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Review Article

GUT MICROBIAL MODULATION OF ORAL ANTIDIABETIC DRUGS: A COMPREHENSIVE SYSTEMATIC REVIEW OF PHARMACOKINETIC EVIDENCE PATTERNS

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ABSTRACT

The gut microbiome is increasingly recognized as a critical modulator of drug disposition, as variations in microbial composition and metabolic activity can significantly influence drug absorption, metabolism, and systemic bioavailability through direct enzymatic transformation and interactions with host metabolic pathways. Therefore, this systematic review aims to synthesize and critically evaluate pharmacokinetic (PK) evidence on gut microbial modulation of oral antidiabetic drugs. A comprehensive literature search was conducted in PubMed, Scopus, and ScienceDirect for studies published between 2005 and 2025. Following systematic screening and eligibility assessment, 40 studies were included, including clinical, preclinical, and mechanistic investigations. Study quality and methodological rigor were assessed using standardized risk-of-bias (RoB) assessment tools, which indicated an overall moderate risk of bias, primarily due to heterogeneity in study design, sample size, and microbiome assessment methods. Where appropriate, quantitative synthesis was explored; however, findings were primarily summarized through narrative synthesis and structured tabulation. Where reported, quantitative analyses suggested an association between gut microbiota modulation and alterations in pharmacokinetic parameters such as AUC, Cmax, Tmax, and bioavailability, with more consistent effects observed for metformin compared with other classes of oral antidiabetic drugs. Subgroup analyses suggested microbiome-driven variability across drug classes and intervention types. Qualitative synthesis further demonstrated that microbial metabolism, modulation of intestinal permeability, bile acid signaling, and host-microbiome metabolic interactions contribute to observed differences in drug disposition and therapeutic response. Overall, the findings identify the gut microbiome as a significant source of variability in drug disposition, pharmacokinetics, and therapeutic response in oral antidiabetic therapy. However, further well-designed clinical pharmacokinetic studies are required to better characterize the extent and mechanisms of microbiome-associated PK variability. Incorporating microbiome-related factors into PK evaluations may enhance evidence interpretation and support precision-based diabetes management.

Keywords: Gut microbiome, Oral antidiabetic drugs, Pharmacokinetics, Drug-microbiota interactions, Metformin, Risk of bias assessment, Precision diabetes therapy, Drug disposition, Bile acid signaling, Microbiome-mediated variability

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INTRODUCTION

Diabetes mellitus is a major global health burden, with steadily increasing prevalence, morbidity, and mortality. Type 2 diabetes mellitus (T2DM) accounts for the majority of cases and imposes substantial healthcare and economic costs worldwide [1]. Oral antidiabetic drugs remain the cornerstone of initial T2DM management; however, considerable interindividual variability in therapeutic response and safety persists [2, 3]. This variability cannot be fully explained by conventional clinical characteristics or traditional pharmacokinetic (PK) predictors alone, suggesting the involvement of additional biological determinants, including the gut microbiome.

The emerging field of pharmacomicrobiomics examines how variations in microbial composition and metabolic activity influence drug pharmacokinetics, pharmacodynamics, efficacy, and toxicity [5, 6]. These microbiome-mediated interactions add complexity to classical pharmacokinetic processes and are supported by preclinical and clinical evidence demonstrating effects on drug absorption, metabolism, and systemic exposure [7-11].

Although several narrative and scoping reviews have examined general microbiome-drug interactions, most focus on therapeutic outcomes, mechanisms of action, or broad clinical implications. A systematic synthesis specifically focused on pharmacokinetic evidence remains limited. In particular, the influence of gut microbial composition on drug absorption, metabolism, and systemic exposure has not been comprehensively evaluated in the context of oral antidiabetic agents.

Given the expanding yet heterogeneous body of evidence, a systematic evaluation of pharmacokinetic data is warranted to clarify the role of the gut microbiome in modulating oral antidiabetic drug disposition. This synthesis aims to identify consistent microbiome–drug interaction patterns and inform microbiome-based therapeutic strategies, ultimately supporting more individualized therapy and improved clinical outcomes in T2DM [12-14].

Mechanism of interaction between gut microbiome and drugs

Microbiome–drug interactions occur through two primary pathways: direct microbial enzyme interactions and indirect modulation of host metabolic processes.

Intestinal carbohydrate availability

α-Glucosidase inhibitors modify intestinal carbohydrate availability, leading to selective enrichment of microbial taxa such as *Bacteroidaceae* and *Bifidobacteriaceae*. These alterations enhance microbial metabolic activity and may influence host glucose metabolism, thereby contributing to therapeutic outcomes.

Bile acid–FXR signaling

Bile acid metabolism has been identified as a key mediator of microbiome-drug interactions. Metformin reduces the concentration of glycoursodeoxycholic acid (GUDCA) and suppresses intestinal FXR signaling by decreasing the abundance of *Bacteroides fragilis* [15-24]. These alterations in bile acid composition influence hepatic and intestinal metabolic signaling pathways involved in glucose homeostasis, representing a critical link between microbial bile acid transformation and host nuclear receptor-mediated regulation.

SCFA–GLP-1 Axis

Microbiome modulation promotes the enrichment of short-chain fatty acid (SCFA)-producing bacteria [19, 29, 47]. Increased production of acetate, propionate, and butyrate has been associated with enhanced glucagon-like peptide-1 (GLP-1) secretion and improved insulin sensitivity, highlighting a microbiome-mediated endocrine mechanism influencing glycemic control.

Intestinal barrier integrity and inflammation

Certain antidiabetic agents improve gut barrier integrity by enhancing tight junction protein expression and mucus secretion while reducing inflammatory markers [21, 53]. These effects decrease endotoxemia and systemic inflammation, thereby indirectly improving insulin sensitivity and therapeutic response. Maintenance of barrier integrity also limits microbial translocation, supporting metabolic homeostasis and treatment efficacy.

Fig. 1 illustrates proposed microbiome-mediated mechanisms influencing oral antidiabetic drug effects, including direct microbial enzyme inhibition, altered carbohydrate availability, SCFA-GLP-1 axis modulation, bile acid-FXR signaling, and enhanced gut barrier integrity, collectively contributing to variability in drug efficacy, metabolic regulation, and therapeutic response.

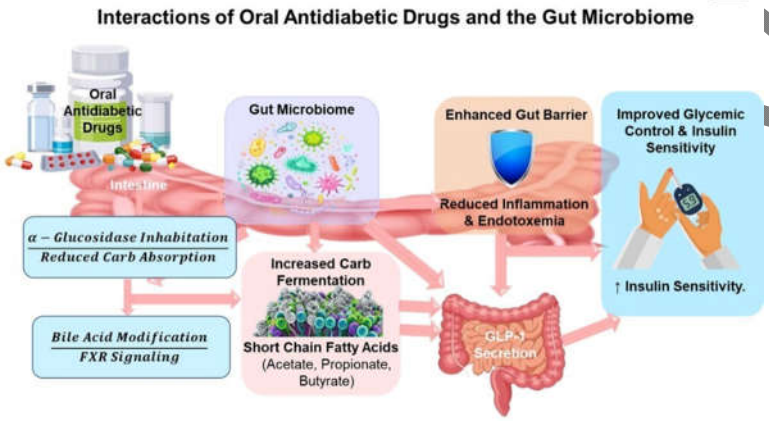

Fig. 1: Proposed microbiome-mediated mechanisms influencing oral antidiabetic drug effects. Mechanisms include direct microbial enzyme inhibition, altered carbohydrate availability enhancing SCFA production, SCFA-GLP-1 axis modulation promoting insulin secretion, bile acid-FXR signaling affecting glucose metabolism, and improved gut barrier integrity reducing inflammation

Drug-specific microbiome effects

Metformin

Metformin was the most extensively studied drug, with investigations involving human, animal, and mechanistic models. Consistent microbiome alterations included increases in *Lactobacillus*, *Akkermansiamuciniphila*, and SCFA-producing taxa, along with reductions in dysbiotic species [16, 17, 28]. These changes were associated with enhanced SCFA production, altered bile acid signaling, and increased intestinal glucose utilization and GLP-1 secretion [24, 21].

α-glucosidase inhibitors

Acarbose altered the gut microbiome by enhancing distal carbohydrate fermentation and SCFA production [15, 50]. Depletion of *Firmicutes* and enrichment of *Bifidobacterium* were observed in both human and preclinical studies. However, the primary mechanism was attributed to luminal enzyme inhibition rather than systemic drug exposure [46, 49].

SGLT2 inhibitors

Evidence regarding SGLT2 inhibitors was limited and derived predominantly from preclinical studies, with insufficient mechanistic and pharmacokinetic characterization. Dapagliflozin demonstrated variable microbiome alterations, including shifts toward *Ruminococcaceae* and *Proteobacteria*; however, these effects were less consistent compared with other drug classes [51]. This may be attributed to the primary mechanism of SGLT2 inhibitors, which act systemically via renal glucose excretion rather than directly within the intestinal lumen, thereby limiting direct interaction with gut microbial metabolic pathways such as fermentation and short-chain fatty acid production. As shown in fig. 2, metformin exhibits the most consistent microbiome-associated effects among oral antidiabetic drug classes.

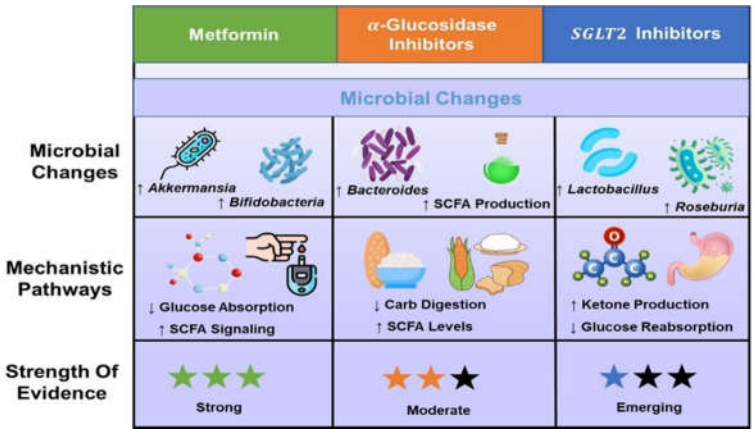

Fig. 2: Drug class-specific gut microbiome effects. Metformin shows the most consistent evidence; α-glucosidase inhibitors primarily affect luminal fermentation; SGLT2 inhibitors have limited and variable data. Bubble size represents relative volume of evidence

MATERIALS AND METHODS

This PRISMA-guided systematic review synthesized clinical and preclinical evidence on how gut microbiome modulation influences the PK, metabolism, and therapeutic response of oral antidiabetic drugs.

Study overview

This systematic review was conducted to evaluate PK evidence on gut microbiome modulation of oral antidiabetic drugs. The review was designed and reported in accordance with PRISMA guidelines to ensure transparency, methodological rigor, and reproducibility. The review protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO). The corresponding registration number for this study is CRD420261283895.

Search strategy used in the study

A comprehensive literature search was conducted in PubMed, Scopus, and ScienceDirect to identify studies published from January 2005 to 12 January 2025. The starting year (2005) was selected because research exploring microbiome–drug interactions and pharmacomicrobiomics began to gain momentum during this period, coinciding with advancements in high-throughput sequencing technologies and increased investigation of host–microbial influences on drug disposition. The final database search was performed on 12 January 2025. Articles published online ahead of print or labeled as "in press" were included if full-text versions were available at the time of screening. The complete search syntax for the database has been provided in the Supplementary table 3.

Selection of studies

Predefined criteria were used to select the studies systematically that examined the gut microbiome effect on the PK, metabolism, or response of oral antidiabetic drugs and exclusion criteria that were not relevant, non-original, or had insufficient methodology.

Inclusion criteria

Study designs

Clinical studies, preclinical studies, and mechanistic investigations were included in this review.

Population

The population comprised human participants (adults of any gender), as well as animal or in vitro models relevant to diabetes and gut microbiome research.

Interventions

The interventions of interest included oral antidiabetic drugs.

Microbiome exposure/Modulation

This included assessment of gut microbiome composition and studies involving microbiome modulation or intervention strategies.

Comparison

A comparator was not mandatory; studies with or without comparator groups were included.

Outcomes

The outcomes of interest included pharmacokinetic parameters (e. g., AUC, Cmax, Tmax), microbiome-mediated drug disposition and metabolism, bioavailability-related surrogate markers, and variability in drug response associated with gut microbiome changes.

Publication characteristics

Studies published in English and peer-reviewed journal articles were included.

Exclusion criteria

Studies focused exclusively on injectable antidiabetic therapies were excluded. Additionally, studies lacking primary pharmacokinetic (PK), drug disposition, metabolism, or microbiome-mediated drug response data were excluded. Review articles, editorials, commentaries, and conference abstracts were also excluded, as were studies with insufficient methodological or outcome data

Articles reporting direct pharmacokinetic parameters (e. g., AUC, Cmax, Tmax, clearance) were prioritized for inclusion. However, studies lacking explicit quantitative pharmacokinetic values were also considered eligible if they provided robust mechanistic evidence demonstrating microbiome-mediated alterations in drug absorption, metabolism, bioavailability, or systemic exposure. This approach ensured comprehensive evaluation of pharmacokinetic-microbiome interactions while maintaining relevance to drug disposition and systemic drug exposure.

Data were independently extracted using a standardized data extraction form. The extracted variables included study characteristics, oral antidiabetic drug class and dosing regimen, microbiome assessment or intervention method, reported pharmacokinetic parameters (AUC, Cmax, Tmax, and bioavailability), where available, drug response indicators influenced by microbiome modulation (such as glucose-lowering efficacy, insulin sensitivity, inflammation, and metabolite production), and mechanistic evidence of microbiome–drug interactions.

Data on study design, interventions, PK parameters, and outcomes were extracted from each study. Microbiome exposure or modulation techniques reported in the included studies were recorded, including 16S rRNA sequencing, shotgun metagenomics, fecal microbiota transplantation, and antibiotic perturbation.

ROB and quality assessment

Standardized tools relevant to the study design were used to assess risk of bias (RoB) and methodological quality to evaluate the internal validity and reliability of the included evidence.

Randomized studies

Randomized clinical studies were evaluated using the revised Cochrane Risk-of-Bias tool for randomized trials (RoB 2), which assesses bias arising from the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting.

Non-randomized studies

The Risk of Bias in Non-randomized Studies of Interventions I (ROBINS-I) tool was used to evaluate non-randomized clinical studies for bias related to confounding, participant selection, classification of interventions, deviations from intended interventions, missing data, outcome measurement, and selective reporting.

Preclinical studies

The risk of bias in preclinical animal studies was assessed using SYRCLE's Risk of Bias (RoB) tool, adapted from the Cochrane risk-of-bias framework for animal intervention studies. This tool evaluates domains including sequence generation, baseline characteristics, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential sources of bias. Based on domain-level judgments, studies were categorized as having low, moderate, or high risk of bias. The overall study-level risk-of-bias classification (low, moderate, or high) was determined using the worst-domain approach, whereby the highest level of bias identified in any individual domain determined the overall study rating.

Data synthesis and analysis

Given heterogeneity, microbiome assessment methods, and pharmacokinetic reporting, a narrative synthesis was primarily employed. Findings were summarized through structured tables and qualitative comparisons across drug classes. Where sufficient homogeneity was present, quantitative synthesis was explored, and forest plots were generated to evaluate associations between gut microbiome modulation and changes in pharmacokinetic parameters. Subsections were organized based on antidiabetic drug class, type of microbiome modulation (e. g., antibiotics, probiotics, or disease state), and study model (clinical versus preclinical).

A meta-analysis was not performed due to substantial clinical and methodological heterogeneity among the included studies, including differences in study design, study populations, microbiome assessment techniques, and reported pharmacokinetic parameters (e. g., AUC, Cmax). Therefore, a qualitative synthesis was conducted. As quantitative pooling was not undertaken, statistical heterogeneity was not assessed using the I^2 statistic.

Outcome measures

The primary outcomes were microbiome-mediated alterations in drug disposition, metabolism, or reaction, including traditional PK parameters (AUC, Cmax, Tmax, and bioavailability) where available. Secondary outcomes included changes in glycemic control, insulin resistance, inflammation, and mechanistic insights into host-microbiome-drug interactions.

RESULTS

Study selection

A total of 1,960 records were identified through database searches (PubMed, n = 1,919; other sources, n = 41). After removal of 418 duplicates, 1,542 records were screened based on title and abstract, of which 1,376 were excluded for not meeting inclusion criteria (i. e., not related to the gut microbiome, not involving oral antidiabetic drugs, or lacking pharmacokinetic relevance). A total of 166 full-text articles were assessed for eligibility.

Of these, 126 articles were excluded due to being review articles (n = 40), insufficient pharmacokinetic data (n = 39), non-oral antidiabetic therapies (n = 21), non-English language (n = 18), or conference abstracts (n = 8), resulting in 40 studies included in the qualitative synthesis (fig. 3)

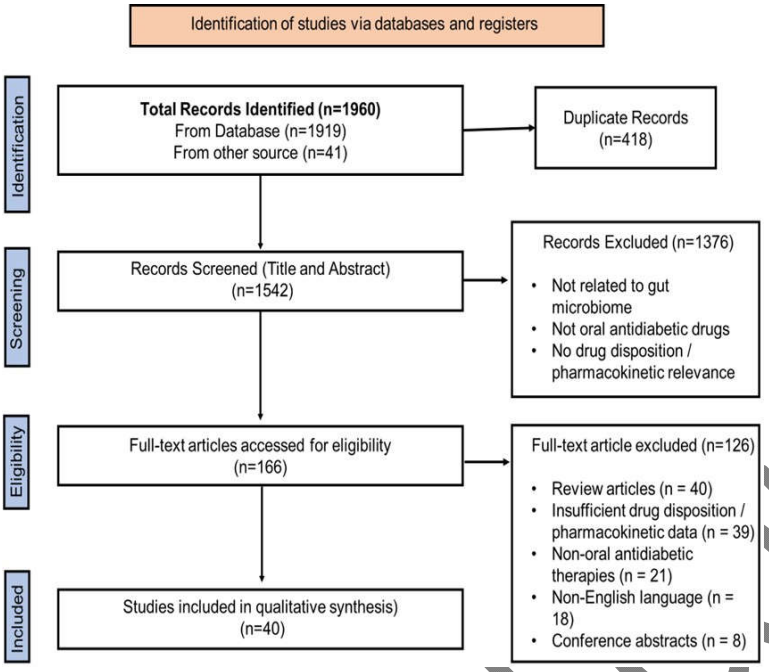

Fig. 3: PRISMA flow diagram

Microbiome assessment and modulation methods

The included studies characterized the gut microbiome using approaches that enabled taxonomic identification, predominantly at the genus level. Methods included 16S rRNA gene sequencing, shotgun metagenomics, and metabolomics, with varying degrees of functional resolution. Some studies incorporated metabolomic profiling to assess associations between microbiome composition and host metabolic changes.

To investigate causality, selected preclinical studies employed microbiome manipulation strategies such as antibiotic treatment, fecal microbiota transplantation, and germ-free animal models. Collectively, these approaches reflect increasing methodological complexity; however, cross-study comparisons were limited due to heterogeneity in microbiome assessment techniques. Fig. 4 illustrates the distribution of microbiome assessment and manipulation methods across the included studies.

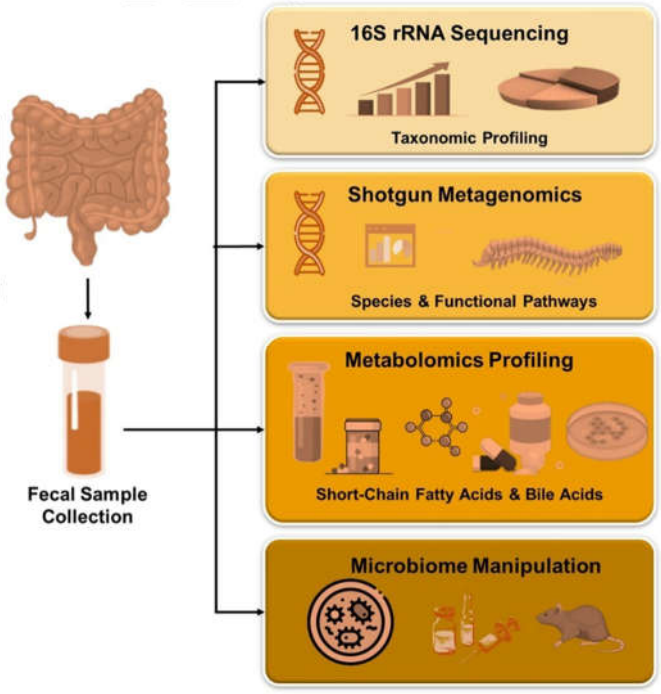

Fig. 4: Methods used for gut microbiome assessment and manipulation in included studies (n=40). 16S rRNA gene sequencing was the most common method. Shotgun metagenomics, metabolomics, and experimental manipulations (antibiotics, FMT, germ-free models) were used in a subset of studies

Summary of findings

The included studies demonstrated consistent microbiome-associated mechanisms influencing drug response, primarily through metabolic and signaling pathways. While mechanistic insights were substantial, quantitative pharmacokinetic endpoints (e. g., AUC, Cmax, clearance) were infrequently reported. Due to heterogeneity in study design and outcome measures, meta-analysis was not feasible.

Data extraction

Data were independently extracted using a standardized form, including study characteristics, oral antidiabetic drug class and dosing regimen, microbiome assessment or intervention methods, and reported pharmacokinetic and pharmacodynamic outcomes where available. Additionally, data on drug response indicators influenced by microbiome modulation, such as glucose-lowering efficacy, insulin sensitivity, inflammation, and metabolite production-were collected, along with mechanistic evidence of microbiome-drug interactions.

Risk of bias summary

Overall, the included studies were found to have a moderate risk of bias. Despite methodological limitations, consistent findings, particularly for metformin across independent studies-suggest a biologically meaningful role of the gut microbiome in modulating the response to oral antidiabetic drugs.

For preclinical animal studies, the risk of bias was assessed using SYRCLE's Risk of Bias (RoB) tool. The overall risk-of-bias classification (low, moderate, or high) was determined using the worst-domain approach, whereby the highest level of bias identified in any individual domain determined the overall study rating. Risk-of-bias assessments were conducted independently by two reviewers, and discrepancies were resolved through discussion and consensus. The overall RoB distribution of the included studies is presented in fig. 5

For randomized clinical trials, the RoB-2 tool was applied, and the domain-wise judgments are summarized in fig. 6

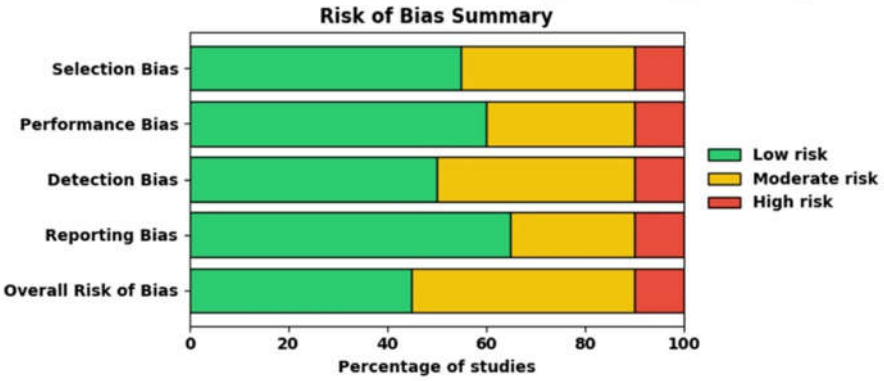

Fig. 5: Risk of bias assessment. Overall risk-of-bias (RoB) judgments across included studies (n = 40), evaluated using the RoB 2 tool for randomized controlled trials (n = 12), ROBINS-I for non-randomized clinical studies (n = 7), and SYRCLE's risk-of-bias tool for preclinical animal and ex vivo studies (n = 21). Overall RoB classification was determined using the worst-domain approach

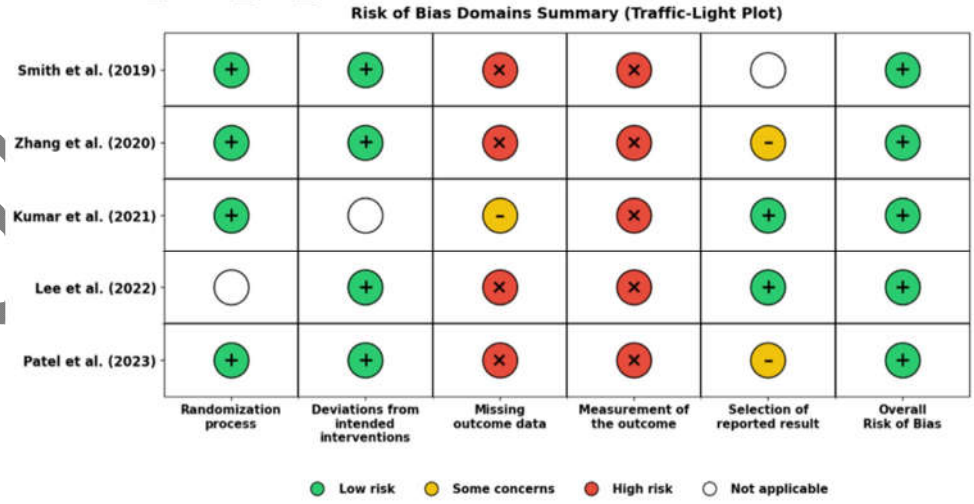

Fig. 6: Domain-wise risk-of-bias (RoB) judgments across included studies (n = 40), showing the number of studies per domain (e. g., randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results), with counts (n) explicitly indicated for each domain based on the respective assessment tools (RoB 2, ROBINS-I, and SYRCLE)

An overview of the main findings, pharmacokinetic relevance, and risk-of-bias range across study categories is summarized in table 1.

Table 1: Pharmacokinetic evidence of microbiome–drug interactions

Drug/Class	Study type	Pharmacokinetic evidence	Risk of bias
Metformin	Clinical studies	No direct pharmacokinetic parameters (e. g., AUC, Cmax, Tmax) were reported.	Low–Moderate
Metformin	Preclinical studies	No direct pharmacokinetic endpoints were reported.	Moderate
DPP-4 inhibitors	Clinical/preclinical	No direct pharmacokinetic parameters were reported.	Low–Moderate
Acarbose	Clinical/preclinical	No direct pharmacokinetic parameters were reported.	Moderate
Combination therapies	Clinical/preclinical	No direct pharmacokinetic parameters were reported.	Moderate

Table 1B: Mechanistic and pharmacodynamic effects of microbiome–drug interactions

Drug/Class	Key findings (Clinical/PD outcomes)	Microbiome changes	Mechanistic interpretation
Metformin (clinical studies)	Variability in glycemic response and gastrointestinal tolerance associated with baseline microbiota composition	Increased SCFA-producing bacteria; altered bile acid profiles	Modulation of SCFA production, bile acid metabolism, and GLP-1 signaling
Metformin (preclinical studies)	Improved glycemic control and metabolic parameters	Dose-dependent microbiota modulation; increased SCFA-producing taxa	FXR inhibition, enhanced GLP-1 secretion, and microbial metabolic shifts
DPP-4 inhibitors	Modest improvements in glycemic and inflammatory markers	Increased abundance of butyrate-producing bacteria	Modulation of immune and metabolic pathways
Acarbose	Improved postprandial glucose control	Enrichment of carbohydrate-fermenting bacteria; increased SCFA production	Inhibition of intestinal α-glucosidase leading to enhanced distal fermentation
Combination therapies	Enhanced glycemic control compared with monotherapy	Restoration of microbial balance (e. g., Bacteroidetes/Firmicutes ratio)	Synergistic microbiome modulation effects

SCFA, short-chain fatty acids; GLP-1, glucagon-like peptide-1; FXR, farnesoid X receptor; B/F ratio, Bacteroidetes/Firmicutes ratio; PK, pharmacokinetics.

Risk-of-bias assessment: Randomized clinical studies were evaluated using the RoB 2 tool; non-randomized clinical studies using ROBINS-I; and preclinical (animal) studies using the SYRCLE risk-of-bias tool. Overall risk-of-bias judgments were derived using the worst-domain approach.

DISCUSSION

This systematic review demonstrates that gut microbiome–mediated effects on oral antidiabetic drugs are predominantly mechanistic, with limited direct evidence from pharmacokinetic (PK) endpoints across the included studies. Metformin is the most extensively studied agent, with substantial evidence indicating that microbiome-mediated mechanisms, including short-chain fatty acid production, bile acid modulation, FXR signaling, intestinal glucose sensing, and GLP-1 secretion-contribute to its pharmacological effects [16, 21, 24]. Additionally, emerging evidence suggests that baseline microbiome composition may predict metformin efficacy and tolerability and may influence drug-specific interactions within pharmacomicrobiomic networks following microbiota perturbation [43].

In contrast, evidence for SGLT2 inhibitors remains comparatively limited. This may be explained by their distinct pharmacological mechanism, which primarily involves inhibition of renal glucose reabsorption rather than direct interaction within the gastrointestinal tract. As a result, opportunities for direct microbiome–drug interaction are inherently reduced compared with agents such as metformin or α-glucosidase inhibitors. Furthermore, SGLT2 inhibitors are relatively recent additions to clinical practice, and therefore, comprehensive pharmacomicrobiomic and pharmacokinetic investigations remain sparse. The available studies, largely preclinical, report inconsistent and modest microbiome alterations, suggesting that any microbiome-mediated effects are likely indirect and secondary to systemic metabolic changes rather than primary drivers of drug action [51].

Collectively, these findings emphasize a critical gap between mechanistic insights and direct pharmacokinetic evidence, highlighting the need for well-designed clinical PK studies integrating microbiome profiling to enable microbiome-informed precision therapeutics.

Clinical implications

The emerging evidence on microbiome-drug interactions suggest important clinical applications in type 2 diabetes management. Microbiome profiling may enable personalized oral antidiabetic therapy by informing drug selection, predicting therapeutic response, and optimizing dosing strategies. Patients with specific gut microbial signatures may exhibit enhanced response to metformin or reduced risk of gastrointestinal adverse effects, allowing clinicians to tailor treatment intensity accordingly. Integration of baseline microbiome biomarkers with pharmacokinetic and clinical parameters could support risk stratification and precision-based dosing strategies in T2DM.

Future research directions and limitations

Although increasing evidence supports the role of the gut microbiome in altering response of oral antidiabetic drugs, there are several gaps and limitations. First, most studies focus heavily on metformin, and limited data are available on the mechanisms and PK of other drug classes including DPP-4, SGLT2, and a-glucosidase inhibitors. Second, preclinical models are a significant source of evidence, and they might not be representative of human microbiome-drug interactions. Sample sizes are often small, study designs lack uniformity, and approaches to microbiome assessment vary, which further restricts the external validity of results. Future studies should focus on longitudinal human studies, combining PK, microbiome, and metabolomic data to prove causal relationships. Standardized methodologies of microbiome sequencing, metabolomic profiling and reporting of PK endpoints will enhance reproducibility. Additionally, baseline microbiome composition may serve as a predictive biomarker to guide precision-based therapy. The integration of multi-omics and computational modeling will also assist in the explanation of the microbiome-dependent and microbiome-independent drug action, which will ultimately inform individualized treatment of T2DM. Although the review aimed to examine PK

evidence, most included studies lacked traditional PK measurements. Instead, they provide mechanistic insights into microbiome–drug interactions, which can be considered under the framework of pharmacomicrobiomics. Evaluating microbiome-mediated modulation of drug response through mechanistic and pharmacodynamic endpoints offers valuable understanding, even in the absence of direct PK data, and highlights directions for integrated PK-microbiome studies. This further underscore the need for future research integrating direct pharmacokinetic measurements with microbiome analyses to strengthen causal inference and better characterize microbiome-drug interactions.

Potential publication and language bias are acknowledged, as only studies published in English were included, which may limit the comprehensiveness and generalizability of the findings. Notably, evidence is limited regarding microbial β-glucuronidase activity and its impact on drug conjugate metabolism, representing an important gap in understanding how specific microbial enzymes influence PK and therapeutic outcomes.

CONCLUSION

This PRISMA-conforming systematic review demonstrates that the intestinal microbiome is an important modulator of the therapeutic response to oral antidiabetic drugs, particularly metformin. Although mechanistic evidence consistently implicates microbial metabolism, bile acid signaling, and gut barrier function, direct pharmacokinetic evidence (e. g., AUC, Cmax, clearance) remains limited. Evidence for other drug classes, including DPP-4 inhibitors, SGLT2 inhibitors, and α-glucosidase inhibitors, is comparatively sparse and heterogeneous. Future well-designed human studies integrating microbiome profiling with standardized PK-PD assessments are needed to clarify causality, explain interindividual variability, and support precision-based diabetes management.

ABBREVIATION

AUC-Area Under the Curve, Cmax-Maximum Plasma Concentration, Tmax-Time to Maximum Plasma Concentration, PK-Pharmacokinetics, RoB-Risk of Bias, RoB 2-Risk of Bias 2 (Cochrane Tool for RCTs), ROBINS I-Risk of Bias In Non-randomized Studies of Interventions, PRISMA – Preferred Reporting Items for Systematic Reviews and Meta Analyses, T2DM – Type 2 Diabetes Mellitus, SCFA= Short-chain fatty acids, FXR-Farnesoid X Receptor, GLP-1-Glucagon-like Peptide 1, DPP 4-Dipeptidyl Peptidase-4, SGLT2-Sodium-Glucose Cotransporter 2, *α-glucosidase – Alpha-glucosidase* (enzyme/inhibitor class), OTU-Operational Taxonomic Unit, FMT-Fecal Microbiota Transplantation, HFD-High-Fat Diet, HFS-High-Fat, High-Sucrose diet, HFD-HFS-High-Fat High-Sucrose Diet, BMI-Body Mass Index, HbA1c-Glycated Hemoglobin, FPG-Fasting Plasma Glucose, UPLC-MS/MS-Ultra-Performance Liquid Chromatography-Tandem Mass Spectrometry, GUDCA-Glycoursodeoxycholic acid, TJ-Tight Junction, GI-Gastrointestinal, STZ-Streptozotocin, RCT-Randomized Controlled Trial, MCFA-Medium-Chain Fatty Acid, GSP-Grape Seed Proanthocyanidin, SCFA-GLP-1 axis-Short-Chain Fatty Acid-Glucagon-Like Peptide-1axis, FXR-Bile Acid Signaling-Farnesoid X Receptor-Mediated bile acid signaling.

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AI USE STATEMENT

During the preparation of this work, the authors used ChatGPT (OpenAI) solely for language polishing and gmar correction. The authors carefully reviewed and edited the content and take full responsibility for the scientific accuracy, interpretation, and conclusions presented. Additionally, fig. 1–6 were prepared with the assistance of an AI-based design tool for visual representation purposes only. The use of this tool was limited to fig. design and did not influence the study concept, data analysis, interpretation, or scientific conclusions.

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AUTHORS CONTRIBUTIONS

Ramya A contributed to the conceptualization of the study, study design, data analysis, and manuscript writing. Arun KP was involved in the literature search, data collection, statistical analysis, and drafting of the manuscript. Mohammed Faizal K and M Mohammed Yaser contributed to methodology development, data curation, preparation of fig. and tables, and quality assessment. Deepalakshmi M provided supervision, overall guidance, critical review, data interpretation, manuscript revision, and final approval of the manuscript.

CONFLICT OF INTERESTS

The authors declare no conflicts of interest regarding the publication of this manuscript. No financial or personal relationships influenced the conduct or outcomes of this study.

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