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Review Article

PPAR-γ as a therapeutic target: role of plant-derived bioactive compounds in diabetes mellitus

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Abstract

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder characterized by insulin resistance, impaired insulin secretion, chronic inflammation, oxidative stress, and dysregulated lipid metabolism. Peroxisome proliferator-activated receptor gamma (PPAR-γ), a ligand-activated nuclear receptor, plays a central role in regulating glucose homeostasis, lipid metabolism, adipocyte differentiation, and insulin sensitivity, making it an important therapeutic target for diabetes management. Although synthetic PPAR-γ agonists, particularly thiazolidinediones, effectively improve glycemic control, their clinical use is limited by adverse effects such as weight gain, fluid retention, cardiovascular complications, hepatotoxicity, and concerns related to long-term safety. Consequently, increasing attention has been directed toward plant-derived bioactive compounds as safer and more selective PPAR-γ modulators. This review summarizes recent advances in the identification and characterization of plant-derived phytochemicals with PPAR-γ modulatory activity and discusses their molecular mechanisms in diabetes management. A diverse range of phytoconstituents, including flavonoids, phenolic acids, terpenoids, alkaloids, lignans, coumarins, stilbenes, and phytosterols, have demonstrated the ability to enhance insulin sensitivity, promote glucose uptake, regulate adipogenesis and lipid metabolism, suppress inflammatory signaling, and reduce oxidative stress through selective or partial modulation of PPAR-γ. Emerging evidence from *in vitro*, *in vivo*, and *in silico* studies highlights their potential as promising alternatives or adjuncts to conventional antidiabetic therapies. Furthermore, advances in computational drug discovery, network pharmacology, molecular docking, artificial intelligence-assisted screening, and nanotechnology-based delivery systems are accelerating the development of novel plant-derived selective PPAR-γ modulators with improved efficacy and bioavailability. Despite these promising findings, well-designed preclinical and clinical studies are required to validate their therapeutic efficacy, safety, pharmacokinetic properties, and long-term clinical applicability for the management of T2DM and its associated metabolic complications.

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Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion, insulin action, or both. The global prevalence of diabetes has increased dramatically over the past few decades, posing a significant public health challenge. According to recent estimates, hundreds of millions of individuals worldwide suffer from diabetes, with type 2 diabetes mellitus (T2DM) accounting for nearly 90–95% of all cases. The pathophysiology of T2DM, is highly complex and involves a network of interrelated mechanisms including insulin resistance, pancreatic β-cell dysfunction, impaired incretin effect, excessive hepatic glucose production, altered adipokine secretion, chronic low-grade

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inflammation, oxidative stress, and dyslipidemia. Progressive insulin resistance in peripheral tissues such as skeletal muscle, adipose tissue, and liver significantly impairs glucose uptake and utilization, while β-cell dysfunction interferes with compensatory insulin secretion, ultimately leading to persistent hyperglycemia. Additionally, obesity-associated inflammation and ectopic lipid accumulation further aggravate metabolic abnormalities and contribute to the development of severe diabetic complications, including cardiovascular disorders, nephropathy, neuropathy, retinopathy, etc. leading to substantial morbidity and mortality (IDF Diabetes Atlas, 2025).

Current management strategies for diabetes focus on achieving a stable glycemic control, preventing complications, and improving quality of life through a combination of lifestyle modifications and pharmacological interventions. Lifestyle measures, including dietary management, regular physical activity, weight reduction, and behavioural modifications, remain the cornerstone of diabetes management. Avoiding calorie-rich processed foods and incorporation of complex carbohydrates in regular diet are also strictly prescribed. Pharmacological therapies include oral antidiabetic agents such as metformin, sulfonylureas, meglitinides, α-glucosidase inhibitors, thiazolidinediones, sodium-glucose cotransporter-2 (SGLT2) inhibitors, and dipeptidyl peptidase-4 (DPP-4) inhibitors, as well as injectable therapies such as glucagon-like peptide-1 (GLP-1) receptor agonists and exogenous insulin. Although these therapeutic options effectively improve glycemic control, many are associated with limitations including hypoglycemia, weight gain, gastrointestinal disturbances, cardiovascular concerns, and loss of efficacy over prolonged use (Inzucchi et al. 2012).

The multifaceted nature of diabetes has highlighted the need for therapeutic agents capable of targeting multiple pathophysiological pathways simultaneously. In this context, nuclear receptors such as peroxisome proliferator-activated receptor gamma (PPAR-γ) have gained considerable attention because of their central role in regulating glucose homeostasis, lipid metabolism, inflammation, and insulin sensitivity. Consequently, the search for safer and more effective PPAR-γ modulators, particularly from plant-derived bioactive constituents, has emerged as a promising strategy for the management of diabetes and its associated metabolic complications, owing to their diverse chemical structures, therapeutic efficacy, and relatively lower toxicity. Medicinal plants have long been utilized in traditional systems of medicine for the treatment of diabetes and related metabolic disorders. Advances in phytochemical and pharmacological research have identified numerous natural compounds capable of interacting with PPAR-γ and regulating its activity. These phytoconstituents include flavonoids, phenolic acids, terpenoids, alkaloids, lignans, coumarins, and stilbenes. Unlike full synthetic agonists, many plant-derived compounds act as selective PPAR-γ modulators (SPPARMs), producing beneficial insulin-sensitizing effects while minimizing adverse outcomes associated with excessive receptor activation (Haeri 2023). These phytoconstituents have demonstrated the ability to enhance PPAR-γ-mediated signaling pathways, improve glucose utilization, suppress inflammatory mediators, and regulate adipogenesis. These effects collectively contribute to improved insulin sensitivity and glycemic control. Furthermore, the antioxidant and anti-inflammatory properties of many phytochemicals provide additional therapeutic advantages in mitigating diabetes-associated complications. The growing body of evidence highlighting the interaction between plant-derived active constituents and PPAR-γ underscores the potential of natural products as promising alternatives or adjuncts to conventional antidiabetic therapies. Understanding the molecular mechanisms underlying PPAR-γ modulation by phytochemicals may facilitate the development of novel therapeutic agents with enhanced efficacy and safety profiles. Therefore, the exploration of plant-derived PPAR-γ modulators represents a promising strategy for the effective management of diabetes and its associated metabolic complications (Moola et al. 2023).

PPAR-γ and Glucose Homeostasis

Peroxisome proliferator-activated receptor gamma (PPAR-γ) is a ligand-activated nuclear transcription factor that plays a crucial role in the regulation of glucose and lipid metabolism. PPAR-γ regulates the transcription of genes responsible for adipocyte differentiation, fatty acid storage, and insulin sensitization. It has two isoforms- PPAR-γ1, which is widely expressed in the key organs involved in insulin sensitivity, such as adipose tissue, pancreatic β-cells, skeletal muscle, and the liver, whereas PPAR-γ2 is specific to adipose tissue (Rangwala and Lazar 2004). Activation of PPAR-γ enhances insulin sensitivity primarily by reducing lipotoxicity and promoting insulin signalling by promoting adipocyte differentiation and increasing the capacity of adipose tissue to store free fatty acids. PPAR-γ also upregulates genes involved in glucose transport,

including Glucose Transporter 4 (GLUT4), thereby improving glucose uptake in peripheral tissues. Mutations in the PPARγ gene, therefore, are responsible in developing insulin resistance, adipocyte hypertrophy, and hepatic steatosis, making it a critical molecular target in the pathophysiology of type 2 diabetes mellitus (Aniello and Amodeo 2023).

The drugs that activate PPAR-γ, known as agonists, most notably the thiazolidinediones (TZDs), improve insulin sensitivity by enhancing glucose uptake in peripheral tissues and reducing hepatic glucose production. These agents exert their antidiabetic effects by modulating adipokine secretion, decreasing levels of pro-inflammatory cytokines, and promoting a shift in lipid storage from ectopic sites to adipose tissue. The ligand-binding domain contains about 270 amino acid residues containing 13 α-helices (H1-H12 and H2) and a four-strand β-pleated sheet. Canonical full agonists bind with a tyrosine residue located on helix H12 and facilitate binding of the co-activator. Antagonists, on the other hand, destabilize the H12. However, partial agonists usually bind with the β-sheet and may not be involved in co-activator binding (Aniello and Amodeo 2023). Beyond glycemic control, PPAR-γ activation has been shown to influence inflammation, oxidative stress, and endothelial function, suggesting broader metabolic and cardiovascular implications. Upon binding to its ligands, either endogenous fatty acid derivatives or synthetic agonists such as thiazolidinediones (TZDs), PPAR-γ undergoes a conformational change and forms a heterodimer with the retinoid X receptor (RXR). This PPAR-γ–RXR complex then binds to specific DNA sequences known as peroxisome proliferator response elements (PPREs) in the promoter regions of target genes, leading to altered gene transcription. In addition, PPAR-γ modulates adipokine secretion by increasing levels of insulin-sensitizing adipokines such as adiponectin while suppressing pro-inflammatory cytokines like tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6). This anti-inflammatory effect further enhances insulin signaling pathways. PPAR-γ activation also decreases hepatic gluconeogenesis and improves β-cell function by reducing glucotoxicity and oxidative stress. Collectively, these molecular and cellular actions lead to improved glycemic control, reduced insulin resistance, and better overall metabolic homeostasis in individuals with type 2 diabetes (Abbas et al. 2012).

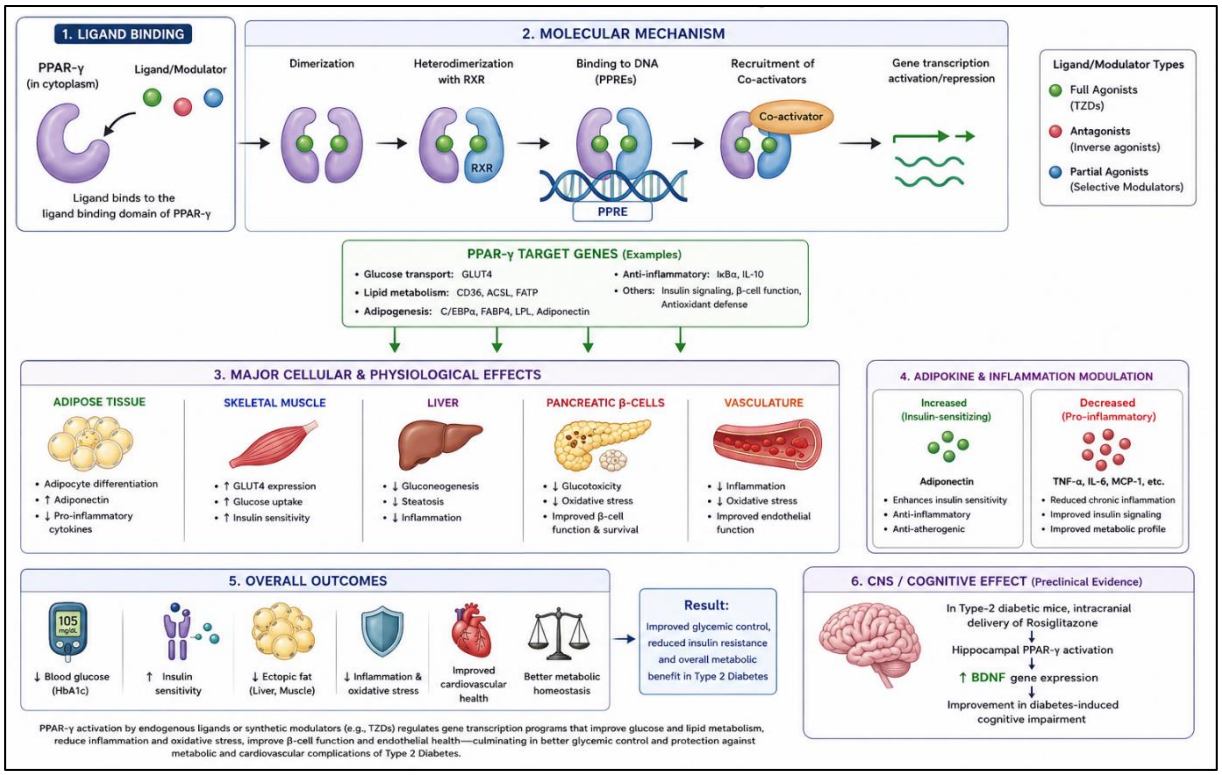

Figure 1. Mechanism of action of PPAR-γ modulators. Schematic illustration showing ligand binding to PPAR-γ, heterodimerization with RXR, binding to PPREs, regulation of target gene transcription, and overall metabolic benefits.

Apart from these, A study with Type-2 diabetic mice showed that direct intracranial delivery of Rosiglitazone induced hippocampal PPAR-γ activation that showed significant improvement in diabetes-induced cognitive impairment by increasing expression of the BDNF gene in the brain (Thiruchelvam et al. 2015). Therefore, understanding the role of PPAR-γ and its modulators remains essential for the development of improved therapeutic strategies for diabetes management. Figure 1 depicts the molecular mechanism of PPAR-γ and its modulators in the metabolic regulation of Diabetes and associated disorders.

Concerns associated with synthetic PPAR modulators

Despite their therapeutic benefits, the clinical use of PPAR-γ modulators is limited by adverse effects including weight gain, fluid retention, fractures, and increased risk of heart failure. For example, Troglitazone, the first generation of TZDs, has been withdrawn from the market due to its potential hepatotoxicity. This in turn has prompted the ongoing research into selective PPAR-γ modulators that retain metabolic benefits while minimizing side effects. Synthesis of Lobeglitazone and Reglitazar as dual activators of PPAR-α and γ, with promising insulin sensitizing and lipid-lowering activities and minimal toxicity in diabetic cases are two such examples (Haeri 2023). However, TZDs are usually metabolized by Cytochrome P450 (CYP) enzymes and transporters whose polymorphic nature affect the drug efficacy and clearance and frequently increase mitochondrial oxidative stress by reducing glutathione levels. Diabetes induced inflammatory reactions further increase the risk of drug-drug interactions and renal impairments (Jangra et al. 2025).

It was also been observed that the frequent genetic mutations, wide polymorphisms, presence of alternative splicing isoforms, post-translational modifications of the PPAR-γ gene that regulate their expression pattern and activities, may contribute the clinical pathophysiology of Diabetes and also influence the pharmacological responsiveness of the drugs. The unwanted effects of existing drugs can also be partially explained in the light of such heterogeneous nature of PPAR-γ transcripts and their tissue-specific activities. Therefore, careful evaluation is required to achieve personalized treatment regime, depending on the nature of the complex signalling network of PPAR-γ (Cataldi et al. 2021). Aprile et al. (2018) identified the presence of PPAR-γΔ5, a naturally occurring splicing isoform of PPAR-γ which lacks the ligand-binding domain. It is highly expressed in adipose tissue and reduces the adipogenic potential of precursor cells through dominant-negative inhibition of PPAR-γ transactivation, which leads to an increased BMI in obese and diabetic patients.

Plant-Derived PPAR-γ modulators: An Overview

The considerable adverse effects and limited selectivity of thiazolidinediones toward endogenous PPAR-γ have stimulated extensive research into the development of selective PPAR-γ modulators capable of improving glucose utilization and alleviating insulin resistance with a reduced risk of adverse events. Natural products constitute a rich source of structurally diverse bioactive compounds with significant potential for development as therapeutic agents or lead molecules. The longstanding ethnopharmacological use of medicinal plants in the management of metabolic disorders, particularly diabetes mellitus, has further strengthened interest in plant-derived therapeutics. As a result, intensive research efforts have been undertaken in recent years to investigate the PPAR-γ modulatory and activation potential of various phytoconstituents. There are several reports that inspected the plant extracts, identified major active compounds, pure secondary metabolites, dietary sources such as fruits, culinary spices and condiments (Abdallah et al. 2020) These compounds can be categorized into two types- a large number of structurally diverse chemicals that possess agonistic behaviour and show their activity in the low micromolar range, while some are inhibitors and antagonists that control overexpression and exert beneficial metabolic regulation (Ammazzalorso and Amoroso 2019). The studies summarized in Table 1 demonstrate a wide variety of plant-derived bioactive compounds including all major classes of secondary metabolites that possess significant PPAR-γ modulatory activity. The search engines “Google Scholar”, “PubMed”, “Scopus” and “Web of Science” was screened for relevant research articles, reviews, book chapters, short communications and conference proceedings from 2010-2025 with the keywords- “phytochemicals as PPAR-γ agonists”, “natural compounds as PPAR-γ modulators”, “PPAR-γ modulatory effects of plant derived compounds”, etc.

Table 1. Plant-derived PPAR-γ modulators and their mechanism of action

Plant name/ Plant parts (Family)	**Active compound (Class)**	**Experimental details**	**Mechanism of action**	**References**
Essential oil of *Piper aduncum* L. and *Anethum graveolens* L.	Dillapiole (phenylpropanoid)	Absorption, Distribution, Metabolism, Excretion (or Elimination), and Toxicity (ADMET) analysis, Baby Hamster Kidney-21 (BHK-21) cell cultures, (High fat diet-Streptozotocin) HFD-STZ induced Type-2 diabetic rats	Partial agonist (EC_{50} of 43.95 μM), reduced oxidative stress and prevented reduction in histone H3 acetylation in BHK-21 cell cultures, reduce plasma glucose level (138.39±12.36 mg/dl), improve renal function and lipid profile diabetic rats	Shafi et al. (2025)
Rhizome of *Curcuma longa* L.	Curcumin (polyphenol diarylheptanoid)	*In vitro* and *in vivo* studies	Increased expression of the PPAR-γ gene, causing its activation in cells to activate Hematopoietic Stem Cells (HSCs) and hepatic fibrosis; exert anti-inflammatory effect by supressing Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) via modulation of PPAR-γ	Majidi et al. (2016)
Fruits of *Malaytea scurfpea* L.	Bavachinin (prenylated flavanone)	*In vivo* study in db/db and diet-induced obese mice, *in silico* molecular docking	Lower blood glucose and triglycerides, Agonist for PPAR-α and γ by binding at an alternative site, synergistic action with synthetic agonists	Feng et al. (2016)
Fruits of *Cucurbita ficifolia* Bouché	4-Hydroxybenzoic Acid (phenolic acid) and β-Sitosterol (phytosterol)	*In vitro*, *in vivo* and *in silico* studies	Dual agonists on PPAR-γ and GPR40 receptors, β-sitosterol and 4-hydroxybenzoic acid (4-HBA), which increased insulin secretion, GLUT4, PPAR-γ, and adiponectin mRNA expression, increased storage of glycogen.	Rosiles-alanis et al. (2022)

Ficus carica L.	Quercetin-3-o-rutinoside (flavonoid) and Angelicin (furocoumarin)	*In silico* molecular docking	G-score −14.22 kcal/mol and −13.56 kcal/mol, respectively with the target PPAR- γ	Deshpande et al. (2025)
Hibiscus sabdariffa L.	α-amyrin and lupeol (triterpenoids)	*In vitro*, *in vivo* and *in silico* studies	Dual agonists on PPAR-α and γ, decreased lipid accumulation in 3T3-L1 adipocytes and blood glucose in mice	Giacoman-Martínez et al. (2019)
Zingiber roseum (Roxb.) Roscoe	β-Sitosterol (phytosterol)	*In silico* molecular docking, Molecular Dynamics (MD) simulations and MMGBSA analysis	Stable binding with PPAR-γ binding affinity (−8.9 kcal/mol)	Amanat et al. (2024)
Leaves of *Hydrangea macrophylla* (Thunb.) Ser.; fruits of *Piper chaba* W. Hunter; rhizomes of *Kaempferia parviflora* Wall. ex Baker.	Hydrangenol (dihydroisocoumarin) and Hydrangeic Acid (stilbenoid); piperlonguminine and retrofractamide A (amide); tetramethyl kaempferol and pentamethylquercetin (flavonoid)	*In vitro* and *in vivo* studies	Agonistic activity for PPAR-γ, improve insulin sensitivity by increasing the levels of adiponectin in 3T3-L1 cells	Matsuda et al. (2014)
Aerial parts of *Mycetia sinensis* (Hemsl.) Craib. and leaves of *Allophylus villosus* (Roxb.) Blume	2,4-Di-butyl phenyl 5-hydroxypentanoate and Diazo acetic acid (1S,2S,5R)-2-isopropyl-5-methylcyclohexyl (esters)	*In vivo* studies on Swiss-albino diabetic model mice, *in silico* molecular docking, ADMET, quantum mechanics based DFT, molecular dynamics simulation	Agonistic activity for PPAR-γ, reduction of blood glucose, serum creatinine and Alkaline Phosphatase in diabetic mice	Azam et al. (2024)
Clerodendrum trichotomum Thunb.	Apigenin 7-O-β-D-glucuronide, apigenin, luteolin, and quercetin (flavonoids)	*In vitro* study	EC_{50} values range 2.3-24.9 μM	Yang et al. (2024)
Whole Grape powder (3% w:w)	Not specified	*In vivo* study in Dahl Salt-Sensitive hypertensive rats	Upregulation of mRNA for PPAR-α, PPAR-γ co-activator-1α, PPAR-γ, and cytosolic NF-κB inhibitor, inhibitor κBα; reduced expression of cardiac TNF-α and TGF-β, increased IκBα expression, and reduced cardiac fibrosis	Seymour et al. (2011)
Fruits of *Viburnum opulus* L.	Chlorogenic acid (phenolic acid), procyanidin, and catechin (Flavan-3-ol)	*In vitro* study in murine 3T3-L1 preadipocyte cell line and pancreatic lipase	Reduced adipogenesis by downregulation of the expression	Zakłos-Szyda et al. (2020)

		activity in triolein emulsion; *in silico* molecular docking	of PPAR-γ, CCAAT/enhancer-binding protein alpha (C/EBPβ/α), and sterol regulatory element-binding protein 1c (SREBP-1c); agonistic binding with PPAR-γ	
Eleutherine Bulbosa (Mill.) Urb.	Anthocyanins (phenolics), quinones	*In vitro* in 3T3-L1 mouse cell line; *in silico* network pharmacology and molecular docking analysis	Improved glucose and lipid metabolism by inhibition of PPAR-γ, Mitogen activated protein kinase 8 (MAPK8), 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), Carnitine Palmitoyltransferase I (CPT-I), and GLP1 expression as well as inhibition of pancreatic lipase α-glucosidase, and α-amylase levels	Permatasari et al. (2024)
Fruits of *Emblica officinalis* Gaertn.	Gallic acid (phenolic acid)	*In vitro* in 3T3-L1 adipocytes, *in vivo* in db/db mice and fructose administered rats	Improved insulin sensitivity and PPAR-γ expression via Akt signalling pathway, increased GLUT4 translocation, reduced obesity and cholesterol and induce adipogenesis	Variya et al. (2020)
Toddalia asiatica (L.) Lam.	Flindersine (pyranoquinoline alkaloid)	*In vivo* study in HFD-STZ induced diabetic rats	Increased plasma insulin concentration, antioxidant enzyme levels and reduced body weight and total cholesterol and increase expression of PPAR-γ in skeletal muscles and adipose tissue	Irudayaraj et al. (2022)
Glycyrrhiza glabra L.	kanzonol X (isoflavonoid) and glabrol (flavonoid)	*In silico* molecular docking and ADMET analysis	Strong binding affinity with PPAR-γ receptor with favourable cellular uptake and bioavailability and no cardiotoxicity	Hosseinpoor et al. (2024)
Garcinia mangostana L.	α-mangostin and γ-mangostin (xanthonoid)	*In silico* molecular docking	Strong binding affinity with PPAR-γ receptor	Mahmudah (2021)

Sisymbrium irio L.	Fatty acid	*In silico* molecular docking	Strong binding affinity with PPAR-γ −7.4 kcal mol^{-1}.	Al-Massarani et al. (2023)
Roasted grains of *Coffea arabica* L. *Coffea canephora* Pierre ex A.Froehner	Caffeine (methylxanthine) and dihydrocaffeic acid (phenolic acid)	*In silico* molecular docking	Strong binding affinity with PPAR-γ ΔG = −39.46 kJ mol−1 and −33.60 kJ mol^{-1}, respectively	Grzelczyk et al. (2020)
Seeds of *Myristica fragrans* Houtt.	Macelignan (polyphenol)	*In vivo* evaluation in alloxan- and glucose-induced hyperglycemic Swiss albino mice; in silico molecular docking	Significant reduction of blood glucose level in a dose-dependent manner; Strong binding affinity with PPAR-α and PPAR-γ (−9.2 and −8.3 kcal/mol, respectively);	Nasreen et al. (2020)
Cordia morelosana Standl.	Rosmarinic acid and methyl Rosmarinate (phenolic acid derivatives)	*In vivo* evaluation in Non-insulin dependent type-2 diabetic (NIDD) model mice, *in silico* molecular docking	Significant inhibition of α-glucosidase and overexpression of PPARγ, PPARα, GLUT-4 and fatty acid transport protein (FAPT) with no toxicity; agonist activity on PPAR-γ	Giles-rivas et al. (2020)
Seeds of *Bixa orellana* L.	Bixin (carotenoid)	*In vivo* evaluation in alloxan-induced diabetic rats; in silico molecular docking and MD simulations	Reduction in blood glucose levels, LDL, total cholesterol and triglycerides, ROS generation in kidney; strong affinity towards PPARγ (−10.6 kcal/mol)	Keita et al. (2020)
Fruits of *Feronia elephantum* Corrêa	22,23-dihydrostigmasterol (phytosterol) and tocopherol (chromanol)	*In vivo* study in HFD-STZ induced diabetic rats; *in silico* molecular docking	Significant reduction in plasma glucose levels and HbA1c; increased plasma insulin levels; restore histological alterations, lipid profile and liver function with no toxicity; strong binding with PPAR-γ (−11.3 and −10.4 kcal/mol)	Reddy et al. (2020)
Aerial parts of *Plantago australis* Lam.	Ursolic acid (pentacyclic triterpenoid)	*In vivo* study in NIDD model mice and *in vitro* study in 3T3-L1 adipocytes	Inhibition of α-glucosidases and the overexpression of PPAR-γ and GLUT-4	Estrada-soto et al. (2023)
Curcuma mangga Valeton & Zijp	Curcumin (diarylhepatonoid)	*In vitro* study in 3T3-L1 adipocytes	Improved glucose uptake via increased GLUT4 expression and	Pujimulyani et al. (2020)

			downregulated PPAR-γ expression	
Leaf and fruit of *Corchorus olitorius* L.	Not specified	*In vivo* study in HFD-STZ induced diabetic rats	Significant reduction in blood glucose level, improved antioxidant and anti-inflammatory response, mediated by increased PPAR-γ expression, positive modulation of Protein Kinase B (Akt), Glycogen synthase kinase-3 beta (GSK-3β), and Glucose Transporter-2 (GLUT-2)	Jeje et al. (2025)
Leaves of *Aegle marmelos* (L.) Corrêa	Aegeline (amine alkaloid)	*In silico* molecular docking analysis	Dual agonistic behaviour for PPAR-α and PPAR-γ	Venkatalakshmi (2025)
Leaves of *Piliostigma thonningii* (Schumach.) Milne-Redh.	Anthracene, 1,2,3,4-tetrahydro-9,10-dimethyl- (polycyclic aromatic hydrocarbon) and tetratriacontyl trifluoroacetate (fatty acid ester)	*In vitro* enzyme inhibitory assay and *in silico* molecular docking analysis	Dose-dependent inhibition of α-amylase and α-glucosidase activities; Dual agonistic behaviour for and PPAR-γ and Cyclooxygenase-2 (COX-2) (binding energy = −7.24 kcal/mol and −7.13 kcal/mol, respectively)	Alabi et al. (2025)
Ocimum tenuiflorum L.	Rosmarinic acid (phenolic acid), permethrin (cyclopropanecarboxylate ester), luteolin and isosakuranetin (flavonoid)	*In silico* molecular docking analysis	Binding energies of −8.3, −8.3, −7.3, and −7.1 kcal/mol, respectively	Rajagopal et al. (2021)
Fruits of *Chrysophyllum albidum* G. Don	Ethanol extract	*In vivo* study with streptozotocin-induced diabetic rats	Hypoglycemic and antioxidative effect via increasing PPAR-γ and decreasing NF-κB expression	Ajayi et al. (2021)
Citrus limon (L.) Burm. f.	Eriocitrin metabolites-eriodictyol, eriodictyol 7-O-glucuronide, eriodictyol 3′-O-glucuronide, homoeriodictyol andhomoeriodictyol 7-O-glucuronide (flavonoid derivatives)	*In silico* molecular docking and molecular dynamics simulation	Partial agonistic behaviour for PPAR-γ	Gangadhariah et al. (2022)
Murraya odorata Blanco	γ-tocopherol, n-hexadecanoic acid, Stigmasterol,22,23-dihydro, Stigmasterol,	*In silico* molecular docking and network pharmacology	Modulation of PPAR-γ activity (−6.4, −5.8, −7.8, −8.0, −5.0, −4.6	Dwivedi et al. (2021)

	Tetradecanoic acid, cis-9-hexadecenal		kcal/mol, respectively)	
Ocimum basilicum L.	Flavonoids	*In vivo* study in HFD-STZ induced diabetic rats	Decreased blood glucose levels and lipid markers, improved hepatorenal antioxidative and anti-inflammatory status by modulation of PPAR-γ activation	Othman et al. (2021)
Leaves of *Moringa oleifera* Lam.	Not specified	*In vivo* study in HFD-STZ induced diabetic rats	Increased insulin sensitivity by increased expression of PPAR-γ	Anwer et al. (2021)
Bark of *Bauhinia purpurea* L.	Bauhiniastatin-1 (dibenzo[b,f]oxepine)	*In vitro* study in 3T3-L1 adipocytes; *in vivo* study in HFD induced obese rats; *in silico* molecular docking	Decreased lipid accumulation in adipocytes; reduced body weight, fat mass and lipid levels in rats; strong binding interaction against PPAR-γ and AMP-activated protein kinase (AMPK)	Sankaran et al.(2021)
Polygonum tinctorium Aiton	Indirubin (bis-indole alkaloid)	*In vitro* study in 3T3-L1 adipocytes	Promotes adipocyte differentiation, basal and peripheral glucose uptake, increase estrogen levels	Konno et al. (2020)
Leaves of *Nelumbo nucifera* Gaertn.	Ethanol extract	*In vivo* study in HFD induced obese C57BL/6J mice	Improve dyslipidemia, inhibit hepatic damage, reduce inflammatory cytokines and downregulates PPAR-γ expression	Wu et al. (2020)
Seeds of *Macrotyloma uniflorum* (Lam.) Verdc.	Rutin, catechin, epicatechin (flavonoids), gallic acid, ferulic acid (phenolic acids), daidzein (isoflavone)	*In vivo* study in HFD-induced Metabolic syndrome (MS) rats	Regulated lipid metabolism, reduced oxidative stress and inflammation by modulating both PPAR-α and PPAR-γ	Malarvizhi et al. (2021)
Seed oil of *Punica granatum* L.	Punicic acid (omega-5 polyunsaturated fatty acid)	*In vitro* and *in vivo* studies	Agonistic behaviour for PPAR-γ; maintained glucose homeostasis, reduced inflammation and oxidative stress	Khajebishak et al. (2019)
Fruit of *Momordica charantia* L.	3,7,25-trihydroxy cucurbita-5,23(E)-dien-19-al (triterpenoid)	*In vitro* study in 3T3-L1 adipocytes; *in silico* molecular docking analysis	Increased glucose uptake by GLUT4 translocation and upregulation of	Adelina et al. (2021)

			PPAR-γ in muscle cells	
Glycine max (L.) Merr.	Isoflavones	*In vivo* study in HFD and high fructose diet induced rats	Prevention of renal damage by activation of PPAR-γ	Pessoa et al. 2020
Husk of Thai Purple Rice - *Oryza sativa* var. Indica (L.) S.Kato ex Matsum. & Nakai)	Protocatechuic acid (phenolic acid) and cyanidin-3-glucoside (phenolic)	*In vivo* study in HFD-STZ induced type 2 diabetic rats	Prevention of diabetic nephropathy by improving mitochondrial function, decreasing lipid peroxidation and increasing antioxidants by regulating Peroxisome proliferator-activated receptor gamma coactivator 1-alpha- Sirtuin 3 - Superoxide dismutase 2 (PGC-1α-SIRT3-SOD2) signaling	Wongmekiat et al. (2021)
Magnolia officinalis Rehder & E.H. Wilson	Magnolol and Honokiol (biphenolics)	*In vivo* study in HFD-induced obese mice.	Promoted browning of adipose tissue and reduce obesity by dual activation of PPAR-α and γ	Chu et al. (2024)
Daucas carota L.	Acetylenic oxylipins	*In vivo* study in HFD-induced diabetic mice	Improved oral glucose tolerance and modulation of gut microbiota by partial agonism for PPAR-γ	Larsen et al. (2024)
Flacourtia jangomas (Lour.) Raeusch.	Rutin (flavonol glycoside) and ostruthin (coumarin)	*In silico* molecular docking	Agonist of PPAR-γ (docking score −9.9 kcal/mol and −7.98 kcal/mol, respectively)	Tomar et al. (2024)
Panax ginseng C.A. Mey.	Ginsenoside Rk1 (saponin)	*In vitro* study in High glucose induced Rat aortic endothelial cells (RAECs) and *in vivo* study HFD-induced C57BL/6 diabetic obese mice	Inhibition of oxidative stress, relieved endothelial dysfunction, increased Nitric oxide (NO) production via activation of PPARs, Protein kinase B/ endothelial nitric oxide synthase (Akt/eNOS) and Nuclear factor erythroid 2-related factor 2/Heme oxygenase-1 (Nrf2/HO-1) pathways	Miao et al. (2024)
Salvia spp. L.	Carnosol and carnosic acid (phenolic diterpene)	*In vivo* study in zymosan-induced peritonitis model	Immunomodulatory effects by agonistic behaviour for	Gazzillo et al. (2025)

		mice; *ex vivo* Surface Plasmon Resonance and *in silico* molecular docking	PPAR-γ and inhibition of inhibitor of the Cyclooxygenase - Microsomal Prostaglandin E Synthase-1 (COX-mPGES-1) pathway	
Not specified	Resveratrol (stilbenoid) and Epigallocatechin gallate (flavonoid)	*In silico* molecular docking analysis	Agonistic behaviour for PPAR-γ (−9.38 kcal/mol and −8.77 kcal/mol, respectively)	Safdar et al. (2025)
Not specified	Maslinic acid (pentacyclic triterpene)	*In silico* network pharmacology	23 overlapping targets including inhibition of PPAR-γ, α-amylase, and α-glucosidase inhibition, glycogen phosphorylase inhibition, reduction in ghrelin concentration, downregulation of Sodium-Glucose Cotransporter 1 (SGLT1) and GLUT2 genes, NF-κB suppression, Nuclear factor erythroid 2-related factor 2 (Nrf2) activation, and AMPK/SIRT 1 pathway activation	Sabarathinam and Satheesh (2025)
Not specified	Ferulic acid, p- coumaric acid (phenolic acids)	*In silico* molecular docking analysis	Potential inhibition of PPAR-γ	Senthil et al. (2020)
Not specified	β-caryophyllene (bicyclic sesquiterpene)	*In vivo* study with high fat/fructose diet induced obese rats	Mitigated insulin resistance, oxidative stress, inflammation and neurological alterations by ligand-independent activation of PPAR-γ	Youssef et al. (2019)
Not specified	1,8-cineole (monoterpene cyclic ether)	*In vitro* study in HAEC cell line, in vivo study in HFD-induced diabetic mice, and in silico molecular docking and molecular dynamics simulation	Amelioration of diabetes-induced endothelial dysfunction via PPAR-γ modulation by deubiquitination	Fu et al. (2025)
Not specified	Quercetin (flavonoid)	*In vivo* study in diabetic rats	Decreased lipid peroxidation by increasing PPAR-γ expression in combination with glibenclamide	Hendrawati and Sulistyoningrum (2025)

Challenges and Recent Advances

Despite the high chemical diversity, pharmacological activity, relatively low toxicity and fewer adverse effects, the translation of plant-derived PPAR-γ modulators from experimental studies to clinical application remains challenging. Their complex isolation and purification, structural complexity, little knowledge about their pharmacokinetics and pharmacodynamics affect the efficacy of testing through biochemical assays. *In silico* virtual screening by computational methods can enhance experimental success rates by predicting the binding pattern of these compounds with specific targets (El-Houri et al. 2015).

Banerjee and his associates (2025) evaluated the antidiabetic effects of a Thai traditional polyherbal formulation (containing 26 medicinal plants) Mathurameha, through *in vitro* study and network pharmacological analysis. The results showed significant modulation in glucose metabolism by interacting with PPAR- γ as a key molecular target and upregulation of GLUT4, AMPK, IRS, PI3K, and AKT genes. Nanotechnology has contributed immensely to the field of target-specific drug delivery of phytoconstituents and helped to overcome the poor solubility and bioavailability. Administration of silver nanoparticles loaded with methanolic leaf extract of *Momordica charantia* successfully restore mitochondrial function, increase insulin sensitivity and reverse inflammatory reactions in the pancreas of Streptozotocin-induced diabetic rats via upregulation of PGC-1α, AMPK, PPARϒ, Akt, insulin and Glut2 mRNA expression and downregulation of Glycogen synthase kinase-3 beta (GSK-3β), Phosphoinositide 3-kinase (PI3K), Interleulin-1B (IL-1B) and TNFα genes (Elekofehinti et al. 2021). El-Marasy and her associates (2024) showed that naringenin-loaded hybridized nanoparticles successfully reduced diabetes-induced depression by regulating brain neurotransmitter secretion and also exerted antioxidative and anti-inflammatory activities by modulating PPAR-γ NLRP3 pathway in experimental rat models.

Conclusion

Plant-derived modulators of the nuclear receptor PPAR-γ have emerged as promising therapeutic candidates for the management of Type-2 Diabetes Mellitus. Numerous phytoconstituents, including flavonoids, terpenoids, alkaloids, phenolics, and fatty acid derivatives, have demonstrated the ability to modulate PPAR-γ activity, thereby improving insulin sensitivity, enhancing glucose uptake, regulating lipid metabolism, and attenuating inflammation and oxidative stress. Unlike conventional synthetic PPAR-γ agonists such as thiazolidinediones, many plant-derived compounds exhibit selective or partial agonistic activity, potentially minimizing adverse effects such as weight gain, fluid retention, and cardiovascular complications.

Despite these encouraging findings, the translation of plant-derived PPAR-γ modulators from experimental studies to clinical application remains challenging. Most evidence is currently limited to *in vitro* studies and animal models, with only a few compounds progressing to clinical evaluation. Major obstacles include poor bioavailability, low potency, limited pharmacokinetic and toxicological data, variability in phytochemical composition, difficulties in standardization of herbal extracts, and insufficient understanding of their precise molecular mechanisms and structure–activity relationships. Furthermore, the pleiotropic nature of PPAR-γ signaling necessitates careful evaluation to avoid undesirable off-target effects and long-term safety concerns.

Future research should focus on the identification and characterization of novel plant-derived selective PPAR-γ modulators (SPPARγMs) with improved efficacy and safety profiles. Advanced approaches such as high-throughput screening, metabolomics, molecular docking, artificial intelligence-assisted

drug discovery, and structure-based drug design can accelerate the discovery of new lead compounds. Additionally, nanotechnology-based delivery systems and formulation strategies may help overcome limitations associated with poor solubility and bioavailability. Rigorous preclinical investigations followed by well-designed clinical trials are essential to establish the therapeutic potential, safety, and efficacy of these natural compounds in diabetic patients.

In conclusion, plant-derived PPAR-γ modulators represent a valuable and largely untapped resource for developing next-generation antidiabetic therapeutics. By addressing current limitations and integrating multidisciplinary research approaches, these natural bioactive compounds hold considerable promise for providing safer, more effective, and mechanistically targeted interventions for the long-term management of diabetes and its associated metabolic complications.

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