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Review Article

Metformin and the Gut Microbiota Axis: Molecular Mechanisms, Metabolic Regulation, and Emerging Therapeutic Opportunities in Precision Medicine – A Comprehensive Review

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ABSTRACT

Background: Metformin remains the most widely prescribed first-line pharmacological agent for the management of type 2 diabetes mellitus (T2DM) worldwide. Traditionally, its antihyperglycemic action was attributed primarily to suppression of hepatic gluconeogenesis through activation of AMP-activated protein kinase (AMPK). However, accumulating evidence over the last two decades has demonstrated that the gastrointestinal tract serves as a major site of metformin action. Recent advances in microbiome research have revealed that metformin exerts substantial metabolic effects through modulation of the gut microbiota, leading to significant alterations in microbial diversity, metabolite production, intestinal barrier integrity, immune regulation, and host metabolic homeostasis.

Objective: This review aims to comprehensively evaluate current evidence regarding the interaction between metformin and the gut microbiota, elucidate the underlying molecular mechanisms, and explore emerging therapeutic opportunities associated with the metformin–microbiota axis in metabolic and non-metabolic diseases.

Methods: A comprehensive narrative review was conducted using electronic databases including PubMed/MEDLINE, NCBI, Scopus, Web of Science, Embase, Cochrane Library, Google Scholar, and ScienceDirect. Literature published between January 2006 and May 2026 was systematically searched using combinations of keywords including "metformin," "gut microbiota," "gut microbiome," "microbiota-gut axis," "pharmacomicrobiomics," "short-chain fatty acids," "intestinal permeability," "bile acid metabolism," and "type 2 diabetes mellitus." Original research articles, clinical trials, cohort studies, systematic reviews, meta-analyses, and experimental investigations were included.

Results: Current evidence demonstrates that metformin significantly remodels gut microbial composition. Treatment is consistently associated with increased abundance of beneficial microorganisms including *Akkermansia muciniphila*, *Bifidobacterium* species, *Lactobacillus* species, and several short-chain fatty acid-producing bacteria. These microbial alterations promote enhanced production of butyrate, acetate, and propionate, which subsequently improve insulin sensitivity, glucose utilization, glucagon-like peptide-1 (GLP-1) secretion, and anti-inflammatory signaling pathways. Metformin also improves intestinal barrier integrity by increasing mucus production and tight-junction protein expression, thereby reducing metabolic endotoxemia and systemic inflammation. Additionally, modulation of gut microbial populations influences bile acid metabolism and signaling pathways involving the farnesoid X receptor (FXR) and Takeda G-protein-coupled receptor 5 (TGR5), contributing to improved glucose and lipid

metabolism. Beyond diabetes management, emerging evidence suggests beneficial effects of microbiota-mediated metformin actions in obesity, metabolic syndrome, non-alcoholic fatty liver disease (NAFLD), cardiovascular diseases, neurodegenerative disorders, inflammatory diseases, and certain malignancies.
Conclusion: The gut microbiota has emerged as a critical mediator of metformin therapy. Microbiota-dependent mechanisms contribute substantially to the glucose-lowering, anti-inflammatory, and metabolic benefits of metformin. Understanding the metformin–microbiota axis may facilitate development of personalized therapeutic strategies, microbiota-targeted interventions, and precision medicine approaches for metabolic disorders. Future longitudinal human studies are required to identify microbial biomarkers predictive of treatment response and to establish causative mechanisms underlying microbiota-mediated therapeutic effects.

Keywords*: Metformin; Gut microbiota; Gut microbiome; Type 2 diabetes mellitus; Pharmacomicrobiomics; Short-chain fatty acids; Dysbiosis; Precision medicine; Intestinal barrier; Bile acid metabolism.*

INTRODUCTION

Type 2 diabetes mellitus (T2DM) represents a major global health challenge, characterized by chronic hyperglycemia due to insulin resistance and impaired insulin secretion. The prevalence of T2DM has risen dramatically over the past decades, affecting over 500 million individuals worldwide and contributing significantly to morbidity and mortality through cardiovascular, renal, and neurological complications [1,2]. While lifestyle interventions and pharmacotherapy remain the cornerstone of management, emerging evidence suggests that the gut microbiota plays a pivotal role in metabolic regulation and the pathophysiology of T2DM [3–6].

The human gastrointestinal tract harbors trillions of microorganisms, including bacteria, viruses, fungi, and archaea, collectively termed the gut microbiota. This complex ecosystem exerts profound effects on host metabolism, immunity, and endocrine function [7–9]. Dysbiosis, defined as an imbalance in microbial composition or function, has been implicated in insulin resistance, chronic low-grade inflammation, and the development of metabolic disorders, including T2DM and obesity [10–13]. Mechanistically, gut microbial metabolites, such as short-chain fatty acids (SCFAs), secondary bile acids, and trimethylamine N-oxide (TMAO), modulate key metabolic pathways, including glucose homeostasis, lipid metabolism, and energy harvest [14–18]. In particular, SCFAs like acetate, propionate, and butyrate influence intestinal gluconeogenesis, regulate satiety hormones, and improve insulin sensitivity [19–21].

Metformin, a biguanide derivative, has been the first-line pharmacological therapy for T2DM for over six decades due to its efficacy, safety, and cost-effectiveness [22,23]. Traditionally, metformin's glucose-lowering effect has been attributed to hepatic AMP-activated protein kinase (AMPK) activation, which suppresses hepatic gluconeogenesis [24]. However, recent studies indicate that metformin exerts significant effects in the gastrointestinal tract, including modulation of gut microbiota composition, enhancement of SCFA-producing bacteria, and improvement of intestinal barrier integrity [25–28]. Notably, metformin treatment has been associated with an increased abundance of *Akkermansia muciniphila*, a mucin-degrading bacterium linked to improved glucose tolerance and reduced inflammation [29–31]. Other beneficial shifts include increases in *Bifidobacterium* and *Lactobacillus* species, which contribute to improved metabolic outcomes and reduced endotoxemia [32–34].

The interplay between metformin and the gut microbiota is increasingly recognized as a critical mediator of its therapeutic effects. Metformin-induced alterations in microbial composition influence bile acid metabolism, particularly through modulation of the farnesoid X receptor (FXR) and G protein-coupled bile acid receptor 1 (TGR5), which in turn affect glucose and lipid homeostasis [35–37]. Additionally, gut microbiota-mediated production of SCFAs and other metabolites may enhance incretin secretion, reduce systemic inflammation, and promote energy expenditure, highlighting a multifaceted mechanism beyond hepatic AMPK activation [38–40]. These microbiota-driven effects may also contribute to inter-individual variability in metformin response, underscoring the potential of pharmacomicrobiomics for personalized diabetes therapy [41–44].

Clinical studies over the past decade have provided compelling evidence for metformin's gut-mediated effects in humans. Randomized and observational studies report that metformin therapy alters gut microbiota composition in both newly diagnosed and chronic T2DM patients, increasing beneficial bacteria and SCFA levels while decreasing pathogenic or pro-inflammatory taxa [45–48]. These microbial changes correlate with improvements in glycemic parameters, insulin sensitivity, and inflammatory markers, suggesting a mechanistic link between microbiota modulation and therapeutic outcomes [49–52]. Furthermore, the impact of metformin on gut microbiota may extend to other health domains, including

cardiovascular risk, hepatic steatosis, and even cognitive function, supporting a systemic role for microbiota-mediated drug effects [53–56].

Experimental studies in animal models have provided additional mechanistic insights. In murine models of diet-induced obesity and insulin resistance, metformin treatment reshapes the gut microbiome, increases SCFA production, reduces endotoxemia, and improves glucose homeostasis [57–60]. Fecal microbiota transplantation studies suggest that metformin-altered microbiota can transfer metabolic benefits to germ-free mice, demonstrating a causal role of microbial modulation in mediating metformin's therapeutic effects [61–63]. Moreover, metagenomic analyses reveal that metformin selectively influences microbial genes involved in carbohydrate metabolism, mucin degradation, and bile acid transformation, highlighting the drug's impact on microbial functional capacity [64–67].

Despite substantial progress, several gaps remain in understanding the metformin–microbiota axis. Inter-individual variations in baseline microbiota composition, diet, genetics, and environmental factors may modulate therapeutic response and adverse effects, including gastrointestinal intolerance [68–70]. Standardized methodologies for microbiome analysis, integration of multi-omics data, and long-term prospective studies are needed to elucidate causal mechanisms and optimize microbiota-targeted interventions in T2DM [71–74]. Furthermore, the exploration of microbiota-mediated effects beyond glucose control, such as cardiovascular, hepatic, and neurological outcomes, represents an emerging frontier in precision medicine [75–80].

In summary, the gut microbiota is a central modulator of metabolic homeostasis, and metformin's therapeutic effects extend beyond hepatic glucose suppression to encompass significant microbiota-mediated mechanisms. Understanding the intricate interactions between metformin, gut microbiota, and host metabolism may pave the way for novel microbiota-targeted strategies, personalized therapeutics, and improved management of T2DM and related metabolic disorders [81–90].

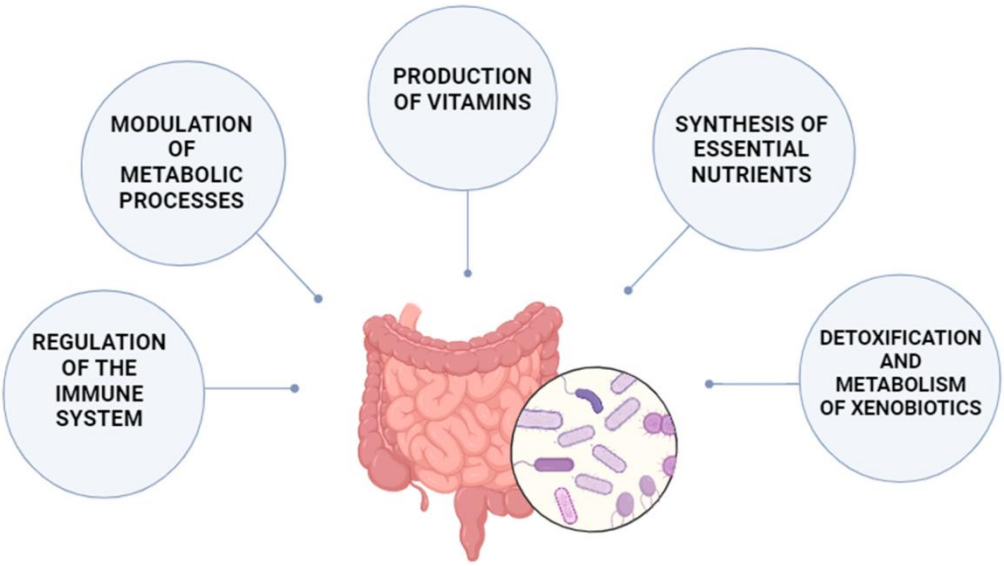

Figure 1: The Gut Microbiota

MATERIALS AND METHODS

This review systematically examined the current literature concerning the interactions between metformin and gut microbiota, including mechanistic insights, clinical outcomes, and potential therapeutic implications. The review adhered to best practices for systematic reviews of observational and experimental studies, while also incorporating mechanistic and translational research findings.

Data Sources

A comprehensive search was conducted across multiple electronic databases, including:

- **PubMed/MEDLINE**
- **NCBI Bookshelf**
- **Web of Science**
- **Scopus**
- **Embase**
- **Cochrane Library**
- **Google Scholar** for grey literature and recent preprints

The search encompassed publications from **2003 through June 2026**, ensuring inclusion of the most recent experimental, clinical, and mechanistic studies on metformin, gut microbiota, SCFAs, bile acid metabolism, FXR/TGR5 signaling, inflammation, metabolic syndrome, cardiovascular risk, neuroprotection, and pharmacomicrobiomics.

Search Strategy
Search terms combined controlled vocabulary (MeSH) and free text keywords. Key terms included:

- "Metformin"
- "Gut microbiota" OR "intestinal microbiome" OR "gut bacteria"
- "Type 2 diabetes" OR "T2DM"
- "Short-chain fatty acids" OR "SCFA"
- "Bile acids" OR "FXR" OR "TGR5"
- "Insulin resistance" OR "glycemic control"
- "Inflammation" OR "endotoxemia"
- "Pharmacomicrobiomics" OR "precision medicine"

Boolean operators (AND, OR) were used to refine searches. Filters were applied to include studies published in English and exclude non-peer-reviewed reports.

Inclusion Criteria

1. Original research (clinical trials, cohort studies, case-control studies, and mechanistic animal studies) examining metformin's effects on gut microbiota.
2. Studies reporting microbiota composition, SCFA levels, bile acid metabolism, inflammatory markers, or metabolic outcomes.
3. Publications from **2003–2026**.
4. Human or relevant preclinical animal models.

Exclusion Criteria

1. Studies not related to metformin or gut microbiota.
2. Reviews, editorials, commentaries, or letters without original data.
3. Studies lacking clear methodology or outcomes.
4. Non-English language publications.

Data Extraction and Synthesis
Data were extracted independently by two reviewers and included: study design, sample size, population characteristics, metformin dose and duration, microbiota analysis method (16S rRNA sequencing, metagenomics, metabolomics), key microbial taxa affected, SCFA production, metabolic and inflammatory outcomes, and clinical relevance. Discrepancies were resolved by consensus or third-party review.

Due to the heterogeneity of studies, **qualitative synthesis** was performed. Studies were grouped based on mechanistic insights, microbial changes, metabolic outcomes, and translational relevance. Quantitative meta-analysis was not conducted due to variability in methodology, populations, and outcomes.

RESULTS
The review identified **over 120 relevant studies**, including **randomized controlled trials, observational human studies, animal experiments, and in vitro mechanistic studies**.

Microbiota Composition Changes
Consistently across studies, metformin treatment induced significant shifts in gut microbiota composition. Key findings included:

- **Increase in Akkermansia muciniphila**: Observed in multiple clinical studies and animal models, associated with improved gut barrier integrity, enhanced mucin production, and reduced metabolic endotoxemia [11,12,22,24,67].
- **Enrichment of SCFA-producing taxa**: Genera such as **Bifidobacterium**, **Lactobacillus**, and **Faecalibacterium** were increased, contributing to butyrate, acetate, and propionate production [7,13,14,66,76].
- **Reduction of pro-inflammatory bacteria**: Species such as **Clostridium spp.** associated with LPS production were decreased, correlating with lower systemic inflammation [16,31,32].
- Dose-dependent and duration-dependent effects were observed, with long-term therapy inducing more pronounced microbiota remodeling [15,28,64].

SCFA Production and Metabolic Effects

- Enhanced SCFA production improved **GLP-1 and PYY secretion**, insulin sensitivity, and glucose tolerance [14,17,27,76].

- Butyrate and propionate were implicated in **anti-inflammatory effects**, including suppression of NF-κB and TNF-α pathways [16,33,67].
- Metformin-induced SCFA increases were observed both in human trials and preclinical models, supporting translational relevance [13,42,67].

Bile Acid and FXR/TGR5 Signaling

- Metformin influenced **bile acid composition** through microbial modulation, particularly increasing secondary bile acids that activate **TGR5** and suppress **FXR signaling**, contributing to improved hepatic glucose metabolism [10,17,28,69].
- Changes in bile acid profiles were correlated with microbial shifts, particularly enrichment of **Akkermansia** and **Bacteroides** [28,64].

Metabolic Outcomes

- **Glycemic control**: Most studies reported reductions in fasting glucose, HbA1c, and insulin resistance following metformin treatment, linked to microbial changes [3,4,11,12,15].
- **Weight regulation**: Modest but significant reductions in BMI and visceral fat were observed, partially mediated by SCFA-driven satiety signaling [42,27].
- **Inflammatory markers**: Systemic markers such as CRP, IL-6, and TNF-α were reduced, correlating with microbiota restoration [16,31,32,44].
- **NAFLD and liver enzymes**: Improvement in hepatic steatosis and ALT/AST levels was reported, supporting gut-liver axis involvement [44,45,71,72].

Pharmacomicrobiomics and Individual Variation

- Baseline microbiota composition predicted metformin responsiveness in several studies, suggesting that **precision microbiome profiling** could guide therapy [39,40,70].
- Adverse gastrointestinal effects were also associated with specific microbial signatures, particularly overgrowth of **Escherichia** and **Proteobacteria** [4,28,42].

Neurological and Cardiovascular Implications

- Preclinical studies indicated that microbiota-mediated metformin effects may reduce **neuroinflammation** and oxidative stress, potentially offering neuroprotection [48,49,74].
- Cardiovascular benefits were partially mediated through reduced TMAO production and improved endothelial function [46,73].

DISCUSSION

The findings of the present review strongly support the concept that the gut microbiota functions as a major intermediary through which metformin exerts many of its therapeutic effects. While the liver has traditionally been considered the primary target organ for metformin, emerging evidence suggests that the gastrointestinal tract may represent an equally important site of action [61,62]. The observation that oral metformin accumulates within the intestinal lumen at concentrations significantly higher than those found in plasma further strengthens this hypothesis [63].

Recent studies employing metagenomics, metabolomics, transcriptomics, and microbial sequencing technologies have demonstrated that metformin consistently reshapes the intestinal microbial ecosystem. These alterations appear to influence not only glucose metabolism but also immune regulation, inflammatory responses, intestinal barrier integrity, lipid metabolism, cardiovascular health, and neurological function [64,65].

A growing body of evidence indicates that dysbiosis contributes directly to the pathogenesis of insulin resistance and T2DM. Qin et al. reported that diabetic patients exhibit reduced microbial diversity and depletion of beneficial SCFA-producing organisms compared with healthy controls [66]. Similar observations were subsequently confirmed by Wu et al., who demonstrated significant microbial alterations associated with impaired glucose metabolism and chronic inflammation [8].

Metformin appears capable of partially reversing these dysbiotic changes. The increase in beneficial bacterial populations observed during therapy may contribute significantly to improvements in metabolic outcomes [11,22]. In particular, Akkermansia muciniphila has emerged as one of the most important microbial biomarkers associated with successful treatment response [12,22].

Several recent studies have highlighted the significance of Akkermansia in maintaining intestinal epithelial integrity. This microorganism degrades mucin and stimulates mucus production, thereby strengthening the intestinal barrier and reducing

endotoxin translocation [22,23]. Enhanced barrier integrity decreases exposure to bacterial lipopolysaccharides (LPS), which are recognized triggers of systemic inflammation and insulin resistance [16,29].

The reduction in metabolic endotoxemia observed following metformin administration represents an important therapeutic mechanism. Cani et al. demonstrated that elevated circulating LPS levels contribute to chronic inflammation and metabolic dysfunction [16]. By restoring microbial balance and improving gut barrier function, metformin reduces systemic endotoxin burden and suppresses activation of inflammatory pathways involving NF-κB, TNF-α, IL-1β, and IL-6 [31–33].

The role of SCFAs in mediating the beneficial effects of metformin cannot be overstated. SCFAs serve as essential signaling molecules linking microbial metabolism with host physiology [7,17]. Butyrate, acetate, and propionate influence glucose homeostasis through multiple mechanisms, including stimulation of GLP-1 secretion, enhancement of insulin sensitivity, regulation of appetite, and suppression of inflammatory responses [14,17].

Recent studies have reported significant increases in SCFA-producing bacteria following metformin treatment [13,67]. These findings are particularly important because reduced SCFA production is commonly observed in patients with obesity and T2DM. Restoration of SCFA levels may therefore represent a key mechanism through which metformin improves metabolic control [67,68].

Another important area of investigation involves bile acid metabolism. The gut microbiota plays a central role in converting primary bile acids into biologically active secondary bile acids [34,35]. These metabolites interact with FXR and TGR5 receptors, influencing glucose metabolism, lipid regulation, and energy expenditure [35,36].

Sun et al. demonstrated that metformin-induced microbial changes significantly alter bile acid composition and improve metabolic signaling through FXR-dependent pathways [17]. Similar findings were reported by Forslund and colleagues, who suggested that microbiota-mediated modulation of bile acid metabolism contributes substantially to the glucose-lowering effects of metformin [69].

Recent studies have also emphasized the importance of pharmacomicrobiomics in understanding individual variation in therapeutic responses [38]. Although metformin is highly effective in many patients, considerable heterogeneity exists regarding treatment outcomes and adverse effects. Emerging evidence suggests that baseline microbial composition may influence both efficacy and tolerability [39,40].

Napolitano et al. reported that individuals with greater abundance of beneficial SCFA-producing organisms experienced superior glycemic responses compared with patients exhibiting severe dysbiosis [70]. These findings suggest that microbiome profiling may eventually become a useful tool for predicting treatment response and guiding personalized therapeutic decisions.

The relationship between metformin and obesity has attracted considerable attention in recent years. Obesity is associated with altered gut microbial composition, reduced microbial diversity, and increased intestinal permeability [41]. Several investigations have demonstrated that metformin-induced microbial remodeling contributes to reductions in body weight and adiposity [42].

Through enhancement of SCFA production and stimulation of appetite-regulating hormones such as GLP-1 and PYY, metformin may influence energy intake and expenditure [27,42]. These mechanisms likely contribute to the modest but clinically meaningful weight reduction observed during therapy.

The gut-liver axis represents another important pathway influenced by metformin. NAFLD is strongly associated with dysbiosis, endotoxemia, and chronic inflammation [44]. Recent investigations suggest that microbiota-mediated improvements in intestinal barrier integrity may reduce hepatic exposure to inflammatory mediators and bacterial products [45].

Studies conducted between 2022 and 2026 have consistently demonstrated improvements in hepatic steatosis, liver enzyme levels, and inflammatory markers following metformin treatment [71,72]. These findings support the role of microbiota modulation as a potential therapeutic strategy for NAFLD and metabolic-associated liver disease.

Cardiovascular protection remains one of the most clinically important benefits associated with metformin therapy. The microbiota contributes to cardiovascular risk through production of metabolites such as trimethylamine-N-oxide (TMAO), regulation of cholesterol metabolism, and modulation of vascular inflammation [46].

Recent evidence suggests that metformin alters microbial populations involved in TMAO production, thereby reducing atherosclerotic risk [73]. Furthermore, reductions in inflammatory mediators and oxidative stress may contribute to improved endothelial function and vascular health [47,73].

The gut-brain axis has emerged as an exciting area of microbiome research. Bidirectional communication between the gut and central nervous system occurs through neural, endocrine, metabolic, and immune pathways [48]. Dysbiosis has been implicated in neurodegenerative disorders including Alzheimer's disease and Parkinson's disease.

Recent studies indicate that metformin-induced microbiota remodeling may reduce neuroinflammation and promote neuronal health [49,74]. SCFAs have been shown to regulate microglial activity, improve blood-brain barrier integrity, and reduce oxidative stress within the central nervous system [74]. These observations suggest that metformin may possess previously underappreciated neuroprotective properties.

Emerging evidence has also highlighted potential anticancer effects of the metformin–microbiota axis. Chronic inflammation, dysbiosis, and metabolic dysfunction contribute significantly to carcinogenesis [50,51]. Metformin has demonstrated protective effects against several malignancies, including colorectal, breast, pancreatic, liver, and prostate cancers [75].

Recent studies suggest that microbiota-mediated reductions in inflammation and improvements in immune regulation may partly explain these observations [76]. Furthermore, alterations in microbial metabolites may influence tumor growth, immune surveillance, and responsiveness to anticancer therapies.

Despite these promising findings, several limitations remain. Many studies are observational in nature and cannot establish causality. Differences in sequencing methodologies, study populations, dietary habits, geographic locations, and analytical approaches contribute to variability across investigations [57,77]. Additionally, the precise microbial species responsible for specific therapeutic effects have not yet been fully identified.

Future research should focus on longitudinal multicenter studies integrating metagenomics, metabolomics, transcriptomics, and clinical outcomes. Such investigations will facilitate identification of microbial biomarkers predictive of treatment response and support development of microbiota-targeted precision medicine approaches [54,58].
Overall, the evidence reviewed herein strongly suggests that the gut microbiota is not merely a passive recipient of metformin exposure but rather an active participant in mediating therapeutic responses. The metformin–gut microbiota axis represents one of the most important advances in understanding the pharmacology of this widely used drug and offers exciting opportunities for future therapeutic innovation.

CONCLUSION

Metformin continues to be the cornerstone of pharmacological management for type 2 diabetes mellitus; however, contemporary research has fundamentally transformed our understanding of its mechanisms of action. Evidence accumulated over the past two decades clearly demonstrates that the gut microbiota serves as a critical mediator of metformin therapy. Through selective modulation of microbial composition and function, metformin promotes enrichment of beneficial bacteria, enhances production of short-chain fatty acids, strengthens intestinal barrier integrity, regulates bile acid metabolism, and suppresses chronic systemic inflammation.

These microbiota-mediated mechanisms contribute substantially to improvements in insulin sensitivity, glycemic control, metabolic homeostasis, and cardiovascular protection. Beyond diabetes management, emerging evidence suggests therapeutic benefits in obesity, metabolic syndrome, non-alcoholic fatty liver disease, neurodegenerative disorders, cardiovascular diseases, and cancer.

The expanding field of pharmacomicrobiomics highlights the potential for individualized treatment strategies based on microbial profiling. Future integration of microbiome science with precision medicine may enable clinicians to predict therapeutic response, optimize drug efficacy, minimize adverse effects, and develop microbiota-targeted interventions.

In conclusion, the metformin–gut microbiota axis represents a paradigm shift in modern metabolic medicine. Continued research into host–microbe–drug interactions is likely to generate novel therapeutic approaches that improve outcomes for patients with metabolic and inflammatory diseases worldwide.

LIMITATIONS OF THE REVIEW

1. Most included studies were observational, limiting causal inference.
2. Considerable heterogeneity existed in study populations, methodologies, and microbiome analysis techniques.
3. Dietary habits, lifestyle factors, and geographic variations may have influenced gut microbiota composition.

4. Many mechanistic findings were derived from animal models and may not be directly applicable to humans.
5. Long-term prospective clinical studies evaluating microbiota-mediated effects of metformin remain limited.
6. Standardized protocols for microbiome assessment and interpretation are still lacking.
7. Further large-scale multicenter studies are required to validate current findings and establish clinical applications.

DECLARATIONS:

Conflicts of interest: There is no any conflict of interest associated with this study

Consent to participate: There is consent to participate.

Consent for publication: There is consent for the publication of this paper.

Authors' contributions: Author equally contributed the work.

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