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REVIEW

Gut Microbiota Targeted Approach by Natural Products in Diabetes Management: An Overview

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Abstract

Purpose of Review This review delves into the complex interplay between obesity-induced gut microbiota dysbiosis and the progression of type 2 diabetes mellitus (T2DM), highlighting the potential of natural products in mitigating these effects. By integrating recent epidemiological data, we aim to provide a nuanced understanding of how obesity exacerbates T2DM through gut flora alterations.

Recent Findings Advances in research have underscored the significance of bioactive ingredients in natural foods, capable of restoring gut microbiota balance, thus offering a promising approach to manage diabetes in the context of obesity. These findings build upon the traditional use of medicinal plants in diabetes treatment, suggesting a deeper exploration of their mechanisms of action.

Summary This comprehensive manuscript underscores the critical role of targeting gut microbiota dysbiosis in obesity-related T2DM management and by bridging traditional knowledge with current scientific evidence; we highlighted the need for continued research into natural products as a complementary strategy for comprehensive diabetes care.

Keywords Bioactive compounds · Diabetes mellitus · Gut microbiota · Inflammation · Molecular mechanisms · Natural products

Introduction

Diabetes mellitus has emerged as one of the most pressing public health issues of the twenty-first century [1••]. According to global estimates, approximately 422 million adults were living with diabetes in 2019, and this number is projected to soar to 551.8 million by 2030 [2•]. The condition is not only accompanied by debilitating microvascular and macrovascular complications but also exerts an immense toll on healthcare systems globally

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[3]. Type 1 diabetes is characterized by autoimmune-mediated destruction of pancreatic β-cells, resulting in absolute insulin deficiency and necessitating lifelong insulin replacement. This pathophysiological process involves complex interactions between genetic predisposition, environmental triggers, and immune dysregulation, leading to the progressive loss of insulin-producing cells [4]. T2DM is driven by insulin resistance and β-cell dysfunction, with inflammation and oxidative stress playing key roles in exacerbating β-cell damage. Markers like C-reactive protein and tumor necrosis factor-alpha highlight the inflammatory aspect, while increased reactive oxygen species indicate oxidative stress, both contributing to the disease's progression [5]. Obesity is a critical epidemiological challenge closely linked with the incidence and progression of T2DM. Current data suggest a tripling in global obesity rates since 1975, making it a leading risk factor for T2DM due to its role in developing insulin resistance [6]. The interplay between obesity and T2DM is mediated through various mechanisms including, but not limited to, adipose tissue inflammation, the release of pro-inflammatory cytokines, and alterations in metabolic function [7]. These pathophysiological changes not only exacerbate insulin resistance but also impair pancreatic β-cell function, further complicating the glycemic control in obese individuals. Furthermore, obesity-induced changes in gut microbiota composition have been shown to influence metabolic pathways related to insulin sensitivity, adding another layer to the complex relationship between obesity and T2DM [7].

Recent advancements in microbiome research have significantly enhanced our understanding of gut microbiota's multifaceted role in human health and disease [8]. A balanced gut microbial ecosystem is fundamental for optimal nutrient absorption and plays an integral part in bolstering innate and adaptive immunity [9]. Furthermore, the gut microbiota is now known to modulate insulin sensitivity and glucose metabolism through several complex signaling pathways, making it a critical factor in metabolic health [10]. In a state of metabolic equilibrium, the gut microbiota aids in the fermentation of non-digestible carbohydrates, producing short-chain fatty acids (SCFAs) like butyrate, acetate, and propionate [11]. These SCFAs serve as energy substrates and modulate inflammatory responses, thus fostering an environment conducive to insulin sensitivity; however, disruptions in this ecosystem can lead to a decrease in the production of SCFAs, thereby impairing insulin signaling pathways and contributing to the development of insulin resistance—a hallmark of type 2 diabetes (T2D) [12, 13]. Emerging evidence indicates that dysbiosis, or imbalances in gut microbiota, has far-reaching implications in the pathogenesis of T2D [14]. Diets high in saturated fats and refined sugars, which are hallmarks of Western dietary patterns, disrupt the microbial equilibrium; this leads to increased gut permeability, thereby enabling endotoxins like lipopolysaccharides (LPS) to enter systemic circulation and initiate inflammatory cascades. Chronic low-grade inflammation is a key factor in insulin resistance and ultimately contributes to the beta-cell dysfunction observed in T2D [15, 16]. The limitations of current pharmacological therapies for T2D, including their financial burden and potential side effects, have invigorated interest in alternative treatment modalities; numerous natural products have demonstrated promise in modulating gut microbiota composition, thereby exerting favorable metabolic effects [17–19]. Particularly intriguing are phytochemicals such as polyphenols, alkaloids, and terpenes, which not only exert antioxidant and anti-inflammatory effects but also have been shown to selectively promote the growth of beneficial gut bacteria [20]. For instance, curcumin, a polyphenol derived from turmeric, has been shown to increase the abundance of butyrate-producing bacteria, thereby enhancing insulin sensitivity [21•]. Similarly, berberine, an alkaloid commonly used in traditional medicine, has been proven to alter gut microbiota in a way that reduces intestinal inflammation and improves glucose metabolism [22, 23].

This review synthesizes the latest findings from both pre-clinical and clinical studies to provide a comprehensive overview of how natural products can be strategically used to manipulate gut microbiota for diabetes management; it delves into the mechanistic interactions between natural products and gut microbiota, offering insights into their potential anti-diabetic effects and clinical applications. By focusing on the intricate relationship between natural bioactive compounds and gut microbiota modulation, this comprehensive review fills a critical gap in the literature, paving the way for innovative dietary interventions in diabetes care.

Review Methodology

We conducted a literature search across specialized databases including PubMed/MEDline, Google Scholar, Scopus, Science Direct, and TRIP ((Turning Research Into Practice) database, employing MeSH terms relevant to diabetes mellitus, dysbiosis, gut microbiota, and natural product interventions. The selection of natural products for inclusion was guided by a thorough review of existing literature, emphasizing compounds with established anti-diabetic properties and their impact on gut microbiota. This encompassed phytochemicals such as polyphenols, alkaloids, and terpenes, recognized for their antioxidant and anti-inflammatory effects, and their ability to modulate gut flora. The selection process considered the frequency of these compounds in scientific research, the strength and consistency of evidence supporting their therapeutic benefits, and their relevance to both current and prospective clinical applications. This strategic approach aimed to provide a comprehensive overview of the most promising natural products for diabetes management through gut microbiota modulation, bridging the gap between traditional medicinal practices and contemporary scientific research. The review covered both preclinical and clinical studies to identify key molecular pathways in type 2 diabetes, focusing on vivo investigations, with tables and figures summarizing significant data. Plant species taxonomy was verified according to World Flora Online [24].

Gut Microbiota and T2DM: A Mutual Physiopathological Interplay

The gut microbiota, a complex ecosystem primarily composed of obligate anaerobes such as *Firmicutes* and *Bacteroidetes*, plays an essential role in metabolic homeostasis [25]; this bacterial community reaches maturity by the age of 3 and serves as a metabolic "organ," converting undigested food into bioactive short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate; these SCFAs are not just metabolic end-products; they are potent signaling molecules with a range of effects, from serving as an energy substrate for colonic epithelial cells to modulating immune responses via anti-inflammatory pathways [25, 26]. These SCFAs serve multiple roles in the context of diabetes management, particularly in T2DM patients: (i) energy substrate for colonic cells, especially butyrate, is a primary energy source for colonic epithelial cells, supporting the integrity and function of the gut barrier [27]; (ii) butyrate and propionate have been shown to influence the secretion of incretin hormones like glucagon-like peptide-1 (GLP-1) which enhances insulin sensitivity and secretion, playing a significant role in the regulation of glucose homeostasis.

In vitro studies have demonstrated that SCFAs can directly modulate the differentiation and function of adipocytes, influencing lipid metabolism and insulin sensitivity [28]. Propionate has been shown to influence lipid metabolism significantly. It is produced during carbohydrate metabolism and has been implicated in various health-promoting effects, such as inhibiting adipogenesis in hepatocytes and reducing fat deposition in vitro [29]. SCFAs interact with G-protein-coupled receptors (GPCRs), such as GPR41 and GPR43, which are important for mediating their effects on energy homeostasis and metabolic health. These receptors are involved in various physiological processes, and their activation by SCFAs has been linked to beneficial metabolic outcomes, including the regulation of immune and inflammatory responses, as well as the maintenance of intestinal homeostasis [29].

Animal models have provided evidence that dietary supplementation with SCFAs or SCFA-producing prebiotics can improve insulin sensitivity, reduce weight gain, and lower inflammatory markers. Butyrate, for instance, has been demonstrated to improve insulin sensitivity and increase energy expenditure in mice, suggesting a potential protective role against diet-induced obesity. This effect is thought to be mediated through mechanisms that are independent of the free fatty acid receptor 3, highlighting the diverse pathways through which SCFAs can influence metabolic health [28]. One study explored the impact of SCFA supplementation on gut inflammation and microbiota composition in a murine colitis model [30]. Although this study did not directly investigate diabetes, it highlighted SCFAs' role in modulating immune responses and gut microbiota, which are relevant to metabolic health. The supplementation with sodium butyrate or a mixture of SCFAs did not significantly change weight or inflammation but did alter T cell differentiation and increased both protective and aggressive gut microbiota [30]. A comprehensive study discussed the effects of SCFAs, such as acetate, propionate, and butyrate, on energy homeostasis and metabolism [31]. It highlighted how SCFAs can positively modulate adipose tissue, skeletal muscle, and liver function, contributing to improved glucose homeostasis and insulin sensitivity. This review underscores the potential of SCFAs as metabolic targets to prevent and counteract obesity and related disorders in glucose metabolism and insulin resistance [31]. A study on high-fat-diet-induced obesity in mice showed that dietary supplementation of SCFAs significantly inhibited body weight gain induced by a high-fat diet. This effect was associated with changes in the expression of G-protein coupled receptors GPR43 and GPR41 in adipose tissue, suggesting a mechanism through which SCFAs can exert their metabolic effects. Additionally, SCFAs were found to alter the gut microbiota composition, further indicating their role in regulating metabolism and inflammation [32]. Clinical studies have investigated the effects of dietary fiber, which is a major source of SCFAs through microbial fermentation in the colon, and these studies have shown beneficial effects on glycemic control, insulin sensitivity, and inflammatory markers in T2DM patients [33]. Interventional studies using direct SCFA supplementation have been more limited, but some evidence suggests potential benefits in improving metabolic health and insulin sensitivity in humans [34].

It is important to highlight that the gut microbiota is not a static entity; it is sensitive to a variety of external factors, including diet, stress, and medication; a disequilibrium in gut microbial composition, often reflected as a disrupted *Firmicutes* to *Bacteroidetes* ratio, can result in "metabolic endotoxemia," marked by elevated systemic levels of lipopolysaccharides (LPS), and this condition can trigger inflammatory cascades involving cytokines such as tumor necrosis factor-alpha (TNFα) and interferon-gamma (IFN-γ) which are implicated in the development of insulin resistance, a key characteristic of T2DM. Polyphenols, natural compounds found in a range of plant foods, have been investigated for their potential to restore healthy gut microbiota [35]. However, their physiopathological relevance extends beyond simple microbial modulation; polyphenols are poorly absorbed in the upper gastrointestinal tract, allowing them to reach high concentrations in the colon where they are metabolized by the microbiota into bioactive metabolites and SCFAs; these SCFAs not only reduce inflammation but also influence incretin hormone secretion, such as GLP-1, which has been shown to enhance insulin sensitivity [36]. Metformin, a frontline anti-diabetic drug, exerts some of its effects by altering the gut microbiota, favoring a shift towards beneficial bacterial species; this action exemplifies the evolving understanding of how medications for T2DM may exert their therapeutic effects, at least partially, by modulating gut microbial composition and function [37].

Effects of Bioactive Compounds and Plant Extracts on the Gut Microbiota in Management of T2DM: Molecular Mechanisms

The modulation and targeting of the intestinal microbiota in the treatment of T2DM is a relatively new concept of primary scientific interest propelling research in this field not only in the prevention and control of diabetes and obesity but also of other pathologies [38, 39]. The makeup and functions of the gut flora are significantly influenced by our diets and the use of drugs [40]. Plant-based bioactive compounds used therapeutically may substantially impact the gut microbial composition. This updated review includes preclinical studies that examine the effects of various plant extracts and bioactive compounds on gut microbial composition and their potential anti-diabetic properties (Fig. 1 and Table 1). This section discusses specific examples of plants, extracts of which have demonstrated beneficial effects on diabetes while also modulating the gut microbiota. The examples were chosen based on the high frequency with which they have been reported in the literature, e.g., the strength and consistency of the evidence supporting their therapeutic benefits and their relevance in ongoing or future clinical studies.

Rhodiola rosea L.

In recent studies, *Rhodiola rosea* has gained attention for its potential effects on diabetes, specifically its interaction with the gut microbiome. Salidroside, one of its bioactive molecules, has been shown to significantly impact glucose and insulin tolerance in obese mice. The compound aids in preventing hyperglycemia and enhances insulin signaling. Furthermore, it was observed to inhibit the production of pro-inflammatory cytokines in the gut, thereby hinting at a direct influence on the gut microbiota [42]. In another in vivo study, salidroside improved the activity of the oxidative defense enzymes superoxide dismutase (SOD), catalase, and glutathione peroxidase when given to streptozotocin (STZ)-induced diabetic mice for 8 weeks. It also decreased blood glucose, urea nitrogen, serum insulin, and creatinine. Salidroside's significant anti-inflammatory and antioxidant properties result from its interference with the TGF-1/Smad2/3 pathway [43]. Jafari et al. reported that *R. rosea* treatment improved fasting blood glucose, modified exogenous insulin, and reduced lipopolysaccharides and hepatic C-reactive protein transcripts; furthermore, we found that the reported changes were due to alterations in the gut microbiota [42]. This is because it also improved the integrity of the intestinal barrier and reduced the translocation of inflammatory biomolecules into the bloodstream. The root extract of *Rhodiola rosea* modestly modulates gut microbiota in a db/db mice model of type 2 diabetes (leptin receptor deletion); it also enhances insulin responsiveness. This study is one of the few to assess the impact of a plant extract on the gut microbiota as type 2 diabetes develops. For 4 weeks, oral gavage with water was administered to leptin receptor-knockout (db/db) mice, whereas *R. rosea* extract was given daily to the db/db mice in the control group. After 4 weeks, hyperglycemia was present in both mice treated with *R. rosea* and untreated db/db mice. *R. rosea* extracts were given to mice via oral gavage, and fasting glucose levels decreased 2 h after the injection. Contrarily, after 30 min, control db/db mice lose their sensitivity to insulin. In diabetic db/db mice, *R. rosea* therapy enhances glucose homeostasis. In feces samples taken from db/db mice before and after treatment with the extract, the gut microbial population was examined using 16S rRNA amplicon next-generation sequencing. The makeup of the gut microbiota was highly heterogeneous, with *Bacteroidetes* and *Firmicutes* dominating in particular, as revealed by *R. rosea* extract [42]. A recent study using *R. rosea* in treating D2TM has shown its anti-inflammatory property to treat diabetic nephropathy and retinopathy and its inhibitory effect on islet B-cell apoptosis, suggesting *R. rosea* as a potential and striking candidate for future research on T2DM management [42].

***Mesembryanthemum crystallinum* (Ice Plant) (MC)**

Extracts of *Mesembryanthemum crystallinum* (commonly known as ice plant), have been shown to exhibit anti-diabetic effects; one of its active constituents D-pinitol, a cyclitol contributes substantially to its anti-diabetic properties because this bioactive compound has been found to regulate

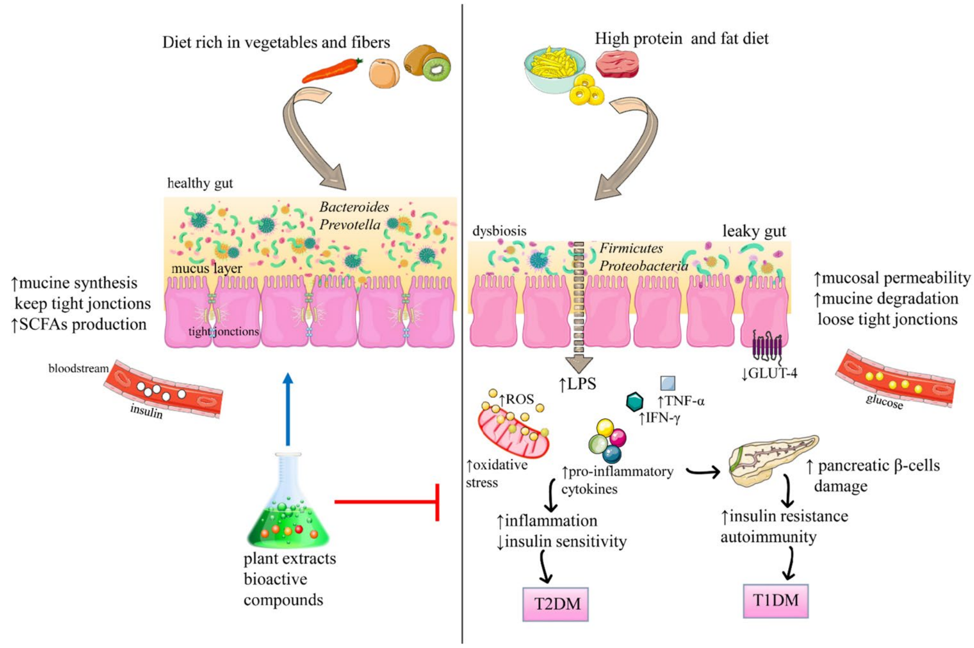

Fig. 1 Dietary impact on gut microbiota and metabolic health. The figure delineates the interplay between diet, gut health, and metabolic outcomes: on one hand, a vegetable and fiber-rich diet promotes a thriving gut, characterized by beneficial bacteria like Bacteroides and Prevotella. This fosters increased mucin production, tight gut junctions, and elevated short-chain fatty acid (SCFA) generation; on the contrary, diets high in protein and fats lead to gut dysbiosis, marked by dominant *Firmicutes* and Proteobacteria. Such imbalance results in a "leaky gut," reduced GLUT-4 (a glucose transporter) expression, and systemic release of inflammatory agents like lipopolysaccharides (LPS). As oxidative stress surges, pro-inflammatory cytokines, notably tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ), get activated; this cascade culminates in reduced insulin sensitivity, paving the way for type 2 diabetes mellitus (T2DM) and even triggering mechanisms of type 1 diabetes mellitus (T1DM). Amidst these pathways, the figure hints at the potential of plant-derived bioactive compounds as a counteracting force against these adverse metabolic shifts. Abbreviations and symbols: SCFA short-chain fatty acid, GLUT-4 glucose transporter type 4, LPS lipopolysaccharides, TNF-α tumor necrosis factor-alpha, IFN-γ interferon-gamma, T2DM type 2 diabetes mellitus, T1DM type 1 diabetes mellitus; ↑, increase; ↓, decrease. (Created with Microsoft PowerPoint using free elements from Freepik [41])

insulin levels, thus potentially offering a complementary treatment option for diabetes [44]. The extract from the ice plant, *Mesembryanthemum crystallinum*, notably rich in d-pinitol, has been recognized for its potential anti-diabetic properties; advanced techniques ensured optimal extraction of d-pinitol from the plant. When tested on type 2 diabetic Goto-Kakizaki rats, this optimized extract showcased a notable ability to regulate blood glucose levels, reducing fasting glucose by 45% and enhancing glucose tolerance. Not only did the extract foster healthier pancreatic structures, promoting the longevity of β-cells and augmenting insulin secretion, but it also displayed prebiotic qualities. There was a marked rise in beneficial gut bacteria like *Bacteroidales S24-7* and *Ruminococcaceae UCG-014*, with a simultaneous decline in potentially less favorable strains such as *Treponema 2* and *Lactobacillus.* Such improvements in both glucose regulation and gut health point to the ice plant extract's potential role as a functional food ingredient that may aid in warding off diabetes [45]. Treatment with D-pinitol in STZ-induced T2DM reduced blood glucose without increasing circulating insulin concentrations [46]. Future studies should aim to examine the impact of MC extract and D-pinitol on the gut microbiota, given its recognized role in metabolic health.

Cinnamon

Cinnamon is widely researched for its antioxidative and anti-inflammatory properties, which have been shown to safeguard pancreatic islet β-cells against oxidative stress and inflammation-induced damage [47]. Recent in vivo studies have suggested a symbiotic role between cinnamon and gut microbiota in managing diabetes [48].

A recent study involving cinnamon on C57BL/6 J mice on a high-fat diet indicated reductions in weight gain, enhanced glucose tolerance, and diminished insulin resistance [51, 93], these benefits were coupled with modifications in the gut microbiota, specifically reductions in *Desulfovibrio* and *Lactococcus* and an increase in *Allobaculum* and *Roseburia* species. While these alterations in the microbiota composition appear promising, it is crucial to clarify that these outcomes do not definitively establish a causal relationship. Enhanced blood glucose control might either be a consequence of

Table 1 Effects of plant extracts and some constituent compounds on in vivo experimental diabetes and the gut microbiome

Bioactive compound/sources	Experimental model	Results		Ref
		Effects on diabetes	Effects on gut microbiota	
Salidroside *Rhodiola rosea* L	In vivo obese mice	↑Insulin tolerance ↓Hyperglycemia ↓Pro-inflammatory cytokines ↓Adipogenesis	↑Integrity of the intestinal barrier	[91] [92]
	In vivo STZ-induced diabetic mice	↓Blood glucose ↓Urea, ↓insulin,↓ creatinine ↓TGF-1/Smad2/3		[43]
Rhodiola root extract	In vivo leptin receptor knockout (db/db) diabetic mice	↓Fasting blood glucose ↓Insulin ↓Reduced lipopolysaccharides ↓Hepatic C-reactive protein transcripts	Modestly modulates the gut microbiota ↑*Bacteroidetes* ↑*Firmicutes* ↓Translocation of inflammatory biomolecules into the bloodstream	[42]
D-pinitol, *Mesembryanthemum crystallinum* (ice plant)	In vivo type 2 diabetic Goto-Kakizaki rats	↓Glucose tolerance ↓Blood sugar ↑Insulin secretion ↑Translocation of glucose transporter 4	↑*Bacteroides S24-7* ↑*Ruminococcaceae* ↑*UCG-014* ↑*Lactobacillus*	[45]
Cinnamon with apple pomace extracts	In vivo C57BL/6 J mice	↓Weight gain ↑Glucose tolerance ↓Insulin resistance	↓*Desulfovibrio* ↓*Lactococcus* ↑*Allobaculum* ↑*Roseburia*	[93]
Cinnamaldehyde	In vivo diabetic mice	↑Leptin, ↑TNF-α, ↑NO ↓SOD, ↓GSH ↑Pancreatic β-cell immunoreactivity	↓Gut barrier dysfunction ↑Remodelling of gut microbiota ↑*Lactobacillus johnsonii*	[94] [95]
	In vivo STZ-induced diabetic mice	↓Inflammatory response ↓Pro-inflammatory cytokines ↑NF-kB	↑Remodelling of the gut microbiota ↑Mucin in colonic epithelial tissues ↑Tight junction proteins: ↑ Muc2, ↑TFF3	[58]
	In vivo STZ-induced diabetic mice	↑AKT ↑E2F1 ↑mRNA insulin receptor substrate 1	↑*Akkermansia*, ↑*Clostridium* III, ↑*Psychrobacter*, ↑*Intestinimonas* ↓*Ruminococcus*, ↓*Escherichia*	[96]
Cinnamon and grape pomace extract	In vivo T2DM C57BL/6 J mice with high-fat diet	↓Adipose tissue inflammation ↓Poor glucose tolerance ↓Insulin resistance	↑Gut barrier function ↓*Peptococcus*, ↓*Desulfovibrio* ↓*Lactococcu*, ↑*Allobaculum*, ↑*Roseburia*	[93]
Polyphenols from grape pomace	In vivo broiler chicks	-	↑Function and structure of the gut microbiota ↑*Lactobacillus* ↑*Clostridium*, ↑*Enterococcus* *Streptococcus* spp., *Clostridium Cluster XIVa*	[97]

Table 1 (continued)

Bioactive compound/sources	Experimental model	Results		Ref
		Effects on diabetes	Effects on gut microbiota	
Polyphenols from grape pomace and grape seed extract	In vivo pigs	↑Gain-to-feed ratio ↓Gut pro-inflammatory cytokines ↓NF-kB	↑Remodelling of the gut microbiota ↓Inflammation of the pigs' gut	[98]
Olive and ginger extract	In vivo healthy rats STZ- induced diabetic rats	hypoglycemic effect ↑SCFAs, ↓appetite ↓Pancreatic β-cell damage	↑Gut bacterial diversity ↓Gut dysbiosis ↑*Firmicutes/Bacteroidetes*, ↑*Lactobacillus* ↑*Prevotella*, ↓*Clostridium*, ↓*Bacteroides*	[99]
6-Gingerol, *Zingiber officinale*	In vivo STZ-induced diabetic rats	↓Fasting blood glucose ↓Hyperlipidaemia, ↓MDA, ↓Pro-inflammatory markers, ↓NF-κB ↑Insulin secretion ↑Insulin exocytosis in pancreatic β-cells ↑Rab27a/Slp4	↑Gut barrier function	
	In vivo db/db T2DM mice	↑GLUT4, ↑GLP-1 ↑Glycogen synthase in skeletal muscles ↓Hyperglycemia ↑cAMP, ↑PKA ↑CREB in pancreatic β-cells ↑Rab27a GTPase, ↑Slp4	↑Gut barrier function	[100]
	In vivo STZ-induced diabetic rats	↓Pro-inflammatory cytokines: Il-1β, IL-6, TNF-α ↓Pro-inflammatory mediators: ↓COX-2, ↓PGE2, ↓NF-kB ↓p38MAPK, ↓TGF-β		[101]
Olive leaves and ginger rhizome aqueous extract	In vivo diabetic and healthy rats	Preventive effect	↑Gut bacterial population ↑*Firmicutes/Bacteroides* ratio ↑*Lactobacillus*, ↑*Prevotella*	[99]
Syringaresinol-di-O-D-glucoside, *Polygonatum sibiricum*	In vivo STZ-induced diabetic rats	Anti-diabetic effects ↓Oxidative stress, ↓ROS ↑Insulin sensitivity ↓Lipid metabolism	↑Gut barrier function	[102]
Saponins, *Polygonatum sibiricum*	In vivo T2DM mice	↓Metabolic profile	↑*Bacteroidetes*, ↓*Firmicutes* ↑*Lactobacillus*, ↓*Lachnospiraceae NK4A136* ↓*Intestinimonas*	[63]
Polygonatum sibiricum (rhizome herb) extracts	In vivo T2DM mice	↓Fasting blood glucose ↓Insulin release	↑*Intestinimonas*, ↑*Lactobacillus* ↑*Lachnospiraceae NK4A136* ↑*Bacteroidetes*	[63]
Gongronema latifolium leaf extracts	In vivo Wistar rats alloxan-induced diabetes	↓Blood glucose ↓Il-2, IL-6, ↓ROS, ↓COX-2 ↑Antioxidant enzymes: ↑CAT ↑SOD, ↑GPx	Modulate gut microbial population ↑*Lactobacillus (L.) johnsonii* ↑*L. reuteri* ↑*Prevotella copri*	[103] [67]

Table 1 (continued)

Bioactive compound/sources	Experimental model	Results		Ref
		Effects on diabetes	Effects on gut microbiota	
Mung bean	In vivo T2DM C57BL/6 mice	Prevented diabetes-induced inflammatory responses ↓ALT, ↓AST, ↓fasting blood glucose ↓Insulin resistance ↓IL-6, ↓IL-10, ↓TNF-α ↓C-reactive protein	↓Gut microbiota imbalance ↓*Firmicutes*, ↓*Bacteroidetes* ↓*Proteobacteria*	[104]
	In vivo prediabetic mice	↓Hyperglycemia, ↓insulin resistance, ↓inflammation ↓Oxidative stress	↓*Firmicutes*, ↓*Bacteroidetes* ↓*Ruminiclostridium 9*, ↓*Intestinimonas* ↑*Lactobacillus*, ↑*Lachnospiraceae* NK4A136 ↑*Akkermansia*	[69]
Whole mung bean (WMB), decorticated mung bean (DMB)	In vivo rats fed with a high-fat diet STZ-induced diabetic rats	↑Control of blood glucose	↓*Staphylococcus*, ↓*Enterococcus* ↑*Bifidobacterium*, ↑ *Akkermansia*	[69]
Anthocyanins, Pg3G, raspberry	In vivo db/db diabetic mice	↓Blood sugar ↑Autophagy ↑Glucose uptake in cells	↑The integrity of the gut barrier ↑Regulating gut microbiota ↑*Prevotella* ↑*Bacteroidetes*/*Firmicutes* ratio	[72]
Astragaloside IV *Astragalus mongholicus* Bunge	In vivo T2DM diabetic mice	Hypoglycemic effect ↓Oxidative stress ↓Blood glucose ↓Insulin resistance	↓*Lactococcus*, ↓*Enterococcus*, ↓*Lactobacillus* ↓*Candidatus-Arthromitus*, ↓*Alistipes* ↓*Odoribacter*, ↓*Rikenella* ↑*Bacteroidetes*, *Firmicutes* ↑*Parabacteroides*, ↑*Roseburia*	[78]
Grape polyphenol	In vivo animal and human study	↓Reduce blood pressure ↑Lipid profile ↓Uric acid levels	↓*Bacteroidetes/Firmicutes ratio* ↑*Akkermansia muciniphila* ↑*Bifidobacteria* ↑*Lactobacillus* ↑*Bacteroides*	[105]
Cranberry polyphenols extract	In vivo animal and human study	↓Insulin resistance ↑Glucose homeostasis, ↑Metabolic health during weight loss	↑*Akkermansia* ↑*Parvibacter* ↑*Barnesiella*	[106]
Resveratrol and quercetin polyphenols	In vivo male Wistar rats	↑High-density lipoprotein, ↑Adiponectin ↓Body weight ↓Low-density lipoprotein, ↓Triglycerides ↓Insulin	↑*Bacteroidales_S24-7 group*, ↑*Christensenellaceae* ↑*Akkermansia* ↑*Ruminococcaceae* ↓*Desulfovibrionaceae*, ↓*Acidaminococcaceae* ↓*Coriobacteriaceae* ↓*Bilophila*	[107]

Table 1 (continued)

Bioactive compound/sources	Experimental model	Results		Ref
		Effects on diabetes	Effects on gut microbiota	
Polyphenols from *Lessonia trabeculate*	In vivo male diabetic C57BL/6 J mice	↓Glucose ↓Cholesterol ↓Triglycerides ↓LDL ↓Insulin	↑*Odoribacter* ↑*Muribaculum* ↑*Alistipes*, *Parabacteroides* ↓*Firmicutes/Bacteroidetes*	[108]
Human clinical studies				
Polyphenols from *Schisandra chinensis* juice	Clinical study 28 obese women BMI ≥ 25	↓Fat mass ↓Triglycerides ↓Glucose	↑*Akkermansia* ↑*Roseburia* ↑*Bacteroides* ↑*Prevotella* ↑*Bifidobacterium* ↓*Ruminococcus*	[109]
Polyphenols from coffee, dark chocolate, polyphenol-rich vegetables	Clinical study 20 men/women with high waist circumference and one component of MetS	↑Glucose tolerance	↑*Clostridium leptum* ↓*Eubacterium rectale* ↓*Blautia coccoides*	[110]

↑Increase, ↓Decrease

ALT alanine aminotransferase, *AST* aspartate transaminase, *IL-6* interleukin-6, *E2F1* insulin-like growth factor 1 receptor, *SCFAs* short-chain fatty acids, *p38 MAPK* ↓P38 mitogen-activated protein kinase, *HepG2* human hepatocyte carcinoma cell line, *Pg3G* pelargonidin-3-O-glucoside, *AS-IV* astragaloside IV, *TNF-α* tumor necrosis factor-α, *CAT* catalase, *SOD* superoxide dismutase, *GPx* glutathione peroxidase improved gut health or an independent factor affecting it, or the two may not be causally related at all. The anti-diabetic efficacy of cinnamon also extends to its essential oil, cinnamaldehyde, which has been found to augment levels of leptin, TNF-α, and NO in STZ-induced diabetic mice [49]. Regarding the increased β-cell immunoreactivity observed with essential oils from cinnamon leaves, the immunoreactivity, meaning that essential oils from cinnamon leaves improve the functional responsiveness of β-cells, not their propensity for an immune response, could, paradoxically, predispose towards diabetes [50]. Other bioactive components in cinnamon, such as non-polar sesquiterpenoids, have exhibited anti-inflammatory and renoprotective qualities. These constituents suppress markers of inflammation and fibrosis, further underscoring the compound's multifaceted roles in diabetes management [51].

Grape Pomace (GP)

Several studies have indicated the anti-diabetic potential of grape polyphenols, emphasizing the role of grape pomace (GP) in glucose regulation. For instance, a recent investigation has reported significant reductions in fasting blood sugar levels following GP supplementation in healthy women [52]. Beyond its anti-diabetic effects, GP also shows promise in modulating gut microbiota. In an in vivo study involving broiler chicks, supplementation with GP products led to a more diverse gut bacterial profile, including higher populations of *Lactobacillus*, *Clostridium*, and *Enterococcus* species [52]. In a pig model, GP dietary supplements rich in polyphenols led to decreased levels of pro-inflammatory cytokines in the intestine, implicating a downregulation of the NF-kB pathway and a reduction in gut inflammation [49]. Although GP appears to have distinct anti-diabetic and gut microbiota-modulating properties, the causal relationship between these effects remains unclear. For example, while GP supplementation led to reduced fasting blood sugar in healthy women, the same study did not report any significant changes in gut microbiota [52]. Therefore, it is essential to consider that the anti-diabetic and microbiota-modulating effects may be independent of each other, warranting further research to uncover the underlying mechanisms.

Olive in Diabetes and Gut Microbiota Management

In STZ-diabetes-induced rat models, olive extract showed promising results in enhancing bacterial diversity [53]. Notably, the extract balanced the *Firmicutes*/*Bacteroidetes* ratio and increased the prevalence of beneficial bacteria such as *Lactobacillus* and *Prevotella*. Additionally, it reduced *Clostridium* and *Bacteroides* diversity. These findings suggest that olive extract may offer beneficial effects in diabetes management through modulation of gut microbiota, increased production of SCFAs, and protection against pancreatic cell damage [54].

Olive oil is renowned for its cardiovascular benefits, which are largely attributed to its phenolic compounds (OOPCs) [55, 56]. These compounds have been shown to influence gut microbiota composition, potentially offering therapeutic avenues for T2DM management. Consumption of olive oil phenolic compounds has been associated with an increase in *Bacteroidetes* and a decrease in the *Firmicutes*/*Bacteroidetes* ratio, a microbial balance linked to atheroprotection and metabolic health [57]. Furthermore, OOPCs have been found to promote the growth of certain beneficial bacteria, enhancing gut bacteria diversity, which is crucial for lipid-immune disorders and obesity management [55, 57]. Mechanistically, the interaction between OOPCs and gut microbiota involves antimicrobial activity, modulation of cholesterol metabolism by gut microbes, and the production of beneficial metabolites [55]. Importantly, OOPCs influence the production of short-chain fatty acids (SCFAs) by gut microbiota, impacting cholesterol metabolism and immune response and potentially aiding in weight management through satiety regulation [55].

Ginger in Diabetes and Gut Microbiota Management

Ginger's active component, 6-gingerol, has demonstrated significant effects on fasting blood glucose levels, lipid parameters, and pro-inflammatory markers in STZ-diabetic rats [58]. Additionally, 6-gingerol improves GLUT4 membrane presentation, positively affecting glucose uptake in skeletal muscles [59]. These studies indicate that ginger can have a role in diabetes management through multiple mechanisms, including anti-inflammatory and antioxidant activities, and could also potentially affect gut microbiota.

Polygonatum sibiricum (PS)

Polygonatum sibiricum (PS) has been shown to have diverse therapeutic effects in diabetes management. Its influence ranges from antioxidant and anti-inflammatory activity to direct hypoglycemic effects and modulation of gut microbiota [60]. PS extract exhibits potent antioxidant activity, evidenced by its ability to scavenge free radicals and protect against lipid peroxidation. This ultimately leads to the restoration of insulin function in diabetic rats. Furthermore, it increases antioxidant enzymes such as SOD and catalase, which mitigates oxidative stress [61]. PS rhizome possesses anti-inflammatory properties. It achieves this through modulation of NGAL expression, KIM-1, and blocking the p38 MAPK/ATF2 pathway, thus reducing cytokine release in the kidneys [62]. The bioactive compounds in PS, including phenolics, flavonoids, and saponins, have been shown to effectively lower blood sugar and lipid levels. Notably, PS flavonoids exhibited hypoglycemic effects comparable to acarbose and gliclazide in T1DM and T2DM rats, respectively [63]. Recent studies highlight PS's ability to modulate gut microbiota in T2DM mice. Saponins from PS increased beneficial bacterial taxa like *Bacteroidetes* while decreasing *Firmicutes* and other bacteria, contributing to better metabolic profiles in diabetic mice [63]. Studies have indicated that PG influences several molecular pathways, including the mitogen-activated protein kinase (MAPK), AMP-activated protein kinase (AMPK), and the Wnt/β-catenin signaling pathway, which plays a crucial role in cell-to-cell communication and tissue regeneration [63].

Gongronema latifolium

Gongronema latifolium (GL) leaf extracts have been shown to effectively combat oxidative stress by enhancing the activities of antioxidant enzymes such as catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx). Furthermore, these extracts help in reducing glucose levels and markers of inflammation, including nitric oxide (NO), malondialdehyde (MDA), and cyclooxygenase-2 (COX-2) in diabetic rats [64]. In a dose-dependent manner, the extract has also been observed to decrease blood glucose levels and inflammatory markers like IL-6 and C-reactive protein [65]. The GL leaf extract enhances insulin sensitivity by possibly increasing insulin receptors and helps regenerate damaged pancreatic β-cells in diabetic rats (Adiga et al., 2010). A study found that a 400 mg/Kg dose of GL extract significantly increased beneficial gut bacteria like *Lactobacillus johnsonii*, *L. reuteri*, and *Prevotella copri*, which are critical for glucose metabolism [66]. Similar results were obtained with *Gongronema latifolium*, diabetic rats treated with different concentrations (200, 400, and 800 mg/Kg body weight) of *G. latifolium* extract. The best result was observed with plant extract at the dose of 400 mg/Kg dose, which resulted in a significant increase in gut microbial population which includes the following bacterial species, i.e., *Lactobacillus (L.) johnsonii*, *L. reuteri*, and *Prevotella copri*; these species play an essential role in glucose metabolism [67].

Mung Bean

In T2DM C57BL/6 mice, mung bean polyphenolic extract showed significant effects on various metabolic parameters; the extract led to decreased blood alanine aminotransferase (ALT) and aspartate transaminase (AST) activities, improved fasting blood glucose levels, and reduced insulin resistance [68]. In terms of inflammation, IL-6 levels, TNF-α, and C-reactive protein were reduced, while IL-10 levels increased, thus attenuating diabetes-induced inflammatory responses. Moreover, sprouted mung bean polyphenol extracts were observed to restore gut microbiota balance in diabetic mice. Specifically, the extract increased the population of beneficial *Bacteroidetes* and Proteobacteria, while reducing the proportion of *Firmicutes*, thus enhancing microbial biodiversity [68]. The authors highlighted the role of modulating intestinal microbiota and inflammation in mitigating T2DM complications. Another recent study [69] showed that administration of mung bean polyphenol supplements for 5 weeks to prediabetic mice reduced hyperglycemia, insulin resistance, inflammation, and oxidative stress. In addition, in prediabetic mice, MBPs reduced the abundance of *Firmicutes* and *Bacteroidetes*, increased the diversity of the gut microbiota, and improved the disparity of the gut microbiota. Along with lowering dangerous bacteria like *Ruminiclostridium 9* and *Intestinimonas*, MBPs also promote the growth of beneficial bacteria like *Lactobacillus* and *Lachnospiraceae NK4A136* associated with prediabetes. Specifically, the helpful bacteria *Lachnospiraceae NK4A136* and *Akkermansia* prevent obesity and prediabetes. In rats fed with a high-fat diet (HFD) and rats that had diabetes induced with STZ, [70] investigated the modulatory effects of whole mung bean (WMB) and decorticated mung bean (DMB) on the control of blood glucose. Results showed that adding WMB and DMB to the diet reduced the number of harmful bacteria (*Staphylococcus* and *Enterococcus)*, increased the abundance of beneficial bacteria like *Bifidobacterium* and *Akkermansia*, and avoided gut microbiota dysbiosis caused by HFD and STZ [69].

Mung bean hull (MBS) polyphenol extracts have been studied in inflammation, diabetes, and digestive health. Mung bean seed husk extract (MSE) was examined for its anti-diabetic, gut microbiota modulation, and anti-inflammatory properties using an in vitro human gut model. Using fresh fecal samples from three healthy individuals and using 16S rRNA next-generation sequencing, it was determined how MSE polyphenols affected the composition of the gut microbiota. MSE alters the makeup of the gut microbiota (*E. coli* and *Shigella)* by encouraging the growth of beneficial bacterial species such as *Enterococcus*, *Ruminococcus*, *Blauti*, and *Bacteroidetes* while restraining the growth of disease-causing bacteria. According to the qPCR data, the quantities of the bacteria *Lactobacillus*, *Faecalibacterium prausnitzii*, *Bifidobacterium*, and *Prevotella* were also elevated. The anti-diabetic effects of ethanolic extract of MSE with concentrations of 100–400 g/mL were investigated in insulin-resistant HepG2 cells. MSE improved glucose absorption and decreased inflammatory markers such as interleukins 1, 6, 8, and TNF-α and decreased intracellular reactive oxygen species (ROS) in insulin-resistant HepG2 cells, demonstrating an anti-diabetic impact [71].

Raspberry

Several studies suggest that anthocyanins from a natural source help prevent chronic diseases, including T2DM. Anthocyanin, a naturally occurring phenolic chemical, is abundant in raspberries. A natural anthocyanin, pelargonidin-3-*O*-glucoside (Pg3G), was isolated and studied for its ability to lower blood sugar levels by promoting autophagy and regulating gut flora. It was shown that Pg3G enhances hepatocytes' ability to absorb glucose (when stimulated with high glucose and fat) and modifies gut microbiota by promoting the growth of helpful bacteria like *Prevotella* and *Bacteroidetes*. Anthocyanin, Pg3G, also increased autophagy and strengthened the integrity of the intestinal barrier in addition to these actions [72]. Postprandial hyperglycemia and other related metabolic abnormalities in diabetes have significantly improved due to the availability of dietary polyphenols and other bioactive substances in berries. Various animal studies have revealed that supplementing with raspberries reduced serum cytokines in T2DM mice [73]. The antioxidant enzymes catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) were all activated by raspberry, and SOD and GPx were boosted in a dose-dependent manner [74]. In mice susceptible to T2DM infection, adding raspberries to the standard diet decreased ROS and increased endogenous antioxidant GPx in erythrocytes and liver tissue [75]. Pelargonidin-3 O glucoside (P3G), produced from wild raspberries, increased glucose tolerance, insulin sensitivity, and autophagy activation [76]. *Prevotella* and the *Bacteroidetes/Firmicutes* ratio are two examples of beneficial microbes enriched in the gut, demonstrating how Pg3G alters gut microbiota composition and improves gut barrier integrity.

Astragalus mongholicus Bunge

Gut health, particularly the balance of beneficial bacteria, is becoming a focal point in diabetes treatment strategies, and recent studies showed that *Astragalus mongholicus* Bunge, a traditional source of Chinese medicine, exerts a hypoglycemic effect by modulating the gut microbial composition [77]. The bioactive compounds found in *Astragalus membranaceus polysaccharides* (AMP) exhibit a promising link with the management of type-II diabetes, with a significant focus on gut microbiota's role. A recent research emphasized AMP's dual role in both rectifying disrupted gut bacteria balance and offering anti-diabetic benefits. When db/db mice, a diabetic model, were treated with AMP, there was a marked improvement in their diabetes symptoms, accompanied by a rebalanced gut ecosystem and an uptick in fecal short-chain fatty acids (SCFA) production. Key insights were drawn on the increased presence of the bacteria *Akkermansia* and *Faecalibaculum*, which showed positive correlations with AMP's hypoglycemic actions and SCFA levels. Another breakthrough was the observation that AMP treatment boosted the levels of glucagon-like peptide-1 (GLP-1) in the bloodstream, a molecule pivotal for glucose regulation. This increase in SCFA, as a result of AMP intervention, potentially acts as a stimulus for GLP-1 secretion. Furthermore, AMP appeared to fortify intestinal health by upregulating receptors and proteins responsible for maintaining gut barriers. Collectively, this suggests AMP's potential in harnessing gut health to mitigate type-II diabetes symptoms. In diabetic mice, astragaloside IV (AS-IV), found in *Astragalus mongholicus* Bunge, was tested for its hypoglycemic effects and mechanisms of action. AS-IV dramatically lowered the levels of oxidative stress, blood glucose, and insulin resistance in T2DM mice. AS-IV boosted butyric acid levels and improved the diversity and richness of the intestinal flora in T2DM mice. In the T2DM model, AMPK/SIRT1 controls the anti-diabetic activity of the AS-IV and PI3K/AKT signaling pathways [78]. On C57BL/6 mice generated by STZ and fed a high-fat, high-sugar diet, in vivo tests of *Astragalus mongholicus* Bunge and *Panax notoginseng* (Burkill) were carried out; this combination boosted the expression of mTOR, Parkin, and Beclin while decreasing the expression of TNF-α, IL-1, and 6 in STZ-induced rats [79]. Another research suggests that plant bioactive chemicals may be employed as an alternative therapeutic source for the restoration of gut microbiota; they also indicate that regulating gut microorganisms may enhance the management of other metabolic illnesses [60, 80].

Role of Polyphenolic Compounds in the Effects of Plant Extracts in the Biological Effects of Plant Extracts in Treating Diabetes

The chemical compositions of plants high in phenols, alkaloids, flavonoids, terpenoids, coumarins, and glycosides have biological effects that typically have positive benefits [81]. The plant's pharmacologically active biocomponents' hypoglycemic action lessens the effects of amylase and numerous blood parameters that directly and indirectly impact the development of diabetes [81]. Among the numerous compounds occurring in plants phenolic/polyphenolic compounds and terpenoids feature prominently, such compounds have been reported to exert positive benefits in experimental diabetes [82]. There are also complex interactions between polyphenolic compounds and other plant constituents and the gut microbiome resulting in alteration in the microbial composition of the gut, as well as metabolism of the compounds by gut microorganisms to produce bioactive molecules [60, 83–85]. Polyphenols constitute a diverse group of compounds having one or more aromatic rings with attached hydroxy groups. The standard classification of polyphenols divides them into two major classes: flavonoids which comprise flavanols, flavanones, anthocyanins, flavonols, flavanones, and isoflavones; and non-flavonoids, i.e., xanthones, lignans, phenolic acids, stilbenes, and tannins [86]. Phenolic acids comprise a phenyl ring and a carboxylic group and are classified as benzoic acid derivatives (gallic and protocatechuic acids) and cinnamic acid derivatives (caffeic, ferulic, and p-coumaric acids). Flavonoids are widely present in plants and make up a diverse group of over 10,000 compounds; these bioactive compounds are water-soluble, have high molecular weight, and display a broad range of structural diversity [87]. Tannins are polyphenolic compounds that serve a defensive function in plants by providing protection against pathogens and herbivores; these compounds have the ability to precipitate proteins, including salivary proteins, which contribute to their astringent properties. Tannins are classified as condensed tannins or proanthocyanidins, which are polymers of flavan-3-ol units, and hydrolysable ones with phenolic acids esters, cyclic polyalcohol [88]. Polyphenolic compounds show their beneficial effects owing to the potential antioxidant capability of polyphenols to interact with primary signaling plus gene regulating pathways, thus, resulting in the modulation of gut microbiota [89]. Dietary polyphenols are naturally occurring compounds and form an utmost part of the diet, such as fruits, vegetables, wine, tea, and coffee. Various reports have evidenced the anti-diabetic, anti-cancer, antioxidant, and neuroprotective role, clearly indicating the link of dietary polyphenols with a decline in incidences of several chronic disorders. However, the bioavailability of polyphenols is less than other nutrients in the diet. However, their poor absorption helps them retain in the intestine for a longer duration, thereby promoting the growth of gut microbiota [90].

Bioavailability and Pharmacokinetics of Polyphenols: Relevance to Disease Prevention

Polyphenols, diverse in their chemical structure, are phytochemicals present in a variety of plants; these compounds hold promise in disease prevention due to their antimicrobial, antioxidant, and anticancer activities [36, 111]. Despite their potential health benefits, the bioavailability of polyphenols varies significantly due to factors such as food matrix, chemical composition, and gut microbiota [112]. For instance, ginger, rich in gingerol, shows rapid absorption in both animal and human models; however, it undergoes extensive metabolism, indicating that bioavailability is a complex interplay of absorption and metabolism [113]. Gut microbiota has been shown to metabolize various polyphenols, further affecting their bioavailability. For example, ellagitannins are metabolized into ellagic acid and urolithins [114]. While anthocyanins from berries and grapes are poorly absorbed, they are still considered essential due to their health benefits [115]. Similarly, quercetin, a flavonol, shows limited absorption but remains studied for its potential health impacts [116]. Flavanones like hesperetin and naringenin from citrus fruits also display limited bioavailability; yet, their hydrolysis by gut microbiota can lead to metabolites with distinct biological activities [117]. As for catechins, they are mainly found in tea and chocolate, and their absorption is influenced by the degree of galloylation [118] Finally, capsaicinoids, primarily capsaicin and dihydrocapsaicin, found in chilies, show high absorption rates but are quickly metabolized in the liver, highlighting the complexity of bioavailability [119]. The bioavailability of polyphenols is complex, affected by factors like gut microbiota and dietary intake and the specific chemical structures of the polyphenols [113]; further studies are required to fully understand the pharmacokinetics and bioavailability of these promising compounds.

Impact of Bioactive Compounds on Gut Microbiota in Diabetic Patients

Polyphenolic compounds, abundantly present in plant-based foods, are metabolized by gut microbiota into bioactive postbiotics; these microbial metabolites are central to understanding how polyphenols can affect the health of diabetic patients [120] (Table 2). Recent studies have highlighted the inter-individual differences in the metabolic transformation of dietary polyphenols, largely driven by the unique gut microbiome of each individual [121]. These differences are especially relevant when considering diabetic patients who often exhibit altered gut microbiota composition [121]. Flavonoids like flavonols, consumed at an average rate of ~25 mg/day, have demonstrated intricate interactions with gut microbiota in diabetic patients, leading to the formation of metabolites like phenylacetic and benzoic acids [122]. Wen et al. [122] found that epigallocatechin gallate and tea polyphenols had a beneficial impact on the gut microbiota composition in diabetic patients, enriching beneficial bacteria like *Akkermansia* and *Bacteroides* [123]. Similarly, supplementation with tea polyphenols was reported to restore microbial diversity disrupted by antibiotics [83]. In terms of other plant extracts, pineapple stem flour has been shown to enhance beneficial microbiota like *Bifidobacterium* and *Lactobacillus, whereas* citrus fruit extracts have indicated positive effects on gut microbial populations due to their rich polyphenol content, including hesperidin and naringenin [124]. Emerging clinical research is increasingly highlighting the intricate relationship between dietary polyphenols and the human gut microbiome; most notably, clinical studies are beginning to reveal how this synergy influences various health conditions, particularly T2DM [90].

Table 2 Impact of natural compounds on gut microbiota in diabetic patients: evidence from human studies and RCTs

Study design	Patients	Intervention	Main outcomes	Significant findings	Reference
Single-center, RCT	Type 2 diabetes	Dietary intervention with functional foods	Gut microbiota composition, metabolic health	Impact on branched-chain amino acids, TMAO levels	NCT03421301
Open-label, RCT	Type 2 diabetes	Diet tailored to influence gut microbiota	HbA1c levels, diabetes remission	Effectiveness against standard dietary advice	[126], NCT05541237
Randomized, placebo-controlled, multi-center (PREMOTE study)	Type 2 diabetes	Probiotics and berberine	Postprandial total and LDL cholesterol levels	Reduced lipid levels, potential cardiovascular benefits	[127]
Clinical study	Diabetic patients	Cinnamon and *Lactobacillus acidophilus*	Fasting glucose levels, antioxidant enzymes, gut microbiome	Improved glucose management, antioxidant status	[128]

RCT randomized controlled trial, *T2D* type 2 diabetes, *TMAO* trimethylamine N-oxide, *LDL* low-density lipoprotein

A clinical trial registered under ClinicalTrials.gov ID NCT03421301 examines the impact of a dietary intervention incorporating functional foods on gut microbiota and metabolic health in individuals with type 2 diabetes [125]. This single-center, randomized, double-blind trial involved a two-stage dietary approach, initially focusing on a calorie-restricted diet followed by the inclusion of a dietary portfolio (DP) or a placebo. The DP comprised various functional foods aimed at modifying gut microbiota, with adherence assessed through dietary recalls and food logs. The research aimed to evaluate the dietary intervention's effectiveness in altering gut microbiota composition and improving metabolic parameters, including branched-chain amino acids and TMAO levels [125].

A recent clinical trial NCT05541237 adopted a broader approach, examining the efficacy of a diet specifically tailored to influence gut microbiota in managing type 2 diabetes [126]. This research was designed as an open-label, randomized control trial, where the diet's impact is measured against standard dietary advice for diabetes management. The key outcomes include monitoring the variation in HbA1c levels, a critical marker for long-term glucose control, alongside assessing the diet's role in achieving diabetes remission, defined by blood glucose normalization without the need for medication [126].

In a study conducted by Shujie Wang and colleagues, the effectiveness of a combined therapy of probiotics and berberine in managing postprandial lipidemia (PL) in type 2 diabetes (T2D) patients was investigated. The study aimed to address the limited treatment options for PL, a significant cardiovascular disease risk factor in T2D. The research was part of the PREMOTE study, a randomized, placebo-controlled, multi-center clinical trial involving 365 T2D patients [127]. It was found that the combination therapy was more effective than either berberine or probiotics alone in reducing postprandial total and LDL cholesterol levels. This effect was attributed to changes in the levels of fecal *Bifidobacterium breve*, particularly due to the activation of fadD genes by berberine, which enhances fatty acid import and metabolism, thereby reducing lipid absorption. The study highlighted the potential of targeting the gut microbiome to improve lipidemia and cardiovascular risk in T2D patients [127].

Another clinical study conducted by Mirmiranpour et al. [127] focused on diabetic patients, assessing the combined effects of cinnamon and *Lactobacillus acidophilus* on the intestinal microbiota. Not only did fasting glucose levels drop, but antioxidant enzymes like SOD, glutathione peroxidase, and catalase also increased, confirming cinnamon's role as a beneficial adjunctive treatment in managing T2DM [128]. Additionally, preliminary results hinted at favorable shifts in the gut microbiome, although further research is needed for confirmation. Although not directly a clinical trial on humans, Sost et al. [128] confirmed that citrus fruit extracts rich in hesperidin and naringenin had a positive impact on gut microbial populations. Future clinical studies could translate these findings to assess potential benefits for human patients with T2DM [129].

Discussion

The escalating global prevalence of type 2 diabetes mellitus (T2DM) necessitates innovative therapeutic strategies that are both effective and affordable [1, 130]. The link between obesity and T2DM underscores the importance of addressing obesity as a means to prevent or manage T2DM, and interventions targeting obesity, including lifestyle modifications, pharmacotherapy, and bariatric surgery, have shown promise in improving insulin sensitivity and reducing the risk of T2DM development [6]. Additionally, the modulation of gut microbiota through dietary changes and the use of prebiotics and probiotics emerge as a novel therapeutic avenue, given the role of gut microbiota in metabolic health. These strategies not only highlight the multifaceted approach needed to tackle the obesity-T2DM nexus but also align with our findings on the potential of natural products in modulating gut microbiota and metabolic health [7]. The findings of our review highlight the emerging role of herbal medicines (HMs) in the management of T2DM. While it is well-known that herbal-based therapies have been employed as complementary treatment options for centuries, our analysis brings to light their interactive effects with gut microbiota in attenuating the disease severity. Several HMs, such as *Scutellaria Radix* and *Coptidis*, were noted for their anti-diabetic and anti-inflammatory properties. Importantly, their therapeutic effects appear to be mediated by interactions with gut microbiota. The gut microbiota is increasingly recognized as a crucial mediator in the pathogenesis of T2DM, particularly through its influence on short-chain fatty acid (SCFA) production, which impacts metabolic inflammation and insulin resistance. A notable feature of our analysis was the range of methodological approaches used to study the impact of HMs on diabetes. These approaches extend from in vitro studies on various cell lines like Rat L6 cells and Hep G2 human hepatoblastoma cells, to animal models, providing a comprehensive view of HMs' anti-diabetic potential. Our review identifies a clear gap in the regulatory approval of HMs for treating T2DM, pointing to an urgent need for standardized clinical trials. Moreover, the existing studies have largely focused on the therapeutic impact of individual HMs, leaving the interactive effects of multiple herbs largely unexplored.

Therapeutic Perspectives, Limitations, and Clinical Pitfalls in the Context of Natural Compounds and Biotics in Diabetes Management

The escalating prevalence of type 2 diabetes mellitus (T2DM) underscores the imperative for innovative, efficacious, and tolerable treatments [1••]. Beyond conventional pharmacotherapy, which may exhibit diminishing efficacy and adverse effects over time, the exploration of natural compounds and biotics presents a promising frontier. Recent advancements have shed light on the antihyperglycemic and gut microbiota-modulating properties of plant-based extracts. For instance, the differential gut microbiota composition in T2DM patients offers a novel management approach [38]. The limited bioavailability of these compounds presents a substantial challenge, underscoring the imperative for forthcoming investigations into nanoformulations to augment absorption. Additionally, the scarcity of extensive human clinical trials that validate the results from animal models underscores the critical necessity for translational pharmacological research. In contrast to natural compounds, biotics—encompassing pro-, pre-, post-, and synbiotics—offer a targeted approach to modulate the gut microbiota, potentially ameliorating T2DM symptoms [48, 131]. Probiotics, for example, introduce beneficial bacteria directly, while prebiotics provide the necessary substrates for these bacteria to flourish [132]. Synbiotics combine both for a synergistic effect, and postbiotics refer to beneficial metabolic byproducts produced by gut microbiota [48]. Despite their promise, the comparative efficacy and safety of these interventions versus natural compounds remain underexplored in human studies. Integrating natural compounds and biotics with standard T2DM management could potentially enhance therapeutic outcomes [133]. However, this necessitates a careful evaluation of interactions and personalized treatment approaches. Future research should focus on head-to-head comparisons, long-term effects, and the exploration of combinational therapies to fully elucidate their therapeutic potential and limitations in T2DM management.

Conclusion

Due to obesity and unhealthy lifestyle choices, diabetes mellitus DM incidence and prevalence are rising everywhere. Effective medications must be created to prevent and treat this chronic metabolic disorder. Gut microbiota may be essential in the etiology of diabetes mellitus, according to an increasing body of research. The need for novel approaches to preventing and treating this illness is vital. However, most medications today, particularly those with a history of success, concentrate primarily on agents created to operate directly on the signaling pathways that change blood sugar levels and frequently cause side effects. Controlling the gut microbiome, however, may be a viable treatment for type 2 diabetes, according to a better knowledge of the disease's root causes. In treating type 2 diabetes, the analogs of plants, particularly therapeutic and functional foods, are of great interest, because they may be given orally, are effective, non-toxic, and have few adverse effects. There have been strategies to prevent T2DM. Gut microbiota management reduces low-grade inflammation, but recent research on gut microbiota influences suggests that this may also be possible. Because people with DM often take anti-diabetic medications, it is essential to consider how these herbal remedies and the ability to develop novel molecules dramatically expand the concept of drug development.

Abbreviations ATF2: Activating transcription factor 2; AMPK/PI3K/Akt/GSK3β: AMP-activated protein kinase/phosphatidylinositol 3-kinase/serine/threonine protein kinase b/glycogen synthase kinase-3 beta; CAT: Catalase; DM: Diabetes mellitus; CRP: C-reactive protein;

FGF2: Fibroblast growth factor 2; FOXO1: Forkhead box protein O1; GSK-3β: Glycogen synthase kinase 3 beta; GPx: Glutathione peroxidase; GLP-1: Glucagon-like peptide 1; GLUT4: Glucose transporter type 4; GSH: Glutathione; H2O2: Hydrogen peroxide; IL-6: Interleukin 6; IRS1: Insulin receptor substrate 1; ICAM1: Intercellular adhesion molecule 1; JNK: Jun N-terminal kinase; MCP-1: Monocyte chemoattractant protein-1; mRNA: Messenger RNA; Muc2: Mucin 2; mTOR: Mammalian target of rapamycin; NO: Nitrous oxide; NF-κB: Nuclear factor kappa B; NRK 52E: Rat renal proximal tubular epithelial cells; PPARG: Peroxisome proliferator-activated receptor gamma; PDX1: Pancreatic and duodenal homeobox 1; p38MAPK: P38 Mitogen-activated protein kinases; ROS: Reactive oxygen species; Rab27a/Slp4: Ras-related protein/synaptotagmin-like protein 4; SOD: Superoxide dismutase; SIRT1: Sirtuin 1; SLC2A4: Solute carrier family 2 member 4; TNFα: Tumor necrosis factor-alpha; TGF-β1: Transforming growth factor beta 1; TFF3: Trefoil factor family 3; T2DM: Type 2 diabetes mellitus

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