



Probiotics, *prebiotics*, synbiotics, and FMT for glycemic control: A systematic review of clinical efficacy and mechanistic readouts in type 2 diabetes and related dysglycemia

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ABSTRACT

Objective: To systematically evaluate the clinical efficacy of probiotics, prebiotics, synbiotics, and fecal microbiota transplantation (FMT) on glycemic control in adults with type 2 diabetes (T2D) and related dysglycemia, and to synthesize associated mechanistic changes in microbial metabolites and composition.

Methods: A systematic review was conducted following PRISMA 2020 guidelines. PubMed/MEDLINE, Scopus, and Web of Science were searched from inception through August 2025 for randomized controlled trials (RCTs) in adults with T2D, prediabetes, or metabolic syndrome. Interventions included probiotics, prebiotics, synbiotics, or FMT compared to control. Outcomes were glycemic indices (e.g., HbA1c, HOMA-IR) and mechanistic biomarkers (e.g., SCFAs, bile acids). Risk of bias was assessed using the Cochrane RoB 2 tool. A narrative synthesis was performed.

Results: Thirty studies were included. Multi-strain probiotics, prebiotics, and synbiotics yielded modest but significant improvements in HbA1c (≈ -0.2 to -0.4%), fasting glucose, and HOMA-IR, particularly with durations ≥ 12 weeks. These benefits were linked to mechanistic shifts, including increased circulating butyrate and ursodeoxycholate, enrichment of SCFA-producing taxa, and reduced endotoxemia. Efficacy was moderated by concomitant medications: metformin use was synergistic, while sulfonyleureas attenuated effects. FMT consistently improved clamp-measured insulin sensitivity in insulin-resistant phenotypes, but its effects on HbA1c were less consistent and donor-dependent.

Conclusion: Microbiome-targeted interventions, especially multi-strain probiotics and substrate-matched synbiotics, are effective adjuncts for improving glycemic control, with effects mediated through microbial metabolite production. FMT primarily modulates insulin sensitivity. Clinical outcomes are context-dependent, influenced by intervention design, duration, and pharmacomicrobiomic interactions.

1. Introduction

Type 2 diabetes (T2D) and related dysglycemic states such as prediabetes and metabolic syndrome remain major drivers of cardiometabolic morbidity despite advances in pharmacotherapy, motivating interest in adjuvant strategies that target causal physiology beyond glucose lowering alone [1,2]. The intestinal microbiome has emerged as a modulator of glucose–insulin homeostasis through multiple pathways, including production of short-chain fatty acids (SCFAs), remodeling of bile acids with downstream FXR/TGR5 signaling,

generation of indole derivatives acting on epithelial and immune receptors, and mitigation or amplification of endotoxemia and low-grade inflammation that influence insulin sensitivity and incretin biology [3, 4].

Human randomized trials increasingly link clinical glycemic improvements to specific microbial metabolites, exemplified by consortia that raise circulating butyrate in parallel with favorable changes in glucose indices [5,6]. In one mechanistic program, ursodeoxycholate (UDCA) increased during probiotic therapy and could be synthesized from chenodeoxycholate by a consortium strain in vitro, suggesting a

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bile acid-mediated component of the host response [6]. Adjunctive administration of a multistrain probiotic alongside metformin reduced glycosylated hemoglobin while enriching SCFA-producing bacteria and shifting bile acid-related metabolites, aligning compositional and metabolomic changes with clinical benefit [7]. Complementing these observations, a resistant-starch prebiotic added to stable metformin therapy increased circulating glucagon-like peptide-1 (GLP-1) and improved fasting and postprandial glycemia and insulin resistance markers over 12 weeks [8]. Symbiotic formulations designed to redirect saccharide flux have reduced serum lipopolysaccharide (LPS) and homeostatic model assessment of insulin resistance (HOMA-IR) while enriching butyrate-producing genera and down-regulating LPS biosynthesis pathways, providing a plausible mechanistic bridge between microbiome shifts and insulin sensitivity in humans [9,10].

Across interventions, probiotics now span from conventional lactic acid bacteria to rationally assembled obligate anaerobe consortia intended to enhance butyrogenesis or bile acid remodeling, with multiple double-blind randomized trials demonstrating feasibility and safety in adults with T2D [9,11]. Prebiotics and synbiotics deploy fermentable substrates such as inulin-type fructans, galacto-oligosaccharides, and resistant starch—often paired with complementary strains—to increase SCFA production and support epithelial barrier function and incretin signaling in clinical settings relevant to dysglycemia [3,12]. Fecal microbiota transplantation (FMT) offers a causal probe and potential therapy by altering recipient community structure and function, with initial studies often conducted in individuals with insulin resistance or metabolic syndrome demonstrating short-term improvements in peripheral insulin sensitivity, while a growing number of trials now directly investigate its effects in established T2D [13–18].

At the level of clinical efficacy, multiple systematic reviews and meta-analyses of randomized controlled trials in adults with T2D report small but statistically significant improvements in glycosylated hemoglobin, fasting plasma glucose, fasting insulin, and HOMA-IR with microbiome-targeted therapies, supporting their role as modest adjuncts to standard care [19–24]. Moderator analyses across these syntheses and earlier quantitative reviews indicate that longer intervention duration (typically ≥ 12 weeks), multispecies formulations, and certain delivery matrices such as fermented milk are associated with larger effects, although between-study heterogeneity remains substantial [19,22,25].

Efficacy appears context dependent: metformin itself remodels the gut microbiome and bile acid pools and, in several trials, coincides with greater probiotic-associated butyrogenic and glycemic responses when background therapy is stable, whereas sulfonylureas may attenuate probiotic effects and even inhibit growth of specific strains *in vitro*, highlighting the importance of pharmacomicrobiomic interactions in trial design and interpretation [26,27]. Beyond medications, baseline microbial features, donor phenotype, and diet shape engraftment and metabolic responses—in particular within FMT studies—suggesting that recipient diversity, functional deficits, and dietary conditioning may help identify responders and optimize outcomes [3,13–15,28].

Prior syntheses have largely emphasized clinical endpoints with limited systematic integration of paired mechanistic biomarkers such as plasma or fecal SCFAs, targeted bile acid profiles, incretin dynamics, and endotoxemia markers, constraining causal inference across heterogeneous interventions [19,21,24,29]. Building on newer randomized trials that report both clinical outcomes and mechanistic readouts, this systematic review evaluates the efficacy of probiotics, prebiotics, synbiotics, and FMT on glycemic control in adults with T2D and related dysglycemia, while mapping associated metabolite and microbiome changes and identifying key moderators—including intervention composition and duration, baseline phenotype and microbiome, diet, and concomitant medications—to inform the rational design of next-generation, mechanism-anchored microbiome therapies.

2. Method

2.1. Reporting guideline

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020) [30] and PRISMA-S guidance [31], with a protocol developed a priori to prespecify eligibility criteria, outcomes, and synthesis plans, and a PRISMA flow diagram will document records identified, screened, excluded with reasons, and included at each stage.

2.2. Research questions

This review asked three prespecified questions: among adults with type 2 diabetes and related dysglycemia (prediabetes or metabolic syndrome), what is the clinical efficacy of probiotics, prebiotics, synbiotics, and fecal microbiota transplantation (FMT) compared with placebo, autologous FMT, or standard care on glycemic outcomes including HbA1c, fasting and postprandial glucose, fasting insulin, HOMA-IR, and where reported, OGTT-derived indices or clamp-measured insulin sensitivity; to what extent do these interventions elicit concurrent mechanistic changes in human-relevant biomarkers and functions, specifically plasma or fecal short-chain fatty acids, targeted bile-acid species or classes, incretin hormones such as GLP-1, endotoxemia markers such as LPS or LBP, and fecal microbiome composition or function measured by 16S rRNA gene sequencing or shotgun metagenomics; and which prespecified moderators, including intervention class and formulation details, duration, delivery matrix, baseline phenotype and microbiome features, diet standardization, and concomitant medications such as metformin and sulfonylureas, appear to modify clinical efficacy or mechanistic signals.

2.3. Eligibility criteria

We included peer-reviewed randomized controlled trials (parallel-group, crossover, or cluster-randomized) and randomized pilot trials in adults aged 18 years or older diagnosed with type 2 diabetes, prediabetes, or metabolic syndrome that compared probiotics, prebiotics, synbiotics, or FMT against placebo, autologous FMT, or standard care and reported at least one prespecified glycemic outcome, with a minimum intervention duration of 8 weeks for probiotic, prebiotic, and synbiotic studies and no minimum duration for FMT if outcomes were justified by design; studies were required to be published in reputable journals indexed in at least one of PubMed/MEDLINE, Scopus, or Web of Science, and to have a clear peer-review policy and an ISSN, and we excluded preprints, non-peer-reviewed materials, conference abstracts without a full peer-reviewed article, single-arm studies without a comparator, animal or *in vitro* studies, pediatric populations, type 1 or gestational diabetes, bariatric surgery cohorts unless microbiome-targeted interventions and glycemic outcomes were analyzed independently of surgical effects, and multifactorial interventions where non-microbiome modulators (for example, berberine, chromium, or high-dose polyphenols) could not be disentangled from the microbiome-targeted component; no geographic restrictions were applied, and studies were limited to English-language publications or those with full English translations.

2.4. Information sources and search strategy

We searched PubMed/MEDLINE, Scopus, and Web of Science Core Collection from database inception through August 31, 2025, and complemented these with manual searches in Google Scholar, including backward and forward citation chasing from included trials and relevant systematic reviews; search strategies combined controlled vocabulary and free-text terms for population, interventions, outcomes, and randomized trial design, applied human and adult limits where available,

and restricted results to English-language journal articles, with the exact, database-specific search strings and limits presented in Table 1.

2.5. Study selection

Two reviewers independently screened titles and abstracts using a prespecified form in Rayyan, advanced any record deemed potentially eligible by either reviewer to full-text assessment, and then independently evaluated full texts against eligibility criteria, with disagreements resolved by consensus or third-party adjudication, reasons for exclusion recorded verbatim at the full-text stage, duplicate records merged before screening, multiple reports from the same study collated with the most complete report designated as primary, and the overall process summarized in a PRISMA 2020 flow diagram spanning database and Google Scholar identification and citation chasing. Inter-rater agreement for study inclusion at the full-text stage, calculated using Cohen’s kappa (κ), was $\kappa = 0.86$, indicating excellent agreement.

2.6. Risk of bias and study quality assessment

Risk of bias for randomized studies was assessed independently by two reviewers using the Cochrane Risk of Bias 2 (RoB 2) tool [32] at the outcome-family level, with glycemic endpoints treated as the primary family and mechanistic biomarkers as a secondary family, disagreements resolved by consensus or third-party adjudication, and judgments justified in domain-level comments; if any eligible nonrandomized controlled trials were encountered within the prespecified scope, they were appraised with ROBINS-I for completeness of quality assessment without altering inclusion decisions, and the methodological quality of any contextual systematic reviews used for citation chasing was appraised with AMSTAR 2 [33] without influencing the primary evidence synthesis.

2.7. Data extraction and synthesis

Two reviewers independently and in duplicate extracted study characteristics, participant demographics and baseline clinical parameters including BMI and diagnostic criteria, medication status and stability with explicit capture of metformin and sulfonylurea use, dietary run-in or standardization, detailed intervention descriptors including for probiotics the exact strain identities with taxonomic designations and CFU per dose and for prebiotics the compound identity and grams per day and for synbiotics the explicit pairing of strains and substrates and for FMT donor screening and delivery route and dose, comparator details, adherence metrics, follow-up duration, prespecified outcomes and measurement methods and time points, analysis sets, and numerical results for all prespecified glycemic outcomes and any reported mechanistic biomarkers and microbiome outputs, alongside funding sources and conflicts of interest, with discrepancies reconciled by consensus and attempts made to contact corresponding authors for clarification when needed, and when necessary figures were digitized using validated software with procedures and assumptions archived.

Because this review does not undertake quantitative pooling, findings were synthesized narratively following SWiM (Synthesis Without Meta-analysis) guidance, grouping studies by intervention class and clinical population, aligning outcomes by common time windows with preference for the longest prespecified follow-up within 24 weeks for comparability, prioritizing intention-to-treat over per-protocol analyses where both were reported, and describing direction and consistency of effects for each outcome alongside risk-of-bias judgments; mechanistic readouts were mapped to clinical outcomes within each study to evaluate concordance between metabolite or microbiome changes and glycemic effects, prespecified moderators such as duration, formulation details, delivery matrix, baseline phenotype and microbiome features, diet standardization, and concomitant medications were used to structure the narrative and explore heterogeneity, and where appropriate we

Table 1
Search strategies for each database (PubMed/MEDLINE; Scopus; Web of Science and Google Scholar).

Database	Limits/filters applied	Exact search strategy
PubMed/ MEDLINE	Humans; Adult: 19+ years; English; Article types: Randomized Controlled Trial, Clinical Trial	((("Diabetes Mellitus, Type 2"[Mesh] OR "type 2 diabetes"[tiab] OR T2D[tiab] OR prediabet*[tiab] OR "Prediabetic State"[Mesh] OR "metabolic syndrome"[tiab] OR "Metabolic Syndrome"[Mesh])) AND ((probiotic*[tiab] OR "Probiotics"[Mesh] OR prebiotic*[tiab] OR "Prebiotics"[Mesh] OR synbiotic*[tiab] OR "fecal microbiota transplant*[tiab] OR "fecal microbiota transplant*[tiab] OR "fecal microbiota transfer"[tiab] OR "Fecal Microbiota Transplantation"[Mesh] OR FMT [tiab])))) AND ((glyc*[tiab] OR HbA1c[tiab] OR "Hemoglobin A, Glycosylated"[Mesh] OR "fasting glucose"[tiab] OR "fasting plasma glucose"[tiab] OR "postprandial glucose"[tiab] OR OGTT[tiab] OR "oral glucose tolerance"[tiab] OR insulin[tiab] OR "Insulin"[Mesh] OR HOMA-IR[tiab] OR "insulin sensitivity"[tiab] OR "hyperinsulinemic-euglycemic clamp"[tiab])) AND (random*[tiab] OR placebo[tiab] OR trial[tiab] OR "double-blind"[tiab] OR controlled [tiab]) NOT (animals[mh] NOT humans[mh])
Scopus	Document type: Article; Language: English; Subject area: Medicine	TITLE-ABS-KEY(("type 2 diabetes" OR T2D OR prediabet* OR "metabolic syndrome") AND (probiotic* OR prebiotic* OR synbiotic* OR "fecal microbiota transplant*" OR "fecal microbiota transplant*" OR "fecal microbiota transfer" OR FMT) AND (glyc* OR HbA1c OR "fasting glucose" OR "postprandial glucose" OR OGTT OR "oral glucose tolerance" OR insulin OR "HOMA-IR" OR "insulin sensitivity" OR clamp) AND (random* OR placebo OR trial OR "double blind" OR controlled)) AND PUBYEAR >1999
Web of Science Core Collection	Document types: Article; Language: English; Timespan: 2000–2025	TS=(("type 2 diabetes" OR T2D OR prediabet* OR "metabolic syndrome") AND (probiotic* OR prebiotic* OR synbiotic* OR "fecal microbiota transplant*" OR "fecal microbiota transplant*" OR "fecal microbiota transfer" OR FMT) AND (glyc* OR HbA1c OR "fasting glucose" OR "postprandial glucose" OR OGTT OR "oral glucose tolerance" OR insulin OR "HOMA-IR" OR "insulin sensitivity" OR clamp) AND (random* OR placebo OR trial OR "double blind" OR controlled))
Google Scholar (manual screening)	First 200 results per query variant; exclude patents and citations; restrict to journal articles	Iterative queries such as "type 2 diabetes probiotic randomized HbA1c," "type 2 diabetes prebiotic randomized fasting glucose," "synbiotic randomized HOMA-IR diabetes," and "fecal microbiota transplantation randomized insulin sensitivity diabetes," with manual screening of titles and abstracts, verification of journal peer review,

(continued on next page)

Table 1 (continued)

Database	Limits/filters applied	Exact search strategy
		and backward and forward citation chasing from included articles and relevant reviews

used structured textual matrices and harvest-style plots to transparently display study-level directions of effect without computing pooled effect sizes.

3. Results

3.1. Study selection process

The systematic search across electronic databases and manual sources initially identified a total of 2077 records. The database-specific yields were as follows: PubMed/MEDLINE (n = 101), Scopus (n = 965), Web of Science Core Collection (n = 863), and manual searches in Google Scholar and through citation chasing (n = 148).

After merging these records and removing 387 duplicates, 1690 unique articles remained for title and abstract screening. During this initial screening phase, 1589 records were excluded as they did not meet the prespecified eligibility criteria, primarily for reasons of wrong study design (e.g., non-randomized trials, reviews, animal studies), wrong population (e.g., type 1 diabetes, healthy subjects), or wrong intervention/comparator.

This process advanced 101 articles to the full-text assessment stage. A thorough review of these full texts against the eligibility criteria led to the exclusion of 71 articles. The primary reasons for exclusion at this stage were:

- **Incorrect study design** (e.g., single-arm trials, non-randomized controlled trials; n = 19)
- **Insufficient intervention duration** (for probiotic/prebiotic/synbiotic studies; n = 16)
- **Wrong population** (e.g., studies focusing solely on NAFLD, obesity without dysglycemia, or pediatric populations; n = 14)
- **Intervention not isolated** (e.g., multi-component supplements where the microbiome-targeted effect could not be disentangled; n = 11)
- **No relevant outcomes reported** (n = 7)

- **Duplicate publication** of an already included study (n = 4)

From the manual search in Google Scholar, 4 additional eligible articles were identified and included. Thus, a total of 30 articles (26 from database searches + 4 from manual searches) were included in the final systematic review. The complete selection process is detailed in the PRISMA 2020 (Fig. 1).

3.1.1. Risk of Bias and study quality assessment results

We present the Risk of Bias (RoB 2) assessments for each study across the five key domains: (D1) bias arising from the randomization process; (D2) bias due to deviations from intended interventions; (D3) bias resulting from missing outcome data; (D4) bias in outcome measurement; and (D5) bias in selection of the reported result. Following each study-specific appraisal, an overall RoB judgment is provided, as illustrated in Fig. 2. Similarly, Fig. 3 displays the methodological quality assessment of systematic reviews using the AMSTAR 2 tool.

3.1.2. Data extraction results

Across the randomized trials and mechanistic ancillaries, probiotic and synbiotic interventions in adults with type 2 diabetes (typically 12–24 weeks; often on stable metformin) showed HbA1c reductions in several studies [7,9,34], improvements in postprandial control in a multicenter proof-of-concept trial [11], and metabolically relevant drug–microbe interactions: HbA1c benefits concentrated in non-sulfonylurea users and coincided with higher plasma butyrate and ursodeoxycholate [5,6], while one mixed prediabetes/recent T2D trial was null overall but improved fasting glucose, HbA1c, and HOMA-IR with increased plasma butyrate and butyrate-pathway genes in metformin users [26]; a symbiotic decreased HOMA-IR and serum LPS with enrichment of SCFA-producing genera [9]. In prediabetes, a 12-week prebiotic (konjac glucomannan + GOS + EPS) lowered HbA1c and shifted the microbiome toward Anaerostipes [35], and a 24-week 20 g/day diverse fiber increased insulin sensitivity and lowered fasting insulin, with HbA1c reduction limited to baseline HbA1c <6.0 % [36]. Fecal microbiota transplantation studies demonstrated donor- and recipient-dependent effects on insulin sensitivity: RYGB-donor material favored clamp-based improvements [13]; after a Mediterranean-diet run-in, lean-donor FMT added little on average [14]; baseline composition and engraftment predicted HOMA2-IR response with bile-acid correlates in secondary analyses [15,28]; an oral-capsule pilot was overall null on clamp but suggested benefit in low-diversity recipients

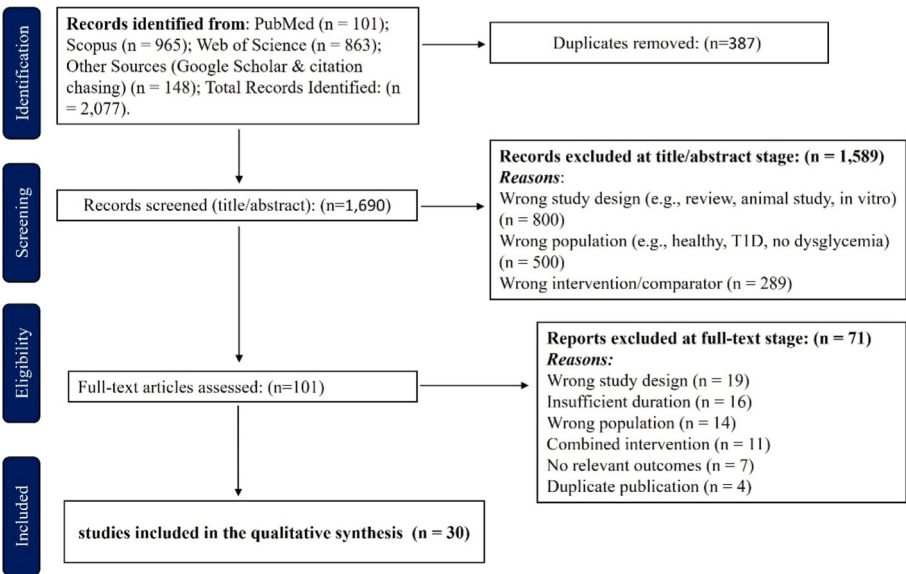


Fig. 1. PRISMA 2020 flow diagram of the study selection process.

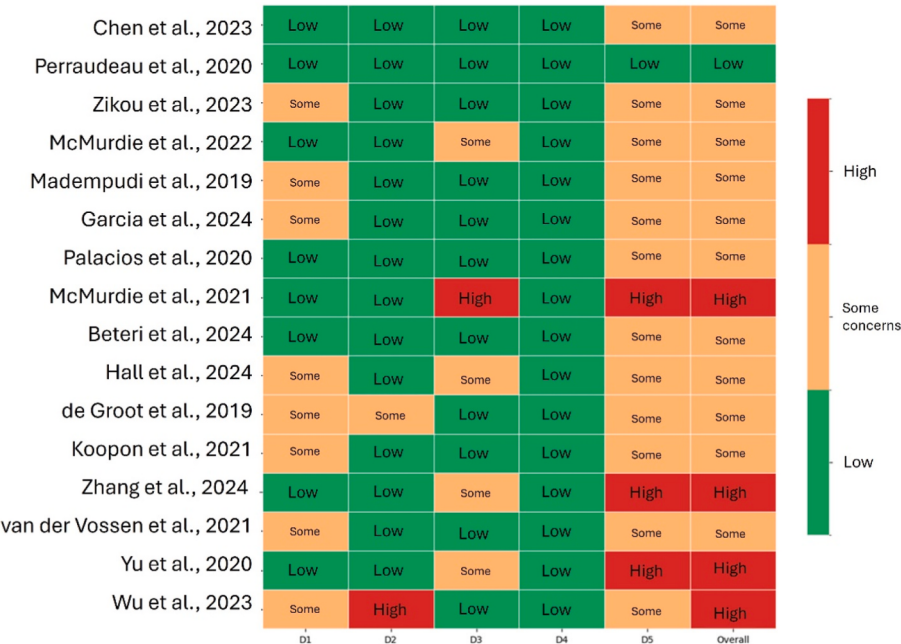


Fig. 2. RoB 2 risk-of-bias heatmap for randomized/experimental studies. Heatmap of Cochrane RoB 2 domain judgments (D1–D5) and overall risk across included trials; green = Low, orange = Some concerns, red = High.

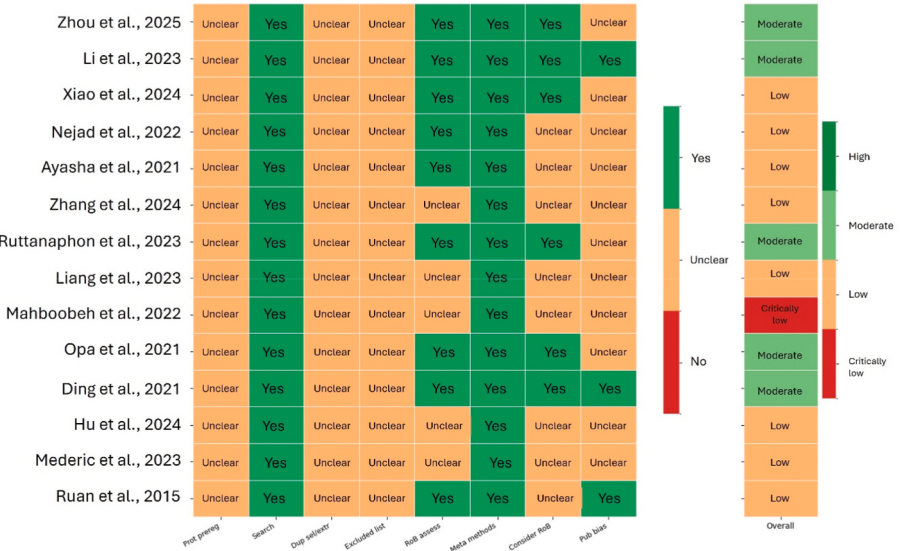


Fig. 3. AMSTAR 2 methodological quality heatmap for included systematic reviews/meta-analyses. Heatmap of AMSTAR 2 items (Yes = green, Unclear = orange, No = red) with a side bar showing the overall confidence rating (Critically low = red, Low = orange, Moderate = yellow-green, High = green).

[37]; and in drug-naïve T2D, 4-week FMT ± metformin improved HOMA-IR/BMI while metformin better reduced FBG/PPG/HbA1c [16]. Meta-analyses consistently reported modest glycemic benefits: probiotics lowered fasting glucose (e.g., MD −7.97 to −17.01 mg/dL), HbA1c (≈−0.31 percentage points; SMD −0.421), and insulin/HOMA-IR with larger effects for multispecies, longer duration, and some carriers (fermented milk) [2,3,12,19–25,29,38–40]. Mechanistic readouts across trials aligned with increased circulating butyrate and UDCA, enrichment of SCFA-producing taxa, and reduced endotoxemia [5–7,9,26,35]. Please refer to **Supplementary File 1** for the full data extraction report.

3.2. Clinical efficacy on glycemic outcomes (HbA1c, fasting/postprandial glucose, insulin, HOMA-IR, OGTT/clamp)

Across randomized trials and meta-analyses in adults with type 2 diabetes (T2D), probiotics, prebiotics, and synbiotics produce modest but statistically significant improvements in glycemic control. Pooled effects consistently show small reductions in HbA1c (typically ≈0.2–0.4 percentage points over ≥12 weeks) alongside decreases in fasting plasma glucose (FPG), fasting insulin, and HOMA-IR; benefits are generally larger with multispecies formulations and longer durations. These findings are robust across several reputable syntheses, though between-study heterogeneity is high [19–21,23–25,29].

Individual T2D probiotic RCTs align with the meta-analytic signal: add-on multispecies products lowered HbA1c versus placebo or standard

care over 12–24 weeks, while a mechanistically designed anaerobe consortium improved postprandial glycemic control over 12 weeks. Importantly, one companion analysis showed that HbA1c benefits were concentrated among participants not using sulfonylureas, highlighting drug–microbe interactions [5–7,9,11,26]. A larger 6-month RCT also reported significant between-group reductions in HbA1c and fasting glucose with a multistrain probiotic under stable background therapy [34].

Prebiotics and synbiotics show comparable glycemic benefits. Network and pairwise meta-analyses indicate prebiotics reduce HbA1c and FPG; synbiotics often perform at least as well as probiotics alone. In prediabetes, two rigorously conducted RCTs reported significant improvements in HbA1c (between-group in one study) and/or fasting glucose over 12–24 weeks, suggesting clinical relevance in related dysglycemia as well [3,12,35,36].

For FMT, human evidence is strongest for improvements in insulin sensitivity measured by hyperinsulinemic–euglycemic clamp in insulin-resistant/metabolic syndrome phenotypes after lean or post-bariatric donor FMT; effects can be transient and donor/recipient dependent. In newly diagnosed, drug-naïve T2D, a 4-week randomized study reported HOMA-IR and BMI improvements after FMT ($\pm$ metformin), whereas metformin better reduced FPG/PPG/HbA1c over that short time frame. Meta-analytic pooling across metabolic diseases suggests HbA1c reduction with FMT, but diabetes-specific RCTs remain few and heterogeneous [13–16,40] (Table 2).

Furthermore, recent FMT trials conducted specifically in drug-naïve or recently diagnosed T2D populations have reinforced these findings. One such study demonstrated that a single FMT infusion from healthy lean donors, compared to autologous FMT, significantly improved peripheral insulin sensitivity (as measured by hyperinsulinemic–euglycemic clamp) and beta-cell function over 18 weeks [18]. Another trial in newly diagnosed T2D patients reported that allogenic FMT, particularly when combined with a personalized, high-fiber diet, was superior to autologous FMT in achieving diabetes remission and improving glycemic control, highlighting the potential of donor microbiota and dietary co-interventions [17]. These T2D-specific trials

provide compelling evidence for FMT's ability to induce durable metabolic improvements in the target population of this review.

3.3. Do these interventions elicit concurrent mechanistic changes (SCFAs, bile acids, incretins, endotoxemia, microbiome)?

Converging human data indicate that clinical improvements are accompanied by mechanism-linked biomarker shifts. In probiotic RCTs, circulating butyrate increased and correlated with stool butyrate and glycemic response; targeted bile-acid changes (e.g., higher plasma ursodeoxycholate) were also observed, with in vitro confirmation of UDCA production by a consortium strain [5,6]. Another adjunctive probiotic trial reported enrichment of fecal butyrate-producing pathways and higher plasma butyrate among metformin users, coinciding with improved fasting glucose/HbA1c in that subgroup [26]. Trials frequently report increases in SCFA-producing taxa under active treatment [7,35]; endotoxemia/barrier readouts show mixed but supportive signals, including reduced serum LPS in a symbiotic trial and decreased zonulin in a metformin-user subgroup, consistent with improved intestinal integrity [9,26,39]. Incretins were measured in some studies (e.g., postprandial GLP-1 alongside FMT plus diet), but large, consistent incretin changes have not been a dominant finding in this literature to date [14] (Table 3).

3.4. Prespecified moderators of efficacy/mechanistic signals

Intervention design matters. Multispecies probiotics outperform single strains in pooled analyses, and longer exposures (≥ 12 weeks, often 24 weeks) are typically needed for HbA1c to change; fermented-milk carriers can be effective matrices in some trials/meta-analyses. Rationally assembled consortia that include obligate anaerobic butyrate producers have shown targeted postprandial benefits and metabolite signatures (butyrate, UDCA). Synbiotics, which match substrate to strain metabolism, frequently perform at least as well as probiotics alone [2,3,6,9,12,19–22].

Baseline phenotype and microbiome features also appear to

Table 2
Summary of clinical efficacy from representative RCTs and meta-analyses.

Intervention (class)	Population/context	Comparator	Duration	Primary glycemic findings	Notes	Key refs
Multistrain probiotic “Probio-X” + metformin	Adults with T2D on stable metformin	Placebo + metformin	12 wk	HbA1c reduced vs placebo ($P < 0.05$)	$\uparrow$ SCFA-producers; bile-acid metabolite shifts (mechanistic details in Part 2)	[7]
Targeted anaerobe consortium (WBF-011)	Adults with T2D (mixed meds)	Placebo	12 wk	Improved postprandial control (design focus)	HbA1c improvement concentrated in non-sulfonylurea users in companion analysis	[5,6,11]
Synbiotic UB0316 + metformin	Adults with T2D on stable metformin	Placebo + metformin	12 wk	HbA1c reduced vs placebo	Multispecies + FOS	[9]
Multistrain probiotic (LactoLevureR)	Adults with T2D; stable meds	Placebo	24 wk	$\downarrow$ HbA1c and $\downarrow$ FPG vs placebo (adjusted analyses)	6-month duration	[34]
Meta-analyses of probiotics (T2D)	Adults with T2D	Placebo/standard care	≥ 4 –12+ wk	Pooled $\downarrow$ HbA1c (≈ 0.2 – 0.4%), $\downarrow$ FPG, $\downarrow$ insulin, $\downarrow$ HOMA-IR	Stronger with multispecies, longer duration	[19–21, 29,38]
Meta-analysis (fermented milk carriers)	Adults with T2D	Placebo/controls	4–12 wk	$\downarrow$ FPG (MD ≈ -17 mg/dL) and $\downarrow$ HbA1c	Matrix may matter	[25]
Prebiotics (NMA and meta-analyses)	Adults with T2D	Placebo/standard care	8–24 wk	$\downarrow$ HbA1c and $\downarrow$ FPG (pooled)	Dose/tolerance considerations	[3,12]
Prediabetes fiber/GOS/ EPS	Prediabetes	Placebo	12 wk (+4-wk FU)	$\downarrow$ HbA1c (between-group), $\downarrow$ FPG (within-group below ADA threshold)	$\uparrow$ butyrate-producers	[35]
Prediabetes diverse fiber 20 g/d	Prediabetes	Cellulose placebo	24 wk	HbA1c reduced in baseline $<6.0\%$ subgroup; $\uparrow$ insulin sensitivity	Well-tolerated	[36]
FMT (lean/RYGB donors)	Insulin-resistant/metabolic syndrome	Autologous or other donors	2–6 wk	Improved clamp-measured insulin sensitivity in selected contexts	Donor/recipient features critical; effects transient	[13–15]
FMT $\pm$ metformin (drug-naïve T2D)	Newly diagnosed T2D	Metformin alone	4 wk	FMT improved HOMA-IR/BMI; metformin better for FPG/PPG/HbA1c over 4 wk	Robust colonization	[16]
Mixed interventions (systematic/meta)	Metabolic diseases incl. T2D	Various	Various	$\downarrow$ FPG, $\downarrow$ HbA1c, $\downarrow$ HOMA-IR (pooled)	Heterogeneous; context-dependent	[23,24]

Table 3
Representative human mechanistic signals observed alongside clinical outcomes.

Study/intervention	Biomarker(s) assessed	Direction of change	Linked clinical signal	Notes
WBF-011 probiotic (T2D) [5,6]	Plasma butyrate (targeted); plasma bile acids incl. UDCA; untargeted metabolomics	↑Butyrate (p = 0.007 in INT); ↑UDCA	HbA1c improvement concentrated in non-SU users	C. butyricum synthesized UDCA in vitro; sulfonylureas inhibited strain growth
Multistrain probiotic + metformin (T2D) [26]	Plasma butyrate; fecal shotgun pathways	↑Plasma butyrate; ↑butyrate-pathway genes	↓FPG, ↓HbA1c, ↓HOMA-IR in metformin subgroup	ITT null; medication-stratified signal
Multistrain probiotic (T2D) [7]	Fecal metagenomics; bile-acid related metabolites	↑SCFA-producers; several BA-related metabolites ↑	↓HbA1c vs placebo	Mechanistic hypothesis: incretin/BAT signaling via BA/SCFA
Symbiotic “Sugar Shift” (T2D) [9]	Serum LPS; 16S + metagenomics	↓LPS; ↓LPS biosynthesis pathways; ↑SCFA-producing genera	↓HOMA-IR	Supports endotoxemia–insulin resistance link
Prediabetes fiber/GOS/EPS [35]	Gut microbiota (16S/metagenomics)	↑Alpha diversity; ↑butyrate-producers (Anaerostipes)	↓HbA1c (between-group), ↓FPG (within-group)	Microbiome enrichment aligned with glycemic improvement
Med-diet ± lean-donor FMT (MetS) [14]	Postprandial GLP-1; clamp insulin sensitivity; microbiota	GLP-1 assessed; no large added effect of FMT over diet	Diet improved indices; limited FMT synergy	Highlights importance of diet context

condition response. In FMT studies, donor characteristics and recipient baseline diversity/functional deficits influence insulin-sensitivity changes and engraftment; in one analysis, lower baseline Prevotella and higher post-FMT richness predicted HOMA-IR improvement. Diet standardization (e.g., Mediterranean diet run-ins) improves signal detection and can itself drive metabolic gains, sometimes overshadowing added FMT effects. In prediabetes, a 24-week diverse-fiber trial found HbA1c reduction primarily among participants with baseline HbA1c <6.0 %, hinting that initial glycemic status modulates responsiveness [13–15,28,36].

Concomitant medications are critical moderators. Metformin interacts positively with some probiotic regimens—enhancing increases in plasma butyrate and butyrate-pathway genes and coinciding with better fasting glucose/HbA1c in subgroup analyses; dedicated add-on trials with stable metformin report clearer HbA1c benefits. Conversely, sulfonylureas may blunt probiotic efficacy: in vitro, several formulation strains exhibited growth inhibition by sulfonylureas, and clinical HbA1c benefits were concentrated in non-sulfonylurea users. These pharmacomicrobiomic interactions argue for prospective stratification by medication class in future trials [6,7,9,26] (Table 4).

Table 4
Moderators with supporting evidence.

Moderator	Effect on outcomes/signals	Examples/evidence
Formulation (multispecies; anaerobic consortia; synbiotics)	Larger HbA1c/FPG/HOMA-IR effects; targeted postprandial benefits	Meta-analyses favor multispecies; WBF-011 postprandial improvement; UB0316 HbA1c reduction [2,6,9,11,19–21]
Duration (≥12–24 wk)	Necessary for HbA1c change; strengthens pooled effects	Long-term RCTs and meta-analytic subgroup findings [20–22]
Delivery matrix (fermented milk)	Meaningful glycemic impact in pooled data	↓FPG and ↓HbA1c with fermented milk carriers [25]
Baseline microbiome/phenotype	Predicts response and engraftment; baseline HbA1c conditions effect size	FMT responder analyses; prediabetes fiber trial (<6.0 % HbA1c subgroup) [28,36,37]
Diet standardization	Improves detectability; may overshadow additive effects	Mediterranean diet run-in before FMT [14]
Concomitant meds (metformin)	Enhances probiotic butyrogenic and glycemic signals	Subgroup benefits; add-on trials with stable metformin [7,9,26]
Concomitant meds (sulfonylureas)	May blunt probiotic efficacy	In vitro growth inhibition; clinical HbA1c signal limited to non-users [6]

4. Discussion

4.1. Summary of intervention effects

Across intervention types, microbiome-targeted therapies demonstrate modest but reproducible improvements in glycemic control among adults with type 2 diabetes (T2D) and related dysglycemia. The overall pattern across randomized controlled trials (RCTs) and meta-analyses shows reductions in HbA1c of approximately 0.2–0.4 percentage points and decreases in fasting plasma glucose (FPG), fasting insulin, and HOMA-IR, particularly when interventions last ≥12 weeks and use multispecies probiotic or synbiotic formulations [19,20,22,38]. These findings are directionally consistent across high-quality syntheses, such as those by Li et al. [19], Xiao et al. [20], and Mederle et al. [24], despite underlying heterogeneity in formulations and populations.

Among probiotics, several studies—including those by Chen et al. [7], Zikou et al. [34], and Chaithanya et al. [41]—report significant HbA1c reductions over 12–24 weeks with multi-strain products, while Perraudeau et al. [11] observed enhanced postprandial glycemic control after 12 weeks of treatment with an anaerobe-inclusive consortium. Meta-analytic comparisons further indicate stronger glycemic effects with longer duration, multispecies formulations, and fermented-milk delivery matrices [15,19,22,42]. Synbiotics that pair complementary substrates with probiotic strains extend these benefits to fasting and postprandial glucose, as seen in trials by Madempudi et al. [41] and Devassy et al. [43].

In contrast, fecal microbiota transplantation (FMT) primarily modulates insulin sensitivity rather than HbA1c in the short term. de Groot et al. [13] and Koopen et al. [14] demonstrated significant clamp-measured improvements in insulin sensitivity following lean or post-bariatric donor FMT, although HbA1c changes were limited during comparable dietary interventions. Wu et al. [16] similarly found improved HOMA-IR and BMI but no incremental fasting or postprandial glucose benefit over metformin during four weeks of treatment. Collectively, these results suggest that probiotic and synbiotic therapies deliver gradual but durable glycemic improvements, whereas FMT produces rapid metabolic shifts with less established long-term durability.

4.2. Mechanistic insights

Beyond clinical endpoints, converging evidence links these interventions to coherent metabolic mechanisms. Probiotics and synbiotics often elevate short-chain fatty acids (SCFAs), particularly butyrate, which enhance insulin sensitivity through activation of G-protein-coupled receptors (GPR41/43) and modulation of hepatic gluconeogenesis [6,26,35]. In the trials by McMurdie et al. [6] and Palacios et al. [26], increased plasma butyrate correlated with reductions in fasting glucose and HbA1c, especially among metformin

users, suggesting synergistic interactions between microbial fermentation and pharmacotherapy.

Bile-acid remodeling provides a complementary pathway. The five-strain consortium studied by McMurdie et al. [6] increased circulating ursodeoxycholate (UDCA), a secondary bile acid capable of signaling through FXR and TGR5 receptors to improve glucose and lipid metabolism. Chen et al. [7] similarly observed enrichment of bile-acid-related metabolites and SCFA-producing taxa, supporting an integrated metabolic effect.

Inflammatory and barrier-integrity pathways also appear central. The symbiotic “Sugar Shift” trial by García et al. [9] documented reductions in serum LPS and enrichment of butyrate-producing genera, consistent with lower endotoxemia and improved insulin resistance. Reduced zonulin and LPS biosynthesis gene expression in metformin-treated participants further indicate restoration of intestinal barrier function [9,26]. Collectively, these findings align with prior mechanistic frameworks suggesting that microbiome modulation influences glucose homeostasis through SCFA signaling, bile-acid receptor activation, and attenuation of inflammation and metabolic endotoxemia [3,39,40].

Recent human and translational studies reinforce these links, showing that microbial metabolites regulate key nodes in host metabolism—such as hepatic gluconeogenic flux, skeletal muscle insulin signaling, and incretin hormone release—via integrated SCFA–bile acid–inflammatory networks [44,45]. The consistent association between butyrate or UDCA enrichment and improved glycemia across multiple RCTs [5–7,9,26,35] underscores the causal plausibility of these microbiota-derived mediators.

4.3. Limitations and future directions

Despite coherent patterns, notable gaps remain. Between-study heterogeneity in strain composition, dosage, duration, and background therapy limits direct comparisons. Medication context, particularly metformin and sulfonylureas, strongly modifies response: metformin appears to potentiate probiotic efficacy via enhanced butyrogenesis [7, 9,26], whereas sulfonylureas may suppress microbial growth and blunt clinical benefit [6]. Additionally, most studies lack standardized dietary control or detailed baseline microbiome profiling, factors known to influence treatment response [13–15,28].

Age- and gender-related subgroup effects were not specifically analyzed in this review. The primary reason for this exclusion was that most randomized controlled trials did not stratify outcomes by sex or age group, and when such data were available, they were inconsistently reported or insufficient for synthesis. Furthermore, given the narrative (non-meta-analytic) nature of our synthesis, quantitative evaluation of demographic moderators was not feasible. Future studies should systematically report age- and sex-stratified outcomes to clarify potential differential responses to microbiome-targeted therapies.

Future work should integrate stratified designs incorporating baseline microbiome features, medication stability, and diet standardization. Multi-omic approaches combining metabolomics and metagenomics would help disentangle which metabolic pathways mediate glycemic improvements. Larger, longer-duration FMT studies are also needed to determine whether transient insulin-sensitivity gains translate into sustained HbA1c reductions.

Overall, microbiome-targeted therapies act through multiple, overlapping metabolic pathways—SCFA and bile-acid signaling, anti-inflammatory modulation, and barrier restoration—to deliver modest but clinically meaningful glycemic improvements. These interventions are best positioned as adjunctive strategies to conventional diabetes management, offering mechanistic opportunities for personalized, microbiome-anchored metabolic care.

5. Conclusion

In conclusion, probiotics, prebiotics, synbiotics, and FMT offer modest, adjunctive benefits for glycemic control in type 2 diabetes and related dysglycemia, primarily by modulating the gut microbiome to increase beneficial metabolites like butyrate and remodel bile acid profiles. Clinical efficacy is context-dependent, influenced by intervention design, duration, concomitant medications, and baseline host characteristics. While these strategies show promise, they should be considered complementary to, not a replacement for, standard diabetes care.

CRediT authorship contribution statement

Neda Shalbaf: Data curation, Conceptualization. **Soheila Sadeghi:** Resources. **Sina Homaei:** Writing – original draft, Visualization. **Farnaz Saberian:** Project administration.

Ethical approval

Ethics approval for conducting this systematic review was not required. No participants were involved in this research.

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Appendix A. Supplementary data

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Data availability

No datasets were generated or analyzed during the current study.

References

- [1] Aw W, Fukuda S. Understanding the role of the gut ecosystem in diabetes mellitus. *J Diabet Investigat* 2018;9(1):5–12.
- [2] Ruan Y, Sun J, He J, Chen F, Chen R, Chen H. Effect of probiotics on glycemic control: a systematic review and meta-analysis of randomized, controlled trials. *PLoS One* 2015;10(7):e0132121.
- [3] Ojo O, Wang X, Ojo OO, Brooke J, Jiang Y, Dong Q, et al. The effect of prebiotics and oral anti-diabetic agents on gut microbiome in patients with type 2 diabetes: a systematic review and network meta-analysis of randomised controlled trials. *Nutrients* 2022;14(23):5139.
- [4] Vitetta L, Gorgani NN, Vitetta G, Henson JD. Prebiotics progress shifts in the intestinal microbiome that benefits patients with type 2 diabetes mellitus. *Biomolecules* 2023;13(9):1307.
- [5] Mcmurdie P, Stoeva MK, Nemchek M, Tyagi S, Gines J, Eid J, et al. 41-LB: changes in circulating metabolites, including butyrate, points to underlying mechanism of a

- probiotic intervention that improves postprandial hyperglycemia in subjects with type 2 diabetes. *Diabetes* 2021;70(Supplement 1):41–LB.
- [6] McMurdie PJ, Stoeva MK, Justice N, Nemchek M, Sieber CM, Tyagi S, et al. Increased circulating butyrate and ursodeoxycholate during probiotic intervention in humans with type 2 diabetes. *BMC Microbiol* 2022;22(1):19.
 - [7] Chen Y, Shen X, Ma T, Yu X, Kwok L-Y, Li Y, et al. Adjunctive probio-X treatment enhances the therapeutic effect of a conventional drug in managing type 2 diabetes mellitus by promoting short-chain fatty acid-producing bacteria and bile acid pathways. *mSystems* 2023;8(1):e01300. 22.
 - [8] Devassy S, S, S, Kumar AKS, Nair B. Efficacy and safety of F-Biotic™ in combination with metformin for type 2 diabetes mellitus: results from a randomized, double-blind clinical trial. *Cureus* 2024;16(12):e76053.
 - [9] García G, Soto J, Netherland Jr M, Hasan NA, Buchaca E, Martínez D, et al. Evaluating the effects of sugar shift® symbiotic on microbiome composition and LPS regulation: a double-blind, placebo-controlled study. *Microorganisms* 2024;12(12):2525.
 - [10] García G, Soto J, Rodríguez L, Nuez M, Domínguez N, Buchaca EF, et al. A randomized placebo controlled clinical trial of a metabolic shifting probiotic, sugar shift, for the treatment of T2DM. *medRxiv* 2022:2022. 12. 06.22283186.
 - [11] Perraudau F, McMurdie P, Bullard J, Cheng A, Cutcliffe C, Deo A, et al. Improvements to postprandial glucose control in subjects with type 2 diabetes: a multicenter, double blind, randomized placebo-controlled trial of a novel probiotic formulation. *BMJ Open Diabet Res Care* 2020;8(1):e001319.
 - [12] Mahboobi S, Rahimi F, Jafarnejad S. Effects of prebiotic and synbiotic supplementation on glycaemia and lipid profile in type 2 diabetes: a meta-analysis of randomized controlled trials. *Adv Pharmaceut Bull* 2018;8(4):565.
 - [13] de Groot P, Scheithauer T, Bakker GJ, Prodan A, Levin E, Khan MT, et al. Donor metabolic characteristics drive effects of fecal microbiota transplantation on recipient insulin sensitivity, energy expenditure and intestinal transit time. *Gut* 2020;69(3):502–12.
 - [14] Koopen AM, Almeida EL, Attaye I, Witjes JJ, Rampanelli E, Majait S, et al. Effect of fecal microbiota transplantation combined with mediterranean diet on insulin sensitivity in subjects with metabolic syndrome. *Front Microbiol* 2021;12:662159.
 - [15] van der Vossen EW, Bastos D, Stols-Gonçalves D, de Goffau MC, Davids M, Pereira JP, et al. Effects of fecal microbiota transplant on DNA methylation in subjects with metabolic syndrome. *Gut Microbes* 2021;13(1):1993513.
 - [16] Wu Z, Zhang B, Chen F, Xia R, Zhu D, Chen B, et al. Fecal microbiota transplantation reverses insulin resistance in type 2 diabetes: a randomized, controlled, prospective study. *Front Cell Infect Microbiol* 2023;12:1089991.
 - [17] Gómez-Pérez AM, Muñoz-Garach A, Lasserrot-Cuadrado A, Moreno-Indias I, Tinahones FJ. Microbiota transplantation in individuals with type 2 diabetes and a high degree of insulin resistance. *Nutrients* 2024;16(20).
 - [18] Su L, Hong Z, Zhou T, Jian Y, Xu M, Zhang X, et al. Health improvements of type 2 diabetic patients through diet and diet plus fecal microbiota transplantation. *Sci Rep* 2022;12(1):1152.
 - [19] Li G, Feng H, Mao X-L, Deng Y-J, Wang X-B, Zhang Q, et al. The effects of probiotics supplementation on glycemic control among adults with type 2 diabetes mellitus: a systematic review and meta-analysis of randomised clinical trials. *J Transl Med* 2023;21(1):442.
 - [20] Xiao R, Wang L, Tian P, Jin X, Zhao J, Zhang H, et al. The effect of probiotic supplementation on glucolipid metabolism in patients with type 2 diabetes: a systematic review and meta-analysis. *Nutrients* 2023;15(14):3240.
 - [21] Nejad L, Al-Naimi S, Rajic A, Ibrahim F. Probiotics as an additional therapeutic approach in the management of type 2 diabetes mellitus: a systematic review and meta-analysis. *Proc Nutr Soc* 2022;81(OCE1):E13.
 - [22] Ayesha IE, Monson NR, Klair N, Patel U, Saxena A, Patel D, et al. Probiotics and their role in the management of type 2 diabetes mellitus (Short-term versus long-term effect): a systematic review and meta-analysis. *Cureus* 2023;15(10).
 - [23] Zhou X, Zheng W, Kong W, Zhang J, Liao Y, Min J, et al. Glucose parameters, inflammation markers, and gut microbiota changes of gut microbiome-targeted therapies in type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. *J Clin Endocrinol Metabol* 2025:dga340.
 - [24] Mederle AL, Dima M, Stoicescu ER, Căpăstraru BF, Levai CM, Hătegan OA, et al. Impact of gut microbiome interventions on glucose and lipid metabolism in metabolic diseases: a systematic review and meta-analysis. *Life* 2024;14(11):1485.
 - [25] Zhong H, Wang L, Jia F, Yan Y, Xiong F, Hidayat K, et al. Effect of probiotic fermented milk supplementation on glucose and lipid metabolism parameters and inflammatory markers in patients with type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. *Biology* 2024;13(8):641.
 - [26] Palacios T, Vitetta L, Coulson S, Madigan CD, Lam YY, Manuel R, et al. Targeting the intestinal microbiota to prevent type 2 diabetes and enhance the effect of metformin on glycaemia: a randomised controlled pilot study. *Nutrients* 2020;12(7):2041.
 - [27] Seicaru EM, Ilie IRP, Căţineanu A, Crăciun AM, Ghervan C. Enhancing metformin effects by adding gut microbiota modulators to ameliorate the metabolic status of obese, insulin-resistant hosts. *J Gastrointest Liver Dis* 2022;31(3):344–54.
 - [28] Zhang Z, Mocanu V, Deehan EC, Hotte N, Zhu Y, Wei S, et al. Recipient microbiome-related features predicting metabolic improvement following fecal microbiota transplantation in adults with severe obesity and metabolic syndrome: a secondary analysis of a phase 2 clinical trial. *Gut Microbes* 2024;16(1):2345134.
 - [29] Rittiphairoj T, Pongpirul K, Janchot K, Mueller NT, Li T. Probiotics contribute to glycemic control in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. *Adv Nutr* 2021;12(3):722–34.
 - [30] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Br Med J* 2021;372.
 - [31] Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al. PRISMA-S: an extension to the PRISMA statement for reporting literature searches in systematic reviews. *Syst Rev* 2021;10(1):39.
 - [32] Minozzi S, Cinquini M, Gianola S, Gonzalez-Lorenzo M, Banzi R. The revised cochrane risk of bias tool for randomized trials (RoB 2) showed low interrater reliability and challenges in its application. *J Clin Epidemiol* 2020;126:37–44.
 - [33] Perry R, Whitmarsh A, Leach V, Davies P. A comparison of two assessment tools used in overviews of systematic reviews: ROBIS versus AMSTAR-2. *Syst Rev* 2021;10(1):273.
 - [34] Zikou E, Dovrolis N, Dimosthenopoulos C, Gazouli M, Makrilakis K. The effect of probiotic supplements on metabolic parameters of people with type 2 diabetes in Greece—A randomized, double-blind, placebo-controlled study. *Nutrients* 2023;15(21):4663.
 - [35] Beteri B, Barone M, Turroni S, Brigidi P, Tzortzis G, Vulevic J, et al. Impact of combined prebiotic galacto-oligosaccharides and bifidobacterium breve-derived postbiotic on gut microbiota and HbA1c in prediabetic adults: a double-blind, randomized, placebo-controlled study. *Nutrients* 2024;16(14):2205.
 - [36] Hall CV, Twelves JL, Saxena M, Scapozza L, Gurry T. Effects of a diverse prebiotic fibre supplement on HbA1c, insulin sensitivity and inflammatory biomarkers in pre-diabetes: a pilot placebo-controlled randomised clinical trial. *Br J Nutr* 2024;132(1):68–76.
 - [37] Yu EW-Y, Liu G, Stastka P, Cheney MC, Mahabamunuge J, Soto MT, et al. OR26-06 fecal microbiota transplantation trial for the improvement of metabolism (FMT-TRIM): a randomized double-blind placebo-controlled pilot trial. *J Endocrin Soc* 2020;4(Supplement_1). OR26-06.
 - [38] Liang T, Wu L, Xi Y, Li Y, Xie X, Fan C, et al. Probiotics supplementation improves hyperglycemia, hypercholesterolemia, and hypertension in type 2 diabetes mellitus: an update of meta-analysis. *Crit Rev Food Sci Nutr* 2021;61(10):1670–88.
 - [39] Ding L-N, Ding W-Y, Ning J, Wang Y, Yan Y, Wang Z-B. Effects of probiotic supplementation on inflammatory markers and glucose homeostasis in adults with type 2 diabetes mellitus: a systematic review and meta-analysis. *Front Pharmacol* 2021;12:770861.
 - [40] Hu D, Zhao J, Zhang H, Wang G, Gu Z. Fecal microbiota transplantation for weight and glycemic control of obesity as well as the associated metabolic diseases: meta-analysis and comprehensive assessment. *Life* 2023;13(7):1488.
 - [41] Madempudi RS, Ahire JJ, Neelamraju J, Tripathi A, Nanal S. Efficacy of UB0316, a multi-strain probiotic formulation in patients with type 2 diabetes mellitus: a double blind, randomized, placebo controlled study. *PLoS One* 2019;14(11):e0225168.
 - [42] Wang X, Chen L, Zhang C, Shi Q, Zhu L, Zhao S, et al. Effect of probiotics at different intervention time on glycemic control in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. *Front Endocrinol* 2024;15:1392306.
 - [43] Devassy S, Sheejamol S, Ak SK, Nair B, Ak IVSK. Efficacy and safety of F-Biotic™ in combination with metformin for type 2 diabetes mellitus: results from a randomized, double-blind clinical trial. *Cureus* 2024;16(12).
 - [44] Tong X, Xu J, Lian F, Yu X, Zhao Y, Xu L, et al. Structural alteration of gut microbiota during the amelioration of human type 2 diabetes with hyperlipidemia by metformin and a traditional Chinese herbal formula: a multicenter, randomized, open label clinical trial. *mBio* 2018;9(3). <https://doi.org/10.1128/mbio.02392-17>.
 - [45] Niu X, Wang Y, Huang L, Guo P, Zhang S, Sun Y, et al. Effect of oral metformin on gut microbiota characteristics and metabolite fractions in normal-weight type 2 diabetic mellitus patients. *Front Endocrinol* 2024;15:1397034.