic fermentation assay, F3 modulated the microbial composition by enriching SCFA-producing genera such as *Acidaminococcus*, *Megasphaera*, *Megamonas*, and *Parabacteroides*. SCFA levels (acetate, propionate, and butyrate) increased by approximately 25–90%. Over 21 days of storage, F3 maintained LAB viability at 6.17×10^8 CFU/mL and YT805 viability at 4.33×10^7 CFU/mL, while inulin decreased by 27.22%, but was reported to remain sufficient to support YT805 activity.	Yang et al., 2025

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A 200 mL/day synbiotic shake for 30 days (2 × 100 mL/day).	Probiotics: *Lactobacillus acidophilus* and *Bifidobacterium bifidum*; Prebiotic: FOS/oligofructose (total 2 g/day).	Relatively "elderly" participants aged 50–60 years; a double-blind, placebo-controlled RCT; n = 20 (10 synbiotic, 10 placebo).	Fasting glycemia decreased significantly from 191.11 to 116.78 mg/dL (−38.89%; $p < 0.05$).	The study assessed lipid parameters and glycemia but did not report gut microbiota composition or SCFA analyses.	Moroti et al., 2012

CONCLUSION

This review emphasizes that alterations in the gut microbiota—particularly reductions in SCFA-producing bacteria and increases in LPS-producing Gram-negative bacteria, contribute to low-grade inflammation, impaired intestinal barrier function, and insulin resistance in T2DM. Based on the synthesis of clinical and preclinical evidence, synbiotic interventions may improve gut microbial composition and increase SCFA production, thereby supporting improved insulin sensitivity and glycemic control, and are relevant for development as adjuvant functional foods, including within livestock-derived food matrices. However, the strength of evidence is still influenced by heterogeneity in formulations (strain selection, prebiotic type, dose, and intervention duration) and limited reporting of microbiota/metabolite endpoints in some studies. Future research should apply clear synbiotic definitions, adequately powered RCT designs, and integrated measurements (microbiota profiles, SCFAs, inflammatory/endotoxin markers, and glycemic outcomes). From a product application perspective, evaluating probiotic viability during processing and storage, as well as prebiotic stability, is essential to ensure consistent biological effects.

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