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Review

Ginkgo biloba L. as a Potential Alternative Therapy to Improve the Management of Diabetes: An Overview on Phytochemical Insights, Mechanisms, and Therapeutic Applications

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Abstract

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia and associated with severe complications, including cardiovascular diseases, neuropathy, nephropathy, and retinopathy. Although synthetic antidiabetic drugs are available, the side effects and limited long-term effectiveness of these medications highlight the urgent need for safer, more potent alternative therapies. *Ginkgo biloba* L., a traditional medicinal plant rich in flavonoids, terpenoids, and bilobalide, has attracted attention for its potential role in diabetes management. This review critically evaluates the antidiabetic potential of *G. biloba* by analyzing evidence from *in vitro*, *in vivo*, and clinical studies. Moreover, this review highlights the pharmacological actions of *G. biloba* and its key bioactive compounds, focusing on their mechanisms of action, including the activation of adenosine monophosphate-activated protein kinase (AMPK), the translocation of glucose transporter type 4 (GLUT4), and the inhibition of protein tyrosine phosphatases. The review also discusses the therapeutic implications of *G. biloba* supplementation and identifies gaps in clinical validation, optimal dosing, and safety profiling. Preclinical studies have demonstrated that *G. biloba* improves glycemic control by enhancing glucose uptake, regulating insulin secretion, inhibiting α-glucosidase activity, and exerting antioxidant and anti-inflammatory effects. Additionally, clinical trials suggest that supplementation with *G. biloba* can reduce oxidative stress, improve lipid profiles, and mitigate diabetes-related complications. However, despite these promising outcomes, inconsistencies remain in present study designs, dosages, and patient populations, which question the validity of results. Furthermore, studies related to the antidiabetic effect and underlying mechanisms of *G. biloba*, such as modulation of AMPK pathways and GLUT4 expression, also remain inadequate and warrant further systematic investigation. *G. biloba* may still be considered a complementary treatment approach in managing diabetes due to its broad pharmacological activities and favorable safety profile. However, well-designed, large-scale clinical trials are crucial for establishing standardized dosing regimens, confirming long-term safety, and fully elucidating the mechanisms of action. Integrating *G. biloba* into therapeutic strategies could offer a natural, and effective adjunct for enhancing glycemic control and reducing diabetes-related complications.

Keywords: diabetes; *G. biloba*; glucose metabolism; insulin resistance; active compound

1. Introduction

Diabetes mellitus (DM) is a common metabolic disorder that affects global health, often leading to mild to severe complications [1]. It has become a significant public health concern in the twenty-first century [2], and is usually described as an emerging global health crisis. In 2021, approximately 537 million people aged 20 to 79 had DM, with figures expected to reach 643 million by 2030 and 783 million by 2045, thus posing significant challenges for patients and healthcare providers [3,4]. DM is characterized by prolonged high blood glucose levels resulting from defective insulin secretion, insulin function, or both [5]. Diabetes is primarily classified into type 1 (T1D) and type 2 (T2D), each characterized by its differences in clinical and mechanistic features. T1D is associated with autoantibodies, loss of β-cell function, and C-peptide deficiency; it is commonly observed in younger individuals as an autoimmune disorder, where the body cannot produce insulin due to a defect in pancreatic β-cells [6,7]. In contrast, type 2 diabetes mellitus (T2DM), responsible for over 90% of cases, is strongly linked to risk factors such as obesity, insulin resistance, metabolic dysfunction, and subclinical inflammation; this leads to impaired insulin secretion or receptor de-

sensitization, resulting in ineffective glucose uptake [7,8]. A sedentary lifestyle and diet with high levels of fat and carbohydrates are major contributors to T2D development [8]. As a chronic disorder, diabetes poses a significant risk of developing microvascular complications such as neuropathy, retinopathy, nephropathy, and macrovascular complications such as stroke, cardiovascular diseases, and peripheral artery disease [9]. Although managing glycemic levels has helped mitigate some complications, the overall morbidity rate still appears to rise. With no definitive cure available, developing novel therapies for diabetes management remains a critical priority [10]. Various antidiabetic agents facilitate the regulation of blood glucose by enhancing insulin activity or inhibiting enzymes such as DPP-4, SGLT-2, and α-glucosidases; however, their effectiveness is often limited by insulin resistance and side effects like weight gain, hypoglycemia, kidney toxicity, and gastrointestinal discomfort [1].

Medicinal plants have been valued in traditional medicine as alternative treatments for decades, mainly when supported by scientific validation. Compared to synthetic drugs, they are often more affordable, with fewer adverse effects, and therapeutic benefits [11]. Despite advancements in phytochemical-based therapies for diabetes, its global prevalence and associated complications remain high, underscoring the urgent need for discovering more effective therapeutic compounds. Phytochemicals derived from herbs are increasingly recognized for their potential in managing metabolic disorders, particularly dyslipidemia and hyperglycemia [12]. *Ginkgo biloba*, the oldest surviving gymnosperm, often called "the living fossil", has been used in traditional Chinese medicine for centuries. This dioecious tree exhibits diverse pharmacological properties, including neuroprotective, antioxidant, anticancer, hepatoprotective, and cardiovascular benefits, attributed to its roles as a free radical scavenger, membrane stabilizer, and platelet-activating factor inhibitor [13,14]. It is widely marketed as a dietary supplement for metabolic disorders; however, its regulatory status and safety can vary depending on the country, thus concerns over potential adverse effects have been raised in some contexts [15]. Numerous preclinical and clinical studies have explored *G. biloba*'s potential for improving metabolic parameters. However, evidence regarding its specific antidiabetic mechanisms, such as adenosine monophosphate-activated protein kinase (AMPK) activation and GLUT4 translocation, remains fragmented and inconclusive, highlighting the need for a comprehensive systematic review [16]. *G. biloba* contains unique bioactive constituents, including acylated flavonol glycosides (ginkgoghrelins), ginkgolic acids, biflavones (ginkgetin), ginkgotides, and terpene trilactones (ginkgolides), making it valuable in herbal medicine. Studies investigating its leaf extracts, seeds, and key compounds like ginkgolide B and C have demonstrated beneficial effects such as weight loss, reduced adipose tissue, improved lipid profiles, enhanced glucose and insulin regulation, and positively impacting kidney function [17]. However, while many investigations have confirmed *G. biloba*'s antioxidant and general metabolic benefits, its direct effects on hyperglycemia, insulin resistance, and glucose metabolism are inconsistently reported across different experimental models [18]. Moreover, specific modulation pathways such as AMPK activation and GLUT4 translocation have not been comprehensively reviewed in the context of *G. biloba* for diabetes therapy, representing a significant knowledge gap. Given the escalating global burden of diabetes and the limitations of current pharmacotherapies, a deeper understanding of plant-based alternatives like *G. biloba* could offer promising complementary strategies. Building on traditional medicine knowledge and emerging antidiabetic research, this study critically reviews *G. biloba*'s role in controlling hyperglycemia and modulating key metabolic pathways. It aims to provide clearer, detailed insights compared to previous general studies, while highlighting future directions for therapeutic development.

2. Methodology

Literature Search Strategy

A comprehensive literature search was conducted using Google Scholar, PubMed, Cochrane Library, ScienceDirect, and Scopus databases. The search utilized the following keyword combinations with Boolean operators to maximize relevance and search coverage: "*G. biloba*" AND ("Diabetes Mellitus" OR "Diabetes" OR "Hyperglycemia") AND ("antidiabetic" OR "insulin resistance" OR "glucose metabolism"). Additional keywords such as "isolated compounds" AND ("*in vitro*" OR "*in vivo*" OR "clinical trials") were also employed to narrow the focus on studies that investigated the antidiabetic properties of compounds isolated from *G. biloba*. This review was limited to English-language studies published up to December 11, 2024, to ensure accessibility and ease of understanding. The selection process adhered to specific inclusion criteria, which included *in vitro* and *in vivo* studies, clinical trials, and research focusing on the antidiabetic effects of *G. biloba* and its isolated compounds. Key data extracted from the selected studies included: year of publication, tested compounds, experimental models (e.g., cell lines, animal models), observed outcomes, results, tested concentrations, and molecular mechanisms underlying the observed effects. Studies that did not meet these criteria or failed to report antidiabetic effects of *G. biloba* or its compounds were excluded from the review.

3. Therapeutic Applications

In this study, 85 articles reported the antidiabetic effects of *G. biloba* through *in vitro*, *in vivo*, and clinical trials. Most of these studies focused on *G. biloba* leaves or its isolated compounds. Tables 1A,1B,1C (Ref. [19–85]) pro-

Table 1A. *In vitro* studies of *G. biloba*.

Test model	Parts	Dose/concentration	Route of administration	Mechanism of action	Formulation	Ref.
α-amylase & α-glucosidase	Leaves	10, 25, and 50 mg/mL	*In vitro*, Enzyme	↓ *α-amylase* inhibitory activities and ↑ α-glucosidase.	Water and Ethanol	[19]
	Leaves	-	*In vitro*, Enzyme	Potent inhibition of α-amylase and α-glucosidase may be a promising natural hypoglycemic and antidiabetic strategy.	Undefined	[20]
α-glucosidase	Seed	20 mg/mL	*In vitro*, Enzyme	α-Glucosidase inhibition offers a potential natural antidiabetic strategy.	Alkali-soluble acid	[21]
AMPK	Leaves	20 and 40 µg/mL	*In vitro*, Enzyme	↑ GLUT4 translocation to the membrane and subsequent ↑ glucose uptake in C2C12 myotubes activated the AMPK pathway.	Petroleum ether	[22]
L6 skeletal muscle cell	Leaves	50 µg/mL	*In vitro*, Cell line	↑ Glucose uptake through both PI 3-kinase and AMPK mediation leads to glucose homeostasis.	Methanol	[23]
SMC	Leaves	0.25 µg/mL	*In vitro*, Cell line	Artificially mimic insulin's effects on glucose metabolism and transport.	Ethanol	[24]
BMSCs	Leaves	200 µg/mL	*In vitro*, Cell line	↑ The effectiveness of BMSCs resulted in ↓ the reversal of blood glucose levels and reversing oxidative stress.	Ethanol	[25]
L-02 cell line	Leaves	10 mg/L	*In vitro*, Cell line	↑ Insulin sensitivity is mainly regulated by ↑ IRS-2 transcription.	Undefined	[26]
INS-1 rat beta cells	Leaves	50 g/mL	*In vitro*, Cell line	↑ Insulin secretion.	Undefined	[27]
Preadipocytes (Swiss 3T3-L1 cells)	Leaves	0.75 and 1.0 mg/mL	*In vitro*, Cell line	↑ Preadipocyte maturation, ↑ expression of mature adipocyte proteins.	Undefined	[28]
Mesangial cell	Leaves	30 mmol/L	*In vitro*, Cell line	↓ Levels of TGF-β1, IGF-1, and CTGF.	Undefined	[29]
HUVECs	Leaves	25, 50, 100 µg/mL	*In vitro*, Cell line	↓ IHG-induced DNA oxidation of endothelial cells.	*G. biloba* extract (EGb 761)	[30]
3T3-L1 cells	Seed	0.4% ginkgo vinegar	*In vitro*, Cell line	↓ C/EBPδ and PPARγ, and inhibited lipid accumulation.	Ginkgo vinegar	[31]
HAECs	Leaves	100 µg/mL	*In vitro*, Cell line	↓ Adhesion molecule expression and endothelial adhesion by ↑ HO-1 via PI3K/Akt/eNOS and p38/MAPK pathways.	Undefined	[32]
HLEC	Leaves	10, 20, and 40 µg/mL	*In vitro*, Cell line	↓ Apoptosis is inhibited by inhibiting oxidative stress, ↓ the Bax/Bcl-2 ratio, and ↓ caspase-3 activity.	Undefined	[33]
EGCs		25, 50, 100 µg/mL	*In vitro*, Cell line	↓ Hyperglycemic.	Undefined	[34]

AMPK, Adenosine monophosphate-activated Protein Kinase; SMC, Smooth muscle cells; BMSCs, Bone marrow mesenchymal stem cells; GLUT4, Glucose transporter type 4; IRS-2, Insulin receptor substrate 2; TGF-β1, Transforming growth factor-beta 1; IGF-1, Insulin-like growth factor 1; CTGF, Connective tissue growth factor; HUVECs, Human umbilical vein endothelial cells; HAECs, Human aortic endothelial cells; HLEC, human lens epithelial cells; EGCs, enteric glial cells. The up sign (↑) indicates an increase, and the down sign (↓) indicates a decrease.

Table 1B. *In vivo* antidiabetic studies of *G. biloba*.

Test model	Parts	Dose/concentration	Route of administration	Mechanism of action	Formulation	Ref.
Wistar rats, STZ induced	Leaves	100, 200, and 300 mg/kg	I.P	Antihyperglycemic, antioxidant, and antihyperlipidemic activities.	Undefined	[35]
Wistar rats, STZ induced	Leaves	-	I.P	↓ Serum glucose.	Undefined	[36]
Wistar rat, STZ induced	Leaves	0.11 g/kg/day	P.O	Protected β-cells, ↑ insulin expression, and antioxidant effects.	Ethanol	[37]
Wistar male rats, STZ induced	Leaves	50, 100, 150 mg/kg/day	Orally	Anti-hyperglycemic effects by upregulated GLUT-4 and IRS-1 in hepatic tissues.	Undefined	[38]
Wistar rats, STZ induced	Leaves	50 mg/kg	I.P	Cardioprotective effects against late complications of diabetes are helpful as an adjuvant therapy for the prevention of diabetic cardiomyopathy.	Ethanol	[39]
Wistar rats, STZ induced	Leaves	200 mg/kg	P.O	Did not improve maternal glycemia, pregnancy rate, antioxidant enzymes, or fetal development in diabetic rats.	Undefined	[40]
Wistar rats, STZ induced	Leaves	0.11 g/kg	I.P	↓ Hyperlipidemia, uremia, oxidative stress, and renal dysfunction.	Undefined	[41]
Wistar rats, STZ induced	Leaves	100 mg/kg	Intragastrically	↓ Blood glucose.	Ethanol	[42]
Wistar rats, STZ induced	Leaves	50 mg/kg	Gavage	Neuroprotective effects on the jejunum and ileum plexuses, supporting enteric nervous system integrity in diabetes.	Undefined	[43]
Male Wistar rats, STZ induced	Leaves	100 mg/kg/day	P.O	↓ Blood glucose and plasma drug concentrations.	Undefined	[44]
Male Wistar rats, STZ induced	Leaves	100 mg/kg/day	P.O	Effects of diabetes on enzyme activities.	Undefined	[45]
Male ApoE$^{-/-}$ mice, STZ induced	Leaves	200 or 400 mg/kg	Gavage	Blocking ERS, ↓ diabetic myocardial damage, including intramyocardial inflammation, interstitial fibrosis, and cardiomyocyte death.	Ethanol	[46]
Mice, STZ induced	Leaves	50 mg/kg	P.O	↓ Blood triglyceride levels, ↑ liver LPL, ↑ liver PPAR-α, and ↓ body weight.	Undefined	[47]
Rats, STZ induced	Leaves	500 mg/kg GBE diluted in 2 mL 0.9%	Gavage	↓ Hyperglycemia, dyslipidemia, ↓ food intake, and body adiposity. ↓ PTP-1B levels in the gastrocnemius muscle, ↑ insulin sensitivity, Akt phosphorylation, and IRS-1.	Undefined	[48]
Albino rats, STZ induced	Leaves	120 mg/kg	P.O	↓ The levels of glucose and fat in the blood.	Undefined	[49]
Albino rats, STZ induced	Leaves	100 mg/kg	P.O	↑ Prostatic changes produced by DM.	Undefined	[50]

Table 1B. Continued.

Test model	Parts	Dose/concentration	Route of administration	Mechanism of action	Formulation	Ref.
Albino rats, STZ induced	Leaves	100 mg /kg daily	Intraperitoneal	↓ Blood glucose level.	The capsule was dissolved in saline	[51]
Albino Wistar rats, STZ induced	Leaves	50 and 100 mg/kg/day,	Orally	↓ FBS and ↑ in blood GSH.	Undefined	[52]
Albino rats, STZ induced	Leaves	100 mg/kg/day	P.O	Protects against diabetes-induced prostate damage.	Undefined	[53]
DBA/2 mice, STZ induced	Leaves	low dose (50 mg/kg/day); high dose (200 mg/kg/day)	P.O	Protected podocytes from hyperglycemia and prevented DN through Nrf-2/HO-1 activation.	Undefined	[54]
OLETF rats	Leaves	100 and 200 mg/kg	P.O	Protects against atherosclerosis and may aid in its prevention.	Undefined	[55]
Male ApoE$^{-/-}$ mice, STZ induced	Leaves	low-dose GBE group (200 mg/kg/day), and high-dose GBE group (400 mg/kg/day)	Intragastric	↓ Serum lipid metabolism levels, blood glucose, and inflammatory cytokines.	Undefined	[56]
Normoglycemic male adult Wistar rats	Leaves	100 mg/kg/day	Orally	↓ Hyperglycemic activity. ↑ Glucose and lipid metabolism act on the expression of key genes.	Undefined	[57]
Wistar albino rats, STZ induced	Leaves	100 mg/kg/day	Orally	Exhibiting antidiabetic, antihypertensive, and antilipidemic effects.	Undefined	[58]
Sprague-Dawley rats	Leaves	40 mg/kg	P.O	Preventive effect against hyperlipidemia.	Undefined	[59]
Adult male Sprague-Dawley rats, STZ induced	Leaves	50, 100, and 200 mg/kg/day	Orally	↓ Blood glucose exhibits glycemic control.	Dissolved in 1% CMC-Na at 10, 20, and 40 mg/mL concentrations.	[60]
Sprague Dawley rats, STZ induced	Leaves	200 mg/kg/day	Orally	Antihyperglycemic and antilipidemic effects, ↑ such as glucose metabolism in the liver by modulating ↑ the hepatic key genes.	Undefined	[61]
Male Sprague-Dawley rats		200 mg/kg	Orally	↑ Pancreatic β-cells, inflammation, and oxidative stress.	Methanol	[62]
HFD-induced Mice	Leaves	100, 200 and 400 mg/kg	P.O	↓ Insulin resistance and ameliorate other symptoms of the metabolic syndrome.	Undefined	[63]

STZ, streptozotocin; I.P, intraperitoneally; P.O, oral administration; OLETF, Otsuka Long-Evans Tokushima Fatty; GLUT-4, glucose transporter type 4; IRS-1, insulin receptor substrate 1; GBE, Ginkgo biloba extract; FBS, fasting blood sugar; GSH, glutathione; Nrf-2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase-1; HFD, high-fat diet; CMC-Na, sodium carboxymethylcellulose.

Table 1C. *In vitro* and *in vivo* antidiabetic studies of isolated compounds of *G. biloba*.

Isolated compounds	Test model	Parts	Dose/concentration	Route of administration	Mechanism of action	Formulation	Ref
Bilobalide (1)	Male Wistar rats, STZ	Leaves	10 mg/kg	Intraperitoneal	↓ Blood glucose and activating insulin secretion.	Undefined	[64]
	3T3-L1 preadipocyte	-	0–200 µM	*In vitro*, Cell line	Inhibited adipogenesis and ↑ lipolysis in 3T3-L1 cells via AMPK activation.	Undefined	[65]
	Female NMRI mice, alloxan-induced	Leaves	100 & 200 mg/kg	Administered orally by gavage (stomach tube)	↑ Effect of glucose and tolbutamide.	Undefined	[66]
	3T3-L1 preadipocytes	-	10, 20 & 50 µM	*In vitro*, Cell line	↓ Inflammatory adipokine secretion, ↑ adiponectin secretion, ↓ NF-κB/JNK activation, and inhibiting serine phosphorylation of IRS-1 receptors of the insulin signaling pathway.	Undefined	[67]
	3T3-L1 preadipocytes	-	10, 20, and 50 µM	*In vitro*, Cell line	Protected adipocytes from hypoxia by ↓ oxidative stress, mitochondrial damage, ↓ and cell death, and inflammation.	Undefined	[68]
	3T3-L1 adipocytes	Leaves	25 µM, 50 µM	*In vitro*, Cell line	Potential novel obesity treatment.	Undefined	[69]
	Male Wistar rats	-	2 mg/kg/day	*In vivo*, Streptozotocin	↑ Glucose uptake is linked to glycogen synthesis.	Distilled water	[70]
2-hydroxy-6-(10′-hydroxypentadec-11′(*E*)-en-1-yl) benzoic acid (2), 2-hydroxy-6-(11′-hydroxypentadec-9′(*E*)-en-1-yl) benzoic acid (3), 2-hydroxy-6-tridecylbenzoic acid (4), 2-hydroxy-6-pentadecylbenzoic acid (5), 2-hydroxy-6-(12′-hydroxyheptadec-13′(*E*)-en-1-yl) benzoic acid (6), and 2-hydroxy-6-(11-hydroxyundecyl) benzoic acid (7)	PTP	Leaves	50 µM	*In vitro*, Protein	Compounds 5–7 inhibited PTPN11, PTPN2, PTP1B, DUSP9, PTPRS, and PTPN9 by over 90%, while compounds 2 and 3 showed significant activity against PTPN11, PTPN2, PTP1B, and DUSP9, targeting PTPs related to insulin resistance.	Aqueous, methanol	[71]
Quercetin (8)	α-Amylase & α-Glucosidase	Leaves	0.061 µM and 0.038 µM	*In vitro*, Enzyme	Potent α-glucosidase and mild α-amylase inhibition make them effective for NIDDM management.	Undefined	[72]

Table 1C. Continued.

Isolated compounds	Test model	Parts	Dose/concentration	Route of administration	Mechanism of action	Formulation	Ref
Rutin (9)	α-Amylase & α-Glucosidase	Leaves	0.043 and 0.037 µM	*In vitro*, Enzyme	Potent α-glucosidase and mild α-amylase inhibition make them effective for NIDDM management.	Undefined	[73]
Ginkgolide C (10)	3T3-L1 cells	Leaves	3–100 µM	*In vitro*, Cell line	Inhibited adipogenesis-related factors, ↑ Sirt1/AMPK activity, ↑ lipolysis, ↑ metabolic syndrome, and insulin resistance.	Undefined	[74]
Kaempferol (11)	INS-1E cells and human islets	-	0.1, 1, and 10 µM	*In vitro*, Cell line	↑ β-cell survival and function through cAMP signaling and antiapoptotic protein expression.	Undefined	[75]
Ginkgetin (12)	3T3-L1 cells	Leaves	5 µM	*In vitro*, Cell line	Inhibited PPARγ and C/EBPα by preventing STAT5 activation in adipogenesis.	Undefined	[76]
	C57BL/6 male mice	Leaves	5 and 10 mg/kg/day	*In vivo*, intraperitoneal injection	Inhibited white adipose hypertrophy, showing potential as an anti-obesity drug.	Undefined	[77]
Isoginkgetin (13), bilobetin (14), ginkgetin (12) and sciadopitysin (15)	pancreatic lipase	Leaves	1, 10, and 100 µM	*In vitro*, Enzyme	Hypolipidemic effects.	Undefined	[78]
Isoginkgetin (13)	3T3-L1 mouse fibroblasts	Leaves	5 mM	*In vitro*, Cell line	↑ Adiponectin production in adipocytes. ↑ Plasma adiponectin levels.	Undefined	[79]
Ginkgolide B (16)	HUVECs	Leaves	0.2, 0.4, and 0.6 mg/mL	*In vitro*, Cell line	Inhibited TLR4-mediated inflammation and JAK2/STAT3, p38 MAPK signaling in high-glucose endothelial cells.	Undefined	[80]
	MPC5	Leaves	0, 5, 10, 20, 40, 80, 100, 200 µM	*In vitro*, Cell line	↓ Total cholesterol, hyperglycemia serum, lipid accumulation, and triglyceride concentrations.	Undefined	[81]
	Male ICR mice, streptozotocin	-	-	*In vivo*	Prevents endothelial dysfunction in the DM aorta. ↑ Aortic SOD1 activity and ↑ NO bioavailability in endothelial cells.	Undefined	[80]
Ginkgolic acid (17)	α-glucosidase	Leaves	13.8 and 40.1 µg mL (–1)	*In vitro*, Enzyme	↑ α-glucosidase inhibitory activity.	Ethyl acetate, n-hexane, n-butanol, and chloroform	[81]

Table 1C. Continued.

Isolated compounds	Test model	Parts	Dose/concentration	Route of administration	Mechanism of action	Formulation	Ref
Amentoflavone (18), bilobetin (14), sequoiaflavone (19), ginkgetin (12), sciadopitysin (15), isoginkgetin (13)	3T3-L1 preadipocytes	Leaves	0.005–100 µM	*In vitro*, Cell line	↑ Lipolysis inhibits cAMP phosphodiesterase.	Undefined	[82]
(2E,4E,1′R,3′S,5′R,8′S)-dihydrophaseic acid 3′-O-β-D-glucopyranoside-anoside. (20), 7,8-dihydro-(R)-7-methoxyconiferyl alcohol (21), (8S)-3-methoxy-8,4′-oxy-neolignan-4,9,9′-triol 3′-O-β-D-glucopyranoside (22).vanillyl alcohol (23),3,4-dimethoxyphenyl β-D-glucopyranoside (24), 3,4-dimethox-yphenyl alcohol-7-O-β-D-glucopyranoside (25), olivil (26),(−)-olivil 4,4′-di-O-β-D-glucopyranoside (27), lariresinol (28),(+)-lariciresinol (29), (+)-8-hydroxypinoresinol (30),(+)-pinoresinol O-β-D-glucopyranoside (31), (+)-cycloolivil(32),22 5-(3-hydroxypropyl)-6-methoxy-2-(3′-methoxy-4′-hy-droxyphenyl)-3-benzofurancarboxaldehyde (33), ginkgolideA (34), and ginkgolide C (10)	Human hepatocarcinoma HepG2 cells	Stem bark	10 ng/mL	*In vitro*, Cell line	Inhibited NF-κB activity and ↓ COX-2 and iNOS expression.	Methanol	[83]
Ginkgolides A, B, C (34, 16, 10), and bilobalides (1).	HFD-induced obese male Wistar rats	-	-	*In vivo*	↓ Adipocyte. ↓ Acetate accumulation tended to ↓ [3H]-oleate incorporation into epididymal adipose tissue.	Undefined	[84]
Rutin (9), quercetin (8)	Adult male Sprague-Dawley rats, STZ		90 mg/kg	*In vivo*	Inhibited the aldose reductase (AR) activity, ↑ production of glutathione, ↓ malondialdehyde (MDA), and advanced glycosylation end products (AGEs).	Undefined	[85]

PTP, Protein tyrosine phosphorylation; GLUT-4, Glucose transporter type 4; MPC5, Mouse renal podocytes; ICR, Institute of Cancer Research; NF-κB, Nuclear factor kappa B; COX-2, Cyclooxygenase-2; iNOS, Inducible nitric oxide synthase; HFD, High-fat diet; MDA, Malondialdehyde; AGEs, Advanced glycosylation end products.

vides an overview of the *in vitro* and *in vivo* studies examining the antidiabetic properties of *G. biloba* and its bioactive compounds.

3.1 Preclinical Studies of G. biloba in Diabetes Management

3.1.1 *In Vitro* Antidiabetic Activity

The aqueous extract of Ginkgo leaves at a 50 mg/mL dose demonstrated significant α-glucosidase inhibition (65%), while the ethanolic extract showed even higher inhibition (95%). Both extracts exhibited comparatively lower α-amylase inhibitory activity (45%). This greater selectivity toward α-glucosidase over α-amylase suggests that Ginkgo leaf extracts could be valuable for managing early-stage hyperglycemia in type 2 diabetes. High α-glucosidase inhibition with moderate α-amylase inhibition is desirable, as excessive α-amylase inhibition may cause undigested starch accumulation in the colon, leading to gastrointestinal discomfort [19]. Similarly, the leaf extracts exhibited potent inhibitory effects on both α-amylase ($>$70%) after the gastric and intestinal phases of digestion, and α-glucosidase ($>$70%) after the intestinal phase, highlighting their potential as natural hypoglycemic agents, although the specific solvent system remains unspecified [20]. Similarly, an alkali-soluble acid extract derived from the seeds at a concentration of 20 mg/mL effectively suppressed α-glucosidase activity, reinforcing its potential as a novel candidate for hypoglycemic intervention [21]. Table 1A (Ref. [19–34]) provides an overview of the *in vitro* studies examining the antidiabetic properties of *G. biloba*.

Skeletal muscle regulates blood glucose levels by facilitating glucose uptake through insulin-dependent and insulin-independent pathways. It serves as the primary site for glucose transport [22]. Two major independent signaling pathways govern this process in response to various stimuli. PI3-kinase, activated by insulin, is essential for promoting glucose uptake, with its impaired activation in skeletal muscle leading to reduced glucose transport. AMPK, another key regulatory protein primarily activated by cellular stress, plays a central role in maintaining energy homeostasis. It consists of two catalytic subunit isoforms, α1 and α2, with phosphorylation of the α subunit being critical for its activation. AMPK α1 is broadly expressed in tissues like skeletal muscle, liver, and pancreas, whereas AMPK α2 is predominantly found in skeletal and cardiac muscle [23]. In support of AMPK's role in glucose regulation, treatment with petroleum ether extracts of Ginkgo leaves at concentrations of 20 and 40 µg/mL was shown to activate the AMPK pathway, thereby promoting GLUT4 translocation to the plasma membrane and enhancing glucose uptake in C2C12 myotubes [22]. Furthermore, methanolic leaf extracts at 50 µg/mL stimulated glucose uptake in L6 skeletal muscle cells through PI 3-kinase and AMPK-mediated pathways, highlighting their contribution to maintaining glucose homeostasis [23]. Similarly, ethanolic extracts of the leaves at a concentration of 0.25 µg/mL successfully mimicked insulin-like effects on glucose metabolism and transport in smooth muscle cells, suggesting their potential application in diabetes management [24]. At a higher concentration of 200 µg/mL, ethanolic leaf extracts significantly enhanced the efficacy of bone marrow mesenchymal stem cells (BMSCs) in lowering blood glucose levels and reversing oxidative stress in diabetic rat models. *In vitro*, BMSCs exposed to H_2O_2 exhibited a significant reduction in cell viability (65.0 $\pm$ 2.45% of the control); in comparison, BMSCs protected by ethanolic *Ginkgo biloba* extract (EGB) showed improved cell viability (94.5 $\pm$ 3.31% of the control), further demonstrating the therapeutic potential of EGB in mitigating oxidative damage [25]. Insulin receptor substrate-2 (IRS-2) is the liver's predominant isoform, compensating for the absent insulin receptor substrate-1 (IRS-1) in IRS-1 knockout models. Hepatic insulin signaling is primarily mediated through IRS-2. Moreover, treatment with leaf extracts at 10 mg/L in the L-02 cell line improved insulin sensitivity, primarily by upregulating IRS-2 transcription, indicating a possible mechanism for alleviating insulin resistance [26]. In pancreatic studies, exposure to 50 µg/mL of the extract exhibited a strong stimulatory effect on insulin secretion in INS-1 rat beta cells, signifying its potential role in improving pancreatic β-cell function [27]. Similarly, leaf extracts at 0.75 mg/mL and 1.0 mg/mL influenced the adipogenesis pathway in Swiss 3T3-L1 preadipocytes, accelerating preadipocyte maturation and stimulating the expression of mature adipocyte-specific proteins, which may have implications for metabolic regulation [28]. Renal studies revealed that treatment with leaf extracts at a concentration of 30 mmol/L significantly reduced the levels of transforming growth factor-β1 (TGF-β1), insulin-like growth factor-1 (IGF-1), and connective tissue growth factor (CTGF) in mesangial cells exposed to high glucose, indicating a protective effect against diabetic nephropathy [29]. Similarly, administration of *G. biloba* extract (EGb 761) at 25, 50, and 100 µg/mL in human umbilical vein endothelial cells (HUVECs) significantly reduced IHG-induced DNA oxidation, a key contributor to diabetes-associated vascular complications [30]. Furthermore, ginkgo vinegar at 0.4% concentration was found to suppress lipid accumulation in 3T3-L1 cells by downregulating the expression of CCAAT/enhancer-binding protein delta (C/EBPδ) and peroxisome proliferator-activated receptor gamma signaling (PPARγ), two crucial regulators of adipogenesis, suggesting its potential role in lipid metabolism modulation [31]. Heme oxygenase-1 (HO-1), also known as heat shock protein 32, was initially identified as the rate-limiting enzyme responsible for degrading heme into equimolar amounts of carbon monoxide (CO), biliverdin, and free iron. The induction of HO-1 is thought to involve the activation of signaling pathways such as mitogen-activated protein kinases (MAPKs) and transcription factors like nuclear factor ery-

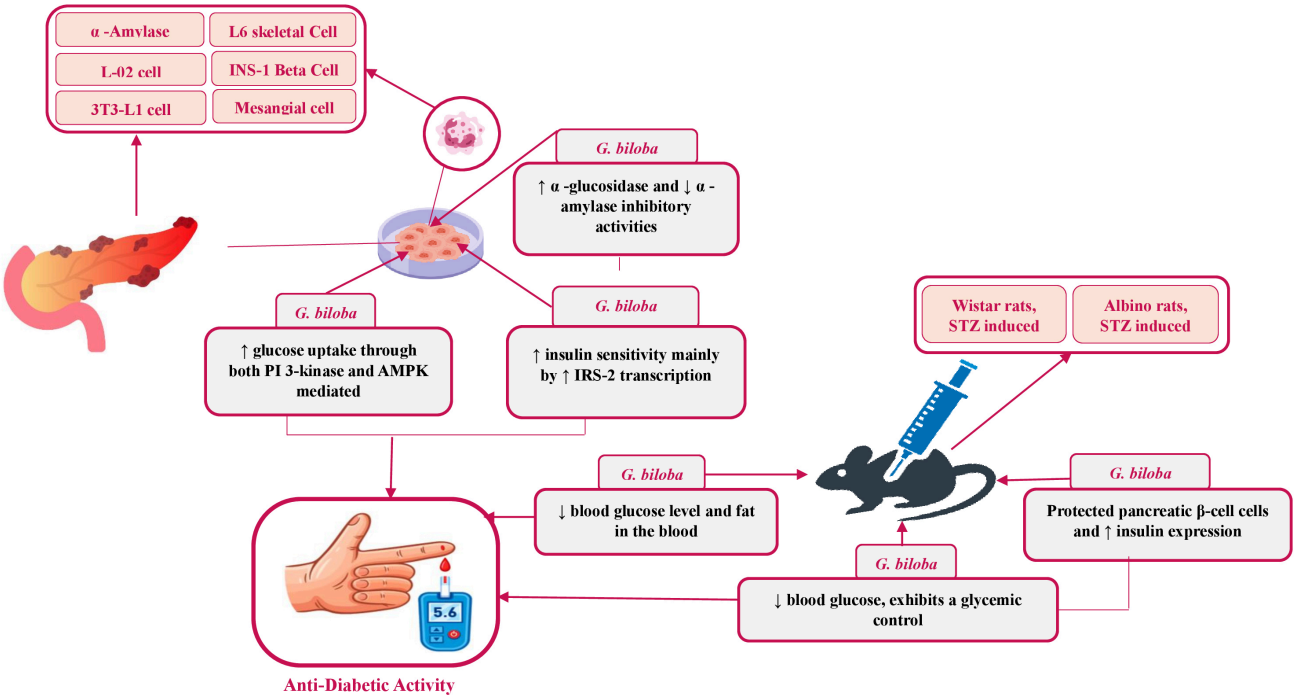

Fig. 1. Proposed *in vivo* and *in vitro* mechanisms of action of *G. biloba* in antidiabetic activity. AMPK, Adenosine monophosphate-activated protein kinase; IRS-2, Insulin receptor substrate 2; PI 3-kinase, Phosphatidylinositol 3-kinase; STZ, Streptozotocin. The up sign (↑) indicates an increase, and the down sign (↓) indicates a decrease.

throid 2-related factor 2 (Nrf2). Notably, treatment with leaf extracts at a concentration of 100 µg/mL significantly reduced high-glucose-induced endothelial adhesion and the expression of adhesion molecules in human aortic endothelial cells (HAECs), primarily through the upregulation of HO-1 via activation of the PI3K/Akt/eNOS and p38/MAPK signaling pathways [32]. In ocular studies, exposure to leaf extracts at 10, 20, and 40 µg/mL protected human lens epithelial cells (HLECs) from high-glucose-induced apoptosis by reducing oxidative stress, lowering the Bax-to-Bcl-2 ratio, and suppressing caspase-3 activity, suggesting their potential in preventing diabetic cataracts [33]. Finally, enteric glial cells (EGCs) treated with 25, 50, and 100 µg/mL of the extract demonstrated attenuation of hyperglycemia-induced damage, highlighting their significance in preserving gastrointestinal homeostasis under diabetic conditions [34]. Proposed *in vivo* and *in vitro* mechanisms of action of *G. biloba* in antidiabetic activity are given in Fig. 1.

3.1.2 *In Vivo* Antidiabetic Activity

G. biloba leaf extract initiates its protective effects primarily through activation of the Nrf-2/HO-1 pathway. The extract inhibits Keap1, a negative regulator of Nrf-2, allowing Nrf-2 to translocate into the nucleus where it binds to antioxidant response elements (ARE) and upregulates the expression of the *HO-1* gene. The HO-1 enzyme catalyzes the conversion of heme into biliverdin, CO, and free iron, which collectively reduce oxidative stress in the cell. Concurrently, *G. biloba* stimulates the GLUT-4/IRS-1 signaling pathway, where it increases phosphorylation of IRS-1, activating downstream PI3K/AKT signaling. This cascade promotes the translocation and expression of GLUT-4 on the cell membrane, enhancing glucose uptake by cells. Additionally, *G. biloba* inhibits endoplasmic reticulum stress (ERS), preventing apoptosis of pancreatic β-cells, which are crucial for insulin secretion. It also reduces inflammatory cytokine levels by modulating the IRE1-JNK pathway, further alleviating cellular stress. Together, these molecular effects improve insulin sensitivity, increase glucose uptake, and provide overall anti-diabetic benefits by reducing oxidative damage, inflammation, and β-cell death (Fig. 2). Streptozotocin (STZ)-induced diabetic Wistar rats treated with intraperitoneal (I.P.) administration of leaf extracts at doses of 100, 200, and 300 mg/kg body weight exhibited significant antihyperglycemic, antioxidant, and antihyperlipidemic activities, demonstrating their potential therapeutic efficacy in diabetes management [35]. Table 1B (Ref. [35–63]) provides an overview of the *in vivo* studies examining the antidiabetic properties of *G. biloba*.

Another study reported that intraperitoneal administration of leaf extracts led to a marked reduction in serum glucose levels. At the same time, the treated diabetic rats maintained a higher body weight than the untreated group, further highlighting the metabolic benefits of the extract [36]. Oral administration of 0.11 g/kg/day of ethanolic leaf extracts effectively preserved pancreatic β-cell integrity, enhanced insulin expression, and improved antioxidant status in type 2 diabetic rats, suggesting its role in mitigat-

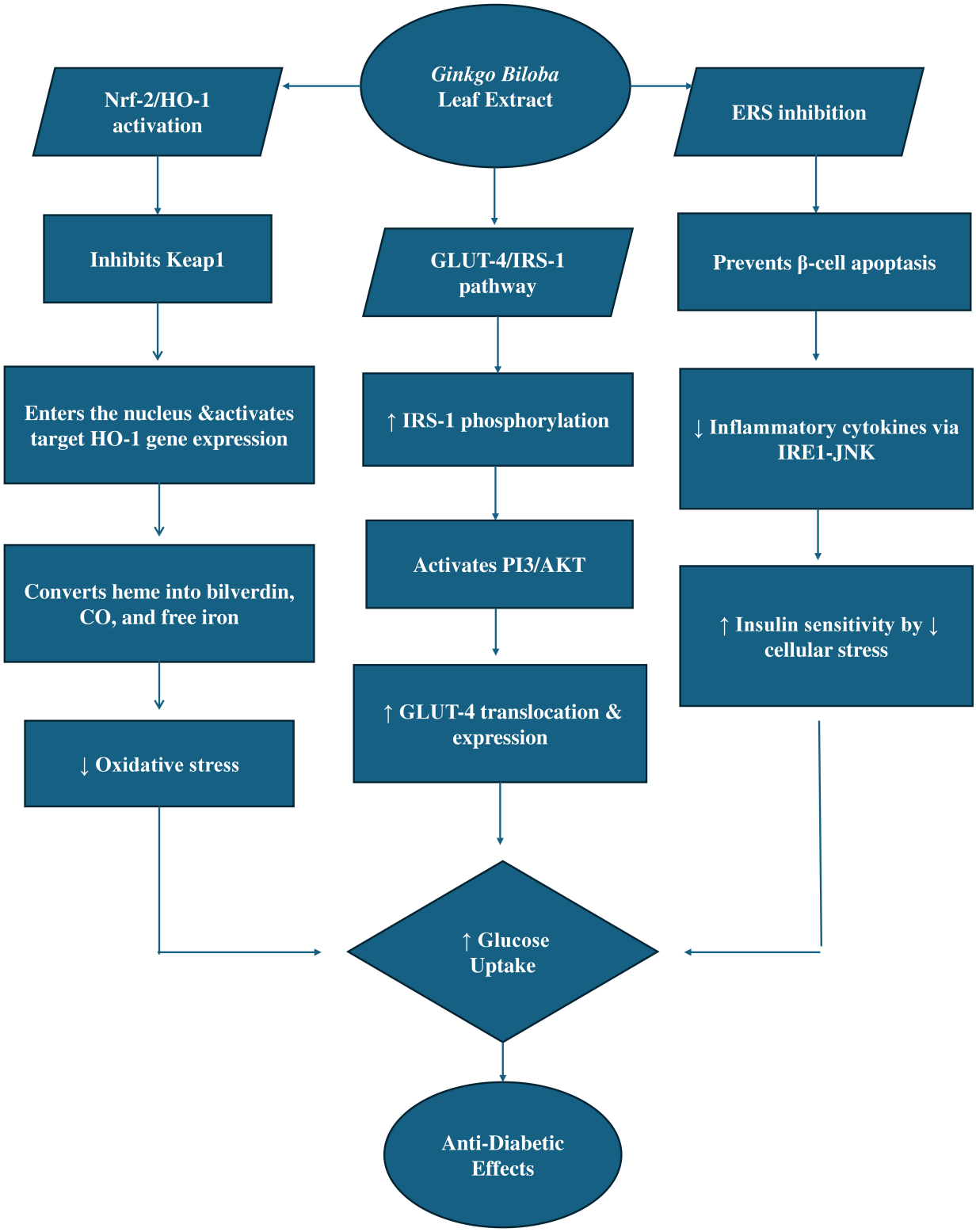

Fig. 2. Mechanistic pathways of *G. biloba* in diabetes management, highlighting Nrf-2/HO-1-mediated antioxidant effects, enhancement of insulin signaling via GLUT-4/IRS-1, and ERS inhibition. GLUT4, Glucose transporter type 4; HO-1, Heme oxygenase-1; Nrf2, Nuclear factor erythroid 2-related factor 2; IRS-1, Insulin receptor substrate-1; ERS, Endoplasmic reticulum stress.

ing diabetes-induced pancreatic dysfunction [37]. Furthermore, supplementation with 50, 100, and 150 mg/kg/day of the extract significantly upregulated GLUT-4 and IRS-1 in hepatic tissues, resulting in pronounced antihyperglycemic effects in STZ-induced diabetic rats [38]. In another experimental setting, Wistar rats receiving 50 mg/kg of ethanolic leaf extracts via intraperitoneal injection exhibited notable cardioprotective effects, which may serve as an adjuvant therapy in preventing diabetic cardiomyopathy and related complications [39]. However, oral administration of 200 mg/kg of the extract throughout pregnancy failed to counteract the diabetes-associated rise in maternal glycemia, reduced pregnancy rates, impaired fetal development, and diminished antioxidant enzyme activity, indicating its limited efficacy in gestational diabetes management [40]. Moreover, intraperitoneal administration of 0.11 g/kg of the leaf extract demonstrated nephroprotective effects in type 2 diabetic rats by alleviating hyperlipidemia, uremia, oxidative stress, and renal dysfunction, suggesting its therapeutic potential in preventing diabetes-induced nephrotoxicity [41]. Proposed *in vivo* and *in vitro* mechanisms of action of *G. biloba* in antidiabetic activity have been given in Fig. 1.

Intragastric administration of 100 mg/kg of ethanolic leaf extract in streptozotocin (STZ)-induced diabetic Wistar rats significantly reduced blood glucose levels, reinforcing its potential as an antidiabetic agent [42]. Similarly, gavage administration of 50 mg/kg of the extract exhibited a neuroprotective effect on the jejunum submucous plexus and the myenteric plexus of the ileum, suggesting its role in preserving enteric nervous system integrity in diabetic conditions [43]. Oral administration of 100 mg/kg per day of the extract in male Wistar rats reduced blood glucose levels and influenced plasma drug concentrations, indicating potential pharmacokinetic interactions [44]. Additionally, another study reported that the same oral dosage modulated enzyme activities affected by diabetes, suggesting a broader metabolic regulatory effect [45]. In ApoE$^{-/-}$ diabetic mice, gavage administration of 200 or 400 mg/kg of the ethanolic extract effectively reduced diabetic myocardial damage by blocking endoplasmic reticulum stress (ERS), thereby preventing cardiomyocyte death, interstitial fibrosis, and intramyocardial inflammation [46]. Furthermore, in STZ-induced diabetic mice, 50 mg/kg of the extract significantly lowered blood triglyceride levels while increasing peroxisome proliferator-activated receptor-alpha (PPAR-α) expression and liver lipoprotein lipase (LPL), alongside a reduction in body weight, demonstrating its lipid-modulating properties [47]. Moreover, gavage administration of 500 mg/kg *G. biloba* extract (GBE), diluted in 2 mL of 0.9% saline to minimize potential toxicity, effectively prevented hyperglycemia and dyslipidemia in diet-induced obese diabetic rats. The treatment also significantly reduced food intake and body adiposity. Additionally, it downregulated protein tyrosine phosphatase-1B (PTP-1B) levels in the gastrocnemius muscle and enhanced insulin sensitivity by promoting Akt phosphorylation and IRS-1 activation, indicating a strong potential for improving insulin signaling and glucose metabolism [48]. Oral administration of 120 mg/kg of *G. biloba* extract (GBE) in STZ-induced diabetic albino rats demonstrated notable antidiabetic effects by significantly reducing blood glucose and lipid levels, potentiating its effect as a possible therapeutic agent for diabetes management [49]. Similarly, 100 mg/kg of GBE administered orally exhibited a protective effect against the destructive structural changes in the prostate gland caused by diabetes, suggesting its role in mitigating diabetic complications beyond glycemic control [50]. Intraperitoneal administration of 100 mg/kg of the extract, dissolved in a saline-based capsule, effectively lowered blood glucose levels in STZ-induced diabetic albino rats, further validating its antihyperglycemic potential [51]. In another study, oral administration of 50 mg/kg/day and 100 mg/kg/day of the extract led to a significant 31% reduction in fasting blood sugar (FBS) and a 57.6% increase in blood glutathione (GSH) levels. However, this reduction in FBS was lower than that achieved with troglitazone (47%) [52]. Additionally, a 100 mg/kg/day oral dose displayed promising therapeutic efficacy in preventing diabetes-induced structural damage in the prostate gland of adult male albino rats [53]. In STZ-induced DBA/2 mice, low (50 mg/kg/day) and high (200 mg/kg/day) oral doses of GBE provided protective effects against hyperglycemia-induced podocyte damage. This prevented diabetic nephropathy by activating the Nrf-2/HO-1 pathway, revealing a potential mechanistic target for diabetic kidney disease treatment [54]. Furthermore, in Otsuka Long-Evans Tokushima Fatty (OLETF) rats, oral administration of 100 and 200 mg/kg of the extract protected against atherosclerosis, highlighting its cardiovascular benefits [55]. In male ApoE$^{-/-}$ diabetic mice, intragastric administration of *Ginkgo biloba* extract (GBE) at 200 mg/kg/day (low dose) and 400 mg/kg/day (high dose) significantly reduced serum glucose, inflammatory cytokines, and lipid levels, highlighting its potential in modulating lipid metabolism and systemic inflammation in diabetes. GBE was dissolved in normal saline for administration, as it offers lower toxicity than organic solvents, making it a suitable vehicle for intragastric delivery in mice [56]. Oral administration of 100 mg/kg/day of *G. biloba* extract (GBE) in normoglycemic male adult Wistar rats demonstrated its ability to enhance glucose and lipid metabolism by modulating the expression of key metabolic genes, suggesting its potential in preventing hyperglycemia and metabolic disorders [57]. Additionally, in STZ-induced Wistar albino rats, GBE at the same dosage exhibited antidiabetic, antihypertensive, and antilipidemic properties, reinforcing its multifaceted role in metabolic regulation [58]. In Sprague-Dawley rats, oral administration of 40 mg/kg of the extract provided a protective effect against hyperlipidemia, further validating its role in cardiovascular health [59]. In STZ-

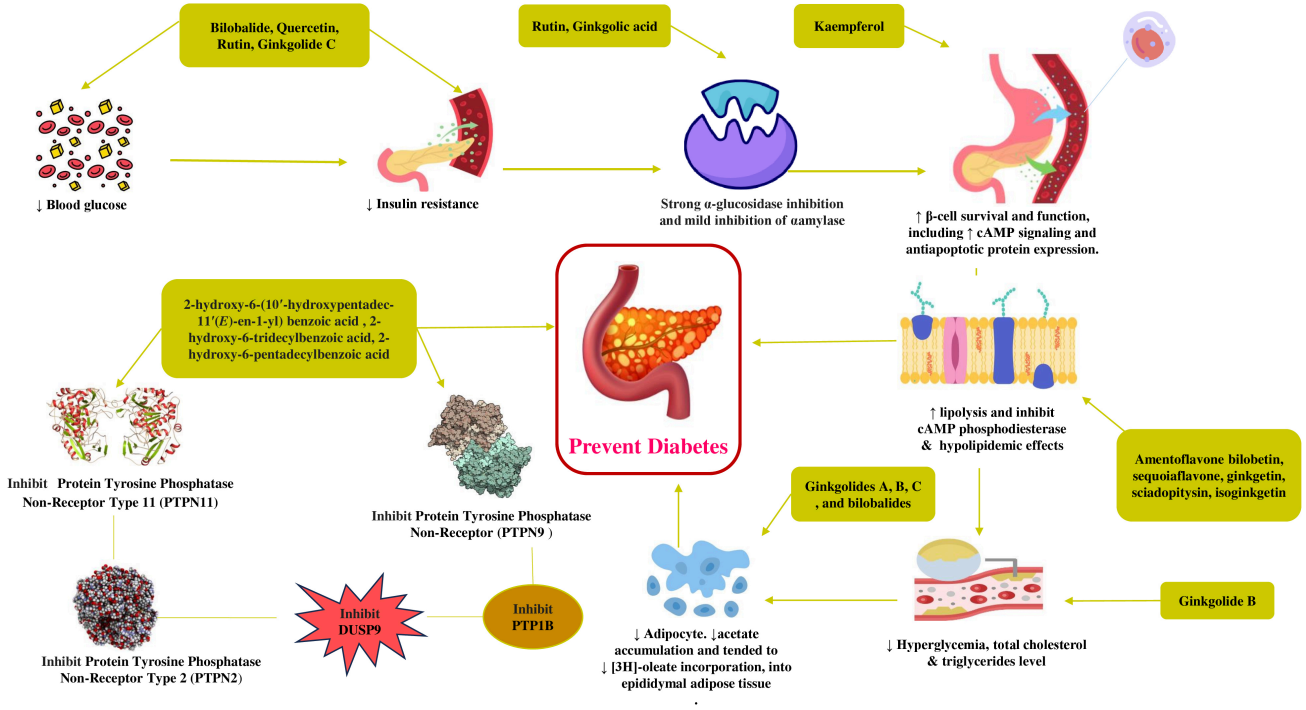

Fig. 3. Proposed mechanism of action of *G. biloba* and its isolated compounds in exerting antidiabetic effects. cAMP, Cyclic adenosine monophosphate; PTPN2, Protein tyrosine phosphatase non-receptor type 2; PTPN9, Protein tyrosine phosphatase non-receptor type 9; PTPN11, Protein tyrosine phosphatase non-receptor type 11.

induced adult male Sprague-Dawley rats, varying doses of 50, 100, and 200 mg/kg/day dissolved in 1% CMC-Na exhibited a dose-dependent reduction in blood glucose levels, supporting its potential application in clinical treatment for type 2 diabetes mellitus (T2DM) [60]. At a higher dosage of 200 mg/kg/day, GBE exerted strong antihyperglycemic and antilipidemic effects while modulating key hepatic genes involved in glucose metabolism. Additionally, it controlled serum liver enzymes, urea, and creatinine levels, suggesting hepatoprotective and nephroprotective benefits [61]. In male Sprague-Dawley rats, oral administration of 200 mg/kg/day of GBE, extracted using methanol, demonstrated a significant role in amino acid metabolism, which was linked to improvements in pancreatic β-cell function, inflammatory response, oxidative stress reduction, and enhanced liver and renal function [62]. Furthermore, in high-fat diet (HFD)-induced obese mice, oral administration of 100, 200, and 400 mg/kg of GBE significantly reduced insulin resistance and alleviated symptoms of metabolic syndrome, indicating its potential for therapeutic intervention in obesity-related metabolic dysfunctions [63].

3.1.3 *In Vitro* and *in Vivo* Antidiabetic Activity of Isolated Compounds

The bioactive derivatives such as bilobalide, quercetin, rutin, and ginkgolide C demonstrated lower blood glucose levels, improving the body's sensitivity to insulin. The subsequent effect of lowered insulin resistance by rutin and ginkgolic acid was potentiated through slow release of glucose to blood after a meal by potent and mild inhibition of digestive enzymes such as alpha-glucosidase and alpha-amylase, respectively. Kaempferol from *G. biloba* protected beta cell damage by expressing antiapoptotic protein and improved insulin function by enhancing insulin signalling by cAMP. The bioactive derivatives 2-hydroxy-6-(10′-hydroxypentadec-11′(E)-en-1-yl) benzoic acid (2), 2-hydroxy-6-(11′-hydroxypentadec-9′(E)-en-1-yl) benzoic acid, 2-hydroxy-6-tridecylbenzoic acid, 2-hydroxy 6-pentadecylbenzoic demonstrated inhibition of multiple protein tyrosine phosphatases (PTPs) involved in insulin resistance such as PTPN11, PTPN2, PTPN9, PTP1B, and DUSP9. Ginkgolides A, B, C, and bilobalide derivatives, especially ginkgolide B, lowered hyperglycemic states, total cholesterol, triglyceride serum levels, and lipid accumulation associated with diabetes, thus maintaining adipose tissue. Amentoflavone, bilobetin, sequoiaflavone, ginkgetin, sciadopitysin, and isoginkgetin exerted hypolipidemic effects by reducing lipolysis and inhibiting the enzyme cAMP phosphodiesterase. A mechanism of action of *G. biloba* on glucose is given in Fig. 3.

Bilobalide, when administered to male Wistar rats at a dose of 10 mg/kg intraperitoneally, demonstrated a remarkable reduction in blood glucose levels, activation of insulin secretion, and alleviation of liver damage caused by streptozotocin (STZ)-induced diabetes. These findings suggest

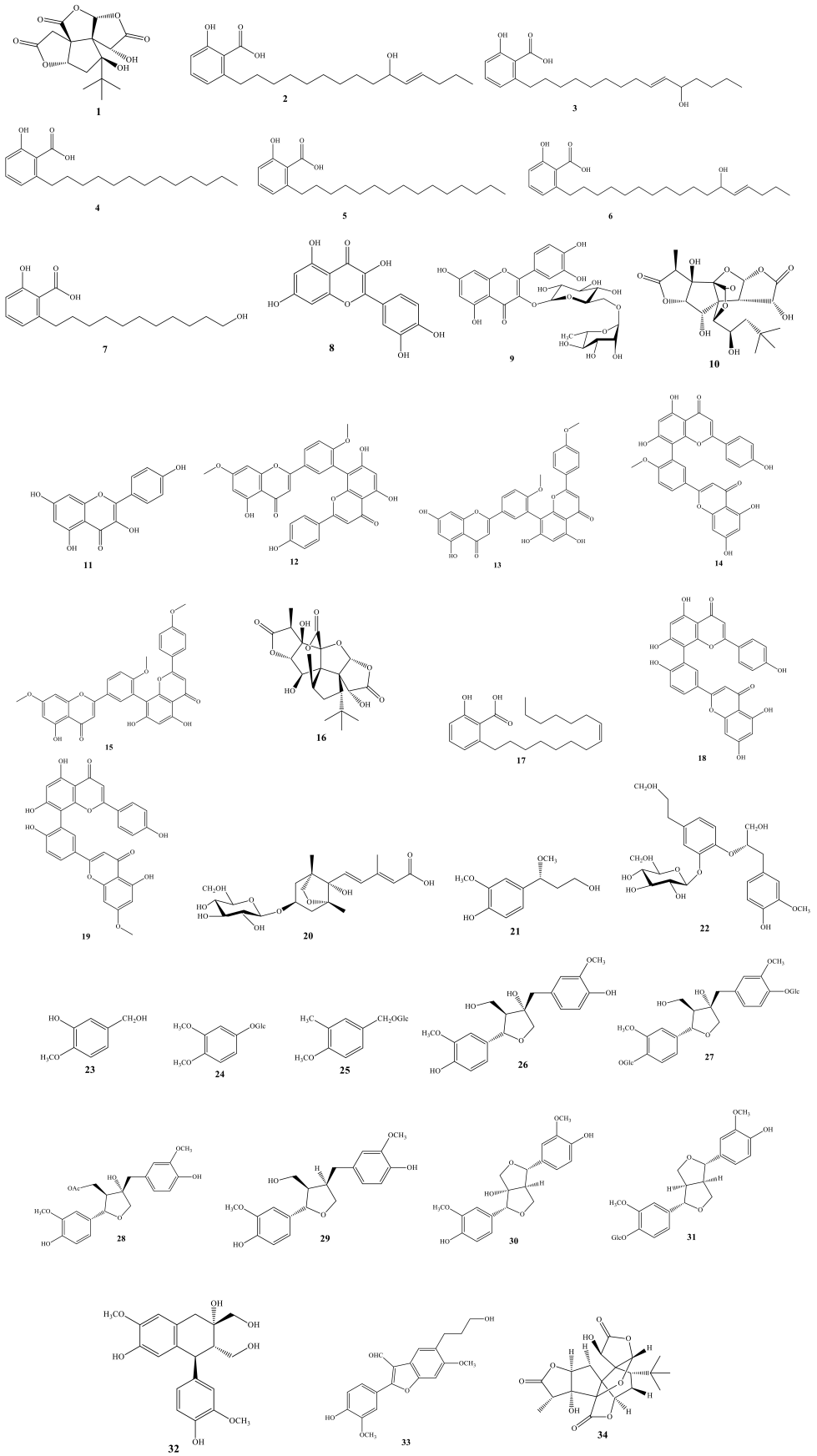

Fig. 4. Chemical structures of compounds isolated from *Ginkgo biloba*.

potential therapeutic effects on diabetes-related complications [64]. *In vitro*, bilobalide has been shown to inhibit adipogenesis and promote lipolysis in 3T3-L1 preadipocytes by activating the AMPK signaling pathway, further supporting its role in modulating metabolic processes [65]. In female NMRI mice subjected to alloxan-induced diabetes, bilobalide administered orally at doses of 100 and 200 mg/kg by gavage, in conjunction with EGb 761, enhanced the activity of beta cells in the presence of glucose, indicating its synergistic effect on glucose regulation and insulin sensitivity [66]. Additionally, bilobalide exhibited protective properties in 3T3-L1 preadipocytes against hypoxia-induced inflammation and insulin resistance. This was achieved by reducing inflammatory adipokine secretion, enhancing adiponectin release, modulating the NF-κB/JNK pathway, and inhibiting serine phosphorylation of IRS-1 receptors, thereby improving insulin signaling [67]. Fig. 4 illustrates the chemical structures of the isolated compounds.

Furthermore, bilobalide provided significant protection to adipocytes from the adverse effects of hypoxia in a dose-dependent manner, inflammation, mitochondrial damage, and attenuating oxidative stress. The treatment significantly reduced cell death, with the highest dose (50 µM) showing a 10% reduction, highlighting its potential in mitigating cellular damage associated with metabolic disorders [68]. In another study, bilobalide induced apoptosis in mature 3T3-L1 adipocytes through a ROS-mediated mitochondrial pathway, offering promising therapeutic avenues for obesity management [69]. Moreover, *in vivo* studies in male Wistar rats treated with bilobalide at a dose of 2 mg/kg/day revealed increased glycogen content in the liver and muscle, in normal and STZ-induced diabetic rats This effect suggests that bilobalide may help mitigate impaired glucose utilization, possibly through its antioxidant properties or by enhancing glucose uptake, further supporting its role in managing diabetes [70]. The compounds 2-hydroxy-6-(10′-hydroxypentadec-11′(E)-en-1-yl) benzoic acid (2), 2-hydroxy-6-(11′-hydroxypentadec-9′(E)-en-1-yl) benzoic acid (3), 2-hydroxy-6-tridecylbenzoic acid (4), 2-hydroxy-6-pentadecylbenzoic acid (5), 2-hydroxy-6-(12′-hydroxyheptadec-13′(E)-en-1-yl) benzoic acid (6), and 2-hydroxy-6-(11-hydroxyundecyl) benzoic acid (7) were tested for their inhibitory effects on protein tyrosine phosphatases (PTPs) relevant to insulin resistance. These compounds exhibited potent enzyme inhibition, with 4–6 showing over 90% inhibition against PTPN11, PTPN2, PTP1B, DUSP9, PTPRS, and PTPN9. Compounds 2 and 3 also displayed significant inhibitory activity against several PTPs, including PTPN11, PTPN2, PTP1B, and DUSP9. These findings underscore the importance of the side chain length and substitutions within the side chain of ginkgolic acid derivatives in determining their inhibitory potency. These derivatives from *G. biloba* leaves may serve as promising therapeutic candidates for managing Type 2 diabetes mellitus (T2DM) due to their potential to inhibit PTPs involved in insulin resistance [71]. Quercetin (8) and rutin (9), both derived from the leaves, exhibited potent α-glucosidase inhibition and mild α-amylase inhibition at concentrations of 0.061 µM and 0.038 µM for quercetin, and 0.043 µM and 0.037 µM for rutin. Their activity makes them suitable candidates as nutraceuticals for managing non-insulin-dependent diabetes mellitus (NIDDM) [72]. In studies with 3T3-L1 cells, Ginkgolide C (10) demonstrated significant inhibition of transcription factors and enzymes associated with adipogenesis, while promoting Sirt1/AMPK activity to enhance lipolysis in differentiated adipocytes. This suggests that ginkgolide C may improve metabolic syndrome and insulin resistance [73]. Kaempferol (11), when tested on INS-1E cells and human islets, enhanced β-cell survival and function. It improved cAMP signaling and upregulated antiapoptotic protein expression, highlighting its potential in supporting pancreatic β-cell health and insulin production [74]. Table 1C (Ref. [64–85]) provides an overview of the *in vitro* and *in vivo* Antidiabetic Activity of isolated Compounds of *G. biloba.*

Ginkgetin (12), a compound derived from *G. biloba* leaves, was found to inhibit the expression of PPARγ and C/EBPα in 3T3-L1 cells, a key event in the initiation of adipogenesis. This inhibition prevents STAT5 activation during the early stages of adipocyte differentiation. This suggests that ginkgetin may serve as a potent modulator of adipogenesis and could be developed as an anti-obesity agent. *In vivo* studies on C57BL/6 male mice further support this notion, as ginkgetin exhibited inhibitory effects on the hypertrophy of white adipose tissue when administered intraperitoneally at doses of 5 mg/kg and 10 mg/kg per day. These findings highlight ginkgetin's potential as an anti-adipogenesis and anti-obesity drug [75]. The compounds isoginkgetin (13), bilobetin (14), ginkgetin (12), and sciadopitysin (15), also derived from *G. biloba* leaves, were evaluated for their inhibitory effects on pancreatic lipase (PL) activity. At concentrations of 1 µM, 10 µM, and 100 µM, these compounds exhibited significant inhibitory activity, providing new evidence for the hypolipidemic effects of *G. biloba*. These findings suggest that these biflavonoids could serve as lead compounds for developing pancreatic lipase inhibitors, offering potential therapeutic benefits for managing lipid metabolism disorders [76]. Isoginkgetin (13) was further investigated in 3T3-L1 mouse fibroblasts, where it was shown to enhance adiponectin production in adipocytes through a novel mechanism involving the AMPK pathway. This mechanism differs from that of rosiglitazone, a known regulator of adiponectin. Isoginkgetin's ability to elevate adiponectin levels could provide new insights into treating metabolic diseases and developing agents that increase plasma adiponectin levels, a biomarker associated with improved metabolic health [77]. Ginkgolide B (16), tested in human umbilical vein endothelial cells (HUVECs), demonstrated protective ef-

fects against high glucose-induced endothelial dysfunction. At concentrations of 0.2, 0.4, and 0.6 mg/mL, ginkgolide B inhibited the TLR4-mediated inflammatory response, which is crucial in the pathogenesis of diabetic vascular complications. The underlying mechanism was linked to the inhibition of JAK2/STAT3 and p38 MAPK phosphorylation, highlighting ginkgolide B's potential as an anti-inflammatory agent for vascular protection in diabetes [78]. Additionally, in mouse renal podocytes (MPC5), ginkgolide B reduced hyperglycemia-induced lipid accumulation and lowered serum levels of total cholesterol and triglycerides at doses ranging from 5 to 200 μM. This effect suggests that ginkgolide B may play a role in managing lipid metabolism disorders in diabetes [79]. *In vivo* studies in streptozotocin-induced diabetic ICR mice further demonstrated that *G. biloba* (GB) protects against endothelial dysfunction in the aorta by increasing superoxide dismutase 1 (SOD1) activity and enhancing nitric oxide (NO) bioavailability in endothelial cells, which may contribute to improved vascular health in diabetic conditions [80]. Ginkgolic acid (36), derived from *G. biloba* leaves, exhibited the highest α-glucosidase inhibitory activity. This study, which represents the first to isolate ginkgolic acids as α-glucosidase inhibitors, suggests that these compounds could manage blood glucose levels, particularly in type 2 diabetes [81]. Amentoflavone (36), bilobetin (14), sequoiaflavone (37), ginkgetin (12), sciadopitysin (15), and isoginkgetin (13) were tested for their effects on lipolysis in 3T3-L1 preadipocytes. These biflavonoids stimulated lipolysis by inhibiting cAMP phosphodiesterase, which could potentially contribute to the management of obesity by promoting fat breakdown [82]. A variety of compounds, including (2E,4E,1′R,3′S,5′R,8′S)-dihydrophaseic acid 3′-O-β-D-glucopyranoside (38), 7,8-dihydro-(R)-7-methoxyconiferyl alcohol (39), and ginkgolides A, B, and C (52), were found to inhibit TNFα-induced NF-κB transcriptional activity in human hepatocarcinoma HepG2 cells. This inhibition led to reduced COX-2 and iNOS gene expression, indicating the potential of these compounds in the prevention and treatment of inflammatory and metabolic diseases [83]. In an *in vivo* study with high-fat diet-induced obese male Wistar rats, a combination of flavone glycosides, terpenoids, and ginkgolides from *G. biloba* led to a reduction in adipocyte size and acetate accumulation, suggesting a potential anti-obesogenic effect that could be beneficial for long-term therapies aimed at obesity management [84]. Rutin (9) and quercetin (20) were tested in adult Sprague-Dawley rats with streptozotocin-induced diabetes. At a 90 mg/kg dose, these flavonoids inhibited aldose reductase activity, stimulated glutathione production, and decreased malondialdehyde (MDA) and advanced glycosylation end products (AGEs). These effects highlight the potential of rutin and quercetin in managing oxidative stress and diabetic complications [85].

4. Clinical Studies and Safety Profile of *Ginkgo biloba* in Diabetes Management

The clinical trials conducted to date with *G. biloba* have primarily targeted its antidiabetic effects and improve lipid profiles, and mitigate diabetes-related complications (Table 2, Ref. [86–100]).

A randomized, placebo-controlled, double-blinded study conducted on 60 patients with type 2 diabetes mellitus (T2DM) over 90 days demonstrated that administering 120 mg/day of GKB extract significantly reduced blood HbA1c and fasting serum glucose levels [86]. Similarly, another randomized, placebo-controlled, double-blinded study involving 24 T2DM patients found that the exact dosage of GKB extract effectively inhibited insulin resistance [87]. In a randomized, double-blind, placebo-controlled crossover study conducted on 10 T2DM patients, *G. biloba* extract (EGb 761) at a dosage of 120 mg/day resulted in a reduction in glycosylated hemoglobin A1c (1c) levels [88]. Additionally, a control treatment study using *G. biloba* extract injection in 60 diabetic nephropathy (DN) patients revealed that administering 20 mL (5 mL per ampule) led to a decrease in urinary albumin excretion rate, regulation of blood lipids, and improvement in renal function and hemorheology [89]. A randomized controlled study with 80 nonproliferative diabetic retinopathy (NPDR) patients over a six-month duration showed that oral administration of 2 mL of GKB extract three times daily significantly decreased the number of retinal microaneurysms and areas of retinal hemorrhage, along with lowering serum total cholesterol, triglycerides, and low-density lipoprotein cholesterol while increasing high-density lipoprotein cholesterol. Furthermore, platelet aggregation and adhesion rates were also reduced [90]. A large-scale, randomized, double-blind, multicenter controlled trial involving 600 type 2 diabetes patients over 24 months indicated that daily intake of 24 mg of *G. biloba* tablets helped attenuate the deterioration of albuminuria in diabetic patients [91]. Similarly, a randomized controlled trial with 68 DN patients over three months showed that an oral dosage of 9.6 mg of *G. biloba* extract (EGB) taken three times daily led to significant reductions in urinary microalbumin (mALB), alpha1-microglobulin (alpha1-MG), immunoglobulin (IgG), transferrin (TF), retinal binding protein (RBP), and N-acetyl-beta-D-glycosaminidase (NAG) levels [92]. A long-term, randomized, double-blind, placebo-controlled study on 210 T2DM patients conducted over three years found that consuming 24 mg of GKB extract three times daily resulted in a lower albumin-to-creatinine ratio (ACR) increase [93]. Another randomized, double-blind, placebo-controlled trial on 250 T2DM patients over 27 months revealed that administering 80 mg of GKB extract capsules twice daily for the first nine months and thrice daily for the following nine months demonstrated moderate improvements in psychological states and significantly enhanced glycemic control [94]. A study on 20 patients with standard glucose tolerance

Table 2. Clinical trail antidiabetic studies of Ginkgo.

Administered material	Study design	Number of Subjects	Health condition of subjects	Duration	Dosage regimen	Findings/Results	Ref
GKB extract	Randomized, placebo-controlled, double-blinded	60	T2DM patients	90 days	120 mg/day	↓ Blood HbA1c, fasting serum glucose	[86]
GKB extract	Randomized, placebo-controlled, double-blinded	24	T2DM patients	-	120 mg/day	Inhibit insulin resistance	[87]
G. biloba extract (EGb 761)	Randomized, placebo-controlled, double-blinded crossover study	10	T2DM patients	-	120 mg/day	↓ Glycosylated hemoglobin A(1c) levels	[88]
G. biloba extract injection	Control treatment	60	DN patients	-	(5 mL/amp) 20 mL	↓ Urinary albumin excretion rate, hemorheology ↑, renal function, and regulated blood lipids	[89]
GKB extract	Randomized controlled study	80	NPDR patients	6 months	2 mL-orally, 3 times/day	↓ Number of retinal micro-aneurysms and areas of retinal hemorrhage, ↓ LDL cholesterol, triglycerides, total cholesterol, ↑ HDL, ↓ platelet adhesion rate, and platelet aggregation rate	[90]
G. biloba Tablets	Randomized, double-anonymized, multicenter, controlled trial	600	Type 2 diabetes	24 months	24 mg/day	Attenuate the deterioration of albuminuria in type 2 diabetes patients	[91]
Extract of *G. biloba* leaf (EGB)	Randomized controlled trial	68	DN	3 months	9.6 mg Orally, 3 times/day	↓ Urinary mALB, alpha1-MG, IgG, TF, RBP, and NAG	[92]
GKB extract	Randomized, double-anonymized, placebo-controlled	210	T2DM	3 years	24 mg, 3 times/day	Less ACR ↑	[93]
GKB extract capsules	Randomized double blind placebo-controlled	250	T2DM	27 months	For the first 9 months, one capsule 80 mg twice/day. For the second 9 months, one capsule 80 mg 3 times/day	Demonstrated a moderate effect on psychological state and Significant ↑ glycemic control in T2DM patients	[94]

Table 2. Continued.

Administered material	Study design	Number of Subjects	Health condition of subjects	Duration	Dosage regimen	Findings/Results	Ref
Ginkgo biloba extract		20	Patients with normal glucose tolerance	3 months	120 mg/day	↓ Blood pressure and an increase in the rate of insulin metabolic clearance	[95]
G. biloba extract (EGb 761)	Not specific	20	NIDDM with hyperinsulinemia, NIDDM with pancreatic exhaustion	3 months	120 mg/day	↓ Insulin-mediated glucose metabolism and ↑ blood glucose levels	[96]
G. biloba (EGb 761®)	Not specific	120	T2DM	6 months	240 mg/day	↑ Brain function and QoL indicators in DM-2 by counteracting insulin resistance	[97]
G. biloba Pills	Randomized, double-blind, placebo-controlled	12	-	58 weeks	Oral *G. biloba* pills or drops, three times/day, five at a time	Regulated glucose, ↓ diabetes risk, and ↓ CVD incidence and mortality	[98]
G. biloba extract	Double-blind, randomized, placebo-controlled crossover study	30	Healthy non-diabetic, glucose tolerant volunteers	3-months	120 mg as a single dose	Modulated hypothalamic-pituitary-adrenal axis, ↓ basal cortisol and stress-induced cortisol response	[99]
Capsule	Randomized double-blind, placebo-controlled trial	60	T2DM	90 days	120 mg	↓ Lipid profile, ↓ inflammatory mediators, leptin level and ↑ the antioxidant status of T2DM patients	[100]

T2DM, Type 2 diabetes mellitus; DN, Diabetic nephropathy; HbA1c, Hemoglobin A1c; EGb 761, Ginkgo biloba extract; mALB, Microalbuminuria; alpha1-MG, Alpha-1-microglobulin; IgG, Immunoglobulin G; TF, Transferrin; RBP, Retinol binding protein; NIDDM, Non-insulin-dependent diabetes mellitus; ACR, Albumin-creatinine ratio; CVD, Cardiovascular disease; QoL, Quality of life.

over three months showed that taking 120 mg of *G. biloba* extract daily reduced blood pressure and increased insulin metabolic clearance rate [95]. Furthermore, research on 20 patients with non-insulin-dependent diabetes mellitus (NIDDM) with hyperinsulinemia or pancreatic exhaustion over three months found that daily intake of 120 mg of *G. biloba* extract reduced insulin-mediated glucose metabolism while elevating blood glucose levels [96]. A six-month study involving 120 T2DM patients revealed that consuming 240 mg/day of *G. biloba* (EGb 761®) positively affected insulin resistance-related factors in the brain, improving overall brain function and enhancing quality of life indicators [97]. A randomized, double-blind, placebo-controlled trial on 12 participants over 58 weeks assessed the impact of *G. biloba* pills, taken three times a day in groups of five, in controlling impaired glucose regulation, slowing diabetes progression, and reducing the incidence and mortality of cardiovascular diseases [98]. A randomized, double-blind, placebo-controlled crossover study on 30 healthy, glucose-tolerant volunteers over three months reported that administering 120 mg of *G. biloba* extract as a single dose affected the hypothalamic-pituitary-adrenal axis by reducing basal cortisol levels and cortisol production in response to acute hyperglycemic challenges [99]. Lastly, a double-blind, randomized, placebo-controlled trial on 60 T2DM patients over 90 days found that consuming 120 mg of *G. biloba* capsules significantly decreased inflammatory mediators and leptin levels while improving antioxidant status and lipid profiles [100].

G. biloba demonstrates a strong safety profile, with multiple animal and human studies reporting no significant toxicity or adverse effects, supporting its use as a safe natural therapeutic agent. In clinical trials, administration of *G. biloba* extract at a dose of 120 mg/day showed no adverse effects on treated individuals' liver, kidney, or hematopoietic functions [86]. Similarly, another study using EGb 761 at the same dose for three months reported it to be safe and well-tolerated in both healthy and diabetic participants, with only minor, non-life-threatening side effects such as changes in appetite, mild headaches, and menstrual bleeding [88]. In animal studies, acute toxicity assessments revealed no toxic effects even at higher doses; for example, oral administration of GKB at 400 mg/kg showed no signs of toxicity [63]. Further supporting its safety, no adverse effects were noted after administering 200 mg/kg body weight over 60 days [61]. In experimental models, to further mitigate any risk of toxicity, high doses of GKB (500 mg/kg) were diluted in normal saline (0.9%) before administration, and no toxicological effects were reported [48]. Similarly, in another study, high doses of *G. biloba* extract, such as 400 mg/kg, were dissolved and delivered in normal saline to minimize potential toxicity [56]. While adverse events—including coronary artery disease, cerebrovascular accidents, and cancer have been reported, no direct causal relationship to *G. biloba* alone has been established. In combination therapy trials, such as those involving *G. biloba* and Liuwei Dihuang (LWDH), the absence of detailed subgroup analyses limits the ability to attribute these events to any single component [91]. These findings are consistent across different formulations and dosages, emphasizing *G. biloba*'s tolerability at both therapeutic and elevated doses. Nonetheless, further investigations, particularly regarding long-term use and potential interactions, are recommended to confirm its safety for broader clinical applications.

5. Nutritional Value of *Ginkgo biloba* in Diabetes Management

There is growing commercialization of products that combine concentrated bioactive compounds from natural sources, known as nutraceuticals. The health benefits of these compounds have attracted significant interest from the scientific community, with some tested through experimental studies [101]. Plant-derived dietary supplements, including antioxidants, essential fatty acids, lipid metabolism enhancers, vitamins, and trace elements, are marketed and recommended to patients as beneficial additions to a diabetic diet and conventional treatments. These supplements aim to enhance glycemic control and minimize the effects of chronic complications [102]. *G. biloba* products were among the top-selling medicinal items in U.S. health food stores. Unlike the leaves, Ginkgo nuts have a long history of use as both food and medicine, with their first mention in herbals around 1350 AD [103]. *G. biloba* leaves and seeds are rich in vitamin, carbohydrates, riboflavin, proteins, amino acid, minerals and other essential nutrients (Table 3, Ref. [103–106]). These nuts are believed to provide health benefits, including diabetes, cancer prevention and treatment for neurological diseases [107]. Carbohydrate compounds in plants, such as oligosaccharides and polysaccharides, have been found to significantly enhance glucose and insulin metabolism in both healthy and diabetic individuals. A study compared three diets in diabetic patients: low-starch (43% carbs, 22% protein, 34% fat), high-starch (55% carbs, 15% protein, 30% fat), and a typical American diet (40% carbs, 20% protein, 40% fat). The low-starch diet resulted in significantly lower plasma glucose and insulin levels. Another trial of over 3200 patients showed that high-fiber, low-fat diets could help prevent diabetic complications. A clinical study also found that high-carb, high-fiber meals improved glycemic control and reduced post-meal lipids in type 2 diabetes patients [108].

6. Limitations

The reviewed studies on the antidiabetic effects of *Ginkgo biloba* leaf extracts exhibited significant heterogeneity, particularly in dosage, administration routes, animal models, and outcome measures, thus making comparisons and generalizations challenging. The dosage range varies considerably for each bioactive derivative from *G.*

Table 3. Nutritional Composition of *G. biloba*.

Class	Component	Leaves (mg/100 g)	Seeds (mg/100 g)	Ref
Macronutrients	Protein	12,270 ± 240	9000–13,000	[103–106]
	Carbohydrate	72,980 ± 200	35,000–72,600	
	Fat	4750 ± 220	2400	
	Fiber	2500	-	
Vitamins	Vitamin C	79.2	15	
	Vitamin E	59.3	-	
	Thiamine (B_1)	1.53	0.22	
	Riboflavin (B_2)	2.98	0.09	
	Niacin (B_3)	2.44	0.16	
	Vitamin (B_6)	3.57	0.33	
Minerals	Sodium	1.65–2.34	7	
	Potassium	4.33–21.11	510	
	Calcium	24.62–40.22	2	
	Magnesium	18.45–69.26	27	
	Phosphorus	4.90–32.65	124	
	Iron	2.63–6.67	1	
	Zinc	0.20–1.85	0.34	
	Copper	0.64–0.79	0.27	
	Manganese	0.63	0.11	
Amino Acids	Leucine	3630	310	
	Lysine	1390	200	
	Valine	2950	280	
	Serine	1510	290	
	Proline	2610	340	
	Glycine	2040	230	
	Glutamic acid	7670	830	
	Histidine	1510	100	
	Phenylalanine	1800	170	
	Arginine	4860	420	
	Cystine	160	20	
	Alanine	2910	240	
	Methionine	750	50	
	Aspartic acid	6420	540	
	Isoleucine	-	200	
	Threonine	2290	260	
	Tryptophan	-	70	
	Tyrosine	1320	60	
Others	Ash	10,010 ± 60	-	
	Water	55,200	-	

biloba (Tables 1A,1B,1C (Ref. [19–85])). This discrepancy raises concerns about the feasibility and safety of translating these doses to human-equivalent doses (HEDs). For instance, a 200 mg/kg rat dose translates to approximately 32 mg/kg in humans, highlighting the need for further research into dose-response relationships and the therapeutic window for human applications. This lack of dose translation between animal models and humans restricts applying preclinical results to clinical practice. Moreover, the heterogeneity in administration routes (e.g., intraperitoneal injection, oral gavage, and oral administration) adds to the variability. For example, intraperitoneal administration of leaf extracts at doses ranging from 50–500 mg/kg showed significant antihyperglycemic, antioxidant, and hypolipidemic effects in STZ-induced diabetic rats (Table 1B). In contrast, 100 mg/kg/day of ethanolic leaf extract oral administration preserved pancreatic β-cell integrity and enhanced insulin expression in type 2 diabetic rats [37]. These discrepancies in administration routes may affect bioavailability, absorption, and efficacy; therefore, they should be carefully considered when interpreting the results. The variation in animal models used across studies, such as STZ-induced diabetes and high-fat diet models, also influences the observed outcomes. For example, STZ models primarily in-

duce β-cell destruction, which may not fully represent insulin resistance in type 2 diabetes. This highlights the need to contextualize findings based on the model used, as the STZ-induced model may not adequately reflect the complex pathophysiology of T2DM (Table 1B). Furthermore, *in vitro* studies that examine α-glucosidase inhibition and adipogenesis are not always validated in *in vivo* systems, weakening their translational potential. The lack of standardization in dosing protocols and extraction methods (e.g., water, ethanol, petroleum ether, and vinegar) complicates the comparison of efficacy across studies. For example, ethanolic extracts have demonstrated more substantial antidiabetic effects than aqueous or petroleum ether extracts, yet the underlying mechanisms remain poorly understood [19,20]. The impact of different solvents on the pharmacological properties of *G. biloba* should be more thoroughly investigated to ensure consistency in therapeutic claims. Another limitation is that the safety data are poorly reported in most studies. Although *G. biloba* extracts demonstrate significant therapeutic potential, the safety profiles of compounds like ginkgolic acids, which have known allergenic and neurotoxic potential, often remain underreported. Long-term toxicity studies are especially lacking, with no precise monitoring of hepatic or renal function in most studies, raising concerns about the safety of these extracts, particularly in vulnerable populations such as cachectic patients or those with liver or kidney disorders. Mechanistic insights from *in vitro* experiments provide a possible rationale for *G. biloba*'s effects but also highlight a disconnect with clinical dosing. For example, certain Ginkgo constituents (such as ginkgolic acids) can activate AMPK signaling and inhibit protein tyrosine phosphatases at ~50 µM concentrations in cell-based models [81], Yet, these concentrations far exceed what is achieved during *in vivo* testing with a typical oral dose of 120 mg of EGb 761 that yields peak plasma levels of key terpene lactones, on the order of only tens of ng/mL (i.e., sub-micromolar) [97]. This disparity suggests that while the proposed molecular mechanisms (e.g., AMPK activation) are biologically plausible, their clinical relevance at standard doses remains unclear, underscoring the need for caution when extrapolating high-concentration *in vitro* findings to expected *in vivo* effects. While *G. biloba* shows promising antidiabetic potential, the current body of literature is hindered by significant heterogeneity in study design, inconsistent reporting, lack of standardization, and insufficient safety data. Future studies should address these limitations by standardizing experimental protocols, clearly defining dosage ranges, and providing detailed safety profiles to better evaluate the therapeutic potential and safety of *G. biloba* for diabetes management.

7. Future Perspectives and Conclusion

G. biloba as a potential alternative therapy for diabetes mellitus (DM) has garnered significant attention due to its promising pharmacological effects, including its antioxidant, anti-inflammatory, and insulin-sensitizing properties. However, the current research scenarios about the antidiabetic activity of the herb present several challenges and gaps that need to be addressed in future studies to understand its full therapeutic potential better. One central area requiring further investigation is the standardization of *G. biloba* dosage. While numerous studies have demonstrated its efficacy in reducing blood glucose levels and improving insulin sensitivity, there is considerable variation in the dosages and forms of *G. biloba* used across clinical trials. This inconsistency makes it difficult to determine an optimal, universally applicable dose for effective diabetes management. Future clinical studies should focus on selecting the most effective doses while considering factors such as the bioavailability of active compounds, patient age, comorbidities, and the duration of treatment. While preclinical studies have provided valuable insights into the mechanisms through which *G. biloba* exerts its effects, such as AMPK activation, GLUT4 translocation, and inhibition of protein tyrosine phosphatases, the detailed molecular pathways remain insufficiently explored. To further validate the therapeutic antidiabetic activity of *G. biloba*, future research must focus on uncovering the exact mechanisms of action behind its potency in managing diabetes. Investigations around molecular interactions of key bioactive compounds, such as bilobalide and flavonoids, will provide deeper insights into their role in regulating glucose metabolism and insulin secretion. These mechanistic studies could lead to more specific therapeutic regimens, which can be used as adjunct therapy alongside other antidiabetic agents. Another possible direction for future research could be to explore the long-term safety and efficacy of *G. biloba* in diabetic populations with comorbid conditions, such as cardiovascular disease, neuropathy, and nephropathy. Focus should be placed on chronic toxicity, herb-drug interactions, and use during pregnancy. While initial clinical studies have suggested that *G. biloba* may help mitigate diabetes-related complications, large-scale, multicenter clinical trials are necessary to establish its role in preventing and treating complications over extended periods. Additionally, the potential of *G. biloba* in managing gestational diabetes and its effects during pregnancy remains largely unexplored, which calls for further investigation.

In conclusion, *G. biloba* L. holds considerable promise as a complementary therapy for diabetes management. Its multifaceted pharmacological activities, such as enhanced glucose uptake, improved insulin secretion, and reduced oxidative stress, make *G. biloba* an ideal candidate for improving glycemic control, thus helping prevent diabetes-related complications. Preclinical and clinical studies have shown encouraging results, suggesting that *G. biloba* can reduce blood glucose levels, improve lipid profiles, and protect against diabetes-induced nephropathy and retinopathy. However, to fully establish its role as an

effective adjunct in diabetes management, future research must address the gaps in clinical trials, optimise dosing regimens, and further elucidate the underlying mechanisms of action. With well-designed, large-scale clinical trials and a deeper understanding of its molecular effects, *G. biloba* could become integral to diabetes treatment strategies, offering a natural, safe alternative to conventional therapies.

Abbreviations

ACR, Albumin-to-creatinine ratio; AMPK, Adenosine Monophosphate-activated Protein Kinase; Alpha1-MG, Alpha1-microglobulin; ApoE, Apolipoprotein E; Bax-to-Bcl-2, ratio of Bcl-2-associated X (Bax) to B-cell lymphoma 2 (Bcl-2) protein expression; BMSCs, Bone marrow mesenchymal stem cells; C/EBPδ, CCAAT/Enhancer-Binding Protein Delta; C-peptide, Connecting peptide; C57BL/6, a specific inbred strain of laboratory mice often shortened as C57, B6 or even 'Black 6'; CTGF, Connective tissue growth factor; GB, *Ginkgo biloba*; DBA/2 mice, a laboratory mice called Dilute Brown Non-Agouti (DBA/2) mice; DM, Diabetes Mellitus; DN, Diabetic nephropathy; DUSP9, Dual Specificity Phosphatase 9; EGb 761, Extract of *Ginkgo biloba* 761; EGCs, Enteric glial cells; ERS, Endoplasmic reticulum stress; FBS, Fasting blood sugar; GLUT4, Glucose Transporter type 4; GSH, Glutathione; HbA1c, Glycosylated hemoglobin A(1c); HAECs, Human aortic endothelial cells; HepG2, Human hepatocarcinoma; HLECs, Human lens epithelial cells; HO-1, Heme Oxygenase-1; HUVECs, Human umbilical vein endothelial cells; I.P., Intraperitoneal; ICR mice, Institute of Cancer Research mice; IGF-1, Insulin-like growth factor-1; IRS-1, Insulin Receptor Substrate 1; IRS-2, Insulin Receptor Substrate 2; INS-1E, a well-characterized rat insulinoma cell line; JAK2/STAT3, Janus kinase 2/Signal transducer and activator of transcription 3; JNK pathway, Jun N-terminal kinase; L-02, Human Fetal Hepatocyte cell line; LPL, Liver lipoprotein lipase; MDA, Malondialdehyde; MPC5, Mouse renal podocytes; NF-κB, Nuclear Factor kappa B; NF-κB/JNK pathway, signaling pathways involving two protein complexes (i.e., NF-κB and JNK); NAG, N-acetyl-beta-D-glucosaminidase; NMRI Mice, Naval Medical Research Institute Mice; NO, Nitric oxide; Nrf-2/HO-1 pathway; NPDR, Non-proliferative diabetic retinopathy; PPAR-α, Peroxisome proliferator-activated receptor-alpha; PPARγ, Peroxisome Proliferator-Activated Receptor Gamma signaling; PI 3-kinase, Phosphatidylinositol 3-kinase; PI3K/Akt/eNOS, Phosphatidylinositol 3-kinase/protein kinase B/endothelial nitric oxide synthase; PKB (Akt), Protein kinase B; PL, Pancreatic lipase; PTPs, Protein Tyrosine Phosphatases; PTP1B, Tyrosine protein phosphatase non-receptor type 1 (1B); PTPN2, a protein tyrosine phosphatase non-receptor type 2; PTPN9, a protein tyrosine phosphatase non-receptor type 9; PTPN11, a protein tyrosine phosphatase non-receptor type 11; PTPRS, Protein Tyrosine Phosphatase Receptor Type S; ROS, Reactive Oxygen Species; RBP, Retinal binding protein; SIRT1, coordinated activity of Sirtuin 1; SOD1, Superoxide dismutase 1; STZ, Streptozotocin; T1D, Type 1 Diabetes; T2D, Type 2 Diabetes; TGF-β1, Transforming growth factor-β1; TF, Transferrin; TLR4, Toll-like Receptor 4; TNFα, Tumor Necrosis Factor alpha; ULETF, Otsuka Long-Evans Tokushima Fatty rats.

Author Contributions

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Conflict of Interest

The authors declare no conflict of interest.

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