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Recent advances in the therapeutic potential phytochemicals in managing diabetes

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Abstract

Diabetes and diabetic complications have been a global menace for a long time, putting a heavy burden on an individual, the health sector, and governments. Diabetic complications attributed to persistent hyperglycemia create a challenge in managing diabetes, considering the nature of the disease as a group of metabolic disorders. Various phytochemicals target different metabolic pathways and molecules through different mechanisms of action, acting individually or synergistically to achieve therapeutic goals. Phytochemicals such as alkaloids, saponins, glycosides, terpenoids, and flavonoids were reported to exert different anti-diabetic effects, including anti-hyperglycemic, anti-hyperlipidemic, anti-inflammatory, antioxidant, and insulinotropic activities. The present review focused on the recent advances in the therapeutic potentials of phytochemicals in managing diabetes and diabetic complications, emphasizing their in vitro and in vivo studies.

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Highlights

What is current knowledge?

Phytochemicals from medicinal plants attenuate diabetic symptoms *via* different mechanisms of action including anti-hyperglycemic, anti-hyperlipidemia, anti-inflammatory, and antioxidant effects. However, attaining glycemic control and treatment of diabetic complications still remains a challenge.

What is new here?

Some of the phytochemicals reported here might be sources for the development of novel anti-diabetic drugs.

Introduction

Diabetes is a group of metabolic disorders that have gone beyond glycemic control requiring multiple approaches to manage and emerging as a global menace leading to reduced life expectancy and complications that might be fatal (1). This disease requires prevention strategies for acute complications and decreasing the risks associated with chronic disease complications. Clinical diagnosis of diabetes may be achieved by testing for plasma glucose levels using two approaches; fasting plasma glucose (FPG) value or 75-g oral glucose tolerance test of (OGTT) 2h plasma glucose (PG) value or hemoglobin test (HbA1c) approach (2). For the FPG approach, an FPG level of $\geqslant$ 126 mg/dL (7.0 mmol/L) for an individual with at least eight post-calorie intakes signifies diabetes, while in the OGTT approach, a PG level of $\geqslant$ 200 mg/dL (11.1 mmol/L) after 2h of the OGTT signifies diabetes. When utilizing the HbA1c criteria, an HbA1c level $\geqslant$ 6.5% is considered an indicator of diabetes. However, for an individual manifesting classic symptoms of unstable glycemic control, a random glucose test approach with PG $\geqslant$ 200 mg/dL (11.1 mmol/L) is regarded as the diagnosis for diabetes mellitus (DM). Diabetes can be classified into type 1 DM, type 2 DM, gestational DM, and other diabetes conditions manifesting as a result of other causes (3).

Worldwide, the number of people with diabetes has risen to half a billion, up to 10.5% of the world's adult population (4). In 2021, young adults between the ages of 20-29 rank up to 10.5% of the prevalence of DM, estimated to be up to 536.6 million. This figure is projected to rise to 12.2% by 2045, including 783.2 million people (4). The prevalence in both genders was similar in 2021, though higher within 75-79 years. A higher prevalence was in urban areas (12.1%) and high-income countries (11.1%) than the rural areas (8.3%) and low-income countries (5.5%), with an expected projection within middle-income countries than both high- and low-income countries (4). This represents a huge burden on the healthcare system and government expenditures on a country's health, especially considering the expected rise in cases. In 2021, the world expenditure on diabetes-related expenses was estimated to be 966 billion USD, with an expected rise of up to 1.054 billion USD by 2045 (4). The necessity for alternative medical options that are inexpensive and accessible, such as plant-based phytochemicals, is particularly vital for individuals residing in rural areas with inadequate healthcare facilities.

Different strategies exist for managing diabetes, with exercise being the recommended practice. Anti-diabetic agents used in diabetic management range from insulin therapy to anti-diabetic drugs used singly or combined therapies and are often associated with some side effects and high costs (5). The nature of diabetes as a multiple disorder makes it a target for different therapy. However, long-term continuous use of anti-diabetic agents might lead to further complications due to disturbance of metabolic pathways (5). Medicinal plants are often preferred as alternatives for managing diabetes, especially for people in low-income countries and rural duelers due to availability and low cost with a synergistic mode of action. These plants comprise phytochemicals such as alkaloids, saponins, and flavonoids attributed to different pharmacological activities to achieve glycemic control, evidenced by their use in traditional folkloric medicine (6). With the rising cost of treatment of diabetes worldwide, which is projected to rise more by 2045, and the obvious burden on government expenditures on healthcare, there is continuous exploitation of natural cheap and affordable sources for novel therapeutics, especially in the low-income countries where there is poor or no access to proper healthcare facilities. Thus, the present review explores the recent advances in the therapeutic roles of phytochemicals in managing diabetes.

Alkaloids

Alkaloids are naturally occurring compounds composed of one or more nitrogen atoms, usually within the compound's ring structure, giving it alkaline properties. These compounds are widely found in plants and classified into different classes, including indoles, quinolines, and isoquinolines (7). These compounds are associated with several pharmacological activities, and a notable example is morphine attributed with clinical applications. Although alkaloids are used as pain relievers, their uses are somehow limited due to addiction. Other clinical applications of these compounds include cardiac stimulants (morphine), muscle relaxants (tubocurarine), anticancer (vincristine and vinblastine), and ephedrine employed in bronchial asthma and the common cold (7). Alkaloids in many medicinal plants were attributed to their pharmacological activities. Thus, their

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use in folkloric medicine includes anti-microbial, anti-diabetic, anticancer, analgesic, and sedatives (8-10). Alkaloids were previously reported to exert anti-diabetic effects via different modes of action, such as stimulating insulin secretion, inhibiting digestive enzymes and forming advanced glycation end products (AGEs), and promoting glucose uptake by cells (11).

The quinoline alkaloid berberine from the roots and stem bark of Tinospora cordifolia was reported to exhibit hypoglycemic properties by inhibiting sucrose activity in Caco-2 cells after 72h of preincubation via decreased glucose absorption in the intestinal epithelium and blocking α-glucoside (12). Oral administration of hypoglycemic alkaloids catharanthine, vindoline, and vindolinine from ethanol extract of Catharanthus roseus combined with sitagliptin showed hypoglycemic effects with significant anti-diabetic activities in hyperlipidemic and diabetic mice (13). 5-hydroxymethylfurfural identified from Lobelia chinensis was reported to exert anti-diabetic activity in silico by attenuating insulin resistance via acting on GSK3B, TNF, MAPK1, and INSR, DPP4, and GSK3B regulating insulin resistance (14). Schulzeines A, B, and C, three iso-quinoline alkaloids from Penares Schulzei, exerted hypoglycemic properties in vitro via alpha glucosidase suppression (15). Another alkaloid palmitine was reported to inhibit the key enzymes of carbohydrate digestion in silico; alpha-amylase and alpha-glucosidase. Studies on palmitine via molecular docking revealed that palmitine exerts its activity by competitive inhibition (16).

Carbazole alkaloids extracted from Murraya koenigii L. and Vindogentianine from Catharanthus roseus inhibited α-glucosidase when p-nitrophenyl glucopyranoside was employed as a substrate (17, 18). In streptozotocin-induced (STZ-induced) diabetic rat models, holaphylline and sarcovagine D (steroidal alkaloids) exerted hypoglycemic potential with minimized diabetic complications (19). Similarly, O-methylmurrayamine A and koenidine exerted more hypoglycemic effects than metformin in STZ-induced diabetic rats (20). Alkaloids also exert pharmacological activities against aldose reductase, a key enzyme of glucose metabolism associated with diabetic complications due to the accumulation of its product (sorbitol) and metabolite (fructose). Isoquinoline alkaloids from Tinospora cordifolia stem the aldose reductase activity from the lens of male Wistar albino rats (21). Canthinone alkaloids exerted inhibitory activity using p-nitrophenyl phosphate against protein tyrosine phosphatase-1B (PTP1B), an enzyme present in several tissues playing an active role in multiple signal transduction pathways (22, 23). Inhibition of PTP1B promotes glucose intake by enhancing insulin receptors and phosphorylation insulin of receptors 1 and 2 (23). Similarly, via a substrate-based mechanism, Vindogentianine from Catharanthus roseus inhibited protein tyrosine phosphatase-1B (18). Another alkaloid, lupanine from the Lupinus species, enhances insulin secretion via glucose-dependent inhibition of ATP-sensitive potassium channels current and enhances gene expression for insulin secretion in rats (24).

Trigonelline was reported to enhance insulin sensitivity in high-fat-fed and low-dose streptozotocin-induced diabetic rats (25). Benzylisoquinoline alkaloids from Ocotea paranapiacabensis inhibited the formation of AGEs responsible for diabetic complications such as nephropathy, retinopathy, and neuropathy via in vitro bovine serum albumin/methylglyoxal reagent assay (26). Diketopiperazine isolated from Aspergillus sp. 16-5c exerted in vitro inhibitory properties against α-glucosidase without inhibiting PTP1B (27). The fumiquinazoline alkaloids scequinadolines D isolated from Scedosporium apiospermum exert its anti-diabetic activity in vitro by enhancing insulin sensitivity in adipocytes promoting triglyceride accumulation in 3T3-L1 cells by stimulating the expression of PPARγ, AMPKα, C/EBPα, LXRα, SCD-1, and FABP4, thereby activating the PPARγ pathway (28). Eurocristatine isolated from Eurotium cristatum exhibited remarkable hypoglycemic activity and improved glucose tolerance, insulin release, and sensitivity and mitigated diabetic liver toxicity in db/db mice (29). Furthermore, in vitro study showed decreased insulin resistance via enhanced glucose uptake and consumption with increased glycogen storage in HepG2 cells subjected to high glucose with enhanced glycogen synthesis (29).

Hernandezine, a natural alkaloid, is an anti-diabetic potential in mouse models via indirect activation of AMP-activated protein kinase by suppressing its dephosphorylation. Additionally, oral administration of hernandezine reduced body weight and hyperglycemia by increasing glucose uptake and decreasing lipogenesis (30). The intestinal oxidative metabolite of berberine, oxyberberine, showed promising potential in alleviating diabetic symptoms by decreasing blood glucose levels, healing pancreatic damage, and exerting anti-inflammatory and antioxidant properties in STZ-induced diabetic rats (31). Furthermore, the intestinal oxidative metabolite oxyberberine exerted a better anti-diabetic activity than berberine by up-regulating the expression mRNA of Nrf2 and PI3K/Akt signaling pathways of the pancreas (31). Coumarin compounds were previously reported to exert anti-diabetic activities both in vitro and in vivo in animal models (32). The anti-diabetic effects of some alkaloids are summarized in Table 1, while their structures are presented in Figure 1.

Table 1: Anti-diabetic alkaloids

Alkaloids	Anti-diabetic action	Effect
Berberine	Anti-hyperglycemic (12)	*In vitro*
Catharanthine	Anti-hyperglycemic (113)	*In vivo* (rats)
Vindoline	Anti-hyperglycemic (114)	*In vivo* (rats)
Vindolinine	Anti-hyperglycemic (113)	*In vivo* (rats)
5-hydroxymethylfurfural	Regulate insulin and attenuate insulin resistance (14)	*In silico*
Schulzeines	Alpha-glucosidase suppression (15)	*In vitro*
Palmitine	Alpha-amylase and alpha-glucosidase inhibition (16)	*In silico*
Carbazole	Alpha-glucosidase inhibition (18)	*In vitro*
Holaphylline	Anti-hyperglycemic (19)	*In vitro*
Sarcovagine D	Anti-hyperglycemic (19)	*In vitro*
O-methyl murrayamine A	Anti-hyperglycemic (20)	*In vivo* (rats)
Koenidine	Anti-hyperglycemic (20)	*In vivo* (rats)
Vindogentianine	Protein tyrosine phosphatase-1B inhibition (18)	*In vitro*
Lupanine	Insulinotropic effects (24)	*In vitro* and *In vivo* (rats)
Trigonelline	Insulinotropic effects (25)	*In vivo* (rats)
Diketopiperazine	Alpha-glucosidase inhibition (27)	*In vitro*
Scequinadolines D	Insulinotropic effects (28)	*In vitro*
Hernandezine	Antihyperglycemic (30)	*In vivo* (mice)
Oxyberberine	Anti-hyperglycemic, anti-inflammatory, antioxidant (31)	*In vivo* (rats)

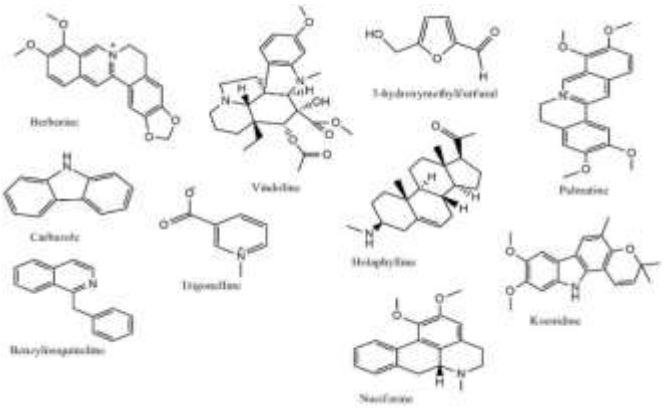

Figure 1. Structures of some anti-diabetic alkaloids

Saponins

Saponins comprise a group of amphiphilic glycosides and steroid terpenes with diverse structural components consisting of a carbohydrate moiety and aglycones originating from plant cells and some marine organisms (33). The diverse structural nature of saponins has been attributed to the various biological and pharmacological effects observed in traditional medicine. Saponins are associated with pharmacological effects such as antioxidant, anticancer, anti-microbial, and anti-diabetic effects, thus attracting attention to their exploration of novel therapeutics in clinical and basic research (34-36). Saponins are attributed to various pharmacological activities in managing diabetes. Notably, the blood glucose-lowering potential is exploited in several clinical studies through different mechanisms of action, making them an alternative hypoglycemic agent (37). Saponins exert anti-diabetic effects in the liver, skeletal muscles, pancreas, and gut via concurrent regulations of different signal pathways (38). Administration of saponins from Momordica charantia showed improved body weight and glucose tolerance in combined high fat- and STZ-induced diabetic rats with reduced fasting blood glucose levels and improved insulin secretion and sensitivity (39). A significant increase in the activity of antioxidants enzymes and expression of p-IRS-1 (Y612) and p-Akt (S473) was also observed with a decrease in malondialdehyde level and p-IRS-1 (S307) expression (39).

Similarly, administering saponins from Momordica charantia to a high-fat diet (HFD) fed C57BLK/6 mice showed improved insulin sensitivity and glucose tolerance (40). Saponin-rich extract of Tithonia diversifolia leaves showed a dose-dependent expression and insulin release by up-regulating the expression of Takeda G-protein bile acid receptor 5 (TGR5) in a dose-dependent manner, subsequently releasing GLP1 with decreased HbAc1 level in diabetic model mice

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(41). Total saponins extracted by ultrasonic microwave-assisted from Corni fructus reduced diabetes in HFD- and STZ-induced diabetic mice by significantly improving glucose and lipid metabolism, reducing oxidative stress, inflammation, hepatic and pancreatic tissue by regulating insulin receptor, glucose transporter 4 (GLUT 4), phosphatidylinositol 3-kinase, and protein kinase B signaling pathways (42). In vitro studies of oleanane-type saponin were observed to be active against α-glucosidase, PTP1B, DPPH, and ATBS assays, potentially a source for the development of anti-diabetic and antioxidant drugs (43). Saponins from Momordica dioica exhibited beta cell protective activity and insulinotropic effect in a dose-dependent manner in STZ-induced diabetic rats (44). Similarly, saponins from Momordica charantia significantly restored body weight, decreased FBG levels and insulin resistance, and increased phosphorylation of liver adenosine monophosphate-activated protein kinase (p-AMPK)/total protein in STZ-induced diabetic mice. Moreover, the mechanism of action of the above was proposed to be through the AMPK/NF-κB signaling via activation of AMPK phosphorylation and regulation of energy metabolism (45).

Saponins isolated from Argania spinosa significantly decreased blood glucose levels in alloxan-induced diabetic mice, equivalent to 2-4 weeks of metformin treatment (46). Furthermore, these saponins showed a strong anti-α-amylase and -α-glucosidase activity in vitro. In another in vitro study, saponins extracted from fruit and seeds of Cupressus sempervirens inhibited α-amylase in starch digestion bioassay (47). Gylongiposide I identified in Gynostemma pentaphyllum exhibited a glucose-dependent insulinotropic effect by stimulating insulin in high glucose concentration with limited effects at low concentration, making it a candidate for developing novel therapeutic with insulinogenic effect (48). Oral administration of entagenic acid to type 2 diabetic db/db mice significantly decreased post-prandial glucose without significantly affecting body weight. Moreover, improved insulin sensitivity, glucose tolerance, and pathological changes in the pancreatic islets were observed. Additionally, in vitro studies showed an improvement in glucose utilization in a dose-dependent manner with enhanced GLUT4 expression and translocation and AMPK phosphorylation (49). Furostanol saponins from Asparagus racemosus reduced the post-prandial glucose level in db/db mice type 2 diabetes model deficient in leptin receptor (50). Furthermore, the AMPK-dependent signaling pathway was activated by the saponins influencing GLUT4 translocation. Additionally, in vivo pharmacological studies demonstrated that these saponins have higher bioavailability and efficacy (50).

Saponins modulated glucose homeostasis via PPARγ-mediated mechanism in type 2 diabetes hypertensive rat model (51). New Nor-triterpenoid saponins exhibited anti-diabetic properties where two of the four compounds activated peroxisome PPAR-α but not the γ (52). Saponin extract from Ziziphus Mauritiana leaves significantly inhibited α-amylase with a strong reduction capacity than ascorbic acid, demonstrating anti-diabetic and antioxidant potential (53). Saponins from Polygonatum sibiricum significantly decreased insulin secretion and FBG levels with significant improvement of lipid profile in type 2 diabetes mice (54). Moreover, the gut microbiota and metabolites of the mice were evaluated and analyzed by 16S rDNA sequencing and metabolic profiling revealing a decrease in Firmicutes, Bacteroidetes, and some bacteria genera. At the same time, a great effect was observed on carbohydrate metabolism and amino acid metabolisms (54). Saponins by-products of Asparagus officinalis L. in STZ-induced type 2 diabetic rats significantly decreased the fasting serum glucose with an accompanied increase in the hepatic glycogen and improved lipid profile (55). Saponins extracted from Panax notoginseng were reported to alleviate insulin resistance in muscles skeletal via regulating GLUT4 expression and IRS1–PI3K–AKT signaling pathway (56). Insulin-induced glucose uptake was increased in the skeletal myoblast cell line, C2C12.

Moreover, blood glucose and serum insulin levels decreased with accompanying glucose and insulin tolerance improvement in KKAy mice. Additionally, the apoptosis and pathological changes of the skeletal muscle cells were reduced with enhanced expression of IRS1 and GLUT4 in C2C12 and KKAy mouse muscle (56). The anti-diabetic effects of some saponins are presented in Table 2, while their structures are shown in Figure 2.

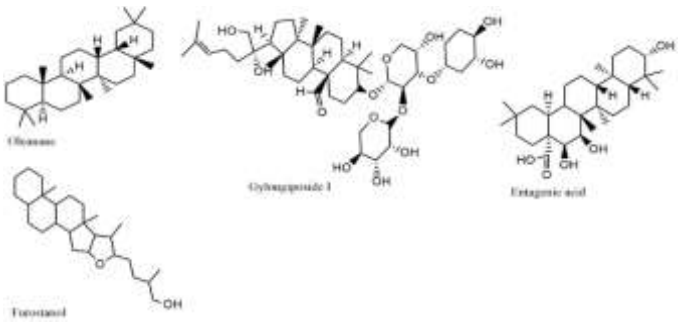

Figure 2. Structures of some antidiabetic saponins

Table 2. Antidiabetic saponins

Saponins	Anti-diabetic action	Effect
Oleanane	Protein tyrosine phosphatase-1B and alpha-glucosidase inhibition (43)	*In vitro*
Gylongiposide I	Insulinotropic (48)	*In vitro*
Entagenic acid	Anti-hyperglycemic and insulinotropic effects (49)	*In vitro* and *In vivo* (mice)
Furostanol	Insulinotropic effects (50)	*In vivo* (mice)

Glycosides

Glycosides are made up of the sugar moiety glycone (saccharide) and the non-sugar moiety aglycon (genin) linked by a glycosidic bond, derived from plant metabolism and attributed with different functions in living organisms, including storage purposes and playing defensives roles against pathogens and herbivores (57). The sugar moiety of glycosides contributes to the solubility, pharmacokinetics, and pharmacodynamic properties, while the non-sugar moiety contributes to the pharmacological effects. Glycosides in the plant are sometimes stored in inactive forms that can be easily transformed into active forms by cleavage to yield the desired. In contrast, in animals, glycosides facilitate the detoxification to remove poisons via binding to the sugar moiety of the glycosides (57). Glycosides are subdivided into four classes depending on the type of glycosidic bond and demonstrate several pharmacological and biological activities, including anti-inflammatory, antipyretic, anti-rheumatic, anti-microbial, and anti-diabetic activities (58). Several studies revealed the anti-diabetic effects of glycosides via a different mode of action to achieve glycemic control and alleviate pathological damages due to diabetes (59, 60).

Steviol glycosides and their metabolites demonstrated anti-diabetic effects in diabetic mice with increasing glucosyl groups in their molecules. This might be due to increased glucose uptake in the myocardium and brain and reduced glucose accumulation in the kidney and liver (61). In a similar study, glycosides from Stevia rebaudiana exhibited anti-diabetic properties exhibiting insulinotropic effects, thereby elevating glucose uptake and the number of glucose transporters (62). In vitro study on flavonol glycosides from Cleome droserifolia against diabetic enzymes revealed a moderate inhibition of α-amylase and α-glucosidase with a remarkably inhibited dipeptidyl peptidase IV (DPPIV) comparable to vildagliptin (63). Furthermore, the aldose reductase enzyme was inhibited, and oxidative stress was suppressed by the flavonol glycosides demonstrating protective action against diabetic complications. Triterpene glycosides from Momordica charantia exhibited anti-diabetic effects by inhibiting α-amylase and α-glucosidase comparable to acarbose (64). Moreover, these compounds inhibited the expression of pro-inflammatory markers and mitochondrial marker COX-2. Wedtrilosides A and B from Wedelia trilobata leave demonstrated anti-diabetic effects by highly and moderately inhibiting the activity of α-glucosidase and α-amylase, respectively (65).

A flavonoid C-glycosides orientin dose-dependently inhibited the specificity of PTP1B in an in silico further subjection to in vitro study showed the inhibition was mixed, agreeing with the in silico study (66). Dietary supplementation with steviol glycosides normalized hyperlipidemia in STZ-induced diabetic rats with an effect on appetite and significant improvement in blood, liver, and kidney function indices with reduced tissue damage (67). However, there was no effect on blood glucose, insulin, insulin resistance, and antioxidant biomarkers. Flavone C-glycosides from Beta vulgaris demonstrated anti-diabetic potential by inhibiting α-glucosidase in vitro, thus a candidate for developing hypoglycemic drugs (68). Steviol glycoside from the aqueous extract of Stevia rebaudiana exhibited anti-diabetic potential in vitro by significantly inhibiting α-amylase comparable to the standard drug acarbose (69). In vitro study of glycoside fraction of Gymnema sylvestre using mouse pancreatic β-cell lines demonstrated a protective effect against H2O2 induced ROS generation with no toxicity on β-cell viability with a glucose dose-dependent insulinotropic effect comparable to glibenclamide and enhanced expression of GLUT2 (70).

Iridoid glycoside loganic acid reduced plasma biomarkers of carbonyl/oxidative stress in STZ-induced diabetic rats and increased the concentration of antioxidant enzymes with an accompanied decrease in the generation of intracellular reactive oxygen species (71). Additionally, loganic acid demonstrated a protective effect against the formation and accumulation of glycation and oxidation protein products and malondialdehyde derivates in plasma. Total glycosides from Cistanche tubulosa exhibited anti-hyperglycemic and anti-hyperlipidemic activities in a combined STZ and diet-induced diabetes in rats by significantly reversing STZ-induced weight loss, reducing FBG and HbA1c levels (72). Moreover, OGTT showed improvement in glucose tolerance, insulin sensitivity, and glycogen storage in the liver and muscles with glucose, a dose-dependent improvement in the activity of regulatory enzymes of carbohydrate metabolism and lipid profile, and antioxidant enzymes with a decrease in oxidative stress and inflammation serum markers (72). Total glycosides from okra fruit demonstrated anti-diabetic and antioxidant properties such as reduced levels of FBG, total cholesterol, triglycerides, and liver index,

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accompanied by elevated oral glucose tolerance and superoxide dismutase in STZ-induced diabetic rats.

Additionally, an obvious recovery was found from a kidney lesion (73). Triterpenoid glycosides from Cyclocarya paliurus exhibited hypoglycemic activity by significantly increasing glucose utilization 3T3-L1 adipocyte, thus, might be the bioactive constituent associated with the traditional application of the plant in diabetic management (74). Figure 3 shows the structures of steviol and loganic acid.

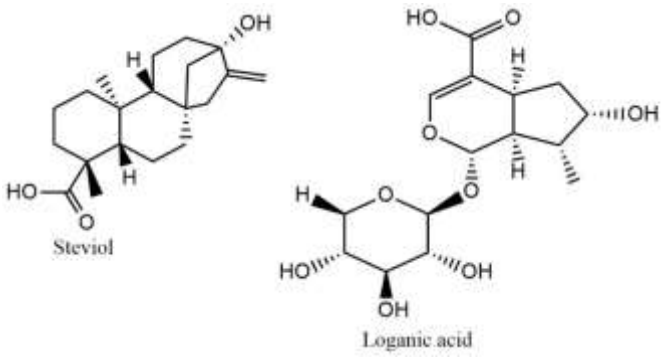

Figure 3. Structures of steviol and longanic acid

Terpenoids

Terpenoids are groups of secondary metabolites, otherwise called isoprenoids, derived from five-carbon isoprene units, mostly originating from plants and animal sources with vast therapeutic applications against different diseases (75). They have diverse backbone structures and functional groups, differentiating them from each other and contributing to their diverse applications, such as flavoring agents, drugs, and nutraceuticals (75). Terpenoids have been attributed with several biological effects such as anti-inflammatory, antiparasitic, antibacterial, antiviral, antimalarial, antioxidant, antiaging, and anti-diabetic activities (75-78). Terpenoids affect their anti-diabetic activities by inhibiting insulin resistance developing enzymes, stabilizing PG, insulin levels, glucose metabolism, and antioxidant actions (79). Furthermore, they inhibit α-amylase, plasma lipase, α-glucosidase, tyrosine phosphatase, aldose reductase, and the expression of SGLT1, GLUT2, DPP4, PTP1B, DGAT, and HSD. Additionally, terpenoids promote the expression of GLUT4, GLP1, HSP, and adiponectin, and also activate PPAR-γ and incretins, and AMPK pathway while they inhibit inflammatory pathways, protein glycation, and formation of AGEs (79).

Terpenoids-rich extract from Dillenia indica exhibited anti-diabetic effects in insulin-resistant C2C12 cells and STZ-induced diabetic mice by reducing oxidative stress (80). The extract demonstrated positive effects in vitro using DPPH and ATBS and strongly inhibited α-glucosidase activity more than acarbose. Moreover, insulin receptor substrate-1 (INS-1) was stimulated, while expression of PDK1 and protein kinase B (Akt) were down-regulated (80). Furthermore, GLUT4 was translocated to the plasma membrane, and increased glucose absorption was observed with a significantly reduced level of ROS and elevated levels of antioxidant enzymes. Terpenoids were reported to activate AMP-activated protein kinase responsible for improving glucose homeostasis in the blood in insulin-resistant rodents, lipid profile, and blood pressure, thus a target for new anti-diabetic drugs (81).

Terpenoids-rich Padina pavonia extract exhibited anti-diabetic and antioxidant activities (82). The extract ameliorated hyperglycemia and dyslipidemia with accompanying improvement in insulin sensitivity and glucose tolerance in combined HFD- and STZ-induced diabetic rats. Moreover, there was an increase in the phosphorylation of glucose and glycogen formation with the suppression of gluconeogenic enzymes. Furthermore, the antioxidant capacity was improved, accompanied by up-regulated expression of the PPARγ gene in the liver. Alzheimer-like alterations induced in diabetic rats were prevented by terpenoid-rich Elettaria cardamomum extract by inhibiting the activity of pro-inflammatory cytokines and GSK3β and generation of ROS (83). Diabetes-induced loss in cognitive functions was reversed, and the increased acetylcholinesterase caspase-3 activity in the hippocampus was significantly lowered with decreased accumulation of the brain Aβ and p-tau. Moreover, the antioxidant defense system and expression of glutamate receptors were enhanced while hippocampal lipid peroxidation marker malondialdehyde was decreased.

Acyclic terpenoids from Annona diversifolia demonstrated in vitro hypoglycemic effects by inhibiting α-glucosidase and selectively inhibiting SGLT-1 in oral glucose, sucrose, lactose tolerance, and glucose excretion (84). Two non-polar terpenoids, betulinic acid, and stigmasterol, exhibited anti-diabetic activity with insulin mimic effects enhancing glucose uptake, significantly inducing and enhancing adipogenesis comparable to rosiglitazone (85). Terpenoid-rich extract of Momordica charantia highly inhibited the activity of α-glucosidase isolated from Saccharomyces cerevisiae in vitro with the Lineweaver-Burk plot showing a partially mixed-type inhibition which was postulated to be the mode of action of the hypoglycemic effect of the plant (86). In another study, triterpenoids and flavonoid fractions of ethanol extract of Canavalia species exhibited significant anti-hyperglycemic and anti-hyperlipidemic effects in HFD and STZ-induced diabetic rats evidenced by the decreased HbA1C and blood glucose levels with improved lipid profile (87). The terpenoids cycloartenol and 24-methylene cycloartenol from Ficus krishnae exhibited a significant glucose-lowering effect in OGTT in HFD-STZ-induced type 2 diabetic rats (88). Additionally, in vitro study showed enhancement in the cell viability of RIN-5F cells, significantly protecting beta cells from glucose toxicity with enhanced insulin release.

Flavonoids

Flavonoids are low molecular weight polyphenolic compounds produced in secondary pathways synthesizing compounds required in trace amounts vastly found in plants and associated with various pharmacological and biological roles influencing different processes, notably in plants in response to environmental factors (89-91). Although flavonoids are mostly associated with antioxidant effects, other pharmacological effects include anti-inflammatory and anti-microbial effects (89). They are derived from 2-phenyl benzyl-pyrone derivatives through the phenylpropanoid pathway with a diphenyl propane backbone made up of 15-carbon atoms with two 6-membered rings attached to 3-carbon units, probably attached to the third ring structure (91). They are classified into different classes depending on the extent of oxidation of the second-ring and the third-ring carbon. Flavonoids were reported to be associated with different pharmacological properties against bacteria, viruses, inflammation, cancer, and oxidative stress, with the anti-diabetic and anti-inflammatory properties attributed to the C2-C3 double bond on the third ring and the hydroxyl groups at the C3', C4', C5, and C7 positions on the other rings (91, 92).

Hesperidin exhibited anti-inflammatory, anti-hypercholesterolemic effects in STZ-induced diabetic rats with a positive effect on hyperglycemia via the Klotho/FGF-23 pathway, which may also inhibit the rise AST, ALT, blood urea nitrogen, and creatinine levels (93). Naringenin demonstrated exerted dual agonistic anti-diabetic effect against PPARγ/GLUT4, strongly regulating metabolism with the significant restoration of body weight, reduced blood glucose, normalized serum lipid profile, and hepatic and pancreatic oxidative stress biomarkers (94). Naringenin possesses anti-diabetic, antioxidant, and antiapoptotic with preventive effects against neurodegeneration of the retina observed in diabetic retinopathy in STZ-induced diabetic rats (95). Eriodictyol was reported to exhibit an insulinotropic effect in diabetic rats in a glucose-dependent manner via the cAMP/PKA pathway improving glucose tolerance and glycemic control (96). In another study, eriodictyol exerted protective effects against oxidative stress, inflammation, and apoptosis induced by hyperglycemia in the retinal ganglial cells of rats (97). The flavone apigenin effectively reduced intracellular ROS generation, DNA damage, and lipid peroxidation, relieved protein carbonylation, and reversed apoptosis induced by STZ in pancreatic β-cells in vitro (98). Moreover, apigenin regulates antioxidant defenses in pancreatic β-cells and is a free radical scavenger. Flavonoids ameliorate diabetic pathogenesis with its complications by regulating glucose metabolism and lipid profile coupled with regulation of the enzymes activities of liver enzymes through different mechanisms (99).

Quercetin was reported to exert type 2 diabetes preventive effects in the Chinese population due to an observed reduction in prevalence (100). Animal studies showed effectiveness at 10, 25, and 50 mg/kg of body weight of quercetin for its hypoglycemic effects (101). Combining quercetin with sitagliptin in STZ-induced diabetic rats improved metabolic profile, β-cell functions, and islet structure with increased SOD, GSH, and decreased NF-κB (102). Rutin exhibits an anti-diabetic and protective effect against hyperglycemia and dyslipidemia via a reduction in intestinal absorption of carbohydrates, inhibition of gluconeogenesis, promote glucose uptake with accompanied insulinotropic effect and protective effects to the Langerhans islet against degeneration (103). Moreover, sorbitol formation, ROS generation, AGEs precursors, and inflammatory cytokines formation was diminished. Kaempferol significantly improved metabolism in STZ-induced diabetic mice by reducing glucose production and increasing its oxidation in the liver and muscles with no alteration in plasma insulin and glucagon levels (104). Kaempferol attenuated diabetic nephropathy in vitro via deactivation of RhoA induced by hyperglycemia and reduced pro-inflammatory cytokines expression, fibrosis, and oxidative stress in NRK-52E and RPTEC cells (105). Treating STZ-induced diabetic rats with fisetin alleviated hyperglycemia, hyperlipidemia, and heart function markers with accompanied minimized myocardium injury (106). Additionally, oxidative stress was suppressed by preventing inflammation and apoptosis and enhancing the antioxidant defenses of the heart.

Dietary luteolin supplementation to HFD-fed menopausal mice reduced adipose tissue inflammation and insulin resistance via suppression of M1-like macrophage polarization in the adipose tissue (107). The antioxidant potential of tangeretin was previously implicated in improving STZ-induced cellular apoptosis in INS-1 cells (108). Additionally, insulin secretion and insulin 1 and 2 expressions were improved with significantly increased antioxidant enzyme activities and decreased ROS generation. Diosmin exerted a hypoglycemic effect in STZ-induced diabetic rats with improved lipid profile by activating the imidazoline I-2 receptor, enhancing β-endorphin secretion and influencing

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metabolic homeostasis (109). Baicalein increased glucose uptake and utilization with increased expression of insulin receptors and proteins and GLUT 2 in insulin-resistant HepG2 cells (110).

Furthermore, the expression of gluconeogenic enzymes was reduced by baicalein to improve glucose metabolism in the hepatocytes. In another study, baicalein was reported to exert protective effects in diabetic cardiomyopathy rats against oxidative stress and inflammation by promoting antioxidant enzymes activities and significantly reducing the level of malondialdehyde via the phosphatidylinositol 3-kinase/AKT pathway (111). Additionally, baicalein exhibited hepatoprotective effects in diabetic liver injury by suppressing the inflammatory cascade in diabetic mice, attenuating the expression of pro-inflammatory proteins, and inhibiting IL-1β, IL-6, and TNF-α (112). Further study on palmitic acid-challenge human hepatic HepG2 cells showed baicalein reversal of the increased insulin, ALT, AST, TG, and TC levels (112). Table 3 summarizes some flavonoids' anti-diabetic effects, while their structures are shown in Figure 4.

Table 3. Antidiabetic flavonoids

Flavonoids	Anti-diabetic action	Effect
Hesperidin	Anti-inflammatory and anti-hypercholesterolemic (93)	*In vivo* (rats)
Naringenin	Anti-hyperglycemic, anti-hyperlipidemic, and antioxidant (94)	*In vivo* (rats)
Eriodictyol	Antioxidant and Insulinotropic effect (96)	*In vivo and In vitro*
Apigenin	Antioxidant and anti-inflammatory (98)	*In vitro*
Quercetin	Anti-hyperglycemic and antioxidant (102)	*In vivo* (rats)
Rutin	Anti-hyperglycemic, anti-inflammatory, and insulinotropic effects (10	*In vivo and In vitro*
Kaempferol	Anti-hyperglycemic and anti-inflammatory (104)	*In vitro*
Fisetin	Anti-hyperglycemic and anti-hyperlipidemic (106)	*In vivo* (rats)
Luteolin	Anti-inflammatory (107)	*In vivo* (mice)
Baicalein	Anti-hyperglycemic, antioxidant, and anti-inflammatory (110-112)	*In vitro*

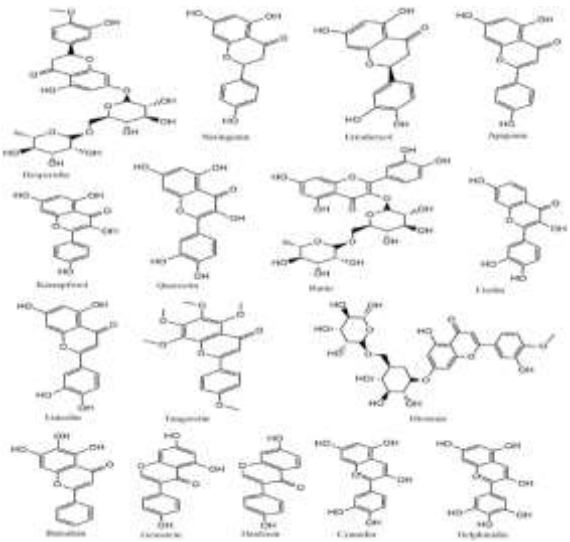

Figure 4. Structures of some antidiabetic flavonoids

Conclusion

Phytochemicals produced by plants as secondary metabolites play various pharmacological roles in diabetes especially considering the complications associated with persistent hyperglycemia. Although attaining glycemic control and treatment of diabetic complications remains a challenge, using different classes of phytochemicals from medicinal plants offers alternatives to achieving therapeutic goals. These phytochemicals act through different mechanisms of action in managing diabetic complications such as nephropathy, retinopathy, dyslipidemia, and poor glycemic control. Some therapeutic roles the phytochemicals play include attenuation of hyperglycemia and hyperlipidemia, α-glucosidase inhibition, insulin secretion regulation, and anti-inflammatory and antioxidant effects to repair tissue injuries. The various phytochemicals reviewed in the present study might provide a source for developing novel anti-diabetic agents.

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Conflict of interest

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