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REVIEW

Recent discovery of plant-derived anti-diabetic natural products

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Covering: 2005 to 2010

This review covers recent discoveries of anti-diabetic compounds. Diabetes mellitus (DM) is a complex disease affecting patients' daily life and elevating patients' risk of developing other diseases. There are several forms of diabetes, including type-1 diabetes (insulin-dependent), type-2 diabetes (noninsulin-dependent), and gestational diabetes. Type-2 diabetes is the most common form and the patient population with type-2 DM rises every year. Current treatments meet some but not all patients' needs. Therefore, new anti-diabetic drugs are in great demand. Traditional herbal medicine provides a rich source for new drug discovery. In this review, recent discoveries of anti-diabetic compounds have been summarized according to their chemical structures and mechanisms of action. Anti-diabetic plant extracts, many of which have been used and marketed as dietary supplements, were also included and discussed, and are classified according to the positive control used in the anti-diabetic animal studies. New anti-diabetic natural products found in the recent patent literature are also summarized.

1 Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by glucose intolerance and changes in lipid and protein metabolism. Further, long-term diabetic patients who are treated ineffectively suffer from complications of retinopathy, nephropathy, and peripheral neuropathy. The risks of acquiring cardiovascular disease, stroke, and cancer are also higher in diabetic patients.[1,2] DM can be found worldwide and the population is increasing. According to World Health Organization projections, around 300 million or more people will be affected by diabetes by the year 2025.[3] The estimated number of diabetic patients in 2030 will be more than double that in 2005.[4] The number of Americans with diabetes approached 24 million in 2007, and the prevalence is still projected to increase due to the high caloric diets and sedentary lifestyles that are common these days.[5] Because type-2 (noninsulin-dependent) diabetes is the most common form of DM, it is the main focus of this review. Unless otherwise indicated, all anti-diabetic compounds and plant extracts summarized in this paper relate to anti-type-2 diabetes. The current therapies for type-2 diabetes include mainly oral anti-diabetic drugs, such as sulfonylureas, biguanides, α-glucosidase inhibitors, thiazolidinediones, and dipeptidyl peptidase-4 (DPP-4) inhibitors *etc*., which are used as monotherapy or in combination. Table 1 summarizes these commonly used therapeutic agents and their mechanisms of action. However, these oral agents have many undesirable side effects (see Table 1) and ultimately cannot control the glycemic level. Therefore, safer and more effective anti-diabetic drugs are still urgently needed.

Herbal medicine has played an important role in treating diabetes in Asia, India and Africa for centuries. In 2006, Jung *et al.* reviewed the hypoglycemic effects of many plants that are used as anti-diabetic remedies, as well as anti-diabetic natural products discovered during 2001–2005.[3] With the rapid advancement of novel technologies and the increased research on anti-diabetic natural products, many new plants, their extracts,

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and their active principles have been found to exhibit anti-diabetic effects, which may provide us with valuable leads to develop as novel anti-diabetic agents to supplement the current chemotherapies. Therefore, this review further summarizes the discovery of novel anti-diabetic natural product extracts, their isolated compounds and possible mechanisms of action from mid 2005 to 2010.

The pathogenesis of type-2 diabetes is complex and involves many mechanisms. Commonly seen drug targets of medicinal plants and natural products are summarized in Table 2. Many pharmaceutical companies and academic laboratories are engaged in the discovery of new targets, pathways, and treatments for type-2 diabetes. For example, endoplasmic reticulum (ER) stress in the pancreatic β-cell was found to play a crucial role in the pathogenesis of diabetes. The core is a triad of stress-sensing proteins: protein kinase R-like endoplasmic reticulum kinase (PERK), inositol-requiring enzyme 1 (IRE1) and activating transcription factor 6.[6] ER stress may also be responsible for the loss of β-cell mass in diabetes.[7] It is clear that the pancreatic β-cell is exquisitely sensitive to perturbations of ER function, due to the large swings in protein flux through its secretory pathway and the significant oxidative stress imposed by

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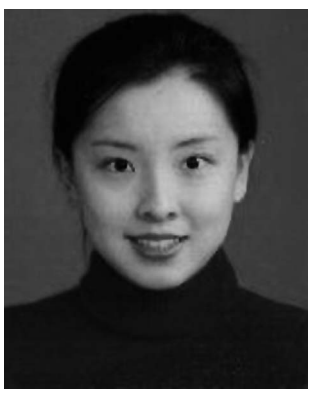

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Table 1 Current oral anti-diabetic drugs, their mechanisms of action and main side effects

Categories	Mechanism	Example	Main Side Effects
Sulfonylureas/insulinotropics	Increase pancreatic insulin production by inhibiting the K_{ATP} channel	Glibenclamide, Glipizide, Tolbutamide, Chlorpropamide	Hypoglycemia, Weight gain
Biguanides	Reduce hepatic glucose production and increase insulin sensitivity	Metformin, Phenformin	GI symptoms (diarrhea, nausea, abdominal pain), Lactic acidosis Metallic taste
α-Glucosidase inhibitors	Interfere with carbohydrate digestion and absorption	Acarbose	GI symptoms (diarrhea, abdominal cramping, flatulence)
Thiazolidinediones	Improve insulin action by activating peroxisome proliferator-activated receptor gamma (PPAR-γ)	Rosiglitazone	Hepatoxicity
DPP-4 inhibitors (Gliptins)	Reduce glucagon and blood glucose levels by inhibiting DPP-4	Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin	Nasopharyngitis, Headache, Nausea, Hypersensitivity, Skin reactions

Table 2 Common targets for anti-diabetic medicinal plants and isolated natural products

Target sites	Description
Sugar Homeostasis	
Glycolysis and Krebs cycle[20]	Glycolysis is an important metabolic pathway in which glucose is oxidized to two pyruvic acids, which enter the Kreb cycle for energy production. Several enzymes that are involved in this pathway, such as hexokinase, phosphofructokinase, pyruvate kinase, succinate dehydrogenase, malate dehydrogenase and lactic acid dehydrognease (under anaerobic condition), would be expected to have regulatory roles.
Gluconeogenesis[20]	The gluconeogenetic pathway generates glucose from non-sugar substrates, keeping blood glucose level. Critical enzymes in this pathway are pyruvate carboxylase, phosphoenolpyruvate (PEP) carboxykinase, fructose-1,6-bisphosphatase, and glucose-6-phosphatase (G-6-Pase).
Hexose monophosphate shunt[20]	Also known as the pentose phosphate pathway, and generates reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) for reductive biosynthesis reaction and 5-carbon sugar. Glucose-6-phosphate dehydrogenase is an important enzyme regulating this pathway.
Glycogen synthesis and glycogenolysis	Storage and release of unused sugar added to glycogen chains are critical in sugar regulation. Glycogen synthase regulated by insulin *via* protein kinase A (PKA) and glycogen phosphorylase involved in glycogen breakdown are the two main control enzymes.
Digestion and absorption of carbohydrate	Carbohydrates, mainly starch and sucrose from diet, are digested into glucose and absorbed *via* the intestine, maintaining blood glucose level. Among all the enzymes involving in the digestion process, α-glucosidase is the most important.
Glucose transporters (GLUT)[15]	Transport glucose in and out of the cell.
Insulin mimetic	
Synthesis, release and degradation of insulin[20]	ATP-gated potassium channel and voltage-gated calcium channel are related with the release of insulin from beta cells. Inhibition of insulinase will affect the degradation of insulin.
Peroxisome proliferator-activated receptor gamma (PPAR-γ)[21]	A subtype of PPAR, a nuclear receptor transcription factor that is involved in insulin resistance. Increase in the expression of PPAR-γ will decrease insulin resistance.
Dipeptidyl peptidase-4 (DPP-4)[22]	An antigenic enzyme expressed on the surface of most cell types. It plays a major role in glucose metabolism and is responsible for the degradation of incretins, such as GLP-1 and GIP.
Downstream signal of insulin	
cAMP	An important second messenger involved in metabolic activities. Increase or decrease of cAMP will correlate with the intensity of insulin.
Phosphoinositide-3 kinase (PI3 kinase)	Involved in several downstream signals of the insulin metabolic pathway.
Protein-tyrosine phosphatase 1B (PTP1B)[23]	Negative regulator of insulin signaling pathway. It can dephosphorylate the activated insulin receptor kinase.

the synthesis of insulin, which will undoubtedly lead to novel strategies for directly treating the actual molecular pathology of diabetes.[6] Meanwhile, obesity and type-2 diabetes are also strongly associated with increased inflammation.[8] As an example, oral or inhaled glucocorticoids are anti-inflammatory therapies targeting diseases such as asthma, arthritis, and colitis. At a molecular level, glucocorticoids bind directly to glucocorticoid receptor (GR), a member of the nuclear receptor family of ligand-activated transcription factors. Activation of GR has pleiotropic effects resulting in hepatic steatosis, hypertriglyceridemia, impaired glucose tolerance, and insulin resistance.[5] It is now clear that chronic low-level inflammation in adipose tissue becomes a strong driving force for the development of systemic inflammation resulting in metabolic syndrome, eventually followed by overt type-2 diabetes.[9] Emerging evidence also suggested that amino acids may potentially be important in the prevention of diabetes and its associated complications.[10] The pathways involved in the pathogenesis of diabetes include increased polyol pathway flux, increased advanced glycation end products formation, activation of protein kinase C, and oxidative and carbonyl stress. Amino acids have modulatory effects on insulin secretion, and some individual amino acids, such as taurine, phenyl alanine, and branched chain amino acids, can improve insulin sensitivity and post-prandial glucose disposal.[10]

In an analysis of 728 patent applications claiming diabetes as an indication during 2008–2010, the highest patent counts were associated with eight anti-diabetic targets: 11β-HSD1, DGAT1, DPP-4, glucokinase (GK), GPR119, PPAR-α, -δ, -γ, SGLT1/2, and stearoyl-CoA desaturase 1 (SCD1).[5] 11β-Hydroxysteroid dehydrogenase 1 (11β-HSD1) localizes to the ER and mediates the inactivation of glucocorticoids (mentioned above), as well as catalyzes the interconversion of cortisone and cortisol.[11] The role of glucocorticoids in the development of whole-body insulin resistance and the overexpression of 11β-HSD1 in visceral adipose has raised the possibility that blockage of 11β-HSD1 can be utilized in the treatment of type-2 diabetes.[5] Glucokinase (GK) catalyzes the initial step in glycolysis and is a key determinant of carbon flux through the glycolytic, glycogen synthesis, pentose phosphate shunt, and gluconeogenic and lipogenic pathways. It is anticipated that activation of GK in the liver and pancreas will be an effective strategy for lowering blood glucose by upregulating hepatic glucose utilization, downregulating hepatic glucose output, and normalizing glucose-stimulated insulin secretion.[5] GPR119 is a lipid-sensing GPCR, and its agonists recapitulated the acute effects of oleoylethanolamide (OEA) on food intake and suppressed weight gain when administered over a 14-day period to rats habituated to a high-fat diet.[12] Synthetic GPR agonists also improved glycemic control in both normal and diabetic mouse models associated with an increase in circulating insulin levels.[13] Renal reabsorption of glucose is critical in the maintenance of plasma glucose levels, and this reabsorption is mediated by two sodium-dependent glucose co-transporters, SGLT1 and 2.[14] The most compelling evidence in support of targeting renal glucose reabsorption for the management of type-2 diabetes comes from human genetics studies, indicating that individuals with renal glycosuria (mutations in SGLT gene) rarely exhibit hypoglycemia or hypovolemia. Phlorizin, a non-selective inhibitor of SGLT1 and 2, lowered blood glucose levels, however, with unwanted side effects,[15,16] while sergliflozin and remogliflozin, which are selective SGLT2 inhibitors, stimulated urinary glucose excretion without any increase in insulin secretion or any discernable effects on normoglycemia or electrolyte balance.[17,18] SCD1 has been implicated in non-alcoholic fatty liver disease, which can often lead to insulin resistance. Global SCD1 inhibition or antisense-mediated SCD1 inhibition in adipose and liver has been shown to decrease lipogenesis and increase fatty acid β-oxidation in rodents maintained on high-fat diets.[5] However, there are side effects associated with the systemic SCD1 inhibitors, such as closed eye fissure and skin barrier dysfunction, which have limited the safety profiles.

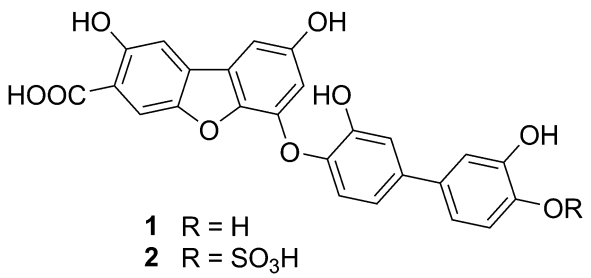
Animal models of diabetes can offer useful and promising information in the development of anti-diabetic drugs, especially with plant extracts for which mechanisms of action are usually unknown. Inbred animal models can also provide homogeneous and controlled environmental factors to avoid other interferences. Thus, a brief classification of the available animal models for diabetes research is further shown in Table 3 to better illustrate their effectiveness, advantages, and drawbacks.[19]

2 Newly isolated anti-diabetic pure plant natural products

The anti-diabetic natural products newly discovered during 2005–2010 are summarized and categorized below according to their chemical structures. Their anti-diabetic activity and mechanism of action are further discussed.

2.1 Lignans

A vanillic acid derivative (**1**) and its sulfate adduct (**2**) isolated from green algae, *Cladophora socialis* (Chlorophyceae), showed potent inhibition of protein tyrosine phosphatase 1B (PTP1B), an important enzyme in regulating the insulin receptor, with IC_{50} values of 3.7 and 1.7 μM, respectively (positive control: N/A).[24]



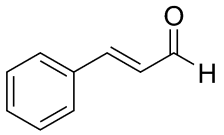
1 R = H
2 R = SO_3H

Cinnamaldehyde (**3**) was identified as the compound responsible for anti-diabetic activity in *Cinnamonum zeylanicum* Blume (Lauraceae). In an STZ-induced diabetic rat model,

Table 3 Current commonly used animal models for anti-diabetic studies

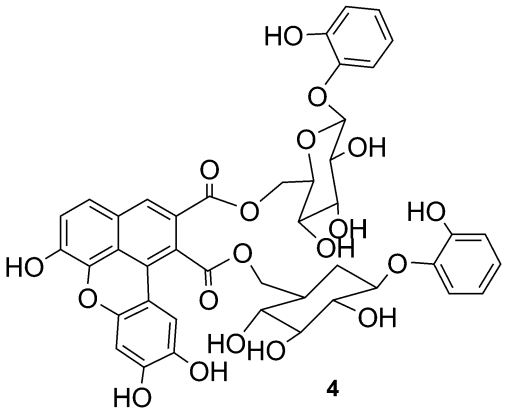
Model	Advantages	Disadvantages
Spontaneous diabetic animals (ex) *ob*/*ob*, *db*/*db* mice, *KK*/*A*^{y} mice	The animals develop DM spontaneously and the disease characteristics are similar to those of human DM.	Expensive and limited availability
	The genetic background is controlled to allow studies on genetic problems.	Mortality rate is high and insulin treatment is required.
Diet-induced diabetic animals	The DM developed in the animal mimics human DM resulting from over-nutrition.	Long term high fat treatment is required.
	No interference from the chemicals used to cause DM.	
Chemical-induced diabetic animals (ex) streptozotocin(STZ)-induced diabetic mice; alloxan (ALX)-induced diabetic mice	Pancreatic beta cells are selectively destroyed.	The DM results from beta cell deficiency rather than insulin resistance.
	Remaining insulin function can help the animals' survival.	The induced DM is less stable and reversible.
	Relatively cheap and easier to handle	Long term experiments should access beta cell function.

administration of **3** at 5, 10, and 20 mg kg^{-1} of body weight (bw) *p.o.* lowered blood glucose level in a dose-dependent manner (63.29%), while glibenclamide, a reference drug (0.6 mg kg^{-1} bw) *p.o.* also produced a significant reduction. In addition, oral administration of **3** (20 mg kg^{-1} bw) significantly decreased glycosylated hemoglobin (HbA_{1C}) and improved lipid profile.[25]



3 Cinnamaldehyde

Two bis(catechol glycoside) esters (**4**, **5**) were isolated from the leaves of *Dodecadenia grandiflora* (Lauraceae), and both compounds (100 mg kg^{-1} bw, *p.o.*) showed significant antihyperglycemic activity in STZ-induced diabetic rats, comparable to the standard drug metformin (100 mg kg^{-1} bw, *p.o.*).[26]



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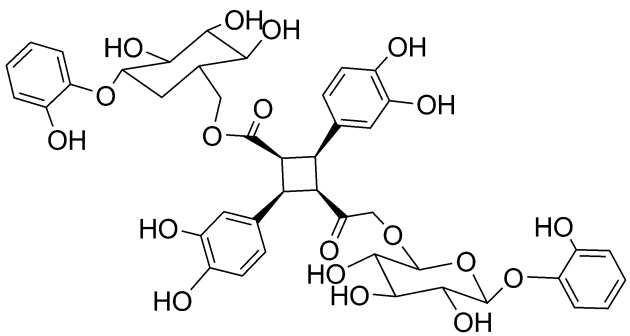

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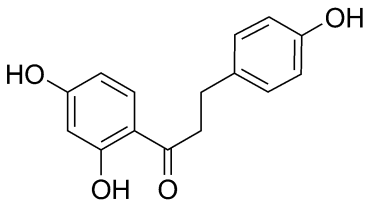
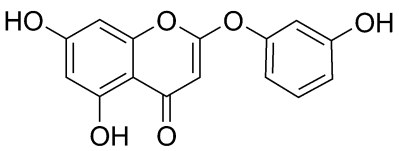
2.2 Flavonoids

Three compounds, identified as davidigenin (**6**), 6-demethoxycapillarisin (**7**), and 2′,4′-dihydroxy-4-methoxydihydrochalcone (**8**), were isolated from *Artemisia dracunculus* L. (Asteraceae), known as Russian tarragon. This extract inhibited aldose reductase (ALR2) activity by 58% to 77% at 3.75 μg mL^{-1}, while quercitrin, a well-known flavonoid and ALR2 enzyme inhibitor, reduced ALR2 activity by 54%.[27] In addition, **7** and **8** inhibited phosphoenol pyruvate carboxykinase (PEPCK) mRNA levels, related to the gluconeogenesis pathway, with IC_{50} values of 43 and 61 μM, respectively (positive control: insulin, 10 nM). Results with LY-294002, a PI3K inhibitor, showed that **7** activated the PI3K pathway, similarly to insulin, while **8** did not, but was dependent on activation of the AMP-activated protein kinase (AMPK) pathway.[28]

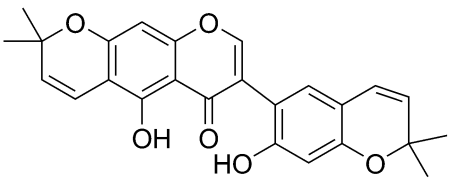


6 Davidigenin, R = H
8 2',4'-Dihydroxy-4-methoxy-dihydrochalcone, R = Me

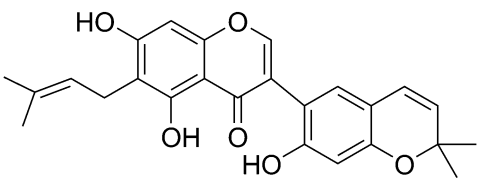


7 6-Demethoxycapillarism

Two main bioactive compounds, kraussianone-1 (**9**) and kraussianone-2 (**10**), from the roots of *Eriosema kraussianum* N. E. Br. (Fabaceae) were studied for their vasodilatory and hypoglycemic properties. Compounds **9** and **10** (20–80 mg kg^{-1} *p.o.*) resulted in dose-dependent hypoglycaemia in rats, with glibenclamide (10 mg kg^{-1} bw, *p.o.*) as the positive control.[29]

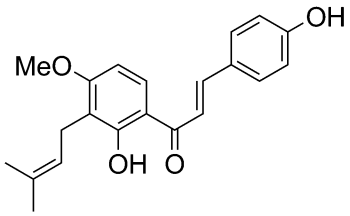


9 Kraussianone 1

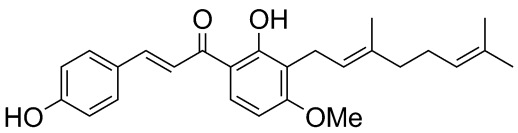


10 Kraussianone 2

Two major chalcones, 4-hydroxyderricin (**11**) and xanthoangelol (**12**), from the ethanol extract of *Angelica keiskei* Koidzumi (Apiaceae/Umbelliferae) were found to have insulin-like activities *via* a pathway independent of the peroxisome proliferator-activated receptor-γ (PPAR-γ) activation. Moreover, **11** (diet with 0.15% of the compound) also prevented progression of diabetes in genetically impaired *KK-A*^{y} mice, which develop diabetes and show hyperglycemia with aging because of insulin resistance (positive control: 0.05% diet of pioglitazone).[30]

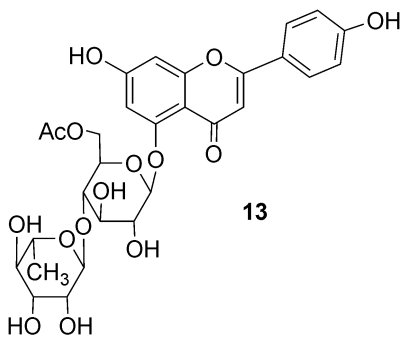


11 4-Hydroxyderricin



12 Xanthoangelol

Three flavonoids, apigenin-5-*O*-[α-L-rhamnopyranosyl-(1→4)-6-*O*-β-D-acetylglucopyranoside] (**13**), apigenin (**14**), and apigenin-5-*O*-[α-L-rhamnopyranosyl-(1→4)-6-*O*-β-D-glucopyranoside] (**15**) were found to be responsible for the anti-hyperglycemic effect of the ethanol extract of the leaves of *Cephalotaxus sinensis* (Rehder & E.H.Wilson) H.L. Li *via* bioassay-guided fractionation. A significantly increased level of glucose transporter GLUT-4 was also seen from mice adipocytes treated with **14** (0.1 mg, 2 mg mL^{-1}, positive control: insulin, 10 nM).[31]



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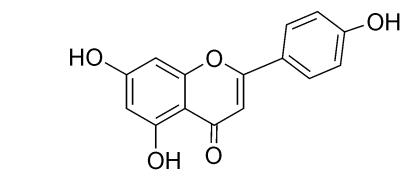

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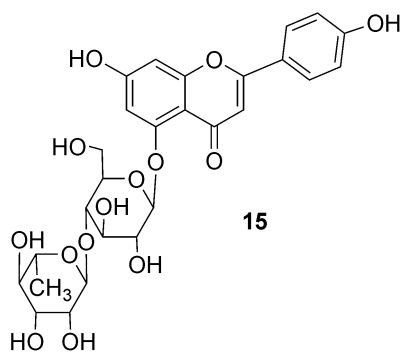

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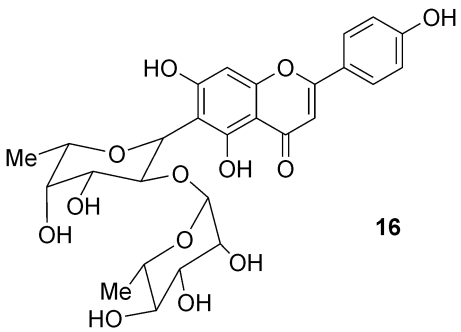
Apigenin-6-C-(2′-*O*-α-L-rhamnopyranosyl)-β-L-fucopyranoside (**16**) isolated from *Averrhoa carambola* L. (Oxalidaceae) leaves showed acute blood glucose lowering effects (50 mg kg^{-1} bw) in ALX-induced diabetic rats and promoted glucose-induced insulin secretion after oral treatment in hyperglycemic rats. In addition, stimulation of ^{14}C-glucose uptake was also observed.[32] Apigenin-6-C-β-L-fucopyranoside (**17**) (50 mg kg^{-1} bw, *p.o.*) from the same plant lowered blood glucose in hyperglycemic rats, promoted glucose-induced insulin secretion, and stimulated glycogen synthesis (positive control: glipizide, 10 mg kg^{-1} bw).[33]



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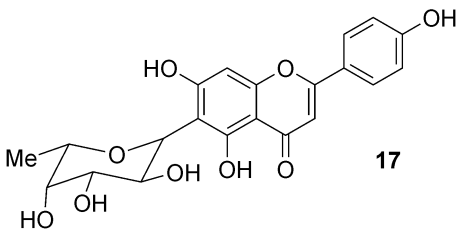

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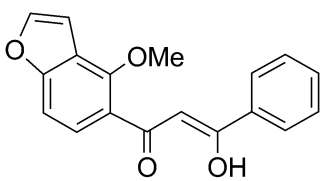
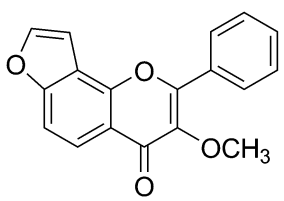
Pongamol (**18**) and karanjin (**19**) found in the fruit of *Pongamia pinnata* (L.) Pierre (Fabaceae) exhibited anti-hyperglycemic activity. In streptozotocin (STZ)-induced diabetic rats, the blood glucose lowering effects of pongamol and karanjin were 22% and 20%, respectively, at a 100 mg kg^{-1} dose *p.o.*, while metformin, a standard anti-diabetic drug, showed 19% reduction at the same dose. Moreover, in type 2 diabetic *db*/*db* mice, the two compounds (100 mg kg^{-1} b.w.) also showed glucose lowering effects of 35% and 30% after 10 days of consecutive administration, while metformin showed 32% activity at the same dose level. Furthermore, in an *in vitro* study, the two compounds also inhibited PTP1B.[34]



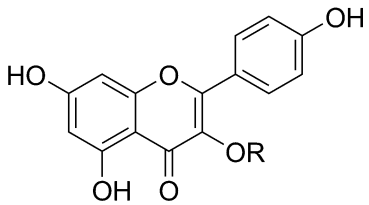
18 Pongamol



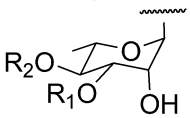
19 Karanjin

Kaempferol (**20**) and quercetin (**21**) isolated from *Euonymus alatus* (Celastraceae), a folk medicine used for treating diabetes

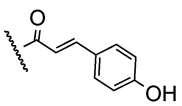
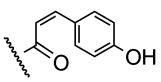
in China, were found to have anti-hyperglycemic effects and were investigated for their mechanism of action. The results showed that **20** and **21** (5–50 μM) significantly improved insulin-stimulated glucose uptake in mature 3T3-L1 adipocytes, and they also served as weak partial agonists in a PPAR-γ reporter gene assay without inducing differentiation of 3T3-L1 preadipocytes, an effect shown by traditional PPAR-γ agonists. Further, **20** and **21** competed with rosiglitazone at the same binding pocket site as PPAR-γ in a competitive ligand-binding assay. Also, inhibition of NO production in response to lipopolysaccharide treatment in macrophage cells was noticed in **20**- and **21**-treated groups, while less inhibition was seen in a rosiglitazone-treated group.[35]

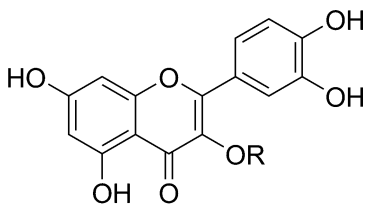


20 R = H, Kaempferol

22 R =  R_1= EC, R_2 = EC

23 R = R_1= EC, R_2 = ZC

EC =  ZC = 



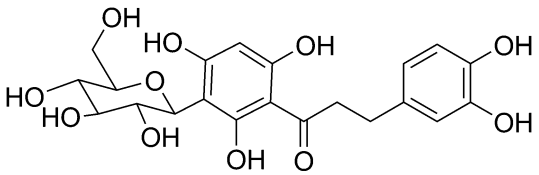
21 Quercetin, R = H
24 Quercetin-3-*O*-glucoside, R = glucose
25 Quercetin-3-*O*-galactoside, R=galactose

Two acylated kaempferol-3-*O*-α-L-rhamnopyranosides (**22**, **23**) from *Machilus philippinense* Merr. (Lauraceae) were isolated by bioassay-guided fractionation and found to inhibit α-glucosidase type IV (from *Bacillus stearothermophilus*) with IC_{50} of 6.10 and 1.00 μM, respectively (acarbose, IC_{50} = 0.046 μM). The two acylated compounds were much more active than the unacylated rhamnopyranoside (IC_{50} = 228.11 μM). Several new flavonols were also identified by a HPLC–SPE–NMR hyphenated technique.[36]

Another research study showed that **21** and quercetin 3-*O*-glycosides (**24**, **25**) are responsible for the antidiabetic activity of *Vaccinium vitis-idaea* (Ericaceae) crude berry extract, and the effect is mediated by AMPK. The quercetin glycosides and the aglycon stimulated the AMPK pathway at concentrations of 25–100 mM (positive control: insulin, 100 nM), but only the aglycon inhibited ATP synthase in isolated mitochondria (by 34 and 79% at 25 and 100 mM, respectively). This discrepancy suggests that the activity of the glycosides may require hydrolysis to the aglycon form.[37]

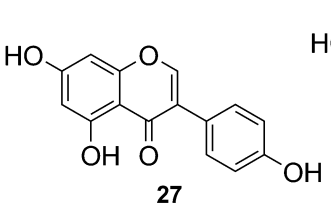
In flavonoid glycosides, the position of the sugar moiety may affect activity. Quercetin 3-*O*-glucoside (**24**) exhibited *in vitro* hepatic glucose-6-phosphatase (G-6-Pase) inhibitory activity, while quercetin 7-*O*-glucoside was inactive.[38]

Aspalathin (**26**) from *Aspalathus linearis* (Fabaceae), the source of rooibos tea, was found to increase glucose uptake by L6 myotubes at 1–100 mM concentrations in a dose-dependent manner, and to increase insulin secretion from cultured RIN-5F cells at 100 mM. In addition, aspalathin lowered fasting blood glucose levels as well as improved impaired glucose tolerance in *db*/*db* mice.[39]



26 Aspalathin

Several known isoflavones, such as genistein (**27**), its derivatives 3′,5′-diprenylgenistein (**28**), 6,8-diprenylgenistein (**29**), derrone (**30**), and alpinumisoflavone (**31**), isolated from branches of *Tetracera scandens* (Dilleniaceae) were found to have glucose-uptake activity in basal and insulin-stimulated L6 myotubes (0–25 μM), acting by AMPK activation and GLUT4 and GLUT1 over-expression. These compounds also inhibited protein tyrosine phosphatase 1B (PTP1B) with IC_{50} values ranging from 20–37 μM (positive control: ursolic acid, IC_{50}: 5 μM).[40]



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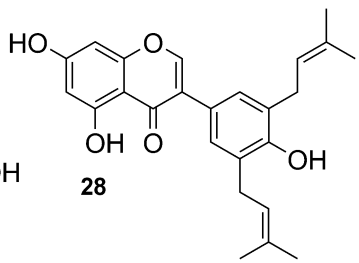

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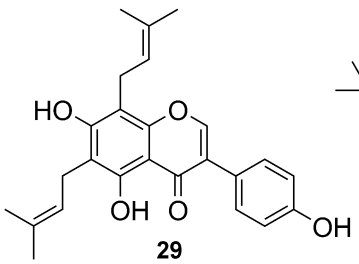

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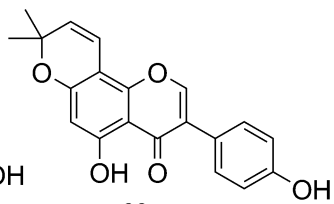

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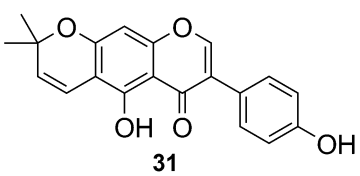
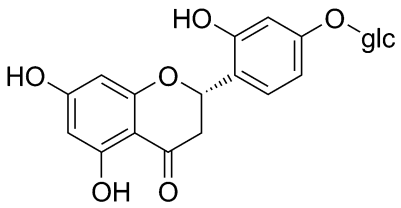


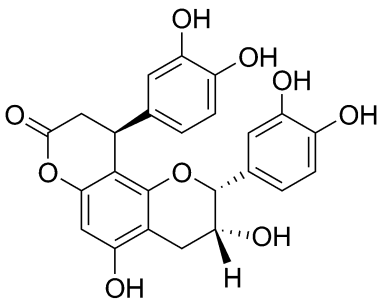
31

Steppogenin-4′-*O*-β-D-glucoside (**32**) isolated from the root bark of *Morus alba* L. (Moraceae) showed a hypoglycemic effect at 50 mg kg^{-1} (*p.o.*) in alloxan-induced diabetic mice.[41]



32 Steppogenin-4'-*O*-β-D-glucoside

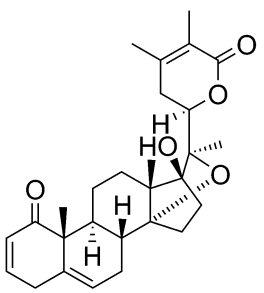
Cinchonain Ib (**33**) from *Eriobotrya japonica* LINDL (Rosaceae) leaves enhanced insulin secretion from INS-1 cells (rat insulinoma cell), as well as reduced plasma insulin level in rats after 108 mg kg^{-1} oral administration, but did not induce any changes in blood glucose level.[42]



33 Cinchonain Ib

2.3 Terpenoids

Five withanolides, identified as coagulin C (**34**), 17β-hydroxywithanolide K (**35**), withanolide F (**36**), (17*S*,20*S*,22*R*)-14α,15α,17β,20β-tetrahydroxy-1-oxowitha-2,5,24-trienolide (**37**), and coagulin L (14*R*,17*S*,20*S*,22*R*)-14,17,20-trihydroxy-3β-(*O*-β-D-glucopyranosyl)-1-oxowitha-5,24-dienolide (**38**), were isolated from the aqueous extract of *Withania coagulans* Dunal (Solanaceae). These compounds significantly inhibited post-diet glucose rise. Compound **38** also lowered fasting blood glucose profile and improved the glucose tolerance of *db*/*db* mice. The median effective dose of **38** was around 25 mg kg^{-1} (*p.o.*) in STZ-induced diabetic rats, which is comparable to the standard dose for the anti-diabetic drug metformin.[43]



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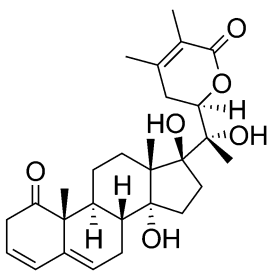

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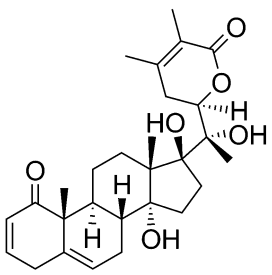

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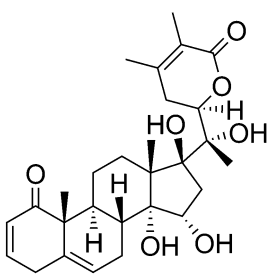

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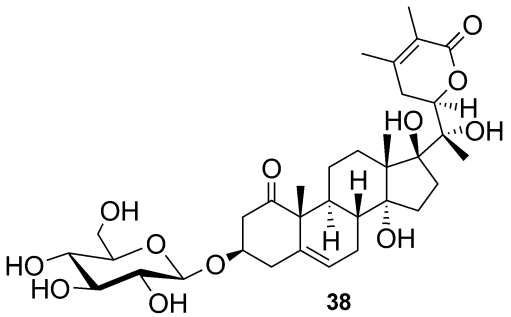
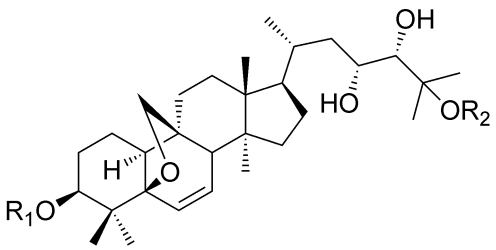
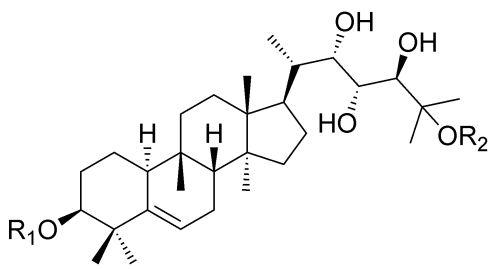


38

Karaviloside XI (**39**) and four cucurbitane glycosides, momordicosides Q, R, S, T, (**40**, **41**, **42**, **43**) were isolated from bitter melon (*Momordica charantia*) and their aglycons stimulated glucose transporter 4 (GLUT4) translocation to the cell membrane, which was associated with increased activity of AMPK.[44]



39 R_1 = All', R_2 = H
40 R_1 = Glc', R_2 = H
41 R_1 = All', R_2 = Glc''

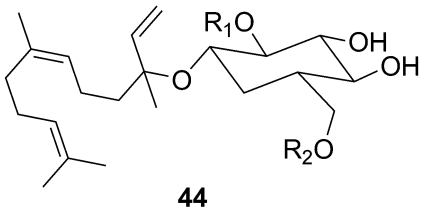


42 R_1 = Glc''(1→6)-Glc', R_2 = Glc'''
43 R_1 = Xyl'''(1→4)-[Glc''(1→6)]-Glc', R_2 = Glc''''

Glc = β-D-glucopyranosyl
All = β-D-allopyranosyl
Xyl = β-D-xylopyranosyl

A sesquiterpene glycoside, nerolidol-3-*O*-α-L-rhamnopyranosyl(1→4)-α-L-rhamnopyranosyl(1→2)-[α-L-rhamnopyranosyl(1→6)]-β-D-glucopyranoside (**44**), was isolated from dried leaves of loquat, *Eriobotrya japonica* (Thunb.) Lindl. (Rosaceae).

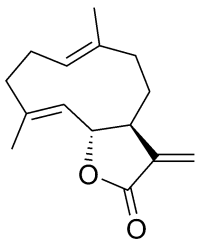
The compound exerted a significant hypoglycemic effect at the doses of 25 and 75 mg kg^{-1} (*p.o.*) in alloxan-induced diabetic mice, using gliclazide as a comparison (50 mg kg^{-1}).[45]



44

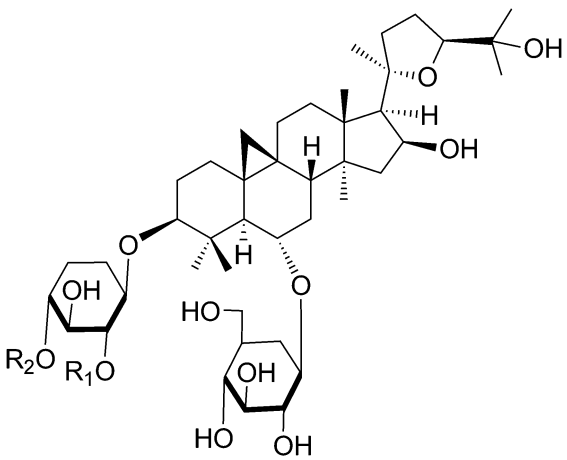
R_1 = Rha(1➛4)Rha, R_2 = Rha
Nerolidol-3-*O*-α-L-rhamnopyranosyl-(1➛4)-α-L-rhamnopyranosyl-(1➛2)-[α-L-rhamnopyranosyl-(1➛6)]-β-D-glucopyranoside

Costunolide (**45**) was isolated by bioassay guided fractionation from the hexane extract of *Costus speciosus* root. A dose-dependent glucose lowering effect was found in costunolide-treated STZ-induced diabetic male wistar rats at different doses (5, 10, 20 mg kg^{-1} bw, *p.o.*). Furthermore, decreased glycosylated hemoglobin (HbA1c), serum total cholesterol, LDL cholesterol, and triglyceride levels were seen as well as increased plasma insulin, tissue glycogen, HDL cholesterol, and serum protein (positive control: glibenclamide, 0.6 mg kg^{-1}).[46]



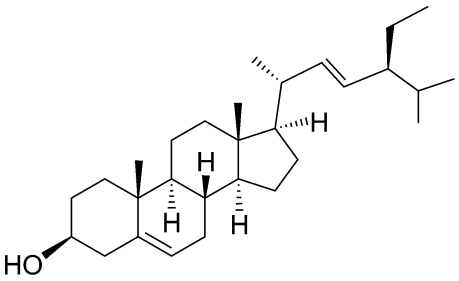
45 Costunolide

At a concentration of 5 μg mL^{-1}, stragaloside II (**46**) and isoastragaloside I (**47**) from the root of *Astragalus propinquus* Schischkin (Fabaceae) selectively increased secretion of adiponectin, an adipocyte-derived insulin-sensitizing hormone, in primary adipocytes without any obvious effects on a panel of other adipokines. These changes were related with a glucose-lowering effect, glucose tolerance, and insulin resistance (positive control: rosiglitazone, 5 μM).[47]



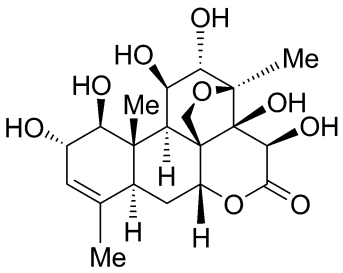
46 Astragaloside II R_1 = Ac, R_2 = H
47 Isoastrogaloside I R_1 = Ac, R_2 = Ac

Stigmasterol (**48**), isolated from the bark of *Butea monosperma* (Lam.) Kuntze (Fabaceae), was administrated to mice at 2.6 mg kg^{-1} d^{-1} *s.c.* for 20 days. Reduced serum triiodothyronine (T3), thyroxin (T4) and glucose concentrations were found as well as decreased activity of hepatic G-6-Pase and increased insulin levels, indicating that **48** exhibits both thyroid-inhibiting and hypoglycemic properties.[48]

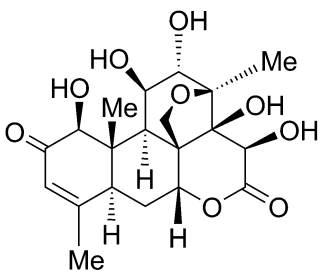


48 Stigmasterol

Two quassinoids, bruceines E (**49**) and D (**50**), isolated from the seeds of *Brucea javanica* (L.) Merr (Simaroubaceae) were administered to normoglycemic mice and STZ-induced diabetic rats (1 mg kg^{-1} bw, *i.p.*). Significantly reduced blood glucose levels were seen in the normoglycemic mice (40% and 48%, respectively) as well as in the STZ-induced diabetic rats (73% and 87%, respectively). These effects were comparable to those with glibenclamide (1 mg kg^{-1} bw).[49]



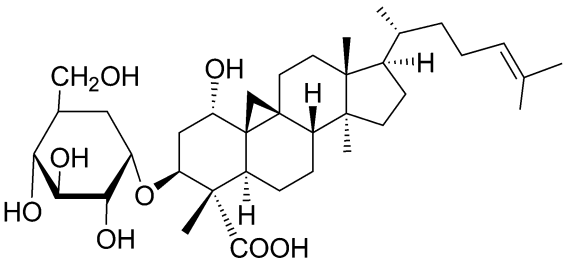
49 Bruceine E



50 Bruceine D

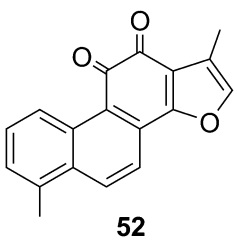
Mollic acid glucoside, a 1α-hydroxycycloartenoid (**51**) from the leaves of *Combretum molle* (R. Br. ex G. Don) Engl. & Diels (Combretaceae), showed a dose-dependent hypoglycemic effect

(5–80 mg kg^{-1} *p.o.*) in normoglycemic and STZ-induced diabetic rats. The LD_{50} value of the compound determined in mice was 183 ± 25 mg kg^{-1} (*i.p.*).[50]

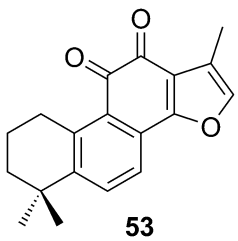


51 Mollic acid glucoside

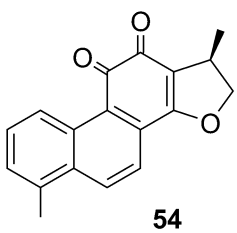
Three tanshinone compounds from the dried root of *Salvia miltiorrhiza* Bunge (Labiatae), a commonly used traditional Chinese medicine for promoting blood circulation, showed insulin-sensitizing activities. The total extract of Danshen (1–10 μg ml^{-1}) and the constituents tanshinone I (**52**), tanshinone IIA (**53**), and 15,16-dihydrotanshinone I (**54**) (10 μM) enhanced low-dose (1 nM) insulin-mediated tyrosine phosphorylation of the insulin receptor β-subunit (CHO/IR cells) as well as the activation of the downstream kinases protein kinase B (PKB), extracellular-signal-regulated kinases (ERK) 1/2, and glycogensynthasekinase (GSK) 3b. In the presence of insulin, the same IR-downstream signaling and the translocation of GLUT4 were also found in adipocytes treated with the three tanshinones.[51]



52 Tanshinone I

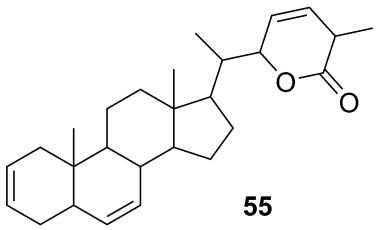


53 Tanshinone IIA



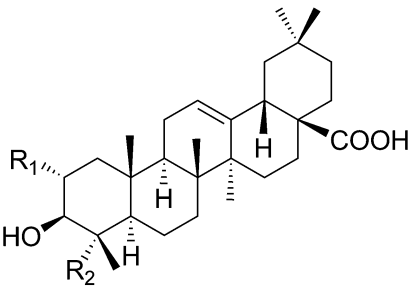
54 15,16-Dihydrotanshinone I

A new steroid, 28-nor-22(*R*)witha-2,6,23-trienolide (**55**), was isolated and identified from the acetone extract of *Elephantopus scaber* L. (Asteraceae), also known as elephant's foot. Oral administration of **55** (2 mg kg^{-1} bw) significantly reduced hyperglycemia in STZ-induced diabetic rats. A maximum reduction of serum glucose level (156.8 mg d^{-1} l^{-1}), about 69% decrease in the blood sugar levels compared to the diabetic control (glibenclamide 0.6 mg kg^{-1}), was observed.[52]

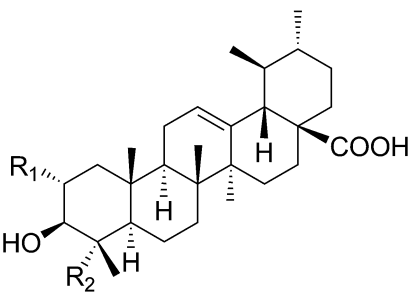


55 28-Nor-22(R)Witha-2,6,23-trienolide

Six pentacyclic triterpenes [oleanolic (**56**), arjunolic (**57**), asiatic (**58**), maslinic (**59**), corosolic (**60**), and 23-hydroxyursolic (**61**) acids] were isolated from the ethyl acetate extract of the leaves of *Lagerstroemia speciosa* (Lythraceae). Their α-glycosidase and α-amylase inhibitory activities were investigated. Among the six compounds, corosolic acid (**60**) showed the best activity against α-glucosidase from *Saccharomyces cerevisiae* (IC_{50} = 3.53 μg mL^{-1}) (acarbose as a positive control showed no inhibition).[53]



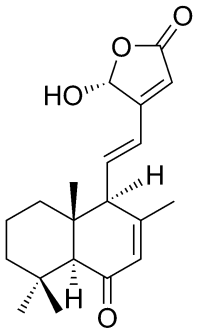
56 Oleanolic acid, R_1 = H, R_2 = CH_3
57 Arjunolic acid, R_1 = OH, R_2 = CH_2OH
58 Maslinic acid, R_1 = OH, R_2 = CH_3



59 Asiatic acid, R_1 = OH, R_2 = CH_2OH
60 Corosolic acid, R_1 = OH, R_2 = CH_3
61 23-Hydroxyursolic acid, R_1 = H, R_2 = CH_2OH

Two new labdane-type diterpenes along with seven known compounds were isolated from rhizomes of *Hedychium spicatum* Ham. Ex Smith (Zingiberaceae) and their intestinal α-glucosidase inhibitory activities were tested. Among the nine isolated compounds, spicatanol (**62**) exhibited the most potent inhibition with an IC_{50} of 34.1 μM.[54]

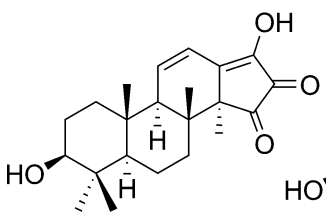
Seven known triterpenes [palbinone (**63**), ursolic acid (**64**), betulinic acid (**65**), β-sitosetol (**66**), daucosterol (**67**),



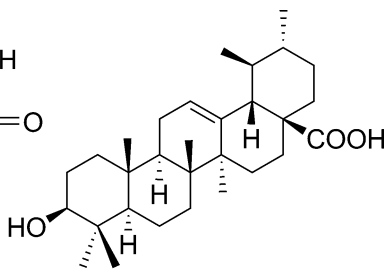
62 Spicatanol

oleanolic acid (**56**), 30-norhederogenin (**68**)] were isolated from Moutan Cortex, the root bark of *Paeonia suffruticosa* Andrew (Paeoniaceae) by bioassay-guided isolation, and their anti-diabetic effects and mechanism were studied. These compounds (10 μM) stimulated AMPK, GSK-3β, and acetyl-coA carboxylase (ACC) phosphorylation as well as increased glucose uptake and enhanced glycogen synthesis (positive control: insulin 100 nM). Among all seven compounds, palbinone (**63**) exhibited the most potent activity by increasing the levels of phospho-AMPK, phospho-ACC, and phospho-GSK-3b in a dose-dependent manner, and triggering glucose uptake and glycogen synthesis in insulin-resistant human HepG2 cells.[55]

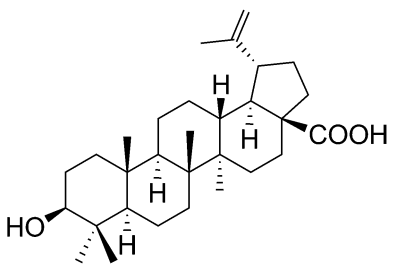
Dihydroxy gymnemic triacetate (**69**) was isolated from *Gymnema sylvestre* (Asclepiadaceae) based on bioassay-guided fractionation and showed a significant anti-diabetic effect by reducing the plasma glucose level more than 50% (20 mg kg^{-1} bw, *p.o.*) in STZ-induced diabetic rats. In addition, it also improved the lipid profile.[56]



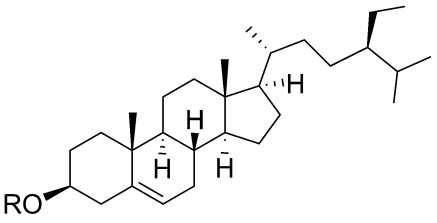
63 Palbinone



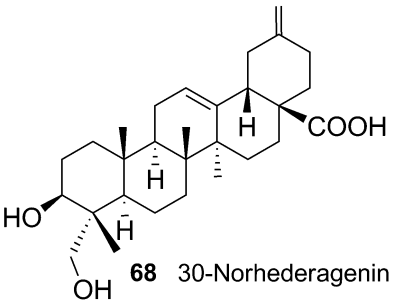
64 Ursolic acid



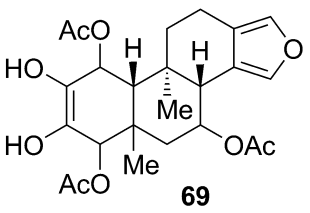
65 Betulinic acid



66 β-Sitosterol, R = H
67 Daucosterol, R = Glc

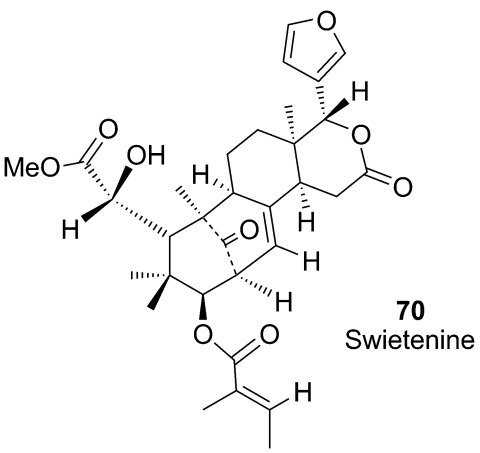


68 30-Norhederagenin



69
Dihydroxygymnemic triacetate

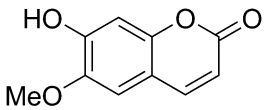
A known tetra-nortriterpenoid, swietenine (**70**), isolated from the seeds of *Swietenia macrophylla* King. (Meliaceae) by bioassay guided fractionation, exhibited significant hypoglycemic activity comparable to that of human insulin in an *in vitro* glucose utilization assay.[57]



70
Swietenine

2.4 Miscellaneous

Scopoletin (7-hydroxy-6-methoxycoumarin) (**71**) was isolated from the leaves of *Aegle marmelos* Linn. Corr (Rutaceae). In levo-thyroxine-treated animals, decreased levels of serum thyroid hormones, glucose, and hepatic G-6-Pase were seen in the scopoletin-administrated group (1 mg kg^{-1}, *p.o.*).[58]



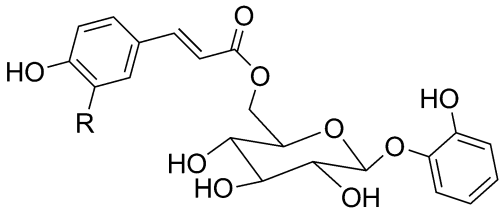
71 Scopoletin

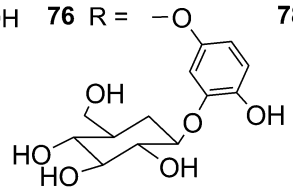
An alcoholic extract of *Morinda citrifolia* L. (Rubiaceae), known as "noni", was associated with a hypoglycemic effect. Two isolated anthraquinones, damnacanthol-3-*O*-β-D-primeveroside (**72**) and lucidin 3-*O*-β-D-primeveroside (**73**), reduced blood glucose level in STZ-induced diabetic mice (100 mg kg^{-1}, *p.o.*), while another anthraquinone, morindone-6-*O*-β-D-primeveroside, (**74**) did not.[59]

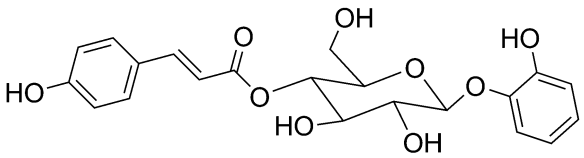
Two phenylpropanoyl esters of catechol glycosides (**75**, **76**) were isolated from the leaves of *Dodecadenia grandiflora* (Lauraceae). Their anti-diabetic activities (100 mg kg^{-1}, *p.o.*) were comparable to metformin (100 mg kg^{-1}).[26] Two related phenolic glycosides [1-[(4′-*O*-(*E*)-*p*-coumaroyl)-β-D-glucopyranosyl]-oxy-2-phenol (**77**) and 1-[(6′-*O*-(*E*)-*p*-coumaroyl)-β-D-glucopyranosyl]-oxy-2-phenol (**78**)] isolated later from *D. grandiflora* leaves exhibited significant *in vitro* G-6-Pase inhibitory activity (63.7 and 66.9%) with IC_{50} values of 88.5 and 81.0 μM, respectively.[38]

4,5-Di-*O*-caffeoylquinic acid (**79**) isolated from *Artemisia dracunculus* L. (Asteraceae) reduced ALR2 activity by 77% at 3.75 μg mL^{-1} (quercitrin,the positive control, reduced ALR2 activity by 54%).[27]

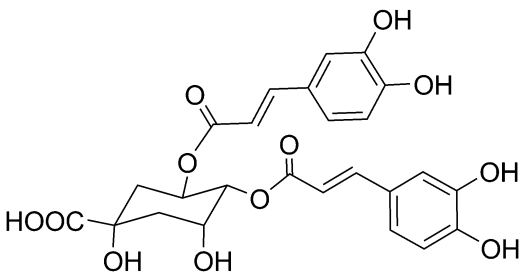
Two stilbenoids, 13-hydroxykompasinol A (**80**) and scirpusin C (**81**), isolated from the seeds of *Syagrus romanzoffiana* (Cham.) Glassman (Arecaceae) showed potent inhibition against α-glucosidase type IV with IC_{50} values of 6.5 and 4.9 μM, respectively (positive control: acarbose, IC_{50}: 40 nM).



75 R = OH **76** R =  **78** R = H

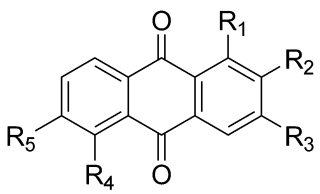


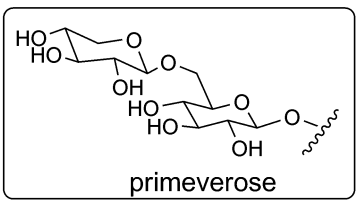
77



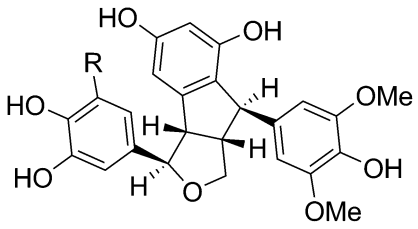
79 4,5-Di-*O*-caffeoylquinic acid

In addition, kompasinol A (**82**) and 3,3′,4,5,5′-pentahydroxy-*trans*-stilbene (**83**) lowered the postprandial blood glucose level (10% and 12% at 10 mg kg^{-1} *p.o.*, respectively).[60]

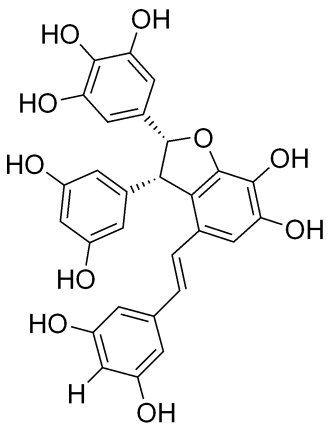




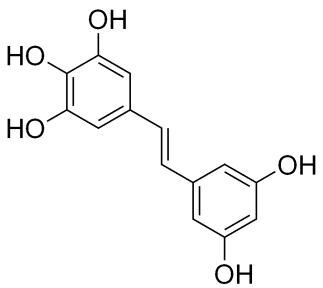
	R_1	R_2	R_3	R_4	R_5
72	OCH_3	CH_2OH	O-primeverose	H	H
73	OH	CH_2OH	O-primeverose	H	H
74	OH	CH_3	H	OH	O-primeverose



80 13-Hydroxykompasinol A
R = OH, *racemate*
82 Kompasinol
R = H, *racemate*

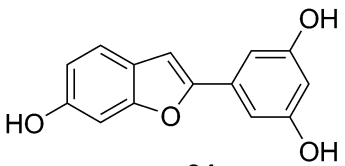


81 Scirpusin C

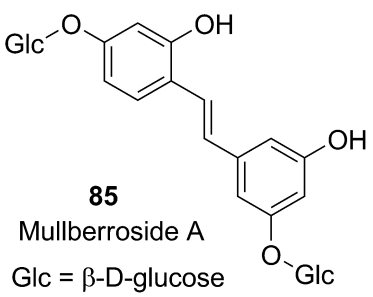


83 3,3',4,5,5'-Pentahydroxy-*trans*-stilbene

Moracin M (**84**) and mullberroside A (**85**) were isolated from the root bark of *Morus alba* L. (Moraceae), and exerted hypoglycemic effects in alloxan-induced diabetic mice. Moracin M (100 mg kg^{-1}, *p.o.*) decreased the fasting blood glucose level (positive control: gliclazide, 50 mg kg^{-1}).[41]



84
Moracin M



85
Mullberroside A
Glc = β-D-glucose

3 Newly discovered anti-diabetic plant extracts

Humans have a long history of using herbal medicines to treat diseases. Approximately 800 plants are used in the folk treatment of diabetes according to ethnobotanical information.[20] To allow easier comparison and evaluation of the potency of the extracts, those anti-diabetic plant extracts newly identified during 2005–2010 have been summarized into six groups based on the positive control used in the experiments (Table 4).

Group 1: Sulfonylureas used as positive control

Sulfonylureas are the most commonly used positive controls in anti-diabetic animal studies. Sulfonylureas can stimulate insulin secretion by binding to the sulfonylurea binding site and closing the ATP-sensitive potassium channel. For plants No. 1 to No. 12 in Table 5, the experiments were conducted in STZ-induced rats and used glibenclamide as a positive control. Among these plant extracts, No. 12 was the most potent, because its anti-diabetic effect was comparable to that of its positive control, glibenclamide 20 mg kg^{-1} bw. This result may reflect the fact that this fraction was further purified from the original crude extract. For plants No. 15 to No. 28, ALX-induced diabetic rats were used with glibenclamide as a positive control. Among these extracts, No. 19 and No. 21 were very potent. Plant extracts No. 31 to No. 38 were tested in STZ-induced rats, but tolbutamide was used as positive control. No. 32 and No. 37 are similar and were the most potent extracts. Finally, extracts No. 39 and 40 were tested in ALX-induced diabetic rats with tolbutamide as a positive control. Extract No. 40 was more potent than No. 39.

Group 2: Biguanides used as positive control

The general mechanism of action of biguanides is to reduce hepatic glucose production (hepatic gluconeogenesis), which is about three times the normal rate in diabetic patients.[107] Several enzymes, such as pyruvate carboxylase, PEP carboxylase; fructose-1,6-biphosphatase and glucose-6-phosphatase are involved in gluconeogenesis.[20] Among all of the extracts using ALX-induced diabetic rats and metformin as positive control, No. 8 from Table 6 was the most potent.

Group 3: α-Glucosidase inhibitors used as positive control

One strategy to control diabetes is to block carbohydrate digestion and absorption. α-Glucosidase, which is involved in the cleavage of glucose from disaccharides and oligosaccharides, is the most important enzyme among those participating in the carbohydrate digestion process.[20] Several natural product

Table 4 The classification of anti-diabetic plant extracts newly identified during 2005–2010

Group	Positive Control
1	Sulfonylureas
2	Biguanides
3	α-glucosidase inhibitors
4	Thiazolidinedione
5	Insulin
6	Positive control unavailable

Table 5 Anti-diabetic plant extracts using sulfonylurea as positive control

No.	Plant Species	Family	Animal Model (administration route)	Extracts Tested	Positive Control (PC)	Ref.
Effects/Constituents/Possible Mechanisms						
1	*Garuga pinnata* Roxb.	Burseraceae	STZ rats (*p.o.*)	Water extract	Glibenclamide (0.25 mg kg^{-1})	61
Increased liver glycogen and serum insulin levels & decreased fasting blood glucose (FBG) and HbA1c						
2	*Orthosiphon stamineus* Benth	Lamiaceae	STZ rats (*p.o.*)	Water extract (containing flavanoid and polyphenols)	Glibenclamide (0.5 mg kg^{-1})	62
In oral glucose tolerance testing (OGTT), extract (0.2–1.0 g kg^{-1}) caused dose-dependent decrease in plasma glucose (PG) concentration; Extract (1.0 g kg^{-1}) and glibenclamide (0.5 mg kg^{-1}) had similar glucose lowering effects; Improved lipid profile.						
3	*Prunella vulgaris* L.	Lamiaceae	STZ rats (*p.o.*)	Aqueous-ethanol extract	Glibenclamide (5 mg kg^{-1})	63
In OGTT, plasma blood glucose was lowered (100 mg kg^{-1}); Plasma insulin level was increased when combined with glibenclamide, indicating increasing insulin sensitivity						
4	Cherukanjuru, *Tragia cannabina* Linn.	Euphorbiaceae	STZ rats (*p.o.*)	Ethanol extract	Glibenclamide (0.5 μg kg^{-1})	64
Reduction of PG was shown; Improvement of lipid profile (250 mg kg^{-1})						
5	*Amaranthus spinosus* L.	Amaranthaceae	STZ rats (*p.o.*)	Methanol extract	Glibenclamide (0.5 mg kg^{-1})	65
Decreased PG level; Also showed anti-hyperlipidemic and spermatogenic effects in STZ-induced diabetic rats (250, 500 mg kg^{-1})						
6	*Ichnocarpus frutescence* (L.) R.Br.	Apocynaceae	Normal rats, glucose-fed rats, STZ rats (*p.o.*)	Methanol and *n*-hexane extracts	Glibenclamide (0.6 mg kg^{-1})	66
Fasting plasma glucose (FPG) was lowed in glucose-fed and STZ-induced diabetic rats; Long term treatment resulted in decreased insulin levels in diabetic rats. (200 mg kg^{-1})						
7	Papatya, *Matricaria chamomilla* L.	Asteraceae	STZ rats (*p.o.*)	Ethanol extract	Glibenclamide (5 mg kg^{-1})	67
Extract reduced postprandial hyperglycemia and oxidative stress (100 mg kg^{-1})						
8	*Begonia malabarica* Lam.	Begoniaceae	STZ rats (*p.o.*)	Methanol extract	Glibenclamide (5 mg kg^{-1})	68
Extract caused reduction in PG level in normal rats as well as diabetic animals; Long term treatment resulted in low FPG and postprandial plasma levels; Serum insulin level was increased (200 mg kg^{-1} bw)						
9	*Diospyros peregrina* Gurke.	Ebenaceae	STZ rats (*p.o.*)	Methanol extract	Glibenclamide (1 mg kg^{-1} bw)	69
Extract (50 and 100 mg kg^{-1} bw) showed dose-dependent hypoglycemic and hypolipidemic activity after long term oral administration to diabetic rats; Fruit contains soluble tannins, flavones, peregrinol, hexacosane, hexacosanol, bsitosterol, betulinic acid, and lupeol						
10	*Genista tenera* (Jacq. ex Murr) O. Kuntze	Fabaceae	STZ rats (*p.o.*)	*n*-Butanol extract	Glibenclamide (0.5 mg kg^{-1} bw)	70
15 day treatment brought blood glucose (BG) level to normal value in diabetic animals (200 mg kg^{-1}, bw); 26 different flavonoid components were characterized in *n*-butanol extract						
11	Olive, *Olea europaea* L.	Oleaceae	STZ rats (*p.o.*)	Ethanol extract	Glibenclamide (0.6 mg kg^{-1})	71
14 day treatment resulted in reduced PG level and improved lipid profile; Also increased insulin level in diabetic rats, but not normal rats						
12	Kalizeeri, *Vernonia anthelmintica* (L.) Willd	Asteraceae	STZ rats (*p.o.*)	Ethanol extract followed by fractionation with silica gel chromatography	Glibenclamide (20 mg kg^{-1})	72
Fraction A2 showed the maximum anti-hyperglycemic effect (100 mg kg^{-1}); Long term treatment with active fraction resulted in reduced PG, HbA1c, and plasma insulin levels and improved lipid profile						
13	*Abutilon indicum* Sweet	Malvaceae	STZ rodents (*p.o.*)	Aqueous extract	Glibenclamide (5 mg kg^{-1} bw)	73
In OGTT, extract (0.5 and 1 g kg^{-1} bw) reduced BG level more quickly than glibenclamide; Further experiments showed that extract can inhibit glucose absorption and insulin secretion						
14	*Caralluma sinaica* L.	Asclepiadaceae	STZ rabbits (*p.o.*)	Ethanol extract	Glibenclamide (5 mg kg^{-1})	74
In OTGG, extract showed PG lowering effects in normal and diabetic animals; After long term experiment, treated diabetic rabbits showed nearly normal glucose levels (100 mg kg^{-1})						

Table 5 (*Contd.*)

No.	Plant Species	Family	Animal Model (administration route)	Extracts Tested	Positive Control (PC)	Ref.
15	Chinese juniper berry, *Juniperus chinensis* L.	Cupressaceae	ALX rats (*p.o.*)	Aqueous and ethanol extracts	Glibenclamide (0.2 mg kg^{-1})	75
Ethanol extract showed antihyperglycemic effect, while aqueous extract showed anti-hyperlipidemia effect (100 mg kg^{-1})						
16	Shoe flower plant, Chinese hibiscus, *Hibiscus rosasinensis*	Malvaceae	ALX rats (*p.o.*)	Ethanol extract	Glibenclamide (10 mg kg^{-1})	76
Hypoglycemic effect (250, 500 mg kg^{-1})						
17	*Butea monosperma*	Papilionaceae	ALX rats (*p.o.*)	Ethanol extract	Glibenclamide (0.4 mg kg^{-1})	77
Single dose (200 mg kg^{-1}) improved glucose tolerance and reduced BG level; 2 wks treatment reduced BG and improved lipid profile						
18	African locust bean, *Parkia biglobosa* (Jacq) Benth	Mimosaceae	ALX rats (*p.o.*)	Water and methanol extracts of fermented seeds	Glibenclamide (0.01 mg per 150 g body weight)	78
Both extracts (6 g kg^{-1}) decreased FPG comparable with glibenclamide; aqueous extract improved lipid profile; seeds contain glycosides and alkaloids						
19	*Trema micrantha* Blume	Ulmaceae	ALX rats (*v.o.*)	Ethanol extract	Glibenclamide (200 mg kg^{-1})	79
Reduced BG level in diabetic rats (250 mg, 1000 mg kg^{-1}), but not normal rats						
20	Walnut leaves, *Juglans regia*	Juglandaceae	ALX rats (*i.p.*)	Ethanol extract	Glibenclamide (0.6 mg kg^{-1})	80
FPG was lowered, insulin level was increased, and Hba1c was decreased (200 mg kg^{-1})						
21	Indian water lily, *Nymphaea stellata*	Nymphaeaceae	ALX rats (*p.o.*)	Ethanol extract	Glibenclamide (2 g kg^{-1})	81
Flower extract (300 mg kg^{-1}) reduced levels of FBG and urine sugar and improved lipid profile; Also showed increase in plasma insulin						
22	*Parinari excelsa*	Chrysobalanaceae	ALX rats (*p.o.*)	Water extract	Glibenclamide (200 μg kg^{-1})	82
In OGTT of normal rats and 7 days treatment of ALX rats, extract exhibited BG lowering effect (300 mg kg^{-1})						
23	*Heinsia crinata*	Rubiaceae	ALX rats (*p.o.*)	Ethanol extract	Glibenclamide (10 mg kg^{-1})	83
Acute and long-term treatment showed hypoglycemic effects in normal and diabetic rats (450–1350 mg kg^{-1})						
24	*Hunteria umbellata* (K. Schum) Hallier	Apocynaceae	ALX-induced, high fructose-and dexamethosone-induced hyperglycemic rats (*p.o.*)	Aqueous extract	Glibencalmide (1 mg kg^{-1})	84
FPG was reduced in treated group; Plasma HbAic and free insulin were decreased in high-fructose-induced hyperglycemic rats; Lipid profile was also improved; Similar results were also seen in dexamethasone group						
25	Dhaman grass, *Tridax procumbens* Linn.	Asteraceae	ALX rats (*p.o.*)	50% Methanol extract	Glibenclamide (10 mg kg^{-1})	85
Reduced BG in diabetic rats, but not normal rats; In OGTT, anti-hyperglycemic effect was shown (250, 500 mg kg^{-1})						
26	*Cecropia pachystachya*	Cecropiaceae	ALX rats (*p.o.*)	Methanol extract	Metformin (120 mg kg^{-1}), Glibenclamide (3 mg kg^{-1})	86
In OGTT, hypoglycemic effect was found (80 mg kg^{-1}); Contains chlorogenic acid and the *C*-glycosylated flavones, orientin and isoorientin						
27	*Leucas cephalotes* (Roth.)Spreng.	Lamiaceae	ALX rats (IDDM) STZ rats (NIDDM) (*p.o.*)	Ethanol extract	Glibenclamide (600 μg kg^{-1}), Metformin (500 mg kg^{-1})	87
Decreased PG, improved lipid profile, and exhibited antioxidant ability (150, 300, 450 mg kg^{-1}); Contains triterpenes, sterols, flavones, glycosides, and alkaloids						
28	*Stachytarpheta angustifoloa*	Verbanaceae	ALX rats (*p.o.*)	Aqueous extract	Chlorpropamide (250 mg kg^{-1}), Glibenclamide (1 mg kg^{-1}), Metformin (500 mg kg^{-1})	88

Table 5 (*Contd.*)

No.	Plant Species	Family	Animal Model (administration route)	Extracts Tested	Positive Control (PC)	Ref.
Reduced BG in normal and diabetic rats (750 mg kg^{-1})						
29	*Kalanchoe crenata*	Crassulaceae	High calories sucrose diet (*p.o.*)	Water–ethanol extract	Glibenclamide (10 mg kg^{-1})	89
Increased insulin sensitivity index (KITT); Lowered FPG; Decreased PG glucose level after long term treatment (200 mg kg^{-1})						
30	*Angelica hirsutiflora* Liu Chao & Chuang	Umbelliferae	High-fat diet-induced diabetic mice (*p.o.*)	Methanol extract	Glibenclamide (10 mg kg^{-1} bw)	90
In vitro HIT-T15 cells, stimulated insulin secretion (150 μg mL^{-1}); *In vivo*, increased insulin level in diabetic mice (10, 30 mg kg^{-1} bw)						
31	Pumpkin, *Cucurbita ficifolia*	Cucurbitaceae	STZ rats (*p.o.*)	70% Methanol extract	Tolbutamide (150 mg kg^{-1})	91
Reduced BG and HbA1c; Increased plasma insulin and total hemoglobin (300 and 600 mg kg^{-1} for 30 days)						
32	*Helicteres isora* Linn.	Sterculiaceae	STZ rat (*p.o.*)	Bark water extract	Tolbutamide (250 mg kg^{-1})	92
Reduced BG level in normal and diabetic rats (100 mg or 200 mg kg^{-1})						
33	*Heliotropium zeylanicum* (BURM.F) LAMK (MEHZ)	Boraginaceae	STZ rats (*p.o.*)	Methanol extract; Chloroform extract	Tolbutamide (10 mg kg^{-1})	93
Reduced BG and thiobarbituric acid reactive substances(TBARS); Increased GSH, SOD, and CAT (150 and 300 mg kg^{-1} day^{-1})						
34	Indian doab, *Cynodon dactylon* (L.) Pers.	Poaceae	STZ rats (*p.o.*)	Aqueous extract	Tolbutamide (250 mg kg^{-1} bw)	94
Lowered FPG as well as BG in glucose tolerance testing (GTT) (500 mg kg^{-1}, the most effective dose, showed similar effect as tolbutamide); Also improved lipid profile						
35	*Helichrysum graveolens*	Asteraceae	STZ rats (*p.o.*)	Aqueous and ethanol extracts	Tolbutamide (100 mg kg^{-1})	95
In OGTT, both extracts (500 mg kg^{-1}) showed hypoglycemic effects slightly better than that of tolbutamide; Total polyphenols and flavonoids were quantified						
36	*Helichrysum plicatum* ssp. *Plicatum*	Asteraceae	STZ rats (*p.o.*)	Aqueous and ethanol extracts	Tolbutamide (100 mg kg^{-1})	96
In OGTT, hypoglycemic effect (500 mg kg^{-1}); total polyphenols and flavonoids were quantified						
37	Cowitch, *Mucuna pruriens*	Fabaceae	STZ rats (*p.o.*)	Water extract	Tolbutamide 250 mg kg^{-1}	97
In OGTT, reduced BG in normal rats; with long term treatment, lowered BG in STZ-treated rats (100 and 200 mg kg^{-1})						
38	Tronadora, *Tecoma stans* (L.) Juss. ex Kunth	Bignoniaceae	*In vitro*, α-glucosidase inhibition *In vivo*, STZ rats (*p.o.*)	Aqueous extract	Acarbose (50 mg kg^{-1}), Tolbutamide (60 mg kg^{-1})	98
In vitro, dose-dependent inhibition of glucose release from starch; *in vivo*, improved lipid profile and decreased the postprandial hyper-glycemic peak, but had no effect on FPG (500 mg kg^{-1})						
39	*Laportea ovalifolia* (Scham and Thonn)	Urticaceae	ALX rat (*p.o.*)	Methanol–methylene chloride (1 : 1) extract	Tolbutamide 80 mg kg^{-1}	99
Decreased fasting serum glucose concentration and improved lipid profile [200 mg kg^{-1} (intragastric gavage)]						
40	*Vitex megapotamica*	Verbenaceae	ALX rats (*p.o.*)	Ethanol extract: hexane, ethyl acetate, butanol, dichloromethane, methanol sub-fractions	Insulin (0.3 IU); Tolbutamide (100 mg kg^{-1})	100
Ethyl acetate sub-fraction resulted in the greatest reduction of PG level (400 and 800 mg kg^{-1})						
41	Black plum, *Eugenia jambolana*	Myrtaceae	ALX rabbit (*p.o.*)	Water extract (more effective); ethanol extract	Tolbutamide (250 mg kg^{-1}, body weight)	101
Fraction from water extract (25 mg kg^{-1}) reduced fasting blood glucose and plasma glucose in glucose tolerance test; increased plasma insulin level; possible mechanism: increase insulin secretion						
42	African potato, *Hypoxis hemerocallidea* Fisch. & C.A. Mey.	Hypoxidaceae	STZ rats (*p.o.*)	Water extract	Chlorpropamide (250 mg kg^{-1} *p.o.*)	102
Reduced blood glucose level (50–800 mg kg^{-1} *p.o.*); also has antinociceptive and anti-inflammatory effects						

Table 5 (*Contd.*)

No.	Plant Species	Family	Animal Model (administration route)	Extracts Tested	Positive Control (PC)	Ref.
43	Red currant, *Rhus chirindensis* (Baker F.)	Anacardiaceae	STZ rats (*p.o.*)	Stem-bark aqueous extract	Chlorpropamide (250 mg kg^{-1})	103
Dose-dependent hypoglycemic effect (50–800 mg kg^{-1}); also had analgesic and anti-inflammatory effects						
44	Tree of heaven, *Ailanthus excelsa* Roxb.	Simaroubaceae	STZ rats (*p.o.*)	Ethanol extract	Glymepiride (5 mg kg^{-1} body weight)	104
No effect in normal rats on fasting BG level; In OGTT, decreased glycemia 90 min after glucose pulse; With long term treatment, hypoglycemic effect was also found (70, 350 mg kg^{-1} bw)						
45	*Cinnamomum parthenoxylon* (Jack) Nees	Lauraceae	STZ rats (*p.o.*)	Polyphenolic oligomer-rich extract	Glymepiride (5 mg kg^{-1} bw)	105
Oral administration of extract (100, 200, and 300 mg kg^{-1} bw) caused body weight loss and decrease in FPG level in normal rats; In OGTT, extract also exerted a decrease in PG; After administration for 14 days in diabetic rats, BG levels were decreased & plasma insulin levels were increased						
46	Karanj, *Pongamia pinnata* (L.) Pierre	Fabacae	ALX mice (*p.o.*)	Petroleum ether extract	Gglyburide (10 mg kg^{-1})	106
Reduced PG in acute and subacute studies (25, 50, 100, 200 and 400 mg kg^{-1})						

extracts were newly discovered to show anti-diabetic activity using α-glucosidase inhibitors as control, and they are summarized in Table 7.

Group 4: Thiazolidinedione (TZD) used as positive control

The thiazolidinedione class of drugs targets peroxisome proliferator-activated receptors (PPARs), which are nuclear receptor transcription factors that induce the proliferation of peroxisomes involved in cell metabolism of sugars, proteins, and lipids.[20] Only a few natural product extracts were tested for their anti-diabetic activity using TZD as control. These extracts are listed in Table 8.

Group 5: Insulin used as positive control

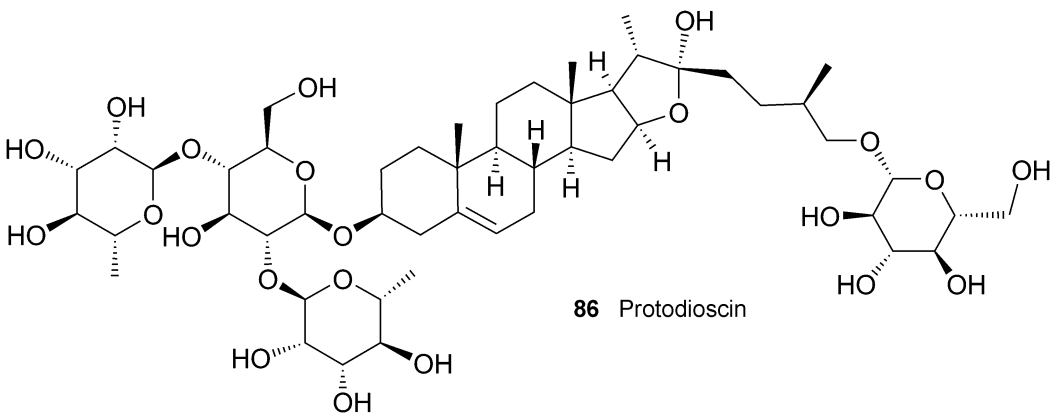
Several new plant extracts are identified as anti-diabetic fractions by using insulin or others as the positive control. They are summarized in Table 9.

Group 6: Positive control not available

These studies did not contain a positive control. Usually plasma glucose level was compared with that of the negative control, a normal animal (Table 10).

4 Recent patents covering new anti-diabetic plant-derived natural products

A novel anti-diabetic compound fraction was discovered from fenugreek seeds.[149] This furostanolic-saponin-rich fraction (>70%) contained approximately 30% protodioscin (**86**) as one of the active principles. Protodioscin is best known as the putative active component of the herbal aphrodisiac plant *Tribulus terrestris*.[150] However, in this patent, the inventor discovered that the described fraction significantly lowered the glucose level in preclinical rat models after two weeks of oral treatment. Further clinical studies in human volunteers indicated that 500 mg is a suitable dosage of the furostanolic-saponin-rich fraction from fenugreek seeds administered once or twice daily alone or in combination with current oral anti-diabetic drugs.



86 Protodioscin

Table 6 Anti-diabetic plant extracts using biguanide as positive control

No.	Plant Species	Family	Animal Model	Extracts Tested	Positive Control (PC)	Ref.
Effects/Constituents/Possible Mechanisms						
1	Siberian ginseng, *Acanthopanax senticosus*	Araliaceae	*Ob*/*ob* mice (*p.o.*)	50% Ethanol extract	Metformin 300 mg kg^{-1}	108
Reduced insulin resistance index by 58% in 400 mg kg^{-1}, *p.o.* mg group (better than metformin at 300 mg) and by 28% in 800 mg kg^{-1}, *p.o.* group						
2	*Salicornia herbacea* L.	Chenopodiaceae	ICR mice (*p.o.*)	50% Ethanol extract	Metformin (250 mg kg^{-1})	109
Prevented the onset of hyperglycemia and hyperlipidemia induced by high-fat diet in a dose-dependent manner (350, 700 mg kg^{-1}); Mechanism may be *via* down-regulation of lipogenesis-related genes (SREBP1a, FAS, GAPT), PEPCK, and glucose 6-phosphatase gene expressions in liver						
3	Chicory, *Cichorium intybus*	Compositae	STZ rats (*p.o.*)	80% Ethanol extract	Metformin (500 mg kg^{-1})	110
In OGTT, hypoglycemic effect was shown (125 mg kg^{-1}); also improved lipid profile; mechanism may be due to decrease in activity of Glc-6-Pase, which lowers hepatic glucose production						
4	*Sclerocarya birrea*	Anacardiaceae	STZ rats (*p.o.*)	Methylene chloride/ methanol extract	Metformin (500 mg kg^{-1})	111
In OGTT, reduced BG level and improved lipid profile; In long term treatment, reduction in blood glucose and increase in insulin level were observed (300 mg kg^{-1})						
5	Nagarmotha, *Cyperus rotundus* L.	Cyperaceae	ALX rats (*p.o.*)	70% Ethanol extract	Metformin (450 mg kg^{-1})	112
Reduced blood glucose level (500 mg kg^{-1} *p.o.* for 7 days), Possible mechanism: strong DPPH radical scavenging action *in vitro*						
6	Umbrella tree, *Musanga cecropioides*	Urticaceae	ALX rats (*p.o.*)	Aqueous and ethanol extracts	Metformin (20 mg kg^{-1})	113
Exerted dose-dependent FPG lowering effect (250, 500, 1000 mg kg^{-1}); ethanol extract had better effect						
7	*Nymphaea stellata* Willd	Nymphaeceae	ALX rats (*p.o.*)	Ethanol extract	Metformin (11.3 mg kg^{-1})	114
Lowered PG level (100, or 200 mg kg^{-1})						
8	*Stachytarpheta angustifoloa*	Verbanaceae	ALX rats (*p.o.*)	Aqueous extract	Metformin (500 mg kg^{-1}), Chlorpropamide (250 mg kg^{-1}), Glibenclamide (1 mg kg^{-1})	88
Reduced BG in normal and diabetic rats (750 mg kg^{-1})						
9	*Cecropia pachystachya*	Cecropiaceae	ALX rats (*p.o.*)	Methanol extract	Metformin (120 mg kg^{-1}), Glibenclamide (3 mg kg^{-1})	86
In OGTT, exhibited hypoglycemic effect (80 mg kg^{-1}); chlorogenic acid and the *C*-glycosylated flavones, orientin and isoorientin were found in the extract						
10	*Leucas cephalotes* (Roth.) Spreng.	Lamiaceae	ALX rats (IDDM), STZ rats (NIDDM) (*p.o.*)	Ethanol extract	Metformin (500 mg kg^{-1}), Glibenclamide (600 μg kg^{-1})	87
Decreased PG, improved lipid profile, and exhibited antioxidant ability (150, 300, 450 mg kg^{-1}); Contains triterpenes, sterols, flavones, glycosides, and alkaloids						
11	*Nigella sativa* L.	Ranunculaceae	*In vitro*: short-circuit current technique; *In vivo*: OGTT in normal rats (*p.o.*)	Aqueous extract	Metformin (300 mg kg^{-1})	115,116
In vitro: inhibited Na-dependent glucose transporter across isolated rat jejunum (0.1 pg mL^{-1} to 100 ng mL^{-1}); *in vivo*: improved glucose tolerance (2 g kg^{-1}); further studies indicated that the extract increases the activity of AKt and AMPK in C2C12 skeletal muscle cell and H4IIE hepatocytes, as well as exhibited agonism of PPAR-γ						
12	Indian kino or Bijasar, *Pterocarpus marsupium* Roxb (Sanskrit: Pitasala)	Leguminosae	ALX rats (*p.o.*)	Butanol subfraction of alcohol extract	Phenformin (300 mg kg^{-1})	117
Hypoglycemic effect and lipid profile improvement (150 mg kg^{-1}); Mechanism may be *via* insulin-like actions						
13	Pi Pa Ye, Folium Eriobotryae, *Eriobotrya japonica* (Thunb.) Lindl.	Rosaceae	ALX rats (*p.o.*)	70% Ethanol extract	Phenformin (100 mg kg^{-1})	118
Hypoglycemic effect (30 g kg^{-1}); Total sesquiterpene fraction (30g kg^{-1}) showed good hypoglycemic effect						

Table 7 Anti-diabetic plant extracts using α-glucosidase inhibitors as positive control

No.	Plant Species	Family	Animal Model	Extracts Tested	Positive Control	Ref.
Effects/Constituents/Possible Mechanisms						
1	Voi, *Cleistocalyx operculatus* (Roxb.) Merr and Perry, *Eugenia operculata* Roxb.	Myrtaceae	*In vitro*, α-glucosidase; *in vivo*, STZ rats (*p.o.*)	Aqueous extract	Acarbose (25 mg kg^{-1}); Guava leaf extract (500 mg kg^{-1})	119
In vitro: inhibited rat-intestinal maltase and sucrase; *in vivo*: reduced BG (500 mg kg^{-1})						
2	*Syzygium cumini* (also called *Eugenia jambolana*) seed kernel	Myrtaceae	*In vitro*, α-glucosidase; *in vivo*, Goto–Kakizaki (GK) rats (*p.o.*)	Acetone extract	Acarbose (*in vitro*); N/A (*in vivo*)	120
In vitro: inhibition by the extract is better than inhibition by acarbose. *in vivo*: inhibited α-glucosidase hydrolysis of maltose (250 mg kg^{-1} bw)						
3	*Rosa damascena* Mill.	Rosaceae	*In vitro*, α-glucosidase; *in vivo*, STZ rats (*p.o.*)	Methanol extract	Acarbose (50 mg kg^{-1})	121
In vitro: inhibited α-glucosidase (2, 5 μg mL^{-1}); *in vivo*: dose-dependent decrease of PG after maltose loading in normal and diabetic rats (100–1000 mg kg^{-1})						
4	Tronadora, *Tecoma stans* (L.) Juss. ex Kunth	Bignoniaceae	*In vitro*, α-glucosidase; *in vivo*, STZ rats (*p.o.*)	Aqueous extract	Aacarbose (50 mg kg^{-1}), Tolbutamide (60 mg kg^{-1})	98
In vitro: dose-dependent inhibition of glucose release from starch; *in vivo*: improved lipid profile and decreased postprandial hyper-glycemic peak, but had no effect on FPG (500 mg kg^{-1})						

Table 8 Anti-diabetic plant extracts using thiazolidinedione as positive control

No.	Plant Species	Family	Animal Model	Extract Tested	Positive Control	Ref.
Effects/Constituents/Possible Mechanisms						
1	Bapanga, *Indigofera mysorensis* Rottl.	Fabaceae	*db/db* mice (*p.o.*)	Ethanol extract	Ttroglitazone (400 mg kg^{-1})	122
Reduced PG, triglyceride, and insulin levels (300 mg kg^{-1} for 10 days); acted as an insulin sensitizer						
2	two variants of *Artemisia princeps* Pampanini, sajabalssuk (SBE) and sajuarissuk (SSE)	Asteraceae	C57BL/KsJ-db/db mice (*p.o.*)	Ethanol extract	Rosiglitazone (0.005 g per 100 g diet)	123
SBE (0.171 g/100 g diet) and SSE (0.154 g/100 g diet) improved glucose and insulin tolerance and lowered HbA1c levels as well as plasma insulin, C-peptide, and glucagon levels; also reversed hepatic glucose-regulating enzyme (GK, G6Pase) activities						
3	*Liriope spicata* var. *prolifera*	Liliaceae	STZ mice (*p.o.*)	Water extract and crude polysaccharide (CP) fraction	Rosiglitazone (2 mg kg^{-1})	124
Both water extract and CP (100, 200 mg kg^{-1}) reduced FPG in diabetic animals, but not normal animals; Also improved lipid profile						

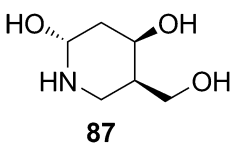
Dubey *et al.* discovered that a hydro-methanolic extraction of at least one out of four plants, *i.e. Salacia roxburghii*, *Salacia oblonga*, *Garcinia indica* and *Lagerstroemia parviflora*, may prevent or manage type-2 diabetes and associated vascular complications.[151] This herbal formulation is prepared by extraction of *S. roxburghii* and *L. parviflora* using a mixed solution of water and methanol (30 : 70) at 70–80 °C, while maintaining the pH of the solution between 7 to 10. When the hydro-methanolic extract of *S. roxburghii* (60 mg kg^{-1}) and *G. indica* (60 mg kg^{-1}) was given to STZ-induced diabetic rats, a significant reduction in blood glucose level was measured, indicating that this herbal extraction can play an anti-diabetic role.

A crude extract containing alkaloids from *Peschiera fuchsiaefolia* (Apocynaceae) within the genus *Tabernaemontana* showed beneficial effects in treating hypercholesterolemic, hypertriglyceridemic, hyperlipidemic and/or dyslipidemic conditions and their related complications linked to metabolic disorders such as obesity and diabetes.[152] This alkaloid extract was used alone or in dual or triple combinations with existing therapeutic approaches inclusive of statins, fibrates, PPAR agonists or dual combination compounds to exert the anti-diabetic effect.

A new compound (2*R*,4*R*)-dihydroxy-5(*R*)-hydroxymethyl piperidine (**87**) was obtained through separation and purification of the total alkaloids from excrements bomboycis from the Chinese medicine Bombyx.[153] Compound **87** showed α-glycosidase inhibiting activity and could be used together with 1-deoxynojirimycin (DNJ) as a medication for treating DM and obesity.

Table 9 Anti-diabetic plant extracts using insulin or others as positive control

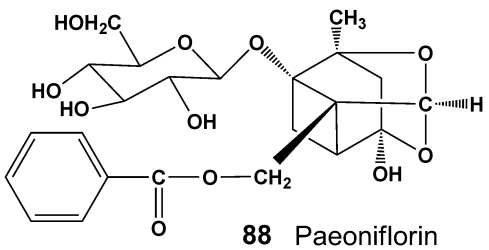
No.	Plant Species	Family	Animal Model	Extracts Tested	Postive Control	Ref.
Effects/Constituents/Possible Mechanisms						
1	Nitobegiku, *Tithonia diversifolia*	Chrysanthemum	*KK-Aγ*-mice (*p.o.*)	80% Ethanol extract	Insulin	125
Decreased BG in an insulin tolerance test (500 mg kg^{-1}, *p.o.*)						
2	Custard apple, *Annona squamosa*	Annonaceae	STZ rats (*p.o.*)	Water extract	Insulin (6 unit kg^{-1})	126
Reduced levels of BG, HbA1c (similar to insulin-treated group), lipids, and lipid peroxidation, but increased plasma insulin and antioxidant enzymes (300 mg kg^{-1}, *p.o.* for 30 days)						
3	*Hemionitis arifolia* (Burm.) Moore	Hemionitidaceae	ALX rats (*p.o.*)	Ethanol extract, subsequently ethyl acetate fraction	Insulin (5 IU kg^{-1}, *i.p.*)	127
Reduced BG level (50 mg kg^{-1})						
4	4 plant extracts were evaluated: *Rhus verniciflua*, *Agrimonia pilosa*, *Sophora japonica*, and *Paeonia suffruticosa*	Anacardiaceae, Rosaceae, Fabaceae, Paeoniaceae	STZ rats (*p.o.*)	80% Ethanol extract	Green tea extract (10 mg kg^{-1})	128
R. verniciflua extract (50 mg kg^{-1}) decreased BG and TBARS; *Sophora japonica* and *Paeonia suffruticosa* extracts also reduced TBARS						
5	*Terminalia superba* Engl. and Diels; *Canarium schweinfurthii* Engl.	Combretaceae; Burseraceae	STZ rats (*p.o.*)	Methanol/methylene chloride (1 : 1) extract	Insulin (3 IU)	129
Both extracts reduced BG level (300 mg kg^{-1})						
6	*Parkinsonia aculeata* L.	Cesalpineaceae	ALX rats (*p.o.*)	Aqueous extract	Insulin NPH (3 U rat^{-1}, *s.c.*)	130
Plasma and urinary glucose levels were lowered, and lipid profile improved (125 or 250 mg kg^{-1})						
7	*Vatairea macrocarpa* (Benth) Ducke	Leguminoseae	STZ rats (*p.o.*)	70% Ethanol extract	Insulin NPH (3 U rat^{-1})	131
In 22 day treatment of the extract, reduced PG and urinary glucose in diabetic rats, but had no effect in normal rats with 22 day treatment; also HOMA-R index (homeostasis model of insulin resistance) was lowered						
8	1. *Schkuhria pinnata* (Lam.) 2. *Euclea undulata* var. myrtina Thunb 3. *Elaeodendron transvaalense* (Burtt Davy)	Asteraceae Ebenaceae Celastraceae	*In vitro* assays: α-glucosidase and α-amylase inhibition in C2C12 myocytes, 3T3-L1 preadipocytes and Chang liver cells	Acetone/ethanol extract	Insulin (1 μM)	132
All three extracts showed *in vitro* hypoglycemic activity						



87

Polysaccharides from the Tibetan medicine Huidouba were reported to prevent or treat DM. Huidouba polysaccharides were obtained by preparations mainly involving soaking Huidouba in water, extracting using 80% ethanol, and vacuum-drying.[154]

The total glucoside fraction from the leaves of *Paeonia lactiflora* or *P. obovata* includes paeoniflorin (**88**), hydroxypaeoniflorin, benzoyl paeoniflorin, and benzoyl-hydroxypaeoniflorin. The total glucoside extraction obtained by water or ethanol extraction can be processed into formulae for treating DM.[155]



88 Paeoniflorin

The ethyl acetate extract of the leaves of *Diospyros kaki* had the following effects, lowering blood pressure, reducing blood lipid, and decreasing blood glucose. The extract could be used for preventing and treating hyperglycemia, DM, and metabolic syndrome.[156]

Euonymus alatus is a deciduous shrub native to eastern Asia, central and northern China, Japan, and Korea. It is a popular ornamental plant in gardens and parks due to its bright pink or orange fruit and attractive fall color. It was reported that the

Table 10 Anti-diabetic plant extracts without positive control

No.	Plant Species	Family	Animal Model	Extracts Tested	Positive Control	Ref.
Effects/Constituents/Possible Mechanisms						
1	African black tea, *Camellia sinensis*	Theaceae	male KK-A^{Y}/TaJcl mice (*p.o.*)	Hot water extract	NA	133
50 mg kg^{-1}, *p.o.* for 4 weeks had significant glucose-lowering effect; suppressed the elevation of BG on oral glucose tolerance (short-term treatment)						
2	Shweta musali (in India), Sutaid musk (in Pakistan), *Asparagus adscendens*	Liliacea	*In vitro* clonal pancreatic β cell line, BRIN-BD11; 3T3-L1 adipocytes	Water extract	NA	134
Increased glucose-dependent insulinotropic action by19–248%; increased glucose uptake in 3T3-L1 adipocytes by81%						
3	*Cinnamomi cassiae*	Lauraceae	C57BIKsj *db/db* mice (*p.o.*)	Water extract (containing 5% cinnamonaldehyde)	NA	135
Decreased BG level in dose-dependent manner (200 mg kg^{-1} group compared with the control); increased serum insulin level; improved lipid profile; decreased some intestinal α-glycosidase activity						
4	4 plants were evaluated: Curry tree (*Murraya koenigii*), Peppermint (*Mentha piperitae*), Holy basil (*Ocimum sanctum*), Bael (*Aegle marmelos*)	Rutaceae, Lamiaceae, Lamiaceae, Rutaceae	STZ rats (*p.o.*)	Ethanol extract	NA	136
M.koenigi I (150 mg kg^{-1}), *O. sanctum*(200 mg kg^{-1}) *A. marmelos* (200 mg kg^{-1}), and *M. piperitae* (300 mg kg^{-1}) decreased levels of BG, HbA1c, and urea, but increased levels of glycogen, hemoglobin, insulin, and C-peptide, also improved glucose tolerance; *M. koenigi I*, *O. sanctum*, and *A. marmelos* decreased activity of carbohydrate-metabolizing enzymes, including hexokinase, glucose-6-phosphate dehydrogenase, and glycogen synthase						
5	*Coix lacryma-jobi*, *Aegle marmelos*, *Artocarpus heterophyllus*, *Vangueria madagascariensis*, *Azadirachta indica*, *Eriobotrya japonica*, and *Syzigium cumini*	Poaceae, Rutaceae, Moraceae, Rubiaceae, Meliaceae, Rosaceae, Myrtaceae	*In vitro*: α-amylase inhibition	Water extract	NA	137
Only *Artocarpus heterophyllus* showed competitive inhibition of α-amylase						
6	*Phyllanthus amarus.* *P. amarus* Schum. and Thonn	Euphorbiaceae	Normal swiss mice (*p.o.*)	Aqueous extract	NA	138
Decreased FPG in a dose-dependent manner (150, 300, 600 mg kg^{-1})						
7	*Plantago ovata* (Psyllium)	Plantaginaceae	STZ rats (*p.o.*)	Aqueous extract	NA	139
Inhibited intestinal glucose absorption and enhanced motility						
8	Lemon grass, *Cymbopogon citratus* Stapf.	Graminaceae	Normal Wistar rats (*p.o.*)	Aqueous extract	NA	140
Lowered FPG (125–500 mg kg^{-1}); improved lipid profile						
9	*Dryopteris fragrans* and *Filix maris*	Aspidiaceae	STZ rats (*p.o.*)	Aqueous extract	NA	141
Improved blood glucose and insulin resistance						
10	*Siraitia grosvenori* Swingle		Goto-Kakizaki (GK) rats	Aqueous extract	NA	142
Improved insulin response and reduced plasma glucose (4 g kg^{-1})						
11	Feremomi, *Clerodendrum capitatum* (Willd) Schumach et. Thonn. var capitatum	Verbenaceae	Normal rats (*p.o.*)	Aqueous extract	NA	143
Lowered FPG in a dose-dependent manner (100, 400, 800 mg kg^{-1}); improved lipid profile						
12	*Posidonia oceanica* (L) Delile	Posidoniaceae	ALX rats (*p.o.*)	Aqueous ethanol extract	NA	144
Oral administration for 15 days (50, 150, and 250 mg kg^{-1} bw) caused a dose-dependent decrease in BG in diabetic animals						
13	Guava, *Psidium guajava* Linn.	Myrtaceae	STZ rats (*p.o.*)	Aqueous and ethanol extracts	NA	145
Long-term treatment (400 mg kg^{-1} bw) reduced BG level, increased insulin level, and promoted hexokinase and glucose-6-phosphate dehydrogenase activities in diabetic rats						

Table 10 (*Contd.*)

No.	Plant Species	Family	Animal Model	Extracts Tested	Positive Control	Ref.
14	Pomegranate, *Punica granatum* Linn.	Punicaceae	STZ rats (*p.o.*)	Aqueous extract	NA	146
Decreased PG and improved lipid profile (250, 500 mg kg^{-1})						
15	*Terminalia belerica*	Combretaceae	ALX rats (*p.o.*)	Methanol extract	NA	147
Reduced PG in diabetic rats and possessed anti-oxidant ability						
16	*Ulva rigida*	Ulvaceae	STZ rats (*p.o.*)	Ethanol extract	NA	148
Polyphenol-rich extract reduced PG and provided protection from genotoxicity						

Table 11 A summary of newly identified compounds during 2005–2010 with anti-diabetic activity

Structure	Compound No.	Mechanism	Animal Model
Lignans	**1**,**2**	PTP1B inhibitor	
	3		STZ rat (glibenclamide)
	4,**5**		STZ rat (metformin)
Flavonoids	**6**,**7**,**8**	ALR2 inhibitor, PEPCK	
	9,**10**		Normal rat (glibenclamide)
	11,**12**	PPAR	KK-Ay mice
	13,**14**,**15**	GLUT transporter	
	16	Insulinotropic effect	
	17	Insulinotropic effect	
	18,**19**	PTP1B inhibitor	STZ rat
	20,**21**	PPAR	
	22,**23**	α-glucosidase	
	24,**25**	AMPK, G-6-Pase	
	26	Insulinotropic, glucose uptake	
	27,**28**,**29**,**30**,**31**	AMPK, PTP1B inhibition	
	32		ALX mice
	33	Enhance insulin secretion, decrease plasma insulin	
Terpenoids	**34**,**35**,**36**,**37**,**38**		Db/db mice, STZ rat (metformain)
	39,**40**,**41**,**42**,**43**	GLUT4, AMPK	
	44		ALX mice (gliclazide)
	45		STZ rat
	46,**47**	Adiponectin secretion	
	48	G-6-Pase activity and insulin level	
	49,**50**		STZ rat (glibenclamide)
	51		STZ rat
	52,**53**,**54**	Insulin sensitizing, GLUT4	
	55		STZ rat (glibenclamide)
	56,**57**,**58**,**59**,**60**,**61**	α-Glucosidase	
	62	α-Glucosidase	
	63,**64**,**65**,**66**,**67**,**68**	AMPK,GSK3b,ACC	
	69		STZ rat
	70	Insulin glucose utility assay	
Miscellaneous	**71**	G-6-Pase, thyroid	
	72,**73**		STZ mice
	75,**76**		metformin
	77,**78**	G-6-Pase	
	79	ALR2	
	80,**81**	α-Glucosidase	
	82,**83**	Postprandial blood glucose	
	84,**85**		ALX mice (gliclazide)

ethyl acetate extraction of *E. alatus* showed excellent anti-diabetic activity.[157] The method for preparing the anti-diabetic extraction powder derived from *E. alatus* involves the following steps: separating leaves, stems, or roots of *E. alatus*; extracting the parts with ethanol, and evaporating ethanol to obtain the extractions; adding distilled water to the extractions, fractionating the mixtures with ether, concentrating the water layer fractions, fractionating with ethyl acetate to obtain the organic solvent layers, and freeze-drying the organic solvent layers to obtain the desired extraction powders.[157]

5 Conclusion

In this review, recent discoveries of pure anti-diabetic compounds from 2005–2010 were categorized by their chemical structures. Because the structures of these natural products are

quite different from those of the currently used anti-diabetic drugs, their mechanisms of action are also likely to be different, which could prove useful for increased clinical effectiveness. Over 100 anti-diabetic plant extracts and fractions, many of which have been used and marketed as dietary supplements, studied during 2005–2010 were also tabulated based on the experimental design. The animal models and commonly used positive controls in diabetic research were summarized for easier interpretation of the experimental data. These descriptions highlight the urgent need for bioactivity-directed fraction and isolation to identify the active constituents as possible leads to develop new drugs for single use or combination therapy for treating DM. Recent patents covering newly isolated fractions or compounds with anti-diabetic activity were also discussed.

Overall, traditional herbal medicine has been used to treat DM for decades. As scientific technologies have been developed and the pathological pathways of DM discovered, specific research can be done to better interpret the traditional usage of herbal medicines, identify the active constitutions for the anti-diabetic activity, and explore the possible mechanisms of action. These studies will significantly facilitate research to discover novel anti-diabetic drugs from novel natural product leads by using medicinal chemistry approaches and to explore their mechanistic functions through pharmacological studies.

6 Appendix

Tabular summary of newly identified compounds during 2005–2010 with anti-diabetic activity (Table 11).

7 Acknowledgements

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8 References

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