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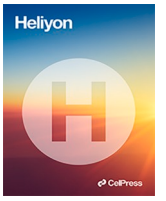

Review article

Clinical applications and mechanism insights of natural flavonoids against type 2 diabetes mellitus

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ABSTRACT

Diabetes is a complex disease that affects a large percentage of the world's population, and it is associated with several risk factors. Self-management poses a significant challenge, but natural sources have shown great potential in providing effective glucose reducing solutions. Flavonoids, a class of bioactive substances found in different natural sources including medicinal plants, have emerged as promising candidates in this regard. Indeed, several flavonoids, including apigenin, arbutin, catechins, and cyanidin, have demonstrated remarkable anti-diabetic properties. The clinical effectiveness of these flavonoids is linked to their potential to decrease blood glucose concentration and increase insulin concentration. Thus, the regulation of certain metabolic pathways such as glycolysis and neoglycogenesis has also been demonstrated. *In vitro* and *in vivo* investigations revealed different mechanisms of action related to flavonoid compounds at sub-cellular, cellular, and molecular levels. The main actions reside in the activation of glycolytic signaling pathways and the inhibition of signaling that promotes glucose synthesis and storage. In this review, we highlight the clinical efficiency of natural flavonoids as well as the molecular mechanisms underlying this effectiveness.

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Table 1
Clinical trials of antidiabetic flavonoids.

Molecules	Models	Experiment	Doses/Periods	Key findings	Authors
Resveratrol	19 T2D patients	A randomized study Double-blind trial (Phase III)	2 × 5 mg/day 4 weeks	Decreased insulin resistance Improved insulin sensitivity	[30]
	62 patients with T2D	A prospective, open-label, randomized, controlled trial	250 mg/day 3 months	Normalized glycaemia and HbA1c levels	[31]
	Non-obese postmenopausal women	A randomized, double-blind, placebo-controlled trial	75 mg/day 12 weeks	Increased resveratrol plasma concentration No effect on insulin sensitivity	[32]
	66 patients with type 2 diabetes mellitus (T2DM)	A randomized placebo-controlled double-blinded parallel clinical trial	1 g/day 45 days	Lowered fasting glycaemia levels, HbA1c, and resistance to insulin	[33]
	12 participants with metabolic syndrome (MetS)	A randomized, double-blind, placebo-controlled clinical trial	500 mg 3 times a day 90 days	Decreased insulin AUC Decreased total insulin secretion	[34]
	8 overweight and sedentary men		A single dose (300 mg) on two separate occasions	Attenuated post-absorption insulin concentrations No changes in insulin signaling	[35]
	60 non-alcoholic subjects with fatty liver disease (FLD)	A double-blind, randomized, placebo-controlled clinical study	2,15 g (twice daily) 3 months	Improved levels of glycaemia, LDL cholesterol, and total cholesterol	[36]
	14 patients with T2D	A double-blind, randomized, crossover design	500 mg (twice daily) 5 weeks	No effect on postprandial and fasting glycaemia, or HbA1c	[37]
	34 subjects suffering from polycystic ovary syndrome	A randomized double-blind, placebo-controlled trial	1500 mg/day 3 months	Lowered fasting insulin content (31.8 %) Augmented insulin sensitivity index (66.3 %)	[38]
	38 obese and overweight subjects	A randomized double-blind study	Resveratrol (80 mg/day) EGCG (282 mg/day) 12 weeks	No impact on insulin-stimulated glucose disposal	[39]
	17 subjects with T2D	A randomized double-blind crossover study	150 mg/day 30 days	No improvement in insulin sensitivity	[40]
	Middle-aged men suffering from metabolic syndrome	A randomized, placebo-controlled, double-blind, parallel group clinical trial	150 and 1000 mg/day 16 weeks	No improvement in glucose homeostasis	[41]
	45 overweight or slightly obese volunteers	A Randomized placebo-controlled trial	150 mg/day 4 weeks	No effect on insulin and plasma glucose levels	[42]
	13 men with T2D	A randomized, placebo controlled, cross-over trial	150 mg/day 1 month	No effect on insulin sensitivity	[43]
	472 elderly diabetic patients	A single-blind randomized controlled clinical trial	500 mg/day 6 months	Improvemed insulin resistance Improvemed blood glucose parameters (decreased G6Pase and HbA1c)	[44]
	110 diabetic patients	A randomized, placebo-controlled trial	200 mg/day 24 weeks	Improved blood glucose as well as insulin synthesis and resistance levels	[45]
Catechin	T2D patients not receiving insulin The participants ingested green tea containing either 582.8 mg of catechins (catechin group; n = 23) or 96.3 mg of catechins (control group; n = 20) per day	A double-blind controlled study	582.8 and 96.3 mg per day 12 weeks	Augmented insulin and adiponectin production No effect on glucose and HbA1c	[46]
	Healthy postmenopausal women (Phase III)		615 mg/350 mL per day 4 weeks	Improved redox homeostasis Improved postprandial glycemic status	[47]
Rutin	50 participants suffering from T2DM	A double blind, placebo-controlled trial	500 mg/day 3 months	Lowered the levels of fasting glycaemia, insulin, insulin resistance, and HbA1c	[48]

(*continued on next page*)

Table 1 (*continued*)

Molecules	Models	Experiment	Doses/Periods	Key findings	Authors
	34 healthy adult participants	A randomized, placebo-controlled, double blind crossover study	200 mg/day 3 weeks	Lowered postprandial glycaemia levels	[49]
Epicatechin	37 healthy women and men	A randomized, double-blind, placebo-controlled study	100 mg/day 4 weeks	Improved insulin resistance Enhanced fasting plasma insulin	[50]
	Erythrocyte membrane AChE in normal and type 2 diabetic patients		–	Pronounced insulin-like effect	[51]
Quercetin	37 healthy women and men	A randomized, double-blind, placebo-controlled study	160 mg/day 4 weeks	No impact on insulin resistance	[50]
Hesperidin and Diosmin	127 diabetic patients with neuropathy and MetS	A randomized controlled trial	1 g/day (for each) 12 weeks	Improved glycaemia, LDL, and triglyceride rates Increased magnitude of enhancement when the two molecules are combined	[52]

1. Introduction

Diabetes is a complex metabolic disorder characterized by disrupted blood glucose regulation [1]. It has several risk factors, including genetics, eating patterns, microbial infections, oxidative stress, metabolism, and epigenetics [2,3]. Type 2 diabetes mellitus (T2DM) is the most common form and typically affects older adults [4–7]. T2DM is initiated by hyperglycemia, which results in a rise in blood glucose concentration [8]. This leads to the glycosylation of proteins, impairing their function and causing several pathophysiological effects [9–11].

Effective diabetes management involves maintaining adequate food intake to stimulate cellular glucose breakdown. One way to achieve this is to inhibit key enzymes involved in the intestinal breakdown of complex sugars into simple sugars that are absorbable [12–14]. These key enzymes include α-amylase and α-glucosidase. Another approach is to stimulate glucose oxidation at the cellular level and its entry through the cell membrane [15,16]. Glucose transport is regulated by insulin, and the deregulation of insulin leads to hyperglycemia and an accumulation of glucose in the blood [17,18]. Thus, stimulating insulin and glucose receptors is a major therapeutic approach for the prevention and treatment of T2DM. Natural substances, particularly the secondary metabolites of medicinal plants, have garnered significant interest as potential antidiabetic drugs due to their rich bioactive molecules [19–26]. Flavonoids are a diverse class of bioactive molecules found in plants that have demonstrated remarkable antidiabetic properties [27–29].

This paper aims to provide an updated overview of natural flavonoids as antidiabetic drugs, their major mechanisms of action, and their clinical applications. Flavonoids have been shown to improve glucose uptake, increase insulin sensitivity, inhibit carbohydrate-digesting enzymes, and decrease hepatic glucose production [27–29]. Furthermore, flavonoids have been reported to have protective effects against diabetes complications, such as nephropathy, neuropathy, and retinopathy [27–29]. Due to these promising findings, natural flavonoids have potential clinical applications as antidiabetic drugs.

2. Clinical investigations of antidiabetic properties of natural flavonoids

Various clinical studies have demonstrated the potential of natural flavonoids in managing diabetes. The findings of clinical trials investigating the antidiabetic effects of these bioactive compounds are summarized in Table 1. The main flavonoids that have been extensively studied in clinical settings include resveratrol, catechin, rutin, epicatechin, quercetin, hesperidin, and diosmin. In the subsequent sections, we will delve into the progress made in clinical investigations concerning these compounds.

2.1. Resveratrol

In a randomized, double-blind trial, Brasnyó et al. [30] investigated the potential of resveratrol in improving insulin sensitivity in T2D patients. Nineteen patients received a 2 × 5 mg daily dose of resveratrol orally for 4 weeks. The results showed a decrease in insulin resistance and an increase in insulin sensitivity and pAkt/Akt ratio. However, no significant effect on parameters associated with β-cell function was observed. In another clinical study conducted by Bhatt et al. [31], a 3-month oral treatment of 62 T2D patients with 250 mg/day of resveratrol normalized glycaemia, HbA1c, systolic blood pressure, total cholesterol, and total protein levels, without any effect on body weight or LDL and HDL cholesterol levels. These results are consistent with the anti-hyperglycemic and anti-hyper-lipidic effects of resveratrol revealed by other *in vitro* and *in vivo* studies.

However, a randomized, placebo-controlled trial conducted by Yoshino et al. [32] on non-obese postmenopausal women with normal GT (NGT) showed that a 12-week treatment with 75 mg/day of resveratrol did not improve insulin sensitivity of adipose tissue, skeletal muscle, or liver, nor did it affect inflammatory markers, plasma lipids, resting metabolic rates, or putative molecular targets (PPARGC1A, NAMPT, SIRT1, and AMPK). This indicates that resveratrol does not have positive metabolic effects in non-obese postmenopausal women with NGT.

Movahed et al. [33] confirmed the results obtained by Bhatt et al. [31] in 2013, showing that a single oral dose of resveratrol (1

g/day) for 45 days reduced fasting glycaemia levels, HbA1c, systolic blood pressure, insulin resistance, and increased HDL levels without affecting markers of renal and hepatic function. Two clinical studies conducted in 2014 also demonstrated the anti-diabetic activity of resveratrol. A three-month treatment of this flavonoid (50 mg) three times a day reduced BMI, weight, waist circumference (WC), fat mass, total insulin secretion, and area under the curve (AUC) of insulin [34]. Another study showed that single-dose supplementation with resveratrol (300 mg) attenuated post-absorption insulin concentrations with elevated p38 MAPK phosphorylation in skeletal muscle, but without any change in insulin signaling from adipose tissue or skeletal muscle [35]. Chen et al. [36]conducted a double-blind, randomized clinical study in 60 non-alcoholic subjects with fatty liver disease (FLD), showing that a three-month treatment with resveratrol (2 capsules, 150 mg) twice per day improved levels of LDL cholesterol, total cholesterol, blood glucose, transaminases, and HOMA-IR index, and augmented the level of adiponectin, with decreased TNF-α, FGF21, and cytokeratin 18 (CK-18) fragment levels. However, Thazhath et al. [37] found that supplementation with resveratrol (500 mg) twice a day for five weeks did not influence fasting and postprandial glycaemia, HbA1c, or total plasma GLP-1 in fourteen participants with T2D.

In a randomized, placebo-controlled study involving 34 subjects with polycystic ovary syndrome, a three-month oral treatment with 1500 mg/day of resveratrol resulted in a significant decrease (31.8 %) in fasting insulin levels and a significant increase (66.3 %) in the insulin sensitivity index. However, no effect was observed on endothelial function or inflammatory markers [38]. In contrast, a combination of resveratrol (80 mg) and epigallocatechin-3-gallate (EGCG) (282 mg) did not improve insulin-stimulated glucose disposal or endogenous glucose production inhibition in 38 obese and overweight subjects after 12 weeks of supplementation. Nonetheless, the combination was shown to enhance the oxidative ability of permeabilized muscle fibers [39]. These findings were consistent with those of Timmers et al. [40], who observed no improvement in hepatic or peripheral insulin sensitivity following one month of oral administration of resveratrol (150 mg/day). Additionally, a randomized, double-blind, clinical trial conducted with middle-aged men suffering from metabolic syndrome showed that daily intake of resveratrol (150 and 1000 mg) for 16 weeks did not improve glucose homeostasis, inflammatory status, or hepatic lipid content [41]. Finally, in a study involving 45 overweight or slightly obese volunteers receiving *trans*-resveratrol or placebo capsules for 4 weeks, separated by a washout period of at least 4 weeks, no changes were noted in fasting or postprandial inflammation, endothelial function, or plasma biomarkers following *trans*-resveratrol supplementation at a dose of 150 mg/day [42].

In 2018, a study investigated the effect of resveratrol on metabolic health in men at high risk of developing T2DM. After administering a daily oral dose of 150 mg for one month, this treatment did not improve insulin sensitivity but enhanced muscle mitochondrial function on a fatty acid-derived substrate [43].

More recently, a single-blind randomized clinical trial evaluated the effects of resveratrol on various parameters in 472 elderly type 2 diabetic patients. After six months of daily oral treatment with resveratrol, beneficial effects were observed, including improved insulin resistance, blood glucose parameters (reduced G6Pase and HbA1c), kidney function, inflammation (decreased pro-inflammatory cytokines, IL-1β, IL-6, and TNF-α), and lipid profile (reduced triglycerides, total cholesterol, and HDL cholesterol) [44].

Another randomized clinical trial in 110 diabetic patients evaluated the effect of daily supplementation with resveratrol (200 mg) on glucose homeostasis and inflammation. After 24 weeks of treatment, significant improvements in glycaemia, insulin synthesis and resistance, TNF-α, and IL-6 levels were achieved [45].

2.2. Catechin

In a study conducted by Nagao et al. [46], the effects of green tea rich in catechins were investigated in patients with T2DM who were not receiving insulin therapy. The study involved a 12-week daily treatment with a beverage containing either 582.8 or 96.3 mg of catechins, which resulted in increased insulin and adiponectin secretion, but had no significant effect on glucose and HbA1c levels. These findings suggest that the consumption of catechin-rich foods by diabetics who are not on insulin therapy could potentially help prevent obesity, maintain low HbA1c levels, and improve insulin secretion capacity.

Similarly, Takahashi et al. [47] examined the effects of catechin-rich green tea on oxidative stress and postprandial hyperglycemia in healthy postmenopausal women. The study involved daily ingestion of catechin-rich green tea (615 mg/350 mL) for 4 weeks, which significantly improved redox homeostasis and postprandial glycemic status.

2.3. Epicatechin

A randomized, placebo-controlled study conducted by Dower et al. [50] aimed to evaluate the impact of pure epicatechin on the cardiometabolic health and vascular function of 37 healthy individuals, both male and female. After four weeks of treatment with 100 mg/day of pure epicatechin, a significant improvement in insulin resistance and fasting plasma insulin was observed, while fasting plasma glucose levels remained unaffected. However, no significant changes were detected in other health-related parameters such as NO levels, blood pressure, blood lipid profile, and flow-mediated dilation.

2.4. Quercetin

The study conducted by Dower et al. [50] also investigated the effects of daily supplementation with quercetin-3-glucoside (160 mg) on cardiovascular disease risk factors in 37 healthy individuals. The results revealed that four weeks of quercetin-3-glucoside supplementation did not lead to any significant changes in insulin resistance, flow-mediated dilation, or other cardiovascular disease risk factors.

Table 2
In vitro/in silico anti-diabetic potential of flavonoids.

Flavonoids	References	Models	Mechanisms
Apigenin	[53,54]	Assessment of high glucose (HG) and tumor necrosis factor α (TNFα) in endothelial cells (ECs)	Reduced the expression of glucose-induced LOX-1 and TNF-α, thereby preventing diabetes complications and mitigating their risk and severity
	[55]	α-glucosidase assay	Inhibited α-glucosidase activity in a non-competitive manner through a monophasic kinetic process
	[56]	α-amylase assay	Inhibited Human and *Aspergillus oryzae* α-amylase activities in a competitive manner
Arbutin	[57]	α-glucosidase and α-amylase assays	Inhibited (dose-dependently) α-amylase (81 %) and α-glucosidase (75 %) activity
	[58]	L6 skeletal muscle cell line	Inhibited *t*-BHP-induced ROS generation Increased glucose uptake
Baicalin	[59]	Skeletal muscles of mice Myotubes of C2C12 cells	Decreased NT-PGC-1α levels Enhanced GLUT4, PGC-1α, pP38MAPK, pAKT and pAS160 contents Increased GLUT4 mRNA, PGC-1α mRNA, PPARγ mRNA, GLUT1 mRNA expression
	[60]	3T3-L1 cells Adipocytes of DIO mice	Decreased HOMA-IR and p-p38 MAPK and pERK levels Enhanced pAKT and PGC-1α contents Increased GLUT4 mRNA, PGC-1α mRNA expression Increased GLUT4 concentration in plasma membranes of adipocytes
	[61]	Hepatocytes of high-fat diet (HFD)-induced obese mice	Decreased HOMA-IR Suppressed p-p38 MAPK, *p*-CREB, FoxO1, PGC-1α, PEPCK and G6Pase expression in liver of obese mice and hepatocytes Inhibited gluconeogenic genes by p38MAPK inhibitor in hepatocytes
	[62]	Skeletal muscle and L6 myotubes	Elevated the levels of PGC-1α, GLUT4, p-p38MAPK, *p*-AKT and p-AS160 in skeletal muscle of obese mice Augmented the activity of PGC1α-GLUT4 axis in myotubes through activation of p38MAPK and AKT pathways
	[63]	Insulin-resistant (IR)-HepG2 cells	Down-regulated IRS/PI3K/Akt signaling pathway Reduced GLUT4 expression and enhanced GSK-3β activity
Catechin	[64]	Human intestinal epithelial Caco-2 cells	Inhibited the intestinal absorption of glucose
	[65]	α-glucosidase assay	Inhibited enzyme activity
	[66]	Hepa 1–6, L6 myoblasts, and 3T3-L1	Activated, in combination with a gallocatechin moiety, LKB1/AMPK signaling pathway
	[67]	Inhibition of mammalian carbohydrate-degrading enzymes: - Rat intestinal maltase - Rabbit glycogen phosphorylase (GP) b	EGCG, catechin 3-gallate (CG), gallocatechin 3-gallate (GCG), and epicatechin 3-gallate (ECG), were good inhibitors of maltase, with IC_{50} values of 16, 62, 67, and 40 μM, respectively GCG, ECG, EGCG, and CG inhibited GP b, with IC_{50} values of 6.3, 27, 34, and 35 μM, respectively
	[68]	α-glucosidase and α-amylase assays	Inhibited α-glucosidase ($IC_{50} = 31$ μg/mL) Inhibited α-amylase ($IC_{50} = 160 \pm 6$ μg/mL)
	[69]	α-amylase assay	Inhibited α-amylase ($IC_{50} = 637.5 \pm 7.81$ μmol/L)
	[70]	α-glucosidase assay	Inhibited α-glucosidase Accessed the active site of the α-glucosidase enzyme and bound to catalytic amino acid residues
	[71]	*In silico* (software analysis)	Presented an optimal combination
	[72]	α-glycosidase assay	Inhibited the activity of α-glycosidase enzyme
Cyanidin	[73]	α-glucosidase assay	Inhibited *α*-glucosidase ($IC_{50} = 19.7 \pm 0.24$ μM)
	[74]	α-glucosidase assay	Inhibited *α*-glucosidase ($IC_{50} = 0.50 \pm 0.05$ mM) Synergistically inhibited intestinal α-glucosidase
	[75]	Intestinal sucrose α-amylase assay	Cyanidin-3-glucoside + Cyanidin-3-galactoside: Inhibited intestinal sucrase ($IC_{50} = 0.50 \pm 0.05$ mM) Inhibited pancreatic α-amylase ($IC_{50} = 0.30 \pm 0.01$ mM)
	[76]	Intestinal maltase and sucrase	Inhibited intestinal maltase ($IC_{50} = 2.323 \pm 14.8$ μM) Inhibited intestinal sucrase ($IC_{50} = 250.2 \pm 8.1$ μM)
	[77]	Adipocytes, 3T3-L1 cells	Decreased TNF-α concentration Activated adipocyte differentiation and insulin signaling
	[78]	Human 3T3-L1 cells and omental adipocytes	Increased adipocyte glucose absorption Increased PPARγ activity Increased adiponectin production
	[79]	Pancreatic β-cells, MIN6N	Decreased DNA fragmentation Reduced ROS generation Increased insulin secretion Prevented cell apoptosis
	[80]	Pancreatic β-cells, MIN6N	Prevented oxidative stress-induced cell apoptosis Reduced H_2O_2-induced cell death
	[81]	3T3-Ll cells	Induced differentiation into smaller adipocytes Reduced TNF-*α* production Activated insulin signaling

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Table 2 (*continued*)

Flavonoids	References	Models	Mechanisms
			Enhanced glucose absorption
			Induced insulin-sensitive adipocytes
	[82]	Hela cells and murine hepatocytes	Activated AMPK signaling pathway by suppressing its downstream kinase
			Improved GT
	[83]	α-glucosidase and α-amylase assays	Inhibited α-amylase activity (IC_{50} = 7.5 μM)
			Inhibited α-glucosidase activity (IC_{50} = 13.72 μM)
	[84]	3T3-L1 adipocytes	Increased glucose absorption
			Enhanced GLUT4 membrane expression
			Enhanced phosphorylation of IRS-1 and Akt
	[85]	Pancreatic INS-1 β-cells	Increased insulin synthesis
			Increased intracellular Ca^{2+} signals
	[86]	α-glucosidase and DPP-4 assays	Inhibited α-glucosidase (IC_{50} = 479.8 μM)
			Inhibited DPP-4 (IC_{50} = 125.1 μM)
	[87]	α-glucosidase assay	Inhibited α-glucosidase activity (IC_{50} = 22.7 ± 7.1 μmol/L)
	[88]	Human hepatocellular carcinoma cell HepG2	Activated the AMPK pathway
	[89]	Liver HepG2 and L02 cells	Promoted glucose consumption via the regulation of the Wnt/β-catenin-WISP1 pathway
	[90]	Pancreatic cells (INS-1 cells)	Enhanced insulin synthesis by intracellular Ca^{2+} signalling
			Activated the PLC-IP3 pathway and the voltage-dependent Ca^{2+} channel
Delphinidin	[91]	Pancreatic cells (INS-1832/13)	Stimulated insulin synthesis
	[92]	L6 myotubes	Increased the absorption of glucose
	[93]	Mouse jejunum samples and human intestinal cells (HT-29, Caco-2, and NCM460)	Decreased glucose uptake
			Affected the function of SGLT1
	[94]	α-amylase, α-glucosidase, and DPP-4 inhibition assays	Inhibited α-glucosidase (44.5 %)
			Inhibited α-amylase (24.2 %)
		Glucose uptake *in vitro*	Inhibited DPP-4 (78.8 %)
			Reduced glucose absorption (37.1 %)
	[95]	Pancreatic RIN-m5F β-cells	Decreased cleaved caspase-3 level, adverse effects of oxidative stress, and apoptosis caused by high glucose concentrations
			Enhanced AMPKα Thr172 level phosphorylation
Epicatechin	[96]	Islets of Langerhans	Stimulated the secretion of insulin
	[97]	Muscle, fat, and liver cells	Increased glycogen content, oxygen and insulin uptake
	[98]	Islets of Langerhans	Stimulated the conversion of (pro) insulin into insulin as well as its release
	[99]	Islets isolation	No impact on insulin release
	[100]	Ins-1E cells	Increased insulin synthesis
			Protected β-cells
	[101]	L6 myoblasts	Promoted glucose absorption and GLUT4 translocation
			Activated PI3K signaling
	[102]	HepG2 cells	(−)-epicatechin + β-glucan exhibited a synergistic effect on the Akt pathway
	[71]	*In silico* (software analysis)	Presented an optimal combination
Hesperetin	[103]	3T3-L1 cells	Inhibited the production of free fatty acids (FFA) stimulated by TNF-α
			Inactivated NF-κB and ERK pathways
	[104]	α-glucosidase assay	Inhibited α-glucosidase (IC_{50} = 0.38 ± 0.05 mM) activity
			K_{slope} = 0.23 ± 0.01 mM
Hesperidin	[105]	RAW 264.7 cells	Normalized inflammation-induced insulin resistance (RAW 264.7 cells)
		3T3-L1 preadipocytes	Inhibited TNF-α-induced synthesis of interleukin-6 (IL-6) and prostaglandin E_2 (PGE_2) (3T3-L1 cells)
Kaempferol	[106]	Mature 3T3-L1 adipocytes	Enhanced insulin-stimulated glucose absorption
	[107]	HIT-T15 cells	Protected HIT-T15 cells via interference with ROS metabolism
	[108]	α-glucosidase assay	Inhibited α-glucosidase (IC_{50} = 19.36 ± 2.43 μM) activity
	[109]	INS-1E cells	Protected β-cells and pancreatic human islets
		Human pancreatic islets	Enhanced insulin synthesis and secretory function
	[110]	INS-1E cells	Inhibited cell apoptosis
		Human pancreatic islets	Decreased caspase-3 activity
			Improved insulin synthesis
	[111]	Pancreatic cells, MIN6	Improved the proliferation of β-cells
	[112]	α-glucosidase assay	Inhibited α-glucosidase (IC_{50} = 1.16 ± 0.04 × 10^{-5} mol/L) activity
	[113]	α-glucosidase and α-amylase assays	Inhibited α-amylase activity (IC_{50} = 51.24 μg/mL)
			Inhibited α-glucosidase activity (IC_{50} = 29.37 μg/mL)
	[114]	α-glucosidase and α-amylase assays	Non-competitive α-glucosidase inhibition
			Competitive α-amylase inhibition
	[115]	RIN-5F cells	Increased anti-apoptotic activity and cell viability
		Pancreatic islets	Stimulated autophagy
			Restored β-cell dysfunction
	[116]	α-glucosidase and α-amylase assays	Inhibited the activity of α-amylase and α-glucosidase
	[115]	RIN-5F cell line	Restored β-cell dysfunction

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Table 2 (*continued*)

Flavonoids	References	Models	Mechanisms
Luteolin	[117]	α-glucosidase and α-amylase assays	Blocked α-glucosidase activity (36 % at 0.5 mg/mL) (stronger than acarbose) Blocked α-amylase activity (less potent than acarbose)
	[118]	Maltase, sucrose, and α-glucosidase activities	Blocked maltase activity (IC_{50} = 2.3 mM) At doses of 100 and 200 mg/kg: No effect was observed on other enzymes
	[119]	3T3-L1 adipocytes	Decreased TNF-α and IL-6 mRNA levels Increased glucose uptake response to insulin stimulation Enhanced Akt2 phosphorylation and PPARγ transcriptional activity
	[120]	Endothelial cells	Increased insulin-dependent nitric oxid production
	[121]	Protein tyrosine phosphatase 1B (PTP1B) assay Aldose reductase (AR) assay	Inhibited AR activities and the PTP1B effect
	[122]	MIN6 cells	Inhibited NF-κB activity Decreased NO production Stimulated insulin secretion
	[123]	*α*-glucosidase assay	Blocked α-glucosidase ($IC_{50} = 1.72 \pm 0.05 \times 10^{-4}$ mol/L) activity A single site of inhibition on the enzyme $K_i = 1.40 \pm 0.02 \times 10^{-4}$ mol/L
	[124]	3T3-L1 cells and RAW264.7 macrophages	Suppressed macrophage cell infiltration
Malvidin-3-*O*-glucoside	[125]	Caco-2 cells	Reduced the absorption of ^{14}C fructose (15 % for the highest concentration)
	[94]	α-glucosidase, α-amylase, and DPP-4 assays Caco-2 cells Glucose absorption (*in vitro*)	Inhibited α-amylase (29.6 %) activity Inhibited α-glucosidase (42.8 %) activity Inhibited DPP-4 (82.4 %) activity Decreased glucose absorption (55.2 %)
	[126]	α-glucosidase, α-amylase, and DPP-4 assays Caco-2 cells	Inhibited α-amylase (29.6 %) activity Inhibited α-glucosidase (42.8 %) activity Inhibited DPP-4 (82.4 %) activity
	[127]	α-glucosidase and α-amylase assays	Inhibited α-glucosidase activity (IC_{50} = 55 μg/mL)
	[128]	α-glucosidase assay	Inhibited α-glucosidase activity in a reversible non-competitive way
Myricetin	[129]	Adipocytes	Enhanced the insulin stimulatory effect Stimulated lipogenesis and uptake of both D-3-*O*-methyl-glucose and D-glucose Increased the V_{max} of glucose transport
	[130]	Rat adipocytes	Increased insulin-stimulated lipogenesis Stimulated glucose transport
	[131]	Rat adipocytes	Inhibited glucose transport and the uptake of methylglucose
	[132]	C2C12 cells	Increased glucose absorption with AMPK and Akt activities Reduced insulin resistance
	[133]	α-amylase and α-glucosidase inhibition assays 3T3-L1 cells	Inhibited both *α*-glucosidase and *α*-amylase activities Enhanced glucose absorption Activated insulin-signaling pathway
	[134]	α-glucosidase and α-amylase assays	Inhibited α-amylase (IC_{50} = 662 μg/mL) activity (reversible and competitive) Inhibited α-glucosidase (IC_{50} = 3 μg/mL) activity (reversible but non-competitive)
	[135]	HepG2 cell line	Increased β-endorphin (BER) and adropin secretion Activated the Glucagon-like peptide-1 (GLP-1) receptor that modulates adropin expression
	[136]	RAW 264.7 cells	Inhibited the expression levels of IFN-γ and IL-2
Naringenin	[137]	Preadipocytes	Stimulated glucose absorption (163 %)
	[138]	α-glucosidase and 11*β*-HSD1 assay	Inhibited 11*β*-HSD1 activity (39.49 %)
	[103]	3T3-L1 cells	Inhibited NF-κB and ERK pathway activation induced by TNF-α as well as the synthesis of Free Fatty Acids (FFA) induced by TNF-α
	[139]	L6 rat myotubes	Increased glucose absorption
	[140]	INS-1E cells	Induced glucose sensitivity Stimulated insulin synthesis Modified gene expression profiles
	[141]	Porcine myotube cultures	Increased the phosphorylation of TBC1D1 by increasing translocation of GLUT4 and absorption of glucose
	[142]	α-glucosidase assay	Decreased postprandial glycaemia levels (*in vitro*)
	[143]	Molecular docking	Exhibited high binding affinity towards GLUT4 and PPARγ
	[144]	α-glucosidase assay	Exhibited an up-regulation of PPARγ receptors Exhibited potent anti-α-glucosidase activity
Naringin	[145]	Differentiated L6 myoblasts	Increased glucose absorption
	[146]	RIN-5F cells	Prevented pancreatic β-cell dysfunction Reduced inhibition of insulin secretion

(*continued on next page*)

Table 2 (*continued*)

Flavonoids	References	Models	Mechanisms
	[147]	HepG2 cells	Stimulated glucose uptake independently of insulin stimulation Increased glucose uptake by inducing AMPK phosphorylation Bound to AMPK γ-subunit
Quercetin	[106]	Mature 3T3-L1 adipocytes	Improved insulin-stimulated glucose absorption
	[148]	α-glucosidase assay	Inhibited α-glucosidase (IC_{50} = 0.017 mmol × L^{-1}) activity
	[149]	C2C12 muscle cells	Improved glucose uptake, by stimulating AMPK pathway
	[150]	11β-HSD1 assay	Inhibited 11β-HSD1
	[151]	Embryonic fibroblasts	Prevented insulin sensitivity impairment
	[152]	INS-1 cells	Enhanced insulin secretion Increased β-cell function
	[153]	C2C12 skeletal muscle cells	Improved insulin sensitivity Improved glucose absorption
	[154]	L6 myoblasts	Reduced ROS production Normalized the level of GSH Increased glucose uptake via GLUT 4 translocation
	[155]	H4IIE hepatocytes	Inhibited G6pase Activated the hepatic AMPK pathway
	[134]	α-glucosidase and α-amylase assays	Inhibited α-amylase (IC_{50} = 770 μg/mL) activity (reversible and competitive) Inhibited α-glucosidase (IC_{50} = 32 μg/mL) activity (reversible but non-competitive)
	[156]	L6 myoblasts	Involvement of the AMPK pathway and p38 MAPK in the uptake of 2-NBDG
	[157]	INS1 cells	Increased the levels of Sirtuin 3 (Sirt3), Catalase (CAT), and Superoxide Dismutase (SOD)
	[158]	α-glycosidase assay	Inhibited α-glycosidase activity
	[159]	α-amylase assay	Inhibited α-amylase (IC_{50} = 0.325 mg/mL) activity in a non-competitive way
Quercitrin	[160]	Rat insulinoma (RINm5F) cells	Protected β-cells against cytokine-induced damage Improved glucose-stimulated insulin secretion (GSIS) Inhibited NF-κB translocation
Isoquercitrin	[161]	NCI–H716 cells	Stimulated GLP-1 production Inhibited DPP-4 competitively (IC_{50} = 96.8 mM) K_i = 236 mM
Rutin	[148]	α-glucosidase assay	Inhibited α-glucosidase (IC_{50} = 0.196 mmol × L^{-1}) activity
	[162]	Isolated soleus muscles from rats	Stimulated the uptake of ^{14}C glucose in diabetic rat soleus muscle
	[154]	L6 myoblasts	Increased glucose uptake, which was related to the translocation of GLUT4
	[163]	C2C12 cells	Enhanced insulin receptor kinase (IRK) activity
	[164]	α-glucosidase and α-amylase assays	Blocked α-amylase (IC_{50} = 0.043 μM) activity Blocked α-glucosidase (IC_{50} = 0.037 μM) activity
	[165]	3T3-L1 and C2C12 mouse cell lines	Down-regulated the expression of protein tyrosine phosphatase-1B (PTP-1B)
	[166]	Human Amylin (hA)	Suppressed hA aggregations causing apoptosis in pancreatic cells
	[71]	*In silico* (software analysis)	Presented an optimal combination
Strictinin ellagitannin	[167]	α-glucosidase assay	Inhibited α-glucosidase (IC_{50} = 2.4 μg/mL) activity
Petunidin	[91]	Pancreatic cells, INS-1832/13	Increased insulin secretion
	[168]	*In vitro* (α-amylase assay) *In silico* (docking study)	Inhibition enzyme activity Slowed glycaemia release

Abbreviations 11β-HSD1: 11-beta-hydroxysteroid dehydrogenase type 1; AMPK pathway: Adenosine Monophosphate-activated Protein Kinase; AMPKα Thr172: Adenosine Monophosphate-activated Protein Kinase Alpha Threonine 172; BER: β-endorphin; CAT: Catalase; CG: Catechin 3-Gallate; DPP-4: Dipeptidyl peptidase-4; ECG: EpiCatechin 3-Gallate; EGCG: EpiGalloCatechin-3-Gallate; ERK: Extracellular Signal-regulated Kinase; FoxO1: Forkhead Box O1; FFA: Free Fatty Acids; GCG: GalloCatechin 3-Gallate; GLP-1: Glucagon-like peptide-1; GSIS: Glucose-Stimulated Insulin Secretion; Glucose Transporter 4: GLUT4; Glutathione: GSH; GP: Glycogen Phosphorylase; HG: High Glucose; hA: Human Amylin; IRK: Insulin Receptor Kinase; IRS-1: Insulin Receptor Substrate 1; IRS/PI3K/Akt: Insulin Receptor Substrate/Phosphoinositide 3-kinase/Akt; IFN-γ: Interferon gamma; IL: Interleukin; LOX-1: Lectin-like Oxidized low-density lipoprotein receptor-1; mRNA: messenger RNA; NF-κB: Nuclear Factor kappa B; NT-PGC-1α: N-terminal fragment of Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha; PPARγ: Peroxisome Proliferator-Activated Receptor Gamma; PPARγ: Peroxisome proliferator-activated receptor gamma; PEPCK: Phosphoenolpyruvate Carboxykinase; PLC-IP3 pathway: Phospholipase C-Inositol trisphosphate pathway; pAKT: Phosphorylated AKT (Protein Kinase B); pAS160: Phosphorylated AS160 (Akt Substrate of 160 kDa); *p*-CREB: Phosphorylated cAMP Response Element-Binding protein; p-P38MAPK: Phosphorylated P38 Mitogen-Activated Protein Kinase; PGE2: Prostaglandin E2; PTP1B: Protein Tyrosine Phosphatase 1B; PTP-1B: Protein Tyrosine Phosphatase-1B; ROS: Reactive Oxygen Species; SGLT1: Sodium/Glucose coTransporter 1; Sirt3: Sirtuin 3; SOD: Superoxide Dismutase; TBC1D 1: Tre-2/BUB2/CDC16 domain family member 1.

2.5. Rutin

Several experiments, both *in vitro* and *in vivo*, have demonstrated the anti-diabetic potential of rutin. In line with these findings, clinical investigations have confirmed the efficacy of this flavonoid in treating diabetes. For instance, a placebo-controlled trial conducted on 50 individuals with T2DM showed that a 3-month administration of rutin (500 mg/day) significantly reduced fasting

Table 3
In vivo anti-diabetic potential of flavonoids.

Flavonoids	References	Model	Mechanisms
Apigenin	[169–171]	Hyperglycemic rats	Stimulated insulin and glycogen synthesis Promoted glucose absorption Regulated key pathways involved in insulin signaling and glucose balance
	[172,173]	Streptozotocin (STZ)-induced diabetic rats (IDR)	Stimulated insulin production Protected pancreatic β-cells Reduced hepatic G6Pase activity
	[174]	STZ-IDR	Preserved pancreatic β-cells Promoted the translocation of GLUT4 to the cell membrane Decreased CD38 expression
	[175]	High fat diet (HFD)-induced obese mice (IOM)	Apigenin improves metabolic disturbances by lowering fasting blood sugar and plasma insulin levels. Apigenin inhibits the inflammatory response mediated by NF-κB.
	[176]	HFD/STZ-IDR	Decreased insulin resistance and glycaemia content
	[177]	STZ-IDR	Decreased ROS levels Restored β-cell apoptosis
	[178]	STZ-IDR	Improved biochemical parameters Repaired destroyed renal and hepatic architecture
Arbutin	[179]	Fasting and healthy dogs	Reduced glycaemia level
	[180]	Alloxan (ALX)-IDR	Decreased insulin and serum glucose concentrations
	[181]	ALX-IDR	Increased glucagon-like peptide 1 (GLP-1) and GLP1R levels
	[182]	STZ-induced diabetic mice (IDM)	Apigenin inhibited increased blood sugar levels and prevented body weight loss. Apigenin activated antioxidant enzymes such as SOD, CAT, and GPX.
Baicalin	[59]	Diet-induced obese (DIO) mice	Decreased food intake and body weight Reversed high fat diet-induced glucose and insulin intolerance, hyperglycemia and insulin resistance
	[60]	DIO mice	Decreased food intake and body weight Reversed HFD-induced glucose intolerance, hyperglycemia, and insulin resistance
	[61]	HFD-induced obese mice	Decreased body weight Alleviated HFD-induced glucose intolerance, hyperglycemia, and insulin resistance
	[62]	Obese mice	Decreased hyperglycemia and insulin resistance Augmented glucose consumption
	[63]	HFD-induced obese and pre-diabetic mice	Damaged the abilities of glycogen synthesis and glucose uptake Ameliorated hyperglycemia and dyslipidemia
Catechin	[183]	Saccharide-dosed rats	Increased insulin activity Inhibited intestinal sucrose and α-amylase activity
	[184]	T2D rats	Improved glucose tolerance (GT) and oxidative status
	[65]	Rats receiving an oral dose of maltose (2 g/kg)	Reduced glycaemia
	[185]	Normal rats	Epigallocatechin-3-gallate (EGCG) increased glycaemia Reduced insulin-stimulated glucose absorption
	[186]	STZ-IDM	Reduced glycaemia level Augmented tissue glycogen Enhanced GLUT4 mRNA
	[187]	HFD-IDM	Stimulated insulin secretion
	[188]	HFD-IDM	Reduced the expression of certain markers of insulin resistance (IR-β and GLUT4)
	[189]	STZ-IDR	Activated insulin receptor (IR) Improved GT
	[190]	STZ-IDM	Decreased glycaemia Protected against oxidative damage
	[71]	ALX- IDM	Prevented hyperglycemia and hypoglycaemia
Cyanidin	[191]	HFD-fed mice	Cyanidin exhibited beneficial effects on hyperinsulinemia, hyperglycemia, hyperleptinemia, and insulin sensitivity. It also reduced insulin resistance and the expression of TNF-α mRNA
	[192]	Rats fed cyanidin-rich diets	Cyanidin decreased glycaemia and the expression levels of the G6Pase gene. It also increased insulin sensitivity, up-regulated GLUT4, and down-regulated RBP4.
	[193]	Diabetic BALB/c mice	Decreased glycated albumin (GA) (46.00 ± 2.50 %) Decreased glycated hemoglobin (HbA1c) (4.95 ± 0.20 %)
	[81]	*db/db* mice	Activated insulin signaling Enhanced glucose absorption Induced insulin-sensitive adipocytes
	[82]	Normal and obese mice	Increased sensitivity to insulin
	[194]	HFD-fed mice	Reduced resistance to insulin Enhanced sensitivity to insulin
	[88]	HFD-fed mice	Inhibited gluconeogenesis
	[89]	Diabetic *db/db* mice	Up-regulated the expression of hepatic GLUT-1
Delphinidin	[195]	Diabetic C57b1/6J mice	No significant hypoglycaemic activity
	[92]	Hyperglycemic obese mice	Lowered glucose production in hepatic cells Reduced fasting glycaemia levels

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Table 3 (*continued*)

Flavonoids	References	Model	Mechanisms
	[193]	BALB/c mice	Reduced GA (30.50 ± 3.46 %) Decreased HbA1c (3.60 ± 0.25 %)
	[194]	HFD-fed mice	Improved insulin sensitivity Decreased insulin resistance
Epicatechin	[196]	ALX-IDR	Decreased glycaemia Protected cells
	[197]	ALX-IDR	Decreased glycaemia Regenerated cells
	[198]	ALX-IDR	Decreased glycaemia
	[199]	STZ-IDR	Failed to reverse DM Failed to halt disease progression
	[99]	STZ-induced β-cell damage Islets isolation	Normalized glycaemia concentrations No impact on insulin release
	[200]	HFD-fed mice	Reduced insulin resistance Enhanced insulin signaling pathway Decreased endoplasmic reticulum stress
	[201]	HFD-fed mice	Decreased glycaemia and insulin contents Augmented blood leptin contents
	[202]	HFD-fed mice	Improved sensitivity to insulin Decreased glycaemia
	[203]	Nicotinamide (NA)/STZ-IDR	Improved insulin resistance and mRNA expression of GLUT4 Epicatechin + gallic acid improved the previous indices
	[102]	Male Kunming mice	(−)-epicatechin + β-glucan exhibited a synergistic effect on the Akt pathway, subsequently enhancing glucose uptake
	[71]	ALX-IDM	Prevented hyperglycemia and hypoglycaemia
Hesperetin	[204]	T2D Goto-Kakizaki (GK) rats	Normalized glucose-regulating enzyme activities Reduced serum and liver lipid levels
	[205]	STZ-IDR	Improved glycaemia Reduced plasma glucose levels
	[206]	STZ-IDR	Improved glycaemia and insulin levels Inhibited insulin resistance development Inhibited enzymes implicated in glucose metabolism
	[207]	STZ-IDR	Improved plasma insulin and glycogen levels
	[208]	ALX-IDM	Restored glycaemia levels
	[209]	NA/STZ-IDR	Improved glucagon, serum glucose, and insulin Decreased activities of G6PD, glucose-6-phosphate (G6P), and fructose-1,6-bisphosphate (FBP)
Hesperidin	[210]	HFD-fed rats	Decreased blood glucose and G6Pase activities Increased glycogen concentration and plasma insulin
	[204]	T2D GK rats	Normalized glucose-regulating enzyme activities Reduced serum and liver lipid levels
	[211]	STZ-IDM	Decreased maternal glycaemia level
	[212]	STZ-induced marginal T1D rats	Decreased blood glucose Altered glucose-regulating enzyme activity
	[213]	HFD/STZ-IDR	Increased serum insulin concentrations Decreased TNF-α expression
	[214]	STZ-IDR	Normalized HbA1c, glucose, serum insulin, hepatic and muscle glycogen levels
	[215]	STZ-IDR	Decreased pancreatic cell degeneration Increased insulin concentrations
	[216]	STZ-IDR	Decreased HbA1c, fructose-1,6-bisphosphatase (FBPase), and G6Pase Improved hepatic glycogen
	[217]	HFD-IOM	Long-term daily treatment (11 weeks): Reduced glycaemia concentration Improved insulin resistance and glucose intolerance
	[218]	HFD/ALX-induced insulin resistance	Improved fasting glycaemia Prevented impaired GT (IGT) development Regulated gluconeogenesis and glycolysis
	[219]	STZ-IDR	Improved the levels of glycaemia, HbA1c, insulin, and lipid profile
Kaempferol	[220]	ALX-IDR	Reduced hyperglycaemia
	[221]	ALX-IDR (soleus muscle)	Increased muscle glycogen content Stimulated glucose absorption
	[222]	Soleus muscle of male Wistar rats	Promoted glycogen synthesis
	[223]	Male Sprague–Dawley rats	Increased the K_M Phlorizin + kaempferol 3-*O*-α-rhamnoside showed an additive inhibitory power on glucose intestinal absorption (GIA)
	[224]	T2D KK-A^y mice	Decreased HbA1c and fasting glycaemia levels
	[225]	STZ-IDR	Reduced insulin resistance and fasting glycaemia Improved disorders related to glucose metabolism

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Table 3 (*continued*)

Flavonoids	References	Model	Mechanisms
	[226]	HFD-IOM	Normalized the hyper-insulinemia, hyper-glycemia Improved insulin sensitivity Inhibited glycogen production and glucose uptake
	[227]	HFD/STZ-IDR	Improved insulin resistance Reduced TNF-α and IL-6 levels
	[228]	HFD-fed mice	Decreased HbA1c and fasting glycaemia levels Improved insulin resistance
	[229]	STZ-IDM	Decreased hyperglycemia Decreased diabetes incidence Decreased liver glucose production Inhibited gluconeogenesis
	[230]	HFD-IOM	Decreased diabetes incidence Decreased hyperglycemia and liver glucose production Improved gluconeogenesis
	[231]	STZ-IDR	Reduced fasting glycaemia levels Increased fasting insulin levels
	[232]	STZ-IDR	Kaempferol + myricetin normalized insulin and glucose levels, inflammatory cytokines, as well as lipid and liver enzymes
Luteolin	[233]	STZ-IDR	Decreased glycaemia contents Increased blood insulin contents
	[118]	Glycaemia determination in an animal model	At doses of 100 and 200 mg/kg: No effect was observed on glycaemia or other enzymes
	[234]	Diabetic KK-A^y mice	Normalized HbA1c, glycaemia, and insulin levels
	[124]	HFD-IOM	Improved insulin resistance
	[235]	Type 2 diabetes mellitus (T2DM) mice	Normalized fasting blood glucose, glycated serum protein, and pancreatic islet function index Restored the pancreas
	[236]	T2DM mice	Normalized pancreatic and hepatic functions, the modulation of intestinal microbiota composition, and the regulation of the PPAR signaling
	[237]	STZ-IDM	Luteolin + diosmin normalized glycaemia, insulin, HbA1c, and glycogen levels
Malvidin-3-*O*-glucoside	[195]	Diabetic mice	Exerted a significant anti-hyperglycemic activity
	[238]	HFD/STZ-IDR	Malvidin + metformin improved glucose and lipid metabolisms with inhibition of inflammation
Myricetin	[130]	STZ-IDM	Reduced hyperglycemia (50 %) Increased the content of G6Pase, hepatic glycogen and glycogen synthase
	[239]	STZ-IDM	Decreased plasma glucose concentrations Stimulated glucose storage in rat soleus muscles Increased expression of GLUT 4
	[240]	STZ-IDM	Decreased plasma glucose level Increased GLUT 4 expression Decreased PEPCK expression in liver
	[241]	Obese rats	Improved insulin sensitivity via an important post-receptor insulin signaling
	[242]	HFD-fed rats	Decreased glycaemia levels Increased sensitivity to insulin Enhanced insulin action
	[243]	Insulin-resistant rats	Decreased plasma glucose levels
	[244]	STZ-IDR	Decreased plasma glucose and HbA1c contents Increased plasma insulin and total haemoglobin contents
	[245]	Rats fed a HF/HS diet	Decreased insulin and glycaemia levels Decreased HOMA-IR values and pro-inflammatory cytokine (TNF-α and IL-6) levels
	[246]	STZ/cadmium-induced diabetic nephrotoxic rats	Ameliorated the levels of glucose, HbA1c, GP, and gluconeogenic enzymes Increased glycogen, GS, insulin, and the expression of insulin signaling molecules Protected pancreas
	[247]	*db/db* mice	Blocked α-glucosidase activity Reduced levels of HbA1c and fasting blood glucose
	[248]	Wistar rats	Exhibited glucoregulatory activity
	[249]	*db/db* mice	Increased adiponectin expression in brown adipose tissue (BAT) Improved insulin resistance by activating BAT
	[135]	T1D rats	Increased β-endorphin (BER) and adropin secretion Decreased hyperglycemia
	[136]	HFD-fed prediabetic mice	Exerted a remarkable hypoglycemic and hypolipidemic effect
	[232]	STZ-IDR	Myricetin + kaempferol normalized insulin and glucose and rates, inflammatory cytokines, as well as lipid and liver enzymes
Naringenin	[138]	Non-insulin-dependent DM (NIDDM)	Reduced plasma glucose
	[250]	NA/STZ-IDR	Reduced the levels of fasting glycaemia and HbA1c Increased serum insulin levels Protected pancreas

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Table 3 (*continued*)

Flavonoids	References	Model	Mechanisms
	[251]	NA/STZ-IDR	Attenuated hematological values, inflammation proteins, and mRNA transcription
	[142]	HFD/STZ-IDR	Inhibited α-glucosidase (*in vivo*) activity
	[252]	HFD/STZ-IDR	Attenuated hyperinsulinemia and hyperglycemia Increased insulin sensitivity Modulated GLUT4 and TNF-α expressions
	[176]	STZ-IDR	Reduced glycaemia and insulin resistance index
	[253]	STZ-IDM	Reduced glycaemia and HbA1c
	[254]	TSOD mice	Decreased hypoglycemic action of pioglitazone No effect on fasting glycaemia level
	[255]	NA/STZ-IDR	Normalized reduced serum insulin concentrations Elevated GP and G6Pase activities
	[143]	STZ-IDR	Attenuated glycaemia levels
	[256]	Insulin-deficient diabetic (IDD) mice induced by STZ	Naringenin + phytoestrogen 8-prenylnaringenin improved glucose homeostasis, STZ-induced disturbances in islet function, and insulin signaling defects
Naringin	[210]	T2D male mice (C57BL/KsJ-*db/db*)	Attenuated glycaemia level Increased glycogen content Augmented plasma insulin and C-peptide
	[257]	STZ-IDR	Decreased glycaemia and HbA1c Augmented plasma insulin level Decreased G6Pase and FBPase activities
	[258]	NA/STZ-IDR	Decreased glycaemia Increased insulin level Decreased HbA1c Reduced FBPase and G6Pase activities
	[213]	HFD/STZ-IDR	Decreased glycaemia level Increased serum insulin level
	[259]	HFD/STZ-IDR	Decreased hyper-insulinemia, hyper-glycemia, insulin resistance, and TNF-α Increased β-cell function Increased PPARγ expression
	[214]	HFD/STZ-IDR	Lowered elevated levels of HbA1c, glucose, serum insulin, hepatic, and muscle glycogen
	[260]	STZ-IDR	Exhibited hypoglycemic effects requiring insulin
	[261]	STZ-IDR	Decreased glycaemia level
	[255]	NA/STZ-IDR	Enhanced expression of adiponectin, IR subunit, and GLUT4 mRNA Reduced levels of hepatic glycogen, serum insulin, HbA1c, and G6Pase
	[262]	HFD/STZ-IDR	Reduced HbA1c and glycaemia levels Augmented plasma insulin content Enhanced activities of carbohydrate metabolism key enzymes
	[263]	STZ-IDM	Normalized hyperglycemia and islet dysfunction Protected β-cell apoptosis
Quercetin	[264]	STZ-IDR	Lowered plasma glucose content Improved GT test Regenerated pancreatic islets
	[265]	STZ-IDR	Ameliorated diabetic status (25 %)
	[266]	STZ-IDR	Protected β-cells Decreased the levels of MDA and nitric oxide (NO) Preserved islet β-cells
	[267]	STZ-IDR	Lowered glycaemia level Augmented insulin level Protected pancreatic β-cell structure
	[268]	ALX-IDR	Reduced glucose level Increased insulin level Inhibited G6Pase activity
	[269]	ALX-IDR	Prevented the rise in glycaemia
	[270]	High fructose diet (HFruD)-fed rats	Improved tyrosine phosphorylation Improved insulin sensitivity
	[271]	STZ-IDM	Lowered glycaemia level Improved plasma insulin level Recovered cell proliferation
	[272]	STZ-IDR	Decreased glycaemia levels Increased antioxidant enzyme activities
	[150]	NA/STZ-IDR	Decreased glycaemia level
	[151]	HFD-fed rats	Inhibited PPARγ expression
	[273]	STZ-IDR	Attenuated glycaemia levels Reduced resistance to insulin
	[274]	STZ-IDR *db/db* mice	Decreased glycaemia level Reduced HbA1c and plasma glucose rates Reduced intestinal maltase activity
	[275]	STZ-IDR	Normalized postprandial hyperglycemia

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Table 3 (*continued*)

Flavonoids	References	Model	Mechanisms
	[276]	NA/STZ-IDR	Increased glycaemia absorption Reduced the activity of glucose transport
	[277]	*db/db* mice	Reduced plasma glucose rates Decreased HOMA-IR
	[278]	STZ-IDR	Reduced glycaemia levels Augmented β-cell number
	[279]	ALX-IDM	Affected (positively) DNA damage Reduced hyperglycemia and enzyme markers (hepatic and renal) Increased expression levels of GLUT4
	[280]	Rats fed a HF/HS diet	Reduced glycaemia, HOMA-IR, and insulin levels
	[281]	STZ-IDR	Improved serum glycaemia levels Enhanced insulin levels Maintained glucose metabolic enzyme activities Preserved β-cell structure
	[282]	Fructose/STZ-IDR	Decreased the levels of glycaemia, hepatic glycogen, and HbA1c Improved the activities of hexokinase and G6Pase
	[283]	STZ-IDR	Exerted remarkable anti-diabetic effects on hyperglycemia
	[284]	STZ-IDR	Quercetin + EGCG restored pancreatic NIT-1 β-cell damage, which subsequently improved insulin secretion
	[157]	Diabetic *db/db* mice	Reduced elevated glycaemia and insulin rates
	[285]	STZ-IDR	Decreased glycaemia level
	[209]	NA/STZ-IDR	Improved serum glucose, glucagon, insulin, hepatic glycogen, and α-amylase Decreased activities of G6PD, FBP, G6P, and glucokinase Improved levels of GLUT2 and GLUT4
	[286]	Hypertensive rats	Reduced serum lipid peroxidation levels Increased insulin sensitivity Increased islet number per section and protein expression of CAT
Quercitrin	[287]	STZ-IDR	Lowered fasting glycaemia level Augmented insulin levels Reduced FBPase and G6Pase activities
	[288]	STZ-IDR	Lowered fasting glycaemia level Augmented insulin contents Protected β-cells
	[289]	STZ-IDR	Lowered fasting glycaemia and HbA1c levels Augmented insulin contents
	[290]	STZ-IDR	Reduced glycaemia levels
Isoquercitrin	[291]	Diabetic rats	Reduced hyperglycemia as a function of time Delayed the glycemic peak (to 30 min)
	[292]	High-calorie diet and STZ-IDR	Improved fasting glycaemia levels, and GT
	[161]	STZ-IDM	Decreased fasting glycaemia, augmented serum insulin contents Inhibited variations in postprandial glycaemia
Rutin	[293]	STZ-IDR	Reduced fasting glycaemia and HbA1c levels Augmented C-peptide and insulin contents
	[294]	STZ-IDR	Decreased fasting glycaemia level Decreased G6Pase and FBPase activities Augmented insulin and glycogen contents
	[295]	STZ-IDR	Reduced fasting glycaemia in a concentration-dependent way
	[276]	NA/STZ-IDR	Decreased glycaemia Augmented glucose absorption Decreased glucose transport activity
	[163]	Insulin resistance model and T2D	Induced a normoglycemic effect
	[296]	HFD/STZ-IDR	Reduced levels of glycaemia, HbA1c, and inflammatory mediators (TNF-α and IL-6) Preserved β-islet cell structure
	[165]	T2D mouse model	Down-regulated the expression of protein tyrosine phosphatase-1B (PTP-1B) Lowered serum glucose contents (*in vivo*)
	[166]	hA transgenic mice	Delayed the progression of diabetes
	[297]	HFD/STZ-IDM	Improved glycaemia and HbA1c levels, as well as pyruvate and GT
	[298]	STZ-IDR	Decreased fasting glycaemia levels Improved pancreatic tissue regeneration
	[71]	ALX-IDM	Prevented hyperglycemia and hypoglycaemia
	[299]	STZ-IDR	Regulated HbA1c and total hemoglobin (tHb) levels Restored STZ-induced damages in pancreas
Strictinin ellagitannin	[167]	OSTT	Enhanced oral sucrose tolerance
Peonidin	[300]	Male Sprague−Dawley rats	Ponidin suppressed the rise in glycaemia, inhibited maltase activity (IC_{50} = 200 μM), and decreased the maximal glycaemia level by 16.5 %.

Abbreviations: ALX: Alloxan; DIO: Diet-induced obese; FBP: Fructose-1,6-Bisphosphate; FBPase: Fructose-1,6-Bisphosphatase; G6P: Glucose-6-Phosphate; G6Pase: Glucose-6-Phosphatase; G6PD: Glucose-6-Phosphate Dehydrogenase; GIA: Glucose Intestinal Absorption; GK: Goto-Kakizaki; GA: Glycated Albumin; HbA1c: Glycated Hemoglobin; HFruD: High Fructose Diet; HFD: High Fat Diet; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; IDM: Induced Diabetic Mice; IDR: Induced Diabetic Rats; IOM: Induced Obese Mice; IR: Insulin Receptor; IDD: Insulin-Deficient

Diabetic; NIDDM: Non-Insulin-Dependent DM; NO: Nitric Oxide; NA: Nicotinamide; PTP-1B: Protein Tyrosine Phosphatase-1B; STZ: Streptozotocin; tHb: total Hemoglobin.

blood glucose, insulin, HbA1c, and insulin resistance levels [48]. Moreover, a recent study on 34 healthy adult participants who received rutin showed a decrease in postprandial glycaemia [49].

2.6. Hesperidin and diosmin

Experimental studies, both *in vivo* and *in vitro*, have demonstrated the anti-diabetic effects of hesperidin and diosmin. Recently, a randomized controlled trial was conducted to investigate the efficacy of these two flavones, administered alone or in combination (1 g/day for each), on 127 diabetic patients with neuropathy and metabolic syndrome (MetS). After 12 weeks of treatment, the separate administration of these flavones improved glycaemia, LDL, and triglyceride levels, with a greater magnitude of improvement observed when combined [52].

3. *In vivo* and *in vitro* anti-diabetic potential of flavonoids: mechanism insights

Flavonoids extracted and isolated from natural sources, particularly medicinal plants, showcase significant antidiabetic properties. Various *in vitro* and *in silico* studies, employing diverse experimental approaches, have been conducted. Tables 2 and 3 provide a comprehensive summary of previous research investigating the effects of flavonoids. In the subsequent section, we will elucidate the antidiabetic actions of each specific natural flavonoid.

3.1. Apigenin

Numerous preclinical studies have demonstrated the anti-diabetic potential of apigenin (Fig. 1 showed the chemical structure of apigenin). *In vivo* hyperglycemia regulation of this compound was evaluated using an alloxan-induced diabetes (AID) mouse model [170,268,301]. Apigenin has been shown to exert various positive effects, including decreasing the activity of G-6-Pase and glucose concentration, as well as reducing the levels of serum insulin [172] and hepatic/muscle glycogen contents [301].

In contrast to the aforementioned studies, Cazarolli et al. [170,171] demonstrated a significant anti-diabetic potential of apigenin in hyperglycemic rats. At doses of 50 and 100 μM, apigenin stimulated the synthesis of glycogen and insulin in the soleus muscle, resulting in an increase in the uptake of 14C-glucose in this tissue. Years later, Cazarolli et al. (2012) [169] elucidated the mechanism underlying the increased glucose uptake in the soleus muscle of hyperglycemic rats. They found that apigenin acts on insulin signaling pathways, including the tyrosine kinase receptor, atypical protein kinase C (aPKC), phosphatidylinositol 3-kinase (PI3K), and MEK.

Hossain et al. [174] investigated the mechanism underlying the anti-diabetic effects of apigenin in a streptozotocin (STZ)-induced diabetes (SID) rat model. They demonstrated that apigenin not only preserved pancreatic β-cells but also enhanced the translocation of GLUT4 in skeletal muscles and decreased the expression of the membrane glycoprotein CD38, thereby improving glucose homeostasis (as shown in Fig. 2). Ren et al. [176] confirmed these findings in T2DM rats caused by a low concentration of STZ as well as a high-fat diet (HFD). They observed a decrease in insulin resistance, glycaemia, and serum lipid levels with improved glucose tolerance (GT) upon treatment with apigenin.

Apigenin has also been shown to have several beneficial effects in HFD-induced obese mice. One study reported an increase in nitric oxide (NO) synthesis mediated by insulin, an improvement of vascular endothelial dysfunction, and inhibition of the inflammatory response associated with nuclear factor-κB (NF-κB). In addition, apigenin decreased the activity of liver enzymes glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK), leading to an improvement in metabolic disturbances such as decreased plasma insulin and fasting blood glucose concentrations [175].

Various *in vitro* methods have been employed to assess the anti-diabetic activity of apigenin, including the inhibition of carbohydrate-hydrolyzing enzymes [53–56,173,177]. Studies have shown that apigenin can inhibit the activity of α-glycosidase and human pancreatic α-amylase [55,56]. In addition, apigenin has been found to inhibit the expression of glucose-induced LOX-1 and

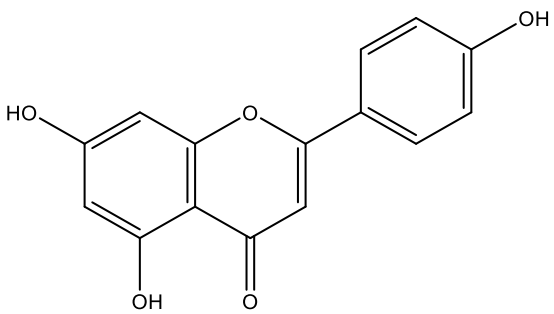

Fig. 1. Chemical structure of apigenin.

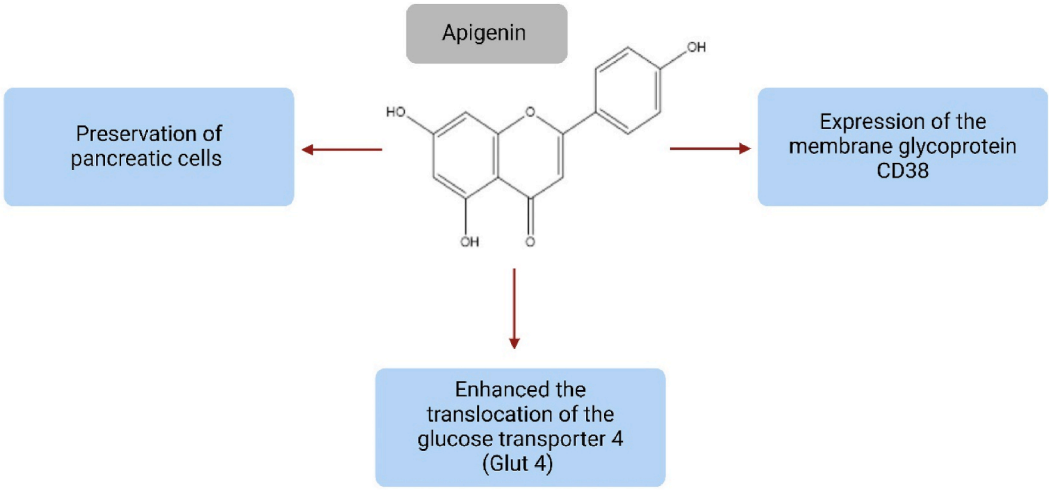

Fig. 2. Effects of apigenin on insulin synthesis and GLUT4 function.

TNF-α, which may help prevent diabetes complications such as arteriosclerosis by regulating NF-κB activity [53,54].

Furthermore, apigenin has been shown to protect pancreatic cells from oxidative stress induced by STZ and promote insulin production [173]. This effect on oxidative stress has also been confirmed through a reduction in ROS levels and the restoration of pancreatic β-cell apoptosis (Fig. 3) [177].

In a recent *in vivo* study, the potential hypoglycemic effect of apigenin was investigated using biochemical and histopathological parameters related to the liver and kidney. The results showed that oral administration of apigenin at a dose of 50 mg/kg/day improved the tested biochemical parameters and also exhibited a protective effect on the renal and hepatic architecture, as confirmed by histological examination. This suggests that apigenin may have therapeutic potential for the treatment of diabetes-associated organ damage [178].

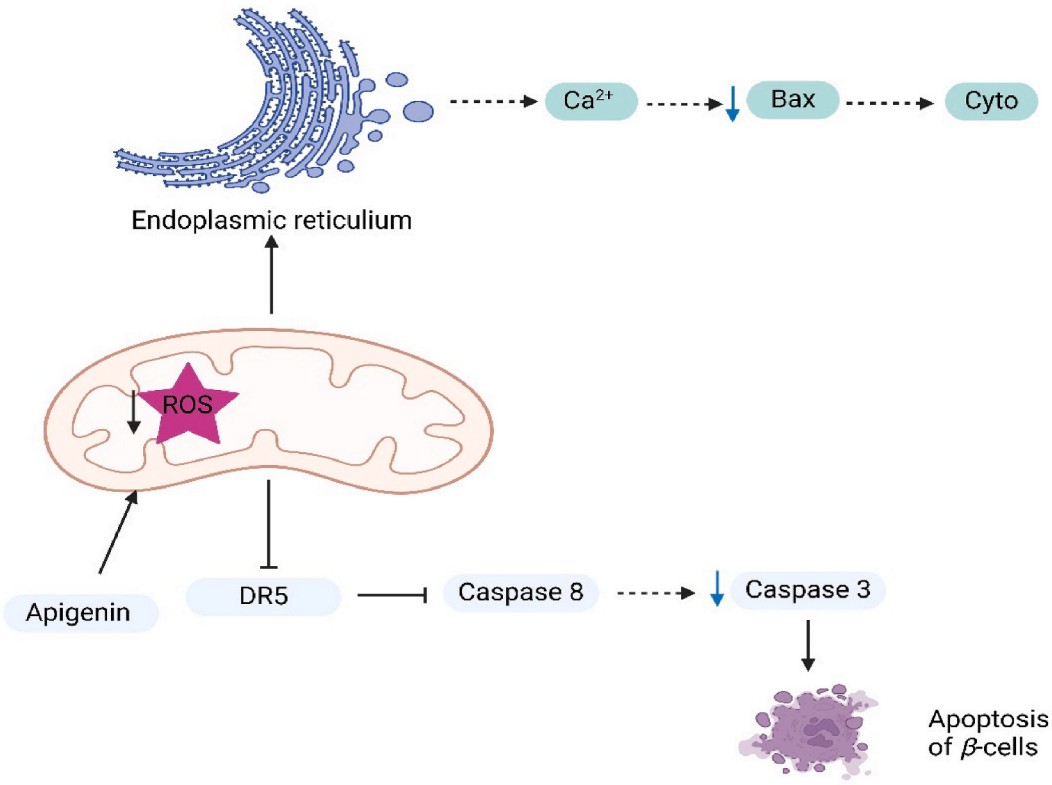

Fig. 3. Protection of beta-cells by apigenin.

3.2. Baicalin

Recently, several preclinical investigations have examined the effect of baicalin on diabetes and insulin resistance, as well as the underlying mechanisms (Tables 2 and 3). Indeed, these studies converge to suggest that baicalin has significant potential as a therapeutic agent for the treatment of obesity and insulin resistance. Their results revealed that this flavone acts through several molecular pathways, including the Akt/AS160/GLUT4 and P38MAPK/PGC1α/GLUT4 pathways, by accelerating the translocation of GLUT4 to the plasma membranes of adipocytes [59,60]. Additionally, baicalin showed an ability to suppress the expression of genes involved in gluconeogenesis and improve hepatic insulin resistance, mainly by inhibiting the p38 MAPK/PGC-1α signaling pathway [61,63]. Furthermore, other studies found that this compound protects against insulin resistance and metabolic dysfunction by activating the GALR2-GLUT4 signaling pathway, while attenuating oxidative stress and AGE production [62]. These results highlight the potential of baicalin as a promising natural treatment for metabolic disorders associated with obesity and prediabetes.

3.3. Arbutin

Arbutin, depicted in Fig. 4, has been investigated for its anti-diabetic properties since 1936, when Michel first reported on its potential therapeutic effects [179]. *In vitro* studies have shown that this flavonoid can dose-dependently inhibit α-amylase (81 %) and α-glucosidase (75 %) activities [57]. These findings were further confirmed *in vivo* using ALX-induced diabetic mice [180,181]. Oral administration of arbutin led to a significant increase in the levels of glucagon-like peptide 1 (GLP-1) and GLP1R, while decreasing serum insulin and glucose concentrations [180,181].

In 2021, a team of Chinese researchers investigated the potential anti-diabetic effects of arbutin in diabetic mice induced by STZ Li et al. [182]. The study revealed that arbutin inhibited increased blood glucose levels and prevented weight loss in the animals, while also increasing plasma insulin concentrations and inducing the activity of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX). These results suggest that arbutin may reduce diabetic symptoms through its antioxidant potential. A year later, Gholami Bahnemiri et al. [58] reported similar findings after pre-treating L6 skeletal muscle cells with arbutin (500 and 1000 μM) before inducing oxidative stress with *tert*-butyl hydroperoxide (t-BHP). Arbutin blocked ROS release and significantly increased glucose uptake, possibly by increasing the expression of glucose transporters GLUT1 and GLUT4 under oxidative stress.

3.4. Catechin

Numerous studies have demonstrated that catechin (Fig. 5) can enhance glucose homeostasis through multiple mechanisms.

Administering catechin orally (*in vivo*) led to a significant increase in 14C-glucose oxidation and a decrease in plasma glucose levels without altering C-peptide or plasma insulin. Additionally, catechin improved the antioxidant defense system and increased GLUT4 mRNA expression. It also restored the alterations of glycogen synthase (GS), G6Pase, glycogen phosphorylase (GP), and glucokinase, along with insulin receptor (IR) activation and improvement in glucose tolerance [186,189,190].

In rats, oral administration of this flavonoid increased insulin activity, decreased plasma glucose levels, and inhibited intestinal sucrose and α-amylase activities before administering soluble starch or sucrose [183]. Imada et al. [188] discovered that in animals made hyperglycemic by a HFD, catechins isolated from tea reduce some markers of insulin resistance. Similarly, in the same experimental protocol, oral administration of this compound stimulated insulin production and improved glucose tolerance (GT) [187]. In rats with T2DM, dietary intake of catechins was found to enhance GT and oxidative status [184].

In vitro tests, particularly those targeting digestive enzyme activity, have shown that catechin has a potent inhibition of α-glucosidase ($IC_{50} = 31$ μg/mL) and α-amylase ($IC_{50} = 160 \pm 6$ μg/mL) [68]. A similar anti-α-amylase effect was observed in the study conducted by Xu et al. [69], with an IC_{50} value of 637.5 ± 7.81 μmol/L.

Studies using cultured cells have revealed significant anti-diabetic effects of catechin. In 2000, Shimizu et al. [64] demonstrated that catechin inhibits intestinal glucose uptake in intestinal epithelial cells (Caco-2). In 2009, Murase et al. [66] found that catechin activates the LKB1/AMPK pathway *in vitro* (using Hepa 1–6, L6 myoblasts, and 3T3-L1 cells) in combination with a gallocatechin moiety. Furthermore, catechin derivatives, such as gallocatechin 3-gallate (GCG), catechin 3-gallate (CG), EGCG, and epicatechin 3-gallate (ECG), inhibit maltase *in vitro*, with IC_{50} values of 6.3, 35, 34, and 27 μM, respectively [67]. In Caco-2 cells, EGCG inhibited

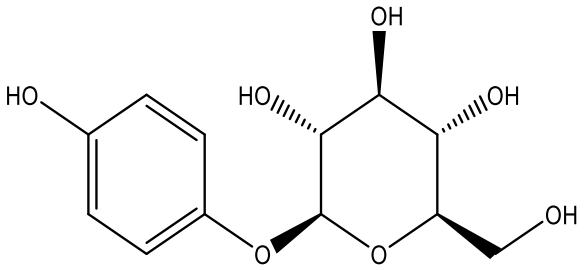

Fig. 4. Chemical structure of arbutin.

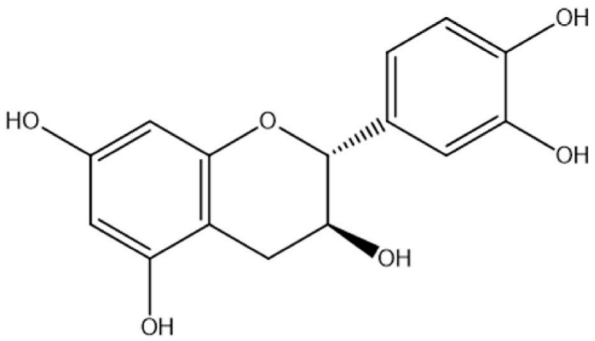

Fig. 5. Chemical structure of catechin.

maltase with an IC_{50} of 27 μM.

Recently, it has been discovered that catechins with a galloyl moiety (GM) have more potent inhibitory properties against α-glucosidase than those without GM [70]. GM was able to bind to catalytic amino acid residues of the α-glucosidase enzyme active site via hydrogen bonds and π-conjugations. In 2021, Mechchate et al. investigated the optimization of the anti-diabetic effects of certain plant flavonoids, including catechins, by developing a safe and potent multi-targeted mixture for the management of diabetes mellitus (DM) and its complications [71]. They found that a mixture containing all these molecules (catechin, epicatechin, and rutin) at 10 mg/kg will produce a new formulation with a powerful anti-hyperglycemic effect in combination, as confirmed *in vivo* (AID mice). Recently, Taslimi et al. [72] demonstrated the anti-diabetic potential of catechin 5-*O*-gallate on the activity of the α-glycosidase enzyme.

3.5. Epicatechin

Epicatechin (Fig. 6) has attracted the interest of many researchers for its potential anti-diabetic activity, both *in vitro* and *in vivo* studies [96–101,196–203]. Regarding the *in vivo* evaluation of anti-diabetic activity, various animal models have been utilized, including STZ-induced diabetic (SID) mice. [99,199,203], ALX-induced diabetic mice [196–198], and HFD-fed mice [200–202].

In diabetic mice, treatment with epicatechin resulted in an improvement in blood glucose levels. This improvement was achieved through enhanced insulin signaling, decreased insulin resistance and endoplasmic reticulum stress, and increased levels of GLUT4, a glucose transporter protein (Fig. 7) and blood leptin concentrations [99,199,203]. Subsequent studies using oral administration of epicatechin to animals fed a high-fructose diet (HFruD) have also reported similar findings, which support the earlier results. These studies showed that epicatechin supplementation improved blood glucose levels and related parameters in animals on a high-fructose diet [200–202].

In contrast to the *in vivo* studies mentioned earlier, some researchers have utilized isolated islets of Langerhans for *in vitro* assessments to evaluate the potential anti-diabetic effects of epicatechin [96–98]. In the study by Ahmad et al. [97], epicatechin was found to increase glycogen content, oxygen uptake, and insulin uptake in muscle, fat, and liver cells. Another study by the same author reported that epicatechin stimulated the conversion of proinsulin into insulin and its secretion from Langerhans islets [98]. Hii and Howell [96]. demonstrated that epicatechin (1 mM) stimulated insulin secretion from isolated islets of Langerhans *in vitro*. In damaged Ins-1E cells, epicatechin (5–20 μM) increased insulin secretion and antioxidant enzyme levels [100]. In skeletal muscle cells, 3-*O*-acyl-epicatechin activated PI3K signaling, leading to increased glucose uptake and translocation of GLUT4 [101].

Furthermore, (−)-epicatechin has shown hypoglycemic effects *in vivo* by modulating glucose metabolism [102]. When combined with β-glucan, it exhibited a synergistic effect on the Akt pathway, enhancing glucose uptake. This synergistic effect was attributed to the inhibition of gluconeogenesis, down-regulation of glycogen synthase kinase-3β (GSK3β), enhancement of glycogen synthesis, and up-regulation of GLUT4. Epicatechin, either alone or in combination with catechin and rutin, has demonstrated a significant

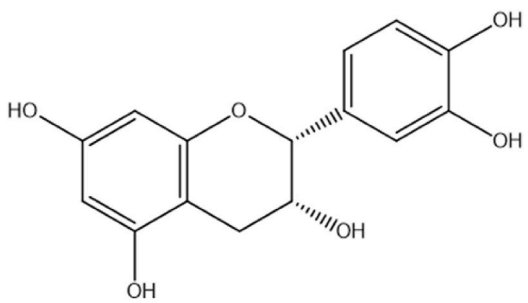

Fig. 6. Chemical structure of epicatechin.

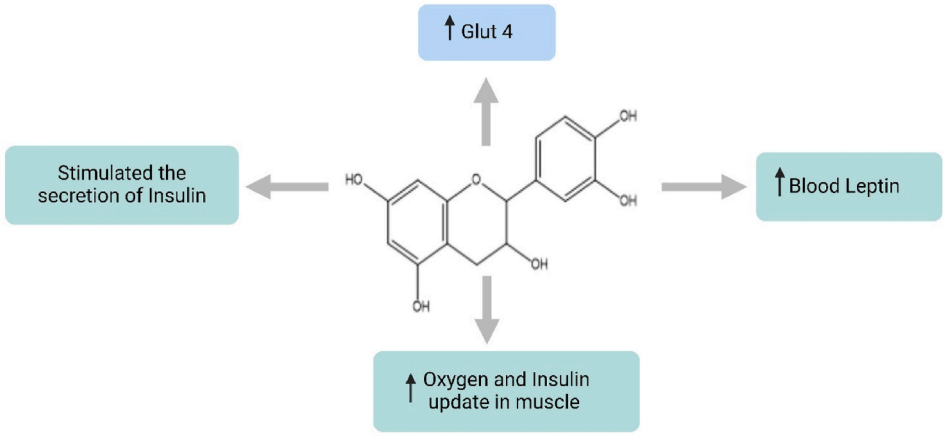

Fig. 7. Antidiabetic mechanisms of epicatechin.

hypoglycemic effect, suggesting its potential as an effective anti-diabetic drug [71].

3.6. Cyanidin

The anti-diabetic activity of cyanidin (Fig. 8) has been investigated by several researchers [73–77,79–86,191–194]. In studies conducted by Daveri et al. and Tsuda et al. [191,193,194], the impact of cyanidin-based treatment on glycemic-related parameters was evaluated in different animal models. In HFD-fed mice, cyanidin improved hyperinsulinemia, hyperglycemia, hyperleptinemia, insulin sensitivity, and decreased insulin resistance and TNF-α mRNA levels [191]. Similarly, in STZ-induced diabetic mice, administration of cyanidin chloride at a dose of 100 mg/kg/day led to a decrease in glycated albumin (GA) levels and glycated hemoglobin (HbA1c) levels [193].

In rats fed cyanidin-rich diets, positive effects on glycemic control were also observed. These effects included a decrease in blood glucose levels, down-regulation of glucose-6-phosphatase (G6Pase) gene expression, improved insulin sensitivity, up-regulation of GLUT4 (glucose transporter 4) expression, and down-regulation of RBP4 (retinol-binding protein 4) in white adipose tissue [192]. These findings suggest that cyanidin has beneficial effects on glycemic control and insulin sensitivity in animal models of obesity and diabetes.

The anti-diabetic potential of cyanidin has been extensively studied both *in vitro* and *in vivo*. In in vitro experiments, cyanidin has shown inhibitory effects on enzymes involved in carbohydrate metabolism, including α-glucosidase, α-amylase, and dipeptidyl peptidase-4 (DPP-4). It has demonstrated inhibitory activity against α-glucosidase and pancreatic α-amylase, as well as sucrase and maltase [73–75]. Cyanidin-3-*O*-glucoside has also exhibited α-glucosidase and DPP-4 inhibition [86] and α-glucosidase and α-amylase inhibition [83].

In cell culture studies, cyanidin has shown positive effects on pancreatic β-cells, promoting cell survival, reducing apoptosis, and increasing insulin synthesis and secretion [80,85]. In adipocytes, cyanidin has been found to enhance glucose uptake, activate insulin signaling pathways, and improve insulin sensitivity [77,81,84]. In hepatocytes and other cells, cyanidin has been shown to activate the AMPK signaling pathway and improve glucose tolerance and insulin sensitivity [82].

Recent studies have further explored the anti-diabetic mechanisms of cyanidin. Fraisse et al. [87] demonstrated its potent inhibitory effect on α-glucosidase, surpassing the activity of acarbose. Jia et al. [88] revealed that cyanidin-3-*O*-glucoside exerts its anti-hyperglycemic effect by activating the AMPK pathway and inhibiting gluconeogenesis. Ye et al. [89] investigated the molecular

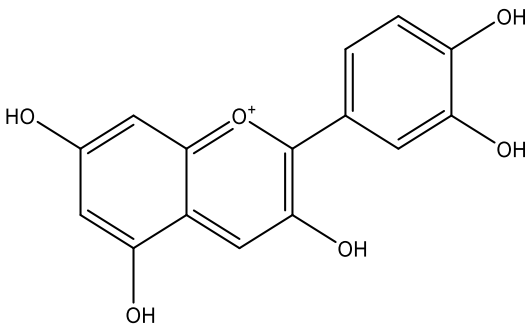

Fig. 8. Chemical structure of cyanidin.

mechanisms of cyanidin-3-*O*-glucoside in liver cells and diabetic mice, highlighting its hypoglycemic effects, up-regulation of liver GLUT-1 expression, and promotion of glucose consumption through the regulation of the Wnt/β-catenin-WISP1 signaling. Indeed, Kongthitilerd et al. [90] elucidated the mechanism of cyanidin-3-rutinoside on insulin secretion in rat pancreatic β-cells, showing that it improves insulin synthesis via intracellular Ca2+ signaling and activation of the PLC-IP3 pathway and voltage-dependent Ca2+ channel.

Overall, these studies provide evidence for the anti-diabetic potential of cyanidin through its effects on carbohydrate metabolism, insulin signaling, glucose uptake, and various cellular pathways involved in glucose homeostasis.

3.7. Delphinidin

Several preclinical investigators have tested the anti-diabetic potential of delphinidin (Fig. 9) [91–93,95,126,193,194]. For this purpose, HFD-fed mice were used as an *in vivo* model [92,193,194]. In fact, in obese C57BL/6J mice, oral treatment of delphinidin 3-sambubioside-5-glucoside (D3S5G) diminished the production of glucose in hepatic cells as well as fasting glycaemia levels, and in parallel, it increased glucose absorption in L6 myotubes (skeletal muscle cells), dose-dependently [92]. A daily dose of delphinidin (100 mg/mL) was able to significantly reduce the values of GA (30.50 ± 3.46 %) and HbA1c (3.60 ± 0.25 %) [193]. Supplementation with this molecule also reduced resistance to insulin and improved its sensitivity [194].

In contrast, *in vitro*, delphinidin-3-glucoside remarkably stimulated insulin synthesis from INS-1832/13 cells (rodent pancreatic β-cells) [91]. In addition, delphinidin recorded other anti-diabetic effects *in vitro* such as inhibition of DPP-4 (34.4 %), α-amylase (35.6 %), α-glucosidase (37.8 %), and a decrease in ROS production (81.6 %) and glucose uptake [94]. This decrease in glucose uptake was confirmed in the same year by Hidalgo et al. [93] in mouse jejunum samples and intestinal cells (Caco-2, HT-29, and NCM460) by affecting sodium-glucose cotransporter 1 (SGLT1) function, a membrane protein involved in the transport of glucose. Moreover, in pancreatic RIN-m5F β-cells, Lai et al. [95] found that delphinidin decreases cleaved caspase-3 level, autophagy, adverse effects of oxidative stress, and apoptosis caused by high glucose concentrations, and increases the level of AMPKα Thr172 phosphorylation.

3.8. Hesperetin

Various methods were used to evaluate the anti-diabetic potential of hesperetin (Fig. 10) [103,104,204–207]. Hesperetin has demonstrated its ability to improve glucose homeostasis in animal models of diabetes. Studies have shown that hesperetin treatment resulted in improvements in glucose levels, insulin levels, glycogen levels, and glucose metabolic enzymes, while also reducing insulin resistance [205–207]. Additionally, hesperetin normalized the activities of glucose-regulating enzymes and reduced serum and liver lipid levels, thereby improving glucose metabolism *in vivo* [204].

Furthermore, hesperetin has been found to inhibit the secretion of free fatty acids (FFA) stimulated by TNF-α and block the activation of the NF-κB and ERK signaling pathways, as demonstrated by Yoshida et al. [103]. It also exhibited inhibitory effects on α-glucosidase, with an IC_{50} value of 0.38 ± 0.05 mM [104]. These findings highlight the potential of hesperetin in improving glucose metabolism and its role in modulating key pathways involved in diabetes pathogenesis.

In recent studies, hesperetin has demonstrated its potential in restoring blood glucose levels in animal models of diabetes. In one study, hesperetin was administered to AID mice, resulting in a significant improvement in blood glucose levels [208]. Another study focused on the use of hesperetin extracted from *Trifolium alexandrinum*, a plant belonging to the Fabaceae family, for the treatment of T2DM in rats [209]. In this experiment, diabetic rats induced by NA/STZ were treated with 50 mg/kg of hesperetin for a duration of 4 weeks.

The treatment with hesperetin showed several beneficial effects in the rats. There was an improvement in serum glucose levels, as well as reductions in glucagon levels and the activities of hepatic glycogen, hepatic function enzymes, lipase enzymes, α-amylase, and lipid profiles. Additionally, the treatment increased the levels of antioxidant enzymes while decreasing the activities of G6PD, glucose-6-phosphate (G6P), fructose-1,6-bisphosphate (FBP), and glucokinase. The levels of GLUT2 and GLUT4, which are glucose transporters, were also improved. Furthermore, the expression levels of various proteins involved in glucose metabolism and signaling pathways were modulated by hesperetin treatment. This included changes in the expression levels of PI3K, AMPK, IR, IL-1β, and

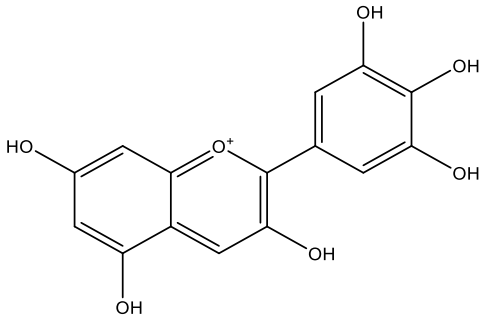

Fig. 9. Chemical structure of delphinidin.

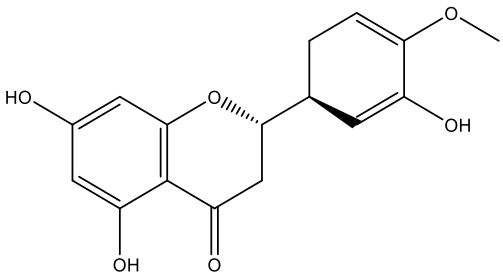

Fig. 10. Chemical structure of hesperetin.

caspase-3. Overall, these recent *in vivo* experiments highlight the potential of hesperetin in improving blood glucose control and various metabolic parameters associated with diabetes.

3.9. Hesperidin

Several studies have experimentally evaluated the anti-diabetic activity of hesperidin (Fig. 11) [105,204,210–216]. *In vivo* evaluation was performed on STZ-induced T1D rats [211,212,215,216], and T2D rats [204,210,213,214].

Hesperidin has been found to enhance glycemic metabolism through various mechanisms. These mechanisms include reducing glycaemia by lowering lipid levels in the blood and liver, modifying the activity of glucose regulatory enzymes [211,212], reducing degeneration of pancreatic cells and levels of TNF-α, increasing insulin concentrations [215], and decreasing fructose-1, 6-bisphosphatase (FBPase), HbA1c, and G6Pase, while improving glycogen content in liver tissue [216]. Additionally, in GK rats with T2DM, hesperidin decreased hepatic lipid and serum levels and altered the activities of glucose regulatory enzymes [204].

In a model of T2DM, the administration of hesperidin demonstrated beneficial effects on serum insulin concentrations and TNF-α expression [213]. Another study revealed that oral treatment with hesperidin (at a dose of 50 mg/kg) normalized HbA1c levels, as well as serum insulin, glucose, hepatic and muscle glycogen levels. It also regulated resistin and adiponectin levels [214].

In rats fed a HFD, hesperidin was found to reduce blood glucose levels and the activity of G6Pase, while increasing glycogen concentration, hepatic glucokinase activity, C-peptide levels, and plasma insulin [210]. Furthermore, an *in vitro* evaluation of hesperidin's anti-diabetic activity utilized 3T3-L1 preadipocytes and RAW 264.7 cells. In RAW 264.7 cells, hesperidin dose-dependently reversed inflammation-induced insulin resistance induced by lipopolysaccharide (LPS), as evidenced by the inhibition of IL-6, TNF-α, and NO. In differentiated 3T3-L1 cells, it inhibited TNF-α-induced production of prostaglandin E2 (PGE2) and IL-6 [105].

Recent experiments investigated the impact of a water-soluble derivative of hesperidin called glucosyl hesperidin on hyperglycemia in HFD-induced obese mice. Long-term daily treatment (11 weeks) with this citrus flavonoid resulted in reduced blood glucose concentration, improved glucose intolerance, and insulin resistance. However, short-term treatment (2 weeks) did not affect blood glucose levels. These findings suggest that hesperidin could potentially be used for the prevention and/or treatment of obesity-related diabetes [217].

Using a rat model of HFD/alloxan-induced insulin resistance, Peng et al. [218] administered hesperidin orally for 35 days at a dose of 100 mg/kg. This treatment improved fasting blood glucose levels without affecting fasting insulin levels, and prevented impaired glucose tolerance (IGT) development. These results suggest that hesperidin can prevent the development of diabetes and insulin resistance by improving insulin sensitivity. The treatment also regulated gluconeogenesis and glycolysis by inducing phosphorylation of the insulin receptor (IR) and increasing glucokinase activity, while decreasing the activities of G6Pase and phosphoenolpyruvate carboxykinase (GTP).

To enhance the sustained release and potency of hesperidin as a potential anti-diabetic agent compared to conventional treatments, a new hesperidin nano-carrier was prepared and characterized. When administered to diabetic rats, this formulation exhibited prolonged production of hesperidin and resulted in improvements in glycemia, HbA1c levels, insulin levels, and lipid profile [219].

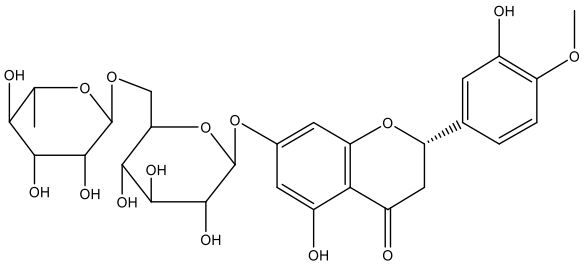

Fig. 11. Chemical structure of hesperedin

3.10. Kaempferol

Regarding the anti-diabetic potential of natural substances, kaempferol (Fig. 12) was one of the most investigated molecules [106–109,112–115,115,116,220–230]. In rats with diabetes induced by ALX (alloxan), oral administration of increasing doses of kaempferitrin (50, 100, and 200 mg/kg) resulted in a significant reduction in hyperglycemia [220]. This effect was further elucidated in a study by Zanatta et al. [221], where administration of kaempferol 3-neohesperidoside (at a dose of 100 mg/kg) via gavage showed increased muscle glycogen content. Additionally, it stimulated glucose uptake in the soleus muscle through the activation of the PI3K (phosphoinositide 3-kinase) and PKC (protein kinase C) pathways.

Various studies have utilized the STZ-induced diabetic animal model to evaluate the anti-diabetic properties of kaempferol [225,227,229]. In one study, oral administration of kaempferol (at doses of 50, 100, and 200 mg/kg) reduced insulin resistance and fasting blood glucose levels, improving glucose metabolism disorders [227]. Another study demonstrated that kaempferol improved insulin resistance, decreased IL-6 and TNF-α levels, and reduced the incidence of hyperglycemia, diabetes, and hepatic glucose synthesis. It also enhanced hexokinase activity in the liver and skeletal muscle, as well as improved gluconeogenesis and hepatic pyruvate carboxylase activity [230]. Furthermore, oral administration of kaempferol (at a daily dose of 50 mg/kg) to rats fed a HFD improved glycemic control by reducing G6Pase and pyruvate carboxylase activity in the liver, increasing protein kinase B (PKB) and hexokinase activity, and enhancing insulin sensitivity [230].

Using the same experimental protocol, dietary intake of kaempferol glycoside (at a concentration of 0.15 %) decreased fasting blood glucose levels, HbA1c, and the expression of sterol regulatory element-binding protein (SREBP-1c) and peroxisome proliferator-activated receptor (PPAR-γ), while improving insulin resistance [228]. Similarly, in obese mice fed a HFD, dietary kaempferol intake (at a concentration of 0.05 %) significantly normalized hyperinsulinemia, circulating lipid profile, and hyperglycemia. This was accompanied by improved insulin sensitivity, altered expression of AMPK and GLUT4 in adipose and muscle tissues, and inhibition of glycogen synthesis and glucose uptake [226]. Kaempferol 3-neohesperidoside promoted glycogen synthesis in rat soleus muscle [222] and reduced HbA1c and fasting blood glucose levels in mice with T2DM [224].

Various *in vitro* methods have been employed to assess the anti-diabetic activity of kaempferol, including tests for α-glucosidase and α-amylase inhibition. Studies have shown that kaempferol exhibits strong inhibitory activity against these digestive enzymes [114,116]. It has been found to possess potent inhibitory activity against α-glucosidase, with IC_{50} values ranging from 19.36 ± 2.43 μM [108] to 1.16 ± 0.04 × 10-5 mol/L (Peng et al., 2016). Additionally, it demonstrates significant inhibitory potential against α-glycosidase and α-amylase, with IC50 values of 29.37 and 51.24 μg/mL, respectively [113].

Several research teams have employed cell culture assays to investigate the mechanisms of kaempferol's anti-diabetic action. In 3T3-L1 adipocytes, this flavonol acts as a weak partial agonist and significantly enhances insulin-stimulated glucose uptake [106]. Studies conducted on INS-1E β-cells and human pancreatic islets have utilized various tests, including measuring caspase-3 activity, cell apoptosis, insulin secretion, and the expression of relevant proteins. These studies have shown that kaempferol reduces caspase-3 activity, inhibits cell apoptosis, improves insulin secretion, and increases the expression of anti-apoptotic proteins such as Bcl-2, Akt, and pancreatic/duodenal homeobox-1 (PDX-1) [109,110]. Moreover, in murine pancreatic islets and RIN-5F cells, kaempferol exhibits anti-apoptotic effects, enhances cell viability, stimulates autophagy via the AMPK/mTOR pathway, and restores *β*-cell function [115]. It is worth noting that the protective potential of kaempferol on β-cells has been observed in various studies. For instance, kaempferol has been shown to protect HIT-T15 cells against oxidative damage induced by 2-deoxy-D-ribose (dRib) by interfering with ROS metabolism [107].

Recent studies have also demonstrated the hypoglycemic effect of kaempferol *in vivo*, with a reduction in fasting glucose levels and an increase in fasting insulin levels observed in a rat model of diabetes [231]. In the same animal model, a recent study reported that a combination of kaempferol and myricetin can normalize glucose levels, inflammatory cytokines, insulin levels, lipid and liver enzymes, as well as oxidative stress markers in diabetic animals [232].

3.11. Luteolin

Luteolin (Fig. 13) is a flavonoid present in several medicinal plants with anti-diabetic activity. *In vitro* and *in vivo* experiments showed its anti-diabetic potential [117,119,120,122–124,233,234,245,300]. In an *in vitro* study conducted by Kim et al. (2000) [117],

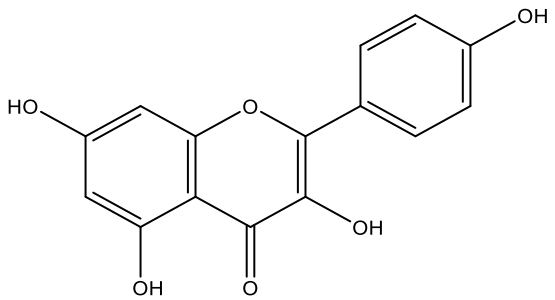

Fig. 12. Chemical structure of kaempferol.

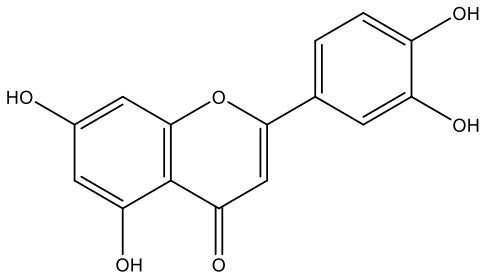

Fig. 13. Chemical structure of Luteolin).

luteolin (0.5 mg/mL) demonstrated superior inhibitory effects (36 %) on α-glucosidase compared to α-amylase and the positive control, acarbose. The inhibitory activity of luteolin on α-glucosidase was further confirmed by Yan et al. [123], who reported a dose-dependent inhibition with an IC50 value of $1.72 \pm 0.05 \times 10-4$ mol/L. Additionally, Yan et al. [123] revealed that luteolin acts as a non-competitive inhibitor (NCI) with a unique binding site on the α-glucosidase enzyme, with a Ki value of $1.40 \pm 0.02 \times 10-4$ mol/L.

Luteolin demonstrated significant anti-diabetic effects in cell culture models. In 3T3-L1 adipocytes, it was found to reduce mRNA levels of TNF-α and IL-6, enhance glucose uptake in response to insulin, promote Akt2 phosphorylation, and increase PPARγ transcriptional activity, indicating its positive impact on glucose metabolism [119]. In endothelial cells, luteolin was shown to improve insulin-dependent nitric oxide production, highlighting its potential in enhancing endothelial function [120]. The compound also exhibited inhibitory effects on aldose reductase (AR) activities and protein tyrosine phosphatase 1B (PTP1B), both of which play significant roles in regulating glucose metabolism [121]. In MIN6 cells, luteolin inhibited NF-κB activity, reduced nitric oxide production, and stimulated insulin synthesis, suggesting its potential in preserving β-cell function [122]. Additionally, in an *in vitro* (3T3-L1 cells and RAW264.7 macrophages) and *in vivo* (HFD-fed mice) study, luteolin suppressed macrophage infiltration and polarization in adipocytes, leading to improved insulin resistance through the activation of the AMPKα1 pathway [124].

Luteolin has been extensively studied for its anti-diabetic effects in various experimental models. In an animal model, it showed significant inhibition of maltase activity, although it did not have an effect on glycaemia or other enzymes such as sucrase and α-glucosidase [300]. In diabetic rats, luteolin decreased blood glucose levels, increased insulin levels, and improved pancreatic function [233]. Another study in diabetic rats reported reduced expression of TNF-α and IL-6 genes, improved insulin-mediated endothelial-dependent relaxation, and restored insulin signaling [120]. Luteolin administration to diabetic KK-Ay mice normalized insulin, glycaemia, and HbA1c levels, demonstrating its anti-hyperglycemic effects [234]. To enhance the anti-hyperglycemic effects of luteolin in a T2DM model, researchers modified its structure and synthesized compounds such as 6,8-(1,3-diaminoguanidine) luteolin (DAGL) and its chromium complex (DAGL·Cr), as well as 6,8-guanidyl luteolin quinone-chromium (GLQ·Cr) [235,236]. DAGL and DAGL·Cr exhibited beneficial effects, including normalization of fasting glycaemia, body weight, glycated serum protein, and pancreatic islet function, with a restorative capacity in the pancreas. The hypoglycemic mechanism was attributed to the regulation of the PI3K/AKT-1 signaling pathway. GLQ·Cr attenuated hyperglycemic symptoms by normalizing pancreatic and hepatic functions, modulating intestinal microbiota composition, and regulating the PPAR signaling pathway. In a recent study, luteolin was combined with another flavone, diosmin, in selenium nanoparticles (SeNPs) to improve diabetes management [237]. The nanospheres containing both flavonoids showed normalization of blood glucose, insulin, HbA1c, lipid profile, and glycogen levels in mice with diabetes. These nanospheres also exhibited antioxidant potential and protective effects against liver damage. Overall, luteolin has

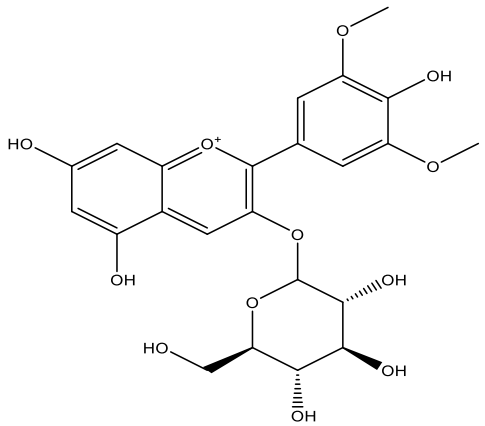

Fig. 14. Chemical structure of malvidin-3-*O*-glucoside.

demonstrated promising anti-diabetic effects through various mechanisms and has been explored for structural modifications and combination strategies to enhance its therapeutic potential in the management of diabetes.

3.12. Malvidin-3-O-glucoside

The compound malvidin-3-*O*-glucoside has shown potential anti-diabetic effects in both *in vivo* and *in vitro* studies. In a study by Grace et al. [195] (Fig. 14), malvidin-3-*O*-glucoside exhibited significant anti-hyperglycemic activity in diabetic mice when administered at a dose of 300 mg/kg. This compound also demonstrated inhibition of α-glucosidase and α-amylase activity in in vitro experiments [127].

In an *in vitro* cell culture model using Caco-2 cells, Mojica et al. [94,126] investigated the molecular markers associated with diabetes and the effects of malvidin-3-*O*-glucoside. Treatment with a 100 μM dose of malvidin-3-*O*-glucoside resulted in the inhibition of α-glucosidase (42.8 %), α-amylase (29.6 %), and DPP-IV (82.4 %) activities. Additionally, it reduced glucose uptake by 55.2 % in Caco-2 cells. Another study on the same cell line demonstrated that malvidin-3-*O*-glucoside reduced 14C fructose absorption by 15 % at the highest concentration tested [125].

A recent *in vitro* study conducted by Xue et al. [128] investigated the interaction between malvidin-3-*O*-glucoside and α-glucosidase, revealing valuable insights into its mechanism of action. The study reported that malvidin-3-*O*-glucoside acts as a reversible non-competitive inhibitor of α-glucosidase. Notably, the binding of malvidin-3-*O*-glucoside to the enzyme induced structural modifications in α-glucosidase, resulting in the regulation of specific amino acid residues and their microenvironment.

Furthermore, a recent study by Zou et al. [238], explored the effects of combined therapy involving malvidin and metformin in a rat model of T2DM induced by a HFD and STZ. The findings demonstrated that the combination therapy of malvidin with metformin exhibited significant improvements in glucose and lipid metabolism. Moreover, the treatment showed efficacy in inhibiting inflammation, suggesting a potential multifaceted therapeutic approach.

3.13. Naringin

Using animal models of SID, several *in vivo* studies have evaluated the anti-hyperglycemic activity of naringin (Fig. 15). Naringin, a molecule found in certain foods, has been shown to have several beneficial effects on glucose regulation and pancreatic beta-cell health. Studies conducted [257,261,263] have demonstrated that this molecule can lower plasma glucose levels in a dose-dependent manner.

Furthermore, naringin has been found to protect beta-cells from apoptosis, which is the programmed cell death, by inhibiting both the extrinsic pathway (mediated by death receptors) and the intrinsic pathway (mediated by mitochondria). In insulin-deficient mice, it has also been observed to improve abnormalities in pancreatic islets.

The specific beneficial effects of naringin on T2DM as opposed to type 1 diabetes (T1D) have been attributed to the requirement of insulin presence, as explained by Xulu and Oroma Owira [260].

In addition, when administered orally to diabetic rats in high concentrations along with vitamin C, naringin has been found to reduce blood glucose levels, HbA1c (glycated hemoglobin), and the activities of enzymes involved in gluconeogenesis (G6Pase and FBPase) in the kidneys and liver. It also increased plasma insulin levels, hepatic glycogen content, and the activity of the enzyme hexokinase, which is involved in glucose metabolism [257].

Oral administration of naringin has been found to have several positive effects, in induced diabetes by nicotinamide (NA) and STZ. These include reducing HbA1c (glycated hemoglobin), blood glucose levels, and the activities of enzymes involved in gluconeogenesis (G6Pase and FBPase). Naringin treatment also stimulated insulin secretion and increased the activities of glucose-6-phosphate dehydrogenase (G6PD) and glucokinase, which are enzymes involved in glucose metabolism [258].

Supplementing naringin to rats with T2DM resulted in enhanced expression of adiponectin, insulin receptor (IR) subunit, and glucose transporter 4 (GLUT4) mRNA. It also reduced hepatic glycogen levels, C-peptides, serum insulin, HbA1c, and G6Pase activity [255]. Similar results were observed in another study using male mice with T2DM (C57BL/KsJ-db/db). Naringin supplementation increased serum insulin levels and decreased glucose, resistin, TNF-α, and free fatty acid (FFA) levels [210].

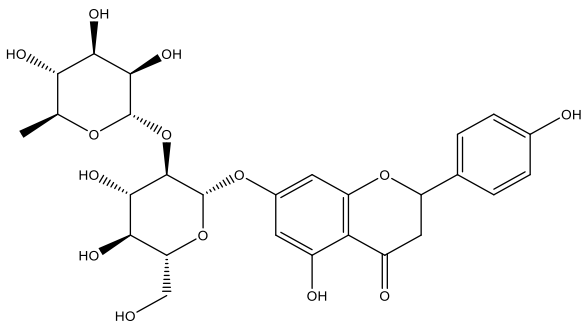

Fig. 15. Chemical structure of naringin.

Many researchers have employed the HFD and STZ-induced diabetic rat model in their experiments. Naringin treatment in these rats resulted in increased serum insulin levels and reduced levels of glucose, resistin, TNF-α, and FFA [213]. In a subsequent study, (Ahmed et al. [214] demonstrated that naringin lowered elevated levels of HbA1c, serum insulin, glucose, hepatic and muscle glycogen, resistin, and adiponectin.

Furthermore, in diabetic rats, naringin was able to decrease HbA1c and blood glucose levels and increase plasma insulin levels in a dose-dependent manner. It also normalized the levels of altered liver enzymes (G6Pase, FBPase, G6PD, GP, hexokinase, and GS), restored the number of insulin-immunoreactive β-cells, and improved glycogen content [262].

In a study conducted by Kumar Sharma et al. [259] on rats with T2DM, naringin exhibited anti-diabetic efficacy. The researchers observed a decrease in hyperglycemia (high blood sugar), hyperinsulinemia (elevated insulin levels), and insulin resistance. Naringin also provided protection to beta-cells in the pancreas by regulating oxidative stress and inflammation (specifically, IL-6 and TNF-α) and influencing the production of dysregulated adipocytokines. The study found that naringin increased the expression of HSP-27, PPARγ, and HSP-72, which are proteins involved in cellular stress response and inflammation regulation.

The anti-diabetic effects of naringin have also been demonstrated *in vitro* studies using cell cultures. Nzuza et al. [146] conducted research on RIN-5F cells, which are pancreatic beta-cell lines, and found that naringin prevented pancreatic beta-cell dysfunction, leading to the reduction of insulin secretion inhibition [145]. investigated the effects of naringin on L6 myoblasts, a type of muscle cell, and observed that naringin increased glucose uptake in differentiated L6 myoblasts, indicating improved glucose utilization by the cells.

Furthermore, Dayarathne et al. [147] studied the relationship between AMPK phosphorylation (activation) and glucose uptake in HepG2 cells, a human liver cell line, treated with high concentrations of glucose. They examined the effects of naringin and its aglycone form, naringenin, both derived from citrus, on glucose uptake. The study revealed that these flavonoids stimulated glucose uptake independently of insulin stimulation by inducing AMPK phosphorylation. Naringin and naringenin bound to the AMPK γ-subunit with high affinities, suggesting their ability to positively modulate AMPK activation and enhance glucose uptake without relying on insulin secretion.

Collectively, these studies highlight the ability of naringin to regulate glucose metabolism, improve insulin sensitivity, protect beta-cells, and enhance glucose uptake, indicating its potential as a therapeutic agent for diabetes management.

3.14. Naringenin

Naringenin (Fig. 16), similar to other compounds, has been extensively studied for its anti-diabetic activity using experimentally induced diabetes in animals. Ortiz-Andrade et al. [138] conducted both *in vitro* and *in vivo* tests to evaluate the effects of naringenin. In in vitro tests, they found that naringenin inhibited the activity of 11β-HSD1 enzyme (by 39.49 %), which is involved in glucocorticoid metabolism, without affecting the activity of α-glucosidase enzyme. In their *in vivo* study using diabetic rats, oral treatment with naringenin (50 mg/kg) for 21 days resulted in reduced fasting blood glucose levels, HbA1c (glycated hemoglobin), and increased serum insulin concentrations. It also demonstrated protective effects on pancreatic beta-cells [251]. In a subsequent study by the same authors using the same experimental protocol, they observed that naringenin attenuated hematological abnormalities, reduced inflammation proteins, and modulated mRNA transcription [251].

Furthermore, Priscilla et al. [142,252] administered naringenin orally to rats with diabetes induced by a HFD and STZ. Their research showed that naringenin attenuated hyperglycemia (high blood sugar) and hyperinsulinemia (elevated insulin levels). It competitively inhibited α-glucosidase, an enzyme involved in carbohydrate digestion, and modulated the expressions of TNF-α (tumor necrosis factor-alpha) and GLUT4 (glucose transporter 4) proteins. Naringenin also improved insulin sensitivity and restored abnormalities in pancreatic tissues.

Multiple studies have confirmed the hypoglycemic efficacy of naringenin in animal models of diabetes induced by STZ. These studies have shown that naringenin reduces HbA1c levels, blood glucose levels, and the insulin resistance index while improving glucose tolerance [143,176,253]. Indeed, Singh et al. [143] conducted molecular studies and reported that naringenin activates the GLUT4/PPARγ pathways, with strong binding affinity to GLUT4 and PPARγ receptors. Additionally, naringenin normalized reduced C-peptide and serum insulin concentrations, elevated GP and G6Pase activities, and restored hepatic glycogen content [255].

In vitro studies have also been conducted to investigate the anti-diabetic effects of naringenin on cultured cells. For instance,

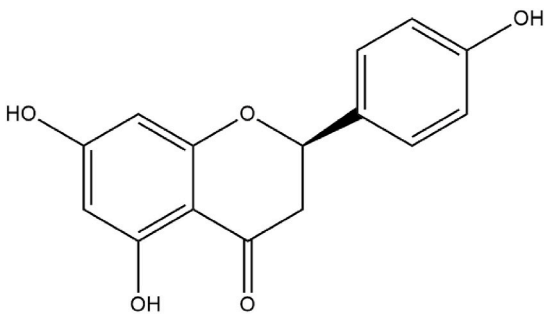

Fig. 16. Chemical structure of Naringenin.

naringenin induced glucose uptake (163 %) in rat adipocytes through various assays, including lipolysis, lipogenesis, and glucose uptake assays [137]. Treatment of 3T3-L1 cells with naringenin inhibited the activation of the NF-κB and ERK pathways induced by TNF-α, as well as the synthesis of free fatty acids (FFAs) induced by TNF-α [103]. Naringenin also increased glucose absorption in muscle cells (L6) by phosphorylating/activating the AMPK pathway [139]. In INS-1E cells, naringenin induced glucose sensitivity, stimulated insulin secretion, and altered gene expression profiles [140]. Another study using porcine myotube cultures showed that naringenin increased the phosphorylation of TBC1D1, leading to GLUT4 translocation and glucose uptake, in a TBC1D1-dependent manner [141].

Recently, Park et al. [256] investigated the anti-diabetic potential of a derivative of naringenin called 8-prenylnaringenin (8-PN) in insulin-deficient diabetic (IDD) mice induced by STZ. Oral treatment with 8-PN and naringenin improved glucose homeostasis, restored islet function, and corrected insulin signaling defects. In the pancreas and liver, 8-PN increased the expression levels of estrogen receptor-alpha (ERα) and fibroblast growth factor 21 (FGF21) specifically in the liver.

In a recent *in vitro* study by Prasad and Srinivasan [144], naringenin was isolated from the ethanolic extract of Tinospora sinensis stems, and its effect on activating PPARγ receptors and inhibiting α-glucosidase enzyme was evaluated. Naringenin demonstrated potent anti-α-glucosidase activity and up-regulation of PPARγ receptors.

These findings collectively demonstrate the hypoglycemic effects of naringenin, both *in vivo* and *in vitro*, and suggest its potential as an anti-diabetic agent. Furthermore, the derivative 8-PN and the identification of naringenin from plant extracts highlight the ongoing research to explore the anti-diabetic properties of these compounds.

3.15. Quercitrin

In studies conducted with STZ-induced diabetic (SID) rats, quercitrin (Fig. 17) has been investigated for its anti-hyperglycemic effects. These studies have shown that quercitrin reduces fasting blood glucose levels and HbA1c, while increasing C-peptide and plasma insulin levels [287–289]. Babujanarthanam et al. [287] observed increased hexokinase activity and glycogen content, decreased G6Pase and FBPase activities, and protection of pancreatic cells with reduced fatty infiltrates and expansion of islets.

In rat insulinoma (RINm5F) cells, quercitrin has shown protective effects on β-cells against cytokine-induced damage, improved glucose-stimulated insulin secretion (GSIS), and inhibition of NF-κB translocation [160].

3.16. Isoquercitrin

Another flavonoid (Fig. 18) has also been studied for its anti-hyperglycemic activity. Paulo et al. [291] conducted the first study on the topic and found that an administered dose of 100 mg/kg of isoquercitrin reduced hyperglycemia in diabetic rats and delayed the glycemic peak. Huang et al. [292] demonstrated that daily oral treatment with isoquercitrin (10 and 30 mg/kg) for 21 days improved fasting blood glucose levels, glucose tolerance, and clinical symptoms in a dose-dependent manner in Wistar rats rendered diabetic by a high-calorie diet and STZ injection.

Inhibition of dipeptidyl peptidase-4 (DPP-4) by isoquercitrin has also been observed. Zhang et al. [161] reported a high inhibition of isoquercitrin on DPP-4 competitively, with Ki and IC50 values of 236 and 96.8 mM, respectively. In an experimental *in vitro* (NCI–H716 cells) and *in vivo* (SID mice) model, isoquercitrin stimulated GLP-1 production *in vitro* and decreased fasting blood glucose levels, increased serum insulin and GLP-1 levels, and inhibited postprandial glycemia variations in a concentration-dependent manner [161].

These studies highlight the potential of quercitrin and isoquercitrin as anti-hyperglycemic agents, with effects on blood glucose levels, insulin secretion, pancreatic cell protection, and DPP-4 inhibition.

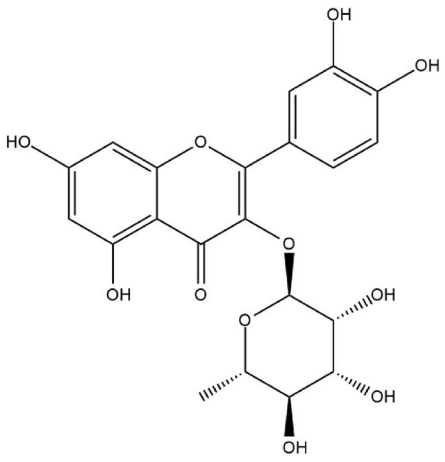

Fig. 17. Chemical structure of Quercitrin.

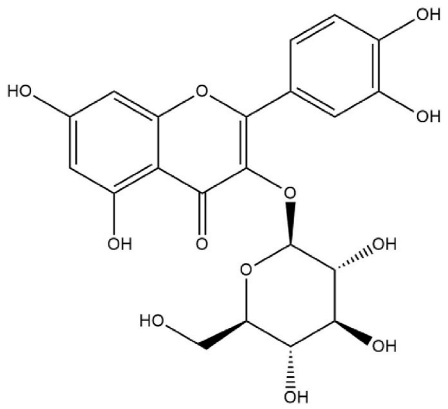

Fig. 18. Chemical structure of Isoquercitrin.

3.17. Rutin

Rutin has been extensively studied for its potential as an anti-diabetic agent (Fig. 19). In studies conducted with STZ-induced diabetic (SID) rats, oral administration of rutin resulted in significant decreases in fasting blood glucose levels and HbA1c, as well as increases in C-peptide and insulin levels [293,294]. These studies also reported improvements in G6Pase and FBPase activities, glycogen content, and hexokinase activity, as well as protection of the pancreas through expansion of islets and reduction of fat infiltration.

Rutin has shown inhibitory effects on α-glucosidase *in vitro*, with an IC_{50} value of 0.196 mmol/L [148]. In SID rats, oral administration of rutin resulted in a concentration-dependent decrease in fasting blood glucose levels [295]. Another study on NA/STZ-induced diabetic rats demonstrated a significant reduction in glycaemia with rutin treatment, along with improvements in glucose uptake and inhibition of glucose transport [276]. The mechanism of action for glucose uptake stimulation by rutin was studied and found to involve the mitogen-activated protein kinase (MAPK), aPKC, and PI3K pathways [162].

Combining rutin with quercetin has shown synergistic inhibitory effects on α-glucosidase and α-amylase activities [164]. Rutin alone exhibited strong inhibition against both enzymes, and its combination with quercetin further enhanced the inhibitory effects. Oral treatment with rutin in HFD/STZ-induced type 2 diabetic rats resulted in reduced glycaemia, HbA1c, and inflammatory mediators, as well as preservation of β-islet cell histological structure and reversal of hepatocyte enlargement [296].

In vitro and *in vivo* studies have demonstrated the anti-diabetic potential of rutin. It has been shown to enhance insulin-dependent translocation of GLUT4 and increase insulin receptor kinase (IRK) activity [163]. Rutin has also been found to increase glucose uptake in L6 myoblasts through GLUT4 translocation under oxidative stress conditions [154]. Other studies have indicated that rutin down-regulates protein tyrosine phosphatase-1B (PTP-1B) expression levels, enhances insulin signaling pathways, and decreases serum glucose levels in animal models [165,166]. Rutin supplementation has also been shown to improve blood glucose levels, HOMA-B%, HbA1c levels, and pancreatic tissue regeneration in diabetic animal models [297].

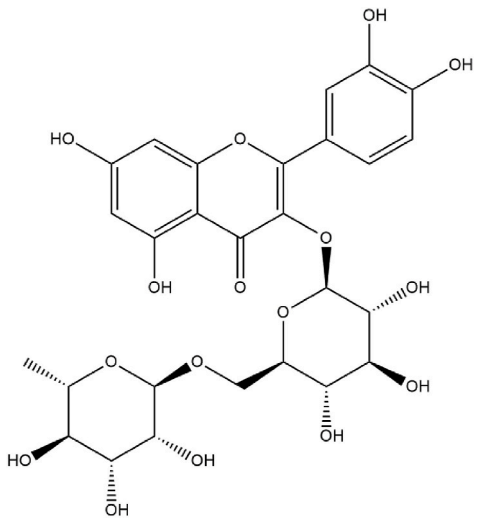

Fig. 19. Chemical structure of Rutin.

To improve the bioavailability and stability of rutin, researchers have explored encapsulating the molecule in nanophytosomes. In SID rats, the encapsulated rutin formulation demonstrated greater efficacy than free rutin in regulating HbA1c and total hemoglobin levels, as well as restoring pancreatic damage induced by STZ [299].

Overall, these studies highlight the anti-diabetic potential of rutin, including its effects on glucose metabolism, insulin secretion, pancreatic protection, and inhibition of key enzymes involved in carbohydrate digestion. Encapsulation techniques may further enhance the therapeutic efficacy of rutin in diabetes treatment.

3.18. Resveratrol

Resveratrol is a natural phytoalexin with multiple health benefits (Fig. 20), including anti-diabetic activities. In various *in vivo* studies, it has shown promising effects in lowering glycaemia levels and improving insulin resistance.

In experimental models of diabetes, including SID rats and NA/STZ-induced diabetic rats, resveratrol demonstrated a concentration-dependent reduction in plasma glucose levels [302]. It also promoted glycogen production in hepatocytes, stimulated glucose uptake, and delayed insulin resistance.

In insulin-deficient diabetic rats, resveratrol improved glucose uptake in skeletal muscle through the PI3K-Akt pathway and lowered plasma glucose levels via insulin-dependent and insulin-independent mechanisms. It also increased the expression of GLUT4 in the soleus muscle and stimulated insulin synthesis [303].

A 30-day oral treatment with resveratrol was found to lower glycaemia levels and HbA1c and normalize plasma insulin contents and certain biochemical parameters [304]. Additionally, resveratrol-induced GLUT4 translocation in the myocardium of SID animals was proposed to be insulin-independent, with increased AMPK phosphorylation, GLUT4 expression, and glucose uptake in myoblastic cells [305].

Resveratrol treatment for 30 days also improved enzyme activities related to carbohydrate metabolism and glucose storage in renal and hepatic tissues. It reduced insulin, HbA1c, and glycaemia levels and improved the activities of FBPase, G6Pase, G6PD, GS, GP, hexokinase, and pyruvate kinase (PK) [306].

Resveratrol has been extensively studied for its anti-diabetic effects, and numerous *in vivo* studies have demonstrated its potential in improving various aspects of diabetes. In male C57BL/6 mice with diet-induced diabetes, long-term intracerebroventricular infusion of resveratrol normalized hyperglycemia and hyperinsulinemia while improving hypothalamic inflammatory NF-κB signaling [307]. Similarly, in diabetic rats, a 30-day oral treatment with resveratrol improved hyperglycemia, insulin secretion, HbA1c, and the expression of pro-inflammatory cytokines [308]. Resveratrol also exhibited antioxidant effects by reducing hydroperoxide, lipid peroxide, and protein carbonyl levels and modulating the activity of antioxidant enzymes (CAT, GPX, SOD, and GST). It protected β-cells from oxidative damage in these studies. In a mouse model of HFD-induced diabetes, resveratrol administration for 35 days decreased glucose intolerance and increased GLP-1 and insulin concentrations, improving insulin sensitivity and reducing β-cell apoptosis [309]. Additionally, resveratrol improved insulin resistance, hyperglycemia, lipid peroxidation, and hepatic steatosis in Wrn mutant mice, with modulation of genes involved in GSH metabolism and the insulin-signaling pathway [310]. Resveratrol treatment in non-obese diabetic (NOD) mice decreased the expression of CCR6, a chemokine receptor, in splenocytes [311]. It also demonstrated anti-diabetic effects by reducing glycaemia levels, increasing glucose uptake, and protecting β-cells in *in vitro* and *in vivo* tests [312]. In various animal models of diabetes, resveratrol normalized dyslipidemia, reduced serum glucose levels, and improved body weight loss [313]. It also improved insulin levels and glucose excursion in an oral glucose tolerance test [314]. The anti-diabetic effects of resveratrol were mediated through activation of the AMPK pathway and its downstream targets, leading to improvements in glycaemia, lipid profiles, adiponectin levels, and insulin sensitivity [315]. Resveratrol exhibited protective effects against apoptosis and oxidative stress in pancreatic cells, preventing diabetes in animal models [316]. It enhanced glucose tolerance, increased β-cell mass, and reduced islet fibrosis and oxidative damage in diabetic mice [317]. Furthermore, resveratrol supplementation showed significant anti-diabetic and antioxidant effects, relieving damage to the pancreas, kidneys, and liver in mice treated with alloxan [318]. It also improved insulin resistance induced by methylglyoxal, reducing serum glucose levels and TNF-α content while increasing insulin and *p*-Nrf 2 protein expressions [319].

In studies conducted in 2015, the combination of resveratrol with vitamin C was found to have beneficial effects in diabetic animals. It improved body weight and restored levels of blood glucose, total protein, MDA, LH, and antioxidant enzymes [320]. Another study in the same year investigated the effect of resveratrol on a mouse model of gestational diabetes mellitus (GDM). Resveratrol at 10

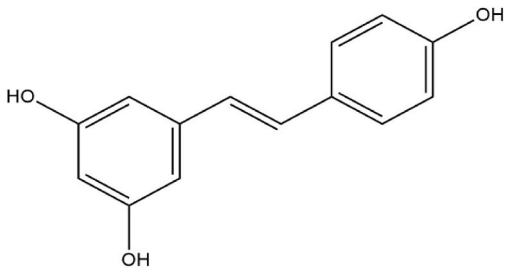

Fig. 20. Chemical structure of Resveratrol.

mg/kg improved insulin tolerance and glucose metabolism by activating AMPK and reducing G6Pase production [321]. Resveratrol also showed the ability to reduce glycaemia and HbA1c levels, stimulate insulin synthesis, and protect β-cells in diabetic rats [322].

In 2018, two experiments explored the combined effect of resveratrol with other compounds on diabetic animals induced by alloxan and STZ. The results showed that resveratrol alone or in combination with vitamin E or quercetin improved insulin sensitivity, normalized blood glucose levels, and preserved pancreatic cell structure [281,323].

Resveratrol has also been nano-encapsulated for the preparation of functional snacks, which exhibited enhanced anti-diabetic properties compared to snacks without or with free resveratrol [324]. In another study, resveratrol derivatives, including *trans*--ε-viniferin and vateriferol, demonstrated significant hypoglycemic effects and inhibited α-glucosidase activity in diabetic mice and *in vitro* experiments [325].

Recent studies in 2021 investigated the impact of resveratrol on insulin production and resistance, GLP-1, and oxidative stress in a rat model of T2DM induced by NA/STZ. The findings showed reductions in insulin resistance, increases in GLP-1, insulin levels, and total antioxidant capacity, along with improvements in intestinal and pancreatic histological alterations [326,327].

3.19. Quercetin

Quercetin (Fig. 21), a natural plant pigment, has shown beneficial effects in various models of diabetes. In a study by Shetty et al. [265] using SID rats, a diet containing quercetin (1 g/kg) improved 25 % of the diabetic state in the animals. One year later, Coskun et al. [266] observed a protective effect on β-cells by measuring antioxidant enzyme activities (CAT, SOD, and GPX) in diabetic rats. Injection of quercetin (15 mg/kg) in diabetic animals increased enzyme activities, reduced levels of MDA and nitric oxide (NO), and preserved β-cells.

In ALX-induced diabetic rats, oral administration of quercetin-3-*O*-glucoside (15 mg/kg/day) for 10 days increased insulin levels, decreased serum glucose concentrations, and inhibited G6Pase activity [268]. Similar results were seen in Lukačínová et al. [269], where oral treatment with quercetin (50 and 100 mg/kg) for 7 days prevented the rise in blood glucose. In an *in vitro* study on mature 3T3-L1 adipocytes, quercetin improved glucose absorption stimulated by insulin, inhibited NO production in macrophage cells, and acted as a partial agonist of PPARγ [106]. Kannappan and Anuradha [270]. showed that a 60-day treatment with quercetin (50 mg/kg) improved tyrosine phosphorylation and insulin sensitivity in an HFruD-induced insulin resistance model.

Kobori et al. [271] evaluated the protective effect of quercetin on BALB/c mice with SID. Rats given a diet containing quercetin (0.5 %) for 14 days showed decreased glycemia, improved plasma insulin levels, and enhanced cell proliferation through the inhibition of Cdkn1a expression, leading to improved liver and pancreas function. In vitro studies on enzyme kinetics by Li et al. [148] confirmed the inhibitory effect of quercetin on α-glucosidase compared to acarbose.

In SID rats, treatment with quercetin (15 mg/kg) for 25 days resulted in decreased glycemia levels and increased antioxidant enzyme activities [272]. In an *in vitro* study on C2C12 muscle cells, Eid et al. [149] found that quercetin 3-*O*-glycosides and quercetin improved glucose uptake in the absence of insulin through the stimulation of the AMPK signaling pathway. Torres-Piedra et al. [150] reported a range of beneficial effects following five days of oral treatment with quercetin (50 mg/kg) in diabetic animals, including the reduction of triglycerides, LDL, HDL, and total cholesterol levels.

In a diabetic rat model, El-Baky [273]. administered quercetin (20 mg/kg) for 8 weeks, resulting in significantly lower glycemia, insulin resistance, NO, and MDA levels. Insulin levels and antioxidant enzyme activities were increased, and β-cell function was improved. Similarly, in an STZ-induced diabetic model, oral administration of quercetin (100 mg/kg) reduced plasma glucose and HbA1c levels [274].

Hussain et al. [275] found that oral doses of quercetin (300 and 600 mg/kg) improved postprandial hyperglycemia in SID rats, with reductions of 32.0 % and 64.0 %, respectively, compared to the positive control acarbose. It also lowered triglyceride and total cholesterol levels compared to the control group [276]. Mechanistically, quercetin reduced glucose transport activity and increased glucose absorption by the hemidiaphragm *in vivo*.

In a C57BL/KsJ-db/db mouse model of T2DM, Jeong et al. [277] demonstrated the hypoglycemic, antioxidant, and hypolipidemic effects of quercetin. After 6 weeks of a quercetin-based diet (at 0.04 % and 0.08 %), plasma glucose, HOMA-IR, triglyceride levels, and TBARS levels were reduced, while HDL-cholesterol and plasma adiponectin were increased. Insulin levels showed no significant effect. Quercetin also reversed pancreatic morphological alterations induced by STZ, established connections between certain islets and

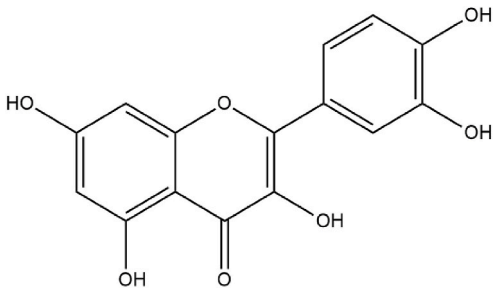

Fig. 21. Chemical structure of Quercetin.

pancreatic ducts, decreased iNOS and caspase 3 immunoreactivity in β-cells, and increased the number of these cells [278].

In C2C12 skeletal muscle cells, quercetin improved glucose uptake in a concentration-dependent manner and attenuated TNF-α-induced insulin resistance by activating the Akt and AMPK pathways [160]. Alam et al. [279] investigated the effect of quercetin on DNA damage and hyperglycemia in alloxan-induced T2D mice. The results showed positive effects on DNA damage, reduced hyperglycemia, enzyme markers, and TBARS levels, and increased expression levels of GLUT4.

Arias et al. [280] administered quercetin (30 mg/kg) for 6 weeks to rats fed a high-fat/high-sucrose (HF/HS) diet and found reduced glycaemia, HOMA-IR, and insulin levels without affecting lipoprotein lipase and lipogenic enzyme activities. In L6 myoblasts, quercetin reduced ROS production and normalized GSH levels, leading to increased glucose uptake via the GLUT4 translocation pathway under TBHP-induced oxidative stress [154]. In H4IIE hepatocytes, quercetin (50 μM) inhibited G6pase and activated the hepatic AMPK pathway, and similar effects were observed in L6 muscle cells and HepG2 hepatocytes [155].

Dhanya et al. [156] elucidated the molecular mechanisms of quercetin's action against T2DM in L6 myotubes. They found involvement of the AMPK pathway and its downstream target, p38 MAPK, in the uptake of 2-NBDG.

Quercetin has been found to inhibit the activity of α-amylase and α-glucosidase, with IC50 values of 770 μg/mL and 32 μg/mL, respectively [134]. The inhibition of these enzymes by quercetin was reversible for α-amylase and competitive, while it was non-competitive for α-glucosidase.

In an animal model of T2D, a 28-day daily treatment with quercetin (25 and 50 mg/kg) reduced glycaemia, hepatic glycogen levels, and HbA1c, while improving hexokinase and G6Pase activities [282]. It also enhanced the activity of antioxidant enzymes (CAT, SOD, and GSH) and decreased TBARS levels. Quercetin restored hepatic and pancreatic damage induced by fructose-STZ in diabetic animals.

Recent studies have shown the anti-diabetic effects of quercetin in SID animals. A 28-day oral treatment with quercetin (100 mg/kg) significantly reduced hyperglycemia [283]. In another study, the combination therapy of quercetin with EGCG protected against β-cell damage in SID animals, improving insulin synthesis through up-regulation of BCL-2 expression and down-regulation of miR-16-5p [284]. Quercetin treatment in INS1 cells and diabetic db/db mice reduced glycaemia and insulin levels, increased the levels of Sirt3, CAT, and SOD, and decreased cleaved caspase-3 levels and the Bax/Bcl-2 ratio, indicating protection against oxidation-induced apoptosis in T2D via Sirt3 [157].

A self-emulsifying drug delivery system containing quercetin and other flavonoids has been developed to optimize the concentration of quercetin for effective reduction of glycaemia in diabetes [285]. This formulation showed a greater hypoglycemic effect compared to the reference drug glibenclamide, potentially due to increased insulin production.

Similar to hesperetin, quercetin extracted from T. alexandrinum exhibited beneficial anti-diabetic effects *in vitro* and *in vivo* study [209]. Another study investigated the antioxidant effects of quercetin on insulin production, signaling, and action in hypertensive rats, showing reduced serum lipid peroxidation rates, improved insulin sensitivity, and increased expression of CAT, VEGF, and M3R [286].

Recent *in vitro* studies have investigated the effects of quercetin on α-glucosidase and α-amylase enzyme activities. Qu et al. [158] found that quercetin and its derivatives extracted from Potentilla bifurca exhibited inhibitory effects on α-glucosidase. However, glycosylation of quercetin weakened this inhibitory effect.

In another study by Shen et al. [159]., the inhibition of α-amylase by quercetin was explored using multi-spectroscopic and molecular docking analyses to examine the structure-activity relationships. The results showed that quercetin inhibited α-amylase activity in a non-competitive manner, with an IC_{50} value of 0.325 mg/mL. Furthermore, quercetin altered the microenvironment of aromatic amino acid residues in the enzyme. Molecular docking analysis revealed that quercetin formed hydrogen bonds with key active site residues (Asp 300, Glu 233, and Asp 197) of the enzyme.

3.20. Myricetin

In an earlier *in vitro* study conducted by Ong and Khoo [129], the impact of myricetin (Fig. 22) on glucose transport and lipogenesis was evaluated using various tests. The study involved determining D-glucose transport, lipogenesis, and 3-*O*-methylglucose transport. The results indicated that myricetin enhanced the insulin-stimulatory effect, stimulating lipogenesis and the uptake of both D-3-*O*-methyl-glucose and D-glucose in rat adipocytes. Additionally, myricetin increased the maximum velocity (Vmax) of glucose transport.

In a subsequent study by Ong and Khoo [130], diabetic mice were intraperitoneally injected with myricetin for four days. The treatment resulted in a 50 % reduction in hyperglycemia in the animals. Furthermore, myricetin increased insulin-stimulated lipogenesis and stimulated glucose transport in adipocytes. Regarding glycogen metabolism, myricetin increased the content of G6Pase, hepatic glycogen synthase, and hepatic glycogen without affecting the total glycogen synthase content.

To investigate the impact of myricetin on lowering plasma glucose levels in diabetes, Liu et al. [239,240] conducted a study where diabetic rats were treated with a daily dose of myricetin for two weeks. The results revealed that myricetin decreased plasma glucose concentrations in a concentration-dependent manner and promoted glucose storage in the soleus muscles of diabetic rats. This effect was accompanied by an increased expression of GLUT4, a glucose transporter protein.

To elucidate the underlying mechanism of this process *in vitro*, rat adipocytes were isolated and exposed to myricetin in a study by Strobel et al. [131]. The findings demonstrated that myricetin inhibited glucose transport and the uptake of methylglucose by these cells.

In contrast, a study conducted by Liu et al. [241] investigated the improvement in insulin sensitivity in obese rats. These rats were given intravenous injections of myricetin three times a day for one week. The treatment resulted in enhanced insulin sensitivity through significant changes in post-receptor insulin signaling.

To further examine the insulin-resistant model, the same research team fed rats a high-fructose diet (HFruD) for six weeks. Oral

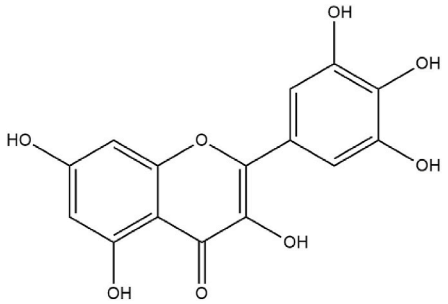

Fig. 22. Chemical structure of Myricetin.

glucose tolerance test (OGTT) results demonstrated that myricetin supplementation reduced blood glucose levels and improved insulin resistance by increasing insulin sensitivity. The activation of insulin receptors was also assessed, revealing that myricetin enhanced insulin sensitivity by improving the activities of GLUT4 and IRS-1-associated PI3-kinase in the rats' soleus muscles [242].

Insulin-resistant rats were subjected to intravenous injections of myricetin (1 mg/kg) three times a day for a duration of two weeks. The treatment resulted in reduced plasma glucose levels accompanied by increased concentrations of plasma β-endorphin [243]. Moreover, an investigation into the activation of insulin receptors (IRs) demonstrated improvements in the signaling intermediates downstream of IRs.

Furthermore, in a study involving C2C12 cells, treatment with myricetin was found to enhance glucose uptake and increase the activities of AMPK and Akt. This led to improved insulin sensitivity by reducing insulin resistance [132].

Kandasamy and Ashokkumar [244,246], conducted studies in which they administered a daily oral dose of myricetin (1 mg/kg) to SID rats. This treatment resulted in several beneficial effects, including reduced blood glucose levels, normalization of carbohydrate metabolic markers (such as HbA1c, gluconeogenic enzymes, and GP), increased insulin levels, and improved expression of glycogen, GS, and insulin signaling molecules (IRS-1, IRS-2, PKB, GLUT2, and GLUT4). Furthermore, histopathological evaluation of pancreatic cells showed that myricetin exerted a protective effect against damage caused by STZ.

In *db/db* mice, myricetin demonstrated inhibition of the digestive enzyme α-glucosidase and reduced levels of HbA1c, fasting blood glucose, and intestinal maltase activity [247].

In a study conducted by Ha-Neul Choi et al. [245], rats were fed a high-fat/high-sucrose (HF/HS) diet supplemented with 0.12 % myricetin for a period of 12 weeks. The myricetin supplementation resulted in decreased levels of insulin and blood glucose, as well as reduced HOMA-IR values, compared to the control group. Additionally, the myricetin-treated group exhibited lower levels of pro-inflammatory cytokines (TNF-α and IL-6).

Meng et al. [134] discovered that myricetin, like quercetin mentioned earlier, inhibits the activity of α-glucosidase and α-amylase. The IC_{50} values for myricetin were found to be 3 μg/mL for α-glucosidase and 662 μg/mL for α-amylase. The inhibitory effect of myricetin on these enzymes was reversible, but it acted competitively on α-amylase and non-competitively on α-glucosidase. Similarly, Arumugam et al. [133] also observed this inhibitory effect of myricetin on both enzymes involved in carbohydrate hydrolysis.

Furthermore, myricetin has demonstrated insulin-like activity in 3T3-L1 cells. It enhances glucose uptake, lipid accumulation, and adiponectin production by activating the insulin-signaling pathway [248]. In addition, Hu et al. [249] found that myricetin increases adiponectin expression in brown adipose tissue (BAT) and improves insulin resistance by activating BAT, highlighting its glucoregulatory properties.

Li et al. [135] conducted experiments involving both acute and chronic treatments with myricetin to assess its hypoglycemic effect in animals with T1D *in vivo* and to understand its mechanism of action in the HepG2 cell line *in vitro*. In the acute treatment, myricetin demonstrated a concentration-dependent increase in β-endorphin (BER) and adropin secretion, leading to a reduction in hyperglycemia. This effect was attributed to the activation of the GLP-1 receptor, which in turn regulated the expression of adropin. It was deduced that the observed rise in plasma adropin levels was mediated by endogenous β-endorphin subsequent to GLP-1 receptor activation.

Early management of predisposition to diabetes and prediabetes is crucial. A recent study by Yang et al. [136], examined the impact of myricetin on prediabetes both *in vivo* and *in vitro*. In RAW 264.7 cells exposed to high glucose levels, a treatment of 10 μM myricetin decreased the expression levels of IL-2 and interferon-gamma (IFN-γ) and reversed the immunosuppressive effects induced by elevated glucose. In prediabetic mice fed a HFD, oral administration of myricetin demonstrated significant hypoglycemic and hypolipidemic effects, and it restored their innate and adaptive immune functions.

Furthermore, as noted above, co-treatment of myricetin and kaempferol has synergistic therapeutic potential in the management of diabetes [232].

4. Conclusion and perspectives

In recent years, there has been a surge in interest surrounding the potential of natural flavonoids as antidiabetic agents. These bioactive compounds, abundant in fruits, vegetables, and other plant sources, have garnered attention for their reported benefits in regulating glucose levels and enhancing insulin sensitivity. Flavonoids, with their diverse biological activities, offer promising

antidiabetic properties by modulating key enzymes in glucose metabolism, improving insulin signaling, and reducing oxidative stress associated with diabetes.

Recent scientific literature highlights specific flavonoids like quercetin, resveratrol, and epigallocatechin gallate, showcasing their potential in lowering blood glucose levels, enhancing insulin sensitivity, and protecting pancreatic beta cells. Their natural origin and generally favorable safety profile make them attractive alternatives to conventional antidiabetic medications, particularly in resource-limited settings where they are readily available and affordable.

Despite the promising outlook, further research is necessary to elucidate the mechanisms of action, optimal dosages, and long-term effects of flavonoids in diabetes management. Rigorous preclinical and clinical studies are crucial to establish their efficacy, safety, and potential interactions with other medications.

In conclusion, while there is optimism regarding the potential of flavonoids as complementary or alternative therapies for diabetes, continued research efforts and clinical trials are imperative to fully harness their therapeutic benefits and integrate them into mainstream diabetes care.

CRediT authorship contribution statement

Abdelhakim Bouyahya: Writing – original draft, Supervision, Resources, Methodology. **Abdelaali Balahbib:** Writing – review & editing, Methodology, Investigation. **Asaad Khalid:** Writing – original draft, Validation, Resources. **Hafiz A. Makeen:** Writing – original draft, Software, Resources, Project administration. **Hassan A. Alhazmi:** Writing – review & editing, Resources, Project administration, Methodology. **Mohammed Albratty:** Writing – original draft, Software. **Andi Hermansyah:** Writing – review & editing, Supervision, Software, Resources, Methodology. **Long Chiau Ming:** Writing – original draft, Supervision, Resources, Project administration. **Khang Wen Goh:** Writing – original draft, Validation, Supervision, Resources, Methodology. **Nasreddine El Omari:** Writing – original draft, Validation, Software, Resources, Project administration, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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