

Antidiabetic Agents from Medicinal Plants

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Abstract: Currently available therapeutic options for non-insulin-dependent diabetes mellitus, such as dietary modification, oral hypoglycemics, and insulin, have limitations of their own. Many natural products and herbal medicines have been recommended for the treatment of diabetes. The present paper reviews medicinal plants that have shown experimental or clinical antidiabetic activity and that have been used in traditional systems of medicine; the review also covers natural products (active natural components and crude extracts) isolated from the medicinal plants and reported during 2001 to 2005. Many kinds of natural products, such as terpenoids, alkaloids, flavonoids, phenolics, and some others, have shown antidiabetic potential. Particularly, schulzeines A, B, and C, radicamines A and B, 2,5-imino-1,2,5-trideoxy-L-glucitol, β -homofuconojirimycin, myrciacitrin IV, dehydrotrametenolic acid, corosolic acid (GlucosolTM), 4-(α -rhamnopyranosyl)ellagic acid, and 1,2,3,4,6-pentagalloylglucose have shown significant antidiabetic activities. Among active medicinal herbs, *Momordica charantia* L. (Cucurbitaceae), *Pterocarpus marsupium* Roxb. (Leguminosae), and *Trigonella foenum graecum* L. (Leguminosae) have been reported as beneficial for treatment of type 2 diabetes.

Keywords: Diabetes, alkaloids, terpenes, flavonoids, phenolics, α -glucosidase, aldose, inhibitor.

INTRODUCTION

Diabetes mellitus is a metabolic disorder of the endocrine system. The disease is found in all parts of the world and is rapidly increasing worldwide. People suffering from diabetes cannot produce or properly use insulin, so they have high blood glucose. Type 2 diabetes, non-insulin-dependent diabetes mellitus, in which the body does not produce enough insulin or properly use it, is the most common form of the disease, accounting for 90%–95% of cases. Type 2 is nearing epidemic proportions as a result of an increased number of elderly people and a greater prevalence of obesity and sedentary lifestyle. The cause of diabetes is a mystery, although both genetic and environmental factors such as obesity and lack of exercise appear to play a role [1]. According to World Health Organization projections, the diabetic population is likely to increase to 300 million or more by the year 2025 [2].

Currently available therapies for diabetes include insulin and various oral antidiabetic agents such as sulfonylureas, biguanides, α -glucosidase inhibitors, and glinides, which are used as monotherapy or in combination to achieve better glycemic regulation. Many of these oral antidiabetic agents have a number of serious adverse effects; thus, managing diabetes without any side effects is still a challenge [3]. Therefore, the search for more effective and safer hypoglycemic agents has continued to be an important area of investigation. The pharmacological agents with the greatest effect on postprandial hyperglycemia include insulin lispro, amylin analogues, and α -glucosidase inhibitors. In hyperglycemia associated with diabetes, the use of aldose reductase inhibitors has been reported for the treatment of

diabetic complications [4]. Aldose reductase as a key enzyme in the polyol pathway has been reported to catalyze the reduction of glucose to sorbitol. Sorbitol does not readily diffuse across cell membranes, and the intracellular accumulation of sorbitol has been implicated in the chronic complications of diabetes such as peripheral neuropathy, retinopathy, and cataracts [5]. A recent study reported that aldose reductase may be involved with another signal transduction pathway in the pathogenesis of diabetic nephropathy [6].

The hypoglycemic effect of several plants used as antidiabetic remedies has been confirmed, and the mechanisms of hypoglycemic activity of these plants are being studied. Recently, two reviews of the chemistry of medicinal plants with antidiabetic potential have been published by Li [1] and Shapiro [7]. New natural products reported from 2001 to 2004 with antidiabetic potential that have potent medicinal activities with diverse structures are reviewed here. This review also focuses on the role of traditional therapeutics and natural medicines from traditional medicinal plants for diabetes. Traditional medicines from readily available medicinal plants offer great potential for the discovery of new antidiabetic drugs.

PLANTS WITH ANTIDIABETIC POTENTIAL

Many traditional plant treatments for diabetes exist, a hidden wealth of potentially useful natural products for diabetes control. Nonetheless, few traditional antidiabetic plants have received scientific or medical scrutiny, despite recommendations by the World Health Organization in 1980 that this should be undertaken. Medicinal plants that are the most effective and the most commonly studied in relation to diabetes and its complications are: *Gentiana olivieri griseb* (Gentianaceae), *Bauhinia forficata koeingii* (Leguminosae), *Eugenia jambolana* L. (Myrtaceae), *Lactuca indica* L.

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(Compositae), *Mucuna pruriens* Bak. (Leguminosae), *Tinospora cordifolia* W. (Menispermaceae), *Momordica charantia* L. (Cucurbitaceae), *Aporosa lindleyana* Baill (Euphorbiaceae), *Cogent db*, *Myrtus communis* L. (Myrtaceae), *Rhizoma Polygonati Odorati* (Liliaceae), and *Terminalia pallida* Brand. (Combretaceae). Most of these plants have shown varying degrees of hypoglycemic and anti-hyperglycemic activity. Among active medicinal herbs, *Momordica charantia* L. (Cucurbitaceae), *Pterocarpus marsupium* Roxb. (Leguminosae), and *Trigonella foenum graecum* L. (Leguminosae) have been reported to be beneficial for treatment of type 2 diabetes.

The following traditional medicinal plants or natural products are commonly used in the control or/and treatment of diabetes and its complications.

Aporosa lindleyana Baill

The aqueous and alcoholic extracts (100 mg/kg) of *Aporosa lindleyana* Baill (Euphorbiaceae) reduced blood glucose in normal rats from 80.49/2.7 to 69.89/2.0 mg% and from 82.69/1.9 to 70.89/3.2 mg%, respectively, 3 h after oral administration of the extract (PB/0.001), and also significantly lowered blood glucose level in alloxan-induced diabetic rats from 3069/3.37 to 1609/2.46 and 3289/4.15 to 1529/3.86 mg%, respectively, 3 h after oral administration of the extract (PB/0.001). The antihyperglycemic activity of *Aporosa lindleyana* Baill (Euphorbiaceae) was compared with that of tolbutamide, an oral hypoglycemic agent [8].

Cogent db

Oral administration of 0.15, 0.30, or 0.45 g/kg body wt. of the aqueous solution of *Cogent db* [9 herbs: *Azadirachta indica* A. juss (Meliaceae), *Phyllanthus emblica* L. (Euphorbiaceae), *Terminalia bellerica* Roxb. (Combretaceae), *Terminalia chebula* Retz. (Combretaceae), *Tribulus terrestris* L. (Zygophyllaceae), *Trigonella foenum graecum* L. (Leguminosae), *Cucuma longa* L. (Zingiberaceae), *Syzygium cumini* L. (Myrtaceae), *Rotula aquatica* Lour. (Lythraceae)] for 40 days exhibited a significant reduction in blood glucose and glycosylated hemoglobin and increased plasma insulin and total hemoglobin along with having antihyperlipidemic effects in diabetic rats. The effective dose was found to be 0.45g/kg body weight (bw). The antidiabetic effect of *Cogent db* was greater than that observed with glibenclamide [9].

Momordica Charantia and Eugenia Jambolana

Plasma glucose concentrations in streptozotocin (STZ)-diabetic mice were reduced by the administration of extracts of *Momordica charantia* (MC) L. (Cucurbitaceae) (200 mg/kg), *Eugenia jambolana* (EJ) L. (Myrtaceae) (200 mg/kg), *Tinospora cordifolia* (TC) W. (Menispermaceae) (200 mg/kg), and *Mucuna pruriens* (MP) Bak. (Leguminosae) (200 mg/kg) by 24.4, 20.84, 7.45, and 9.07%, respectively ($P < 0.005$ for MC, EJ, and MP; $P < 0.05$ for TC). Urine volume was significantly higher ($P < 0.005$) in diabetic controls, and MC, EJ, MP and TC treatment prevented polyuria ($P < 0.001$, 0.0001, 0.01, and 0.001,

respectively). After 10 days of STZ administration, urinary albumin levels (UAE) were over 6-fold higher in diabetic controls as compared to normal controls. Treatment with MC, EJ, MP, and TC significantly prevented the rise in UAE levels from days 0 to 40 in comparison to diabetic controls ($P < 0.0001$, 0.0001, 0.05, and 0.05, respectively). Renal hypertrophy was significantly higher in diabetic controls as compared to non-diabetic controls. MC and EJ partially but significantly ($P < 0.05$) prevented renal hypertrophy as compared to diabetic controls [10a].

Myrtus Communis L. (Myrtaceae)

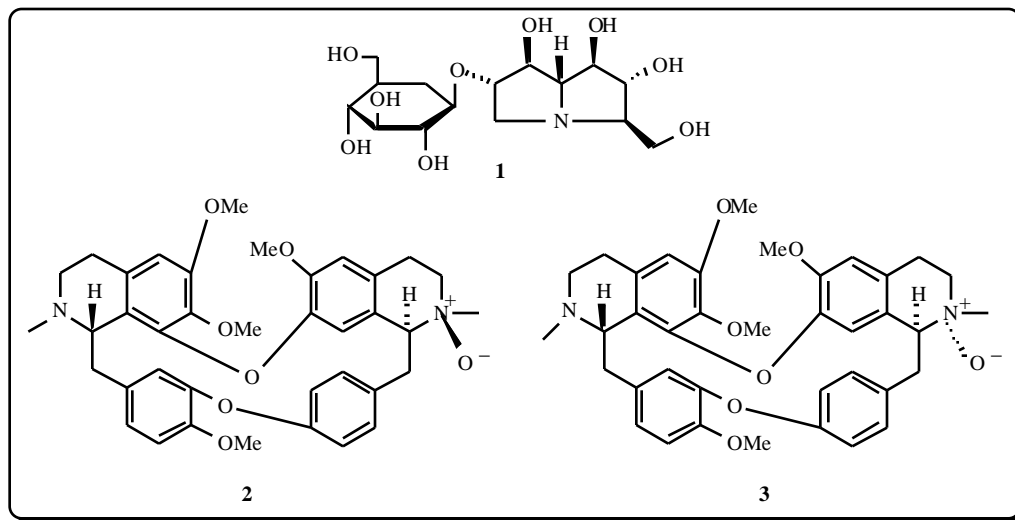
Myrtus communis L. (Myrtaceae) leaves and the volatile oil (Myrtii Oleum; MO) obtained from the leaves are used to lower the blood glucose level in type-2 diabetic patients in Turkish folk medicine. MO significantly lowered blood glucose by 51% in alloxan-diabetic rabbits by 4 h through the following days at a dose of 50 mg/kg ($P < 0.001$). The hypoglycemic dose (50 mg/kg) was also determined by performing the oral glucose tolerance test in normal rabbits. The hypoglycemic effect of the MO was 21% higher in rabbits, which received the glucose load orally, when compared with the control group. However, MO did not affect serum insulin concentrations in normal and alloxan-diabetic rabbits but reduced the serum triglyceride concentrations by 14% in alloxan-diabetic rabbits. The above observations show that MO exerts hypoglycemic as well as mild hypotriglyceridemic activity in diabetic animals [10b].

Pterocarpus Marsupium and Trigonella Foenum-Graecum

The hypoglycemic effect of the aqueous (Aq) extract of the bark of *Pterocarpus marsupium* (PM) Roxb. (Fabaceae) and alcoholic (Alc) extract of seeds of *Trigonella foenum-graecum* L. (Leguminosae) and leaves of *Ocimum sanctum* L. (Lamiaceae) was investigated in both normal and alloxan-induced diabetic rats. The Aq extract of PM (1 g/kg PO) significantly ($P < 0.001$) reduced blood sugar levels from 72.32±5.62 to 61.35±1.2 mg% 2 h after oral administration of the extract and also significantly lowered blood glucose in alloxan-diabetic rats from 202.91±5.44 to 85.22±11.28 mg% 21 days after daily oral administration of the extract ($P < 0.001$). Similarly, reduction was seen with Alc extract of FG (from 74.33±4.77 to 60.56±1.9 in normal rats and from 201.25±7.69 to 121.25±6.25 in diabetic rats) ($P < 0.001$) and OS (from 204.48±11.0 to 131.43±7.86 in normal rats and from 73.54±3.7 to 61.44±2.3 in diabetic rats) ($P < 0.001$). In addition, the extract also showed a favorable effect on glucose disposition in glucose fed hyperglycemic rats [11].

Rhizoma Polygonati Odorati (RPO)

Water soluble extract of *Rhizoma Polygonati Odorati* (RPO) (Liliaceae) may influence glucose or carbohydrate metabolism of diabetic animals in many ways, including inhibiting the activity of α -glucosidase in the digestive canal and improving glucose and triglyceride metabolism. In diabetic rats complicated with hyperlipemia, RPO prevented and reduced both hyperglycemia and hypertriglyceridemia [12].



Terminalia Pallida Brandis

The oral administration of an ethanolic extract of *Terminalia pallida* Brandis (Combretaceae) at a dosage of 0.5g/kg body weight resulted in significant antihyperglycemic activity in alloxan-diabetic rats; in normal rats no hyperglycemic activity was observed [13].

Tinospora Cordifolia

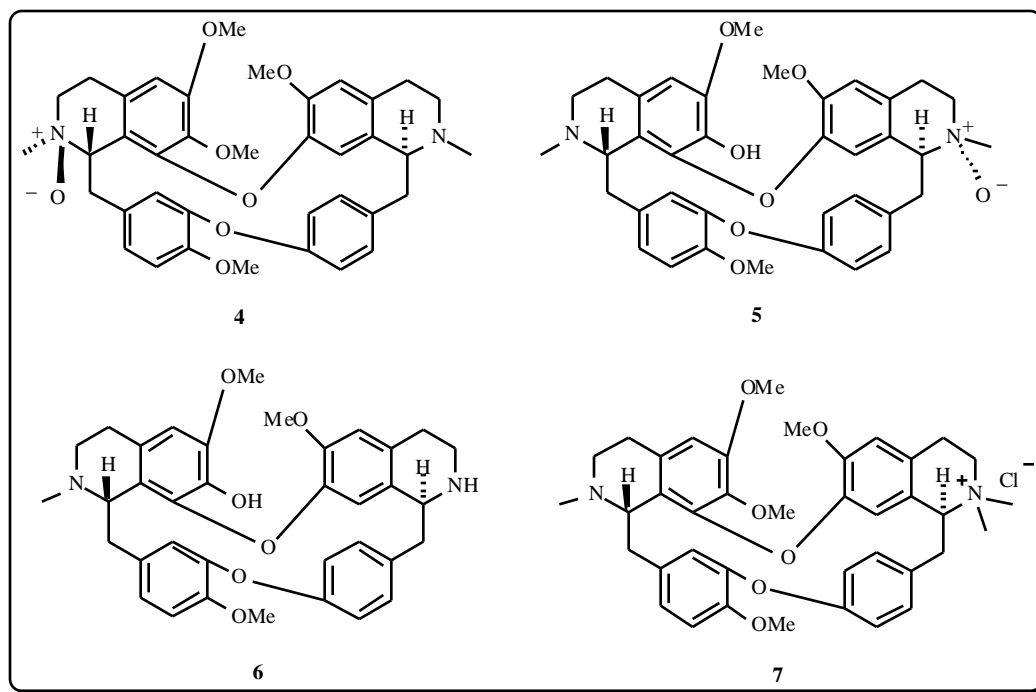
Administration of the extract of *Tinospora cordifolia* W. (Menispermaceae) roots (2.5 and 5.0 g/kg bw) for 6 weeks resulted in a significant reduction in serum and tissue cholesterol, phospholipids, and free fatty acids in alloxan-diabetic rats. The root extract at a dose of 5.0 g/kg bw showed highest hypolipidemic effect. The effect of *Tinospora cordifolia* W. (Menispermaceae) roots at 2.5 and 5.0 g/kg bw was better than that of glibenclamide [14].

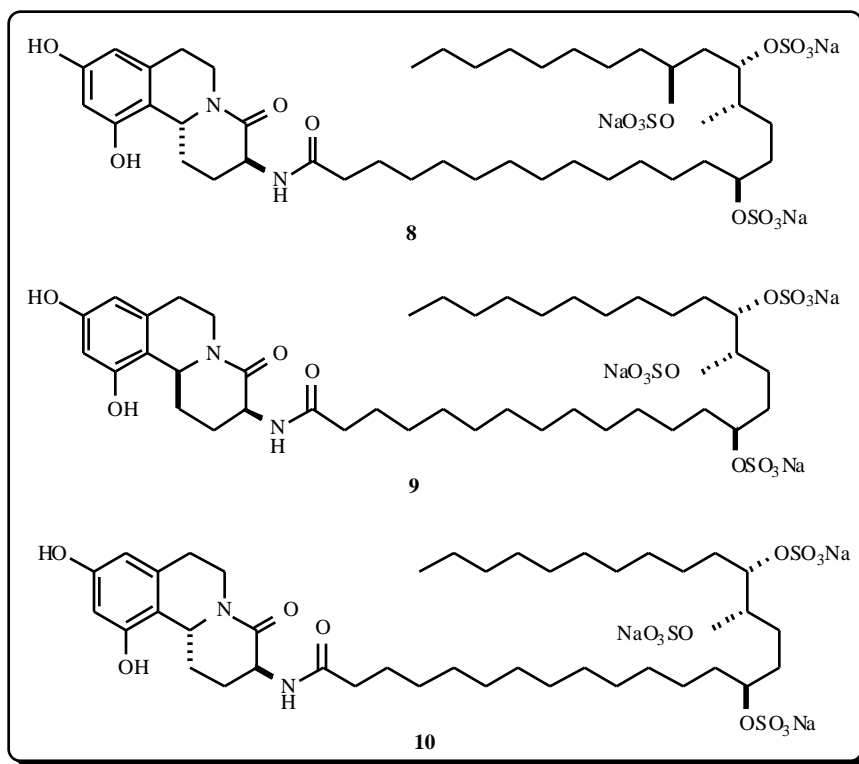
Below, new natural products with antidiabetic potential are categorized according to their chemical structures; those are alkaloids, terpenes, flavonoids, and phenolics as secondary metabolites along with IC₅₀ values. The role of traditional therapeutics of natural medicines is discussed.

ALKALOIDS

Casuarine 6-O-β-glucoside (1) isolated from the MeOH extract of the bark of *Syzygium malaccense* L. Merrill & L.M. Perry (Myrtaceae), inhibited β-glucosidase with IC₅₀ value of 5.7 μg/mL [15].

Six bis-benzylisoquinoline-type alkaloids, tetrandrine 2'-N-oxide (2), tetrandrine 2'-N-oxide (3), tetrandrine 2-N-oxide (4), fangchinoline 2'-N-oxide (5), 2'-N-norfangchinoline (6), and 2'-N-methyltetrandrinium chloride (7) were isolated from *Stephania tetrandra* S. Moore



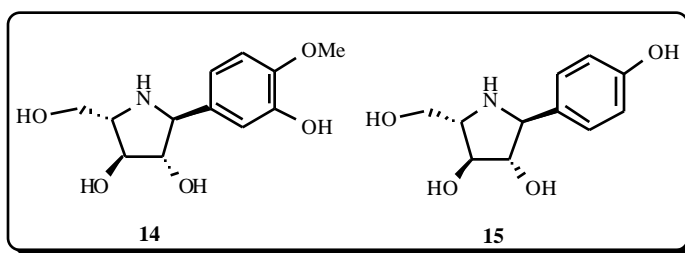
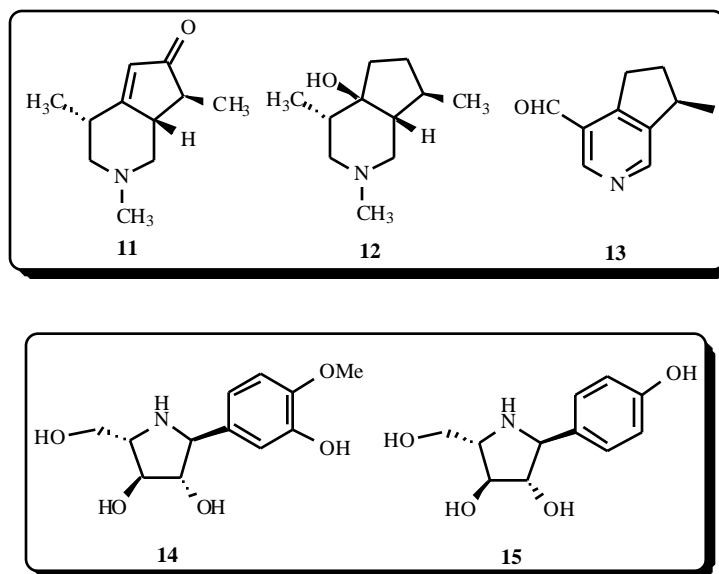


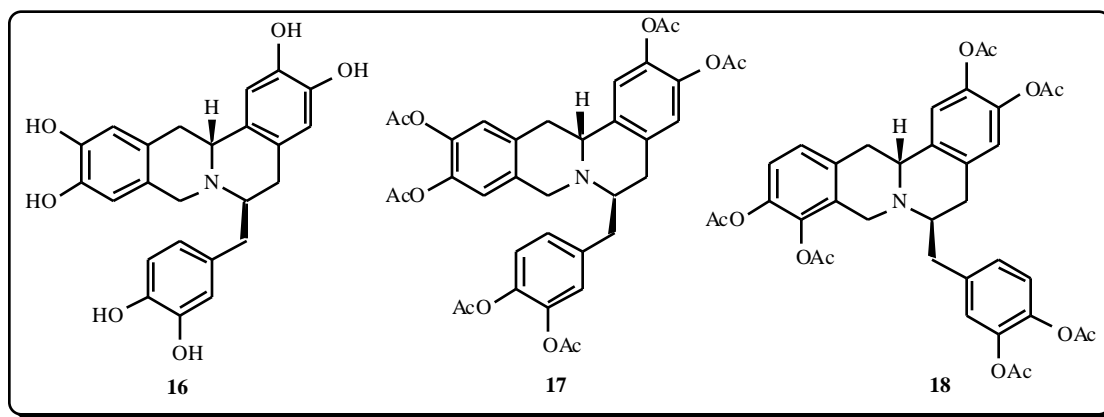
(Menispermaceae). Anti-hyperglycemic effects of compounds (2)–(7), cycleanine, cyclanoline chloride, and stephananthrine were compared with those of fangchinoline and tetrandrine in the STZ-diabetic mice. Fangchinoline, tetrandrine 2'-N-oxide (2), tetrandrine 2'-N-oxide (3), tetrandrine 2-N-oxide (4), fangchinoline 2'-N-oxide (5), and 2'-N-norfangchinoline (6) (1 mg/kg) significantly decreased the high blood glucose to near 50% of original levels in the diabetic mice. However, tetrandrine, 2'-N-methyltetrandrinium chloride (7), and cycleanorine (1 mg/kg) did not affect the high blood glucose level. Cycleanine (1 mg/kg), which has head-to-tail ether bonds, also had a significant antihyperglycemic effect. However, cyclanoline chloride and stephananthrine (1 mg/kg), which

do not have a bis-benzylisopiquinoline structure, did not affect the blood glucose level [16].

Three new isoquinoline alkaloids, schulzeines A (8), B (9), and C (10), were isolated from the marine sponge *Penares schulzei* [17]. Schulzeines A–C encompass two amino acids and a C₂₈ fatty acid, the last of which was sulfated. Schulzeines A–C inhibit α -glucosidase with IC₅₀ values of 48–170 nM [17].

Three compounds, tecomine (11), 5-hydroxyskitanthine (12), and boschniakine (13), were isolated from the *Tecoma stans* (L.) Juss. ex Kunth (Bignoniaceae) harvested in Egypt. Tecomine (11) exerted a potent stimulating effect on the basal glucose uptake rate in rat adipocytes from

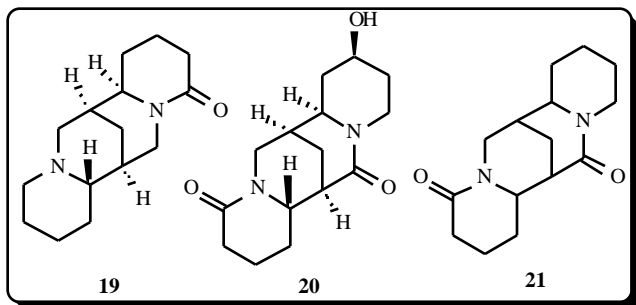




normoglycemic rats, with an EC_{50} value of 6.79×10^{-9} M. On the other hand, the two other alkaloids, (**12**) and (**13**), were inactive up to 100 μ M [18].

Two new pyrrolidine alkaloids, radicamines A (**14**) and B (**15**), were isolated as inhibitors of α -glucosidase from *Lobelia chinensis* LOUR (Campanulaceae). The inhibitory activities of radicamines A (**14**) and B (**15**) and (2*R*,3*R*,4*R*,5*R*)-2,5-dihydroxymethyl-3,4-dihydroxy-pyrrolidine (DMDP) were assayed with respect to α -glucosidase. The IC_{50} values were found to be 6.7×10^{-6} M for (**14**), 9.3×10^{-6} M for (**15**), and 4.9×10^{-6} M for DMDP, respectively. These two new compounds, both polyhydroxy alkaloids having an aromatic ring, have been shown to exhibit very interesting biological activities, similar to that of 1-deoxynojirimycin [19].

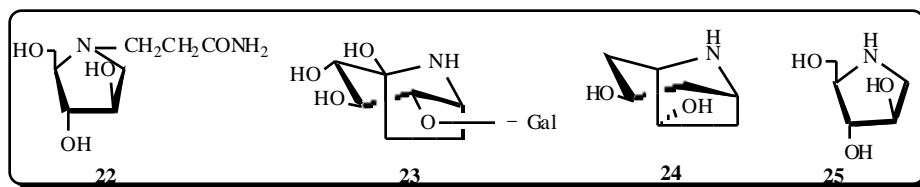
Three quinolizidine alkaloids, javaberine A (**16**), javaberine A hexaacetate (**17**), and javaberine B hexaacetate (**18**), were isolated from *Talinum paniculatum* Gaertner (Portulacaceae); they are inhibitors of TNF- α production by macrophages and fat cells, and *T. paniculatum* is useful as a dieting supplement and for prevention of diabetes [20].

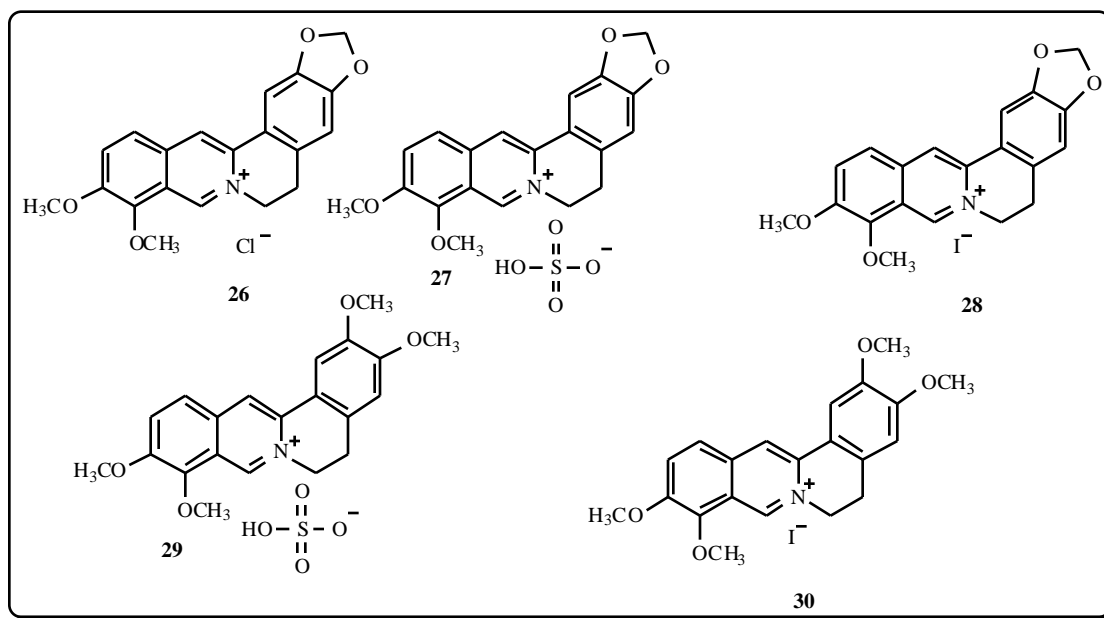


Three quinolizidine alkaloids, lupanine (**19**), 13-OH lupanine (**20**), and 17-oxo-lupanine (**21**), were isolated from *Lupinus perennis* Wild. (Fabaceae). The results show that (**19**)–(**21**), as well as the synthetic 2-thionosparteine, enhanced glucose-induced insulin release from isolated rat islet cells. However, their effect on insulin secretion was

dependent on the glucose concentration in the incubation media. While 2-thionosparteine increased insulin release at every glucose concentration tested, lupanine (**19**) did so only at the two higher concentrations of glucose (8.3 and 16.7 mM), and 13-OH lupanine (**20**) and 17-oxo-lupanine (**21**) only increased insulin secretion at the highest glucose concentration tested (16.7 mM) [21].

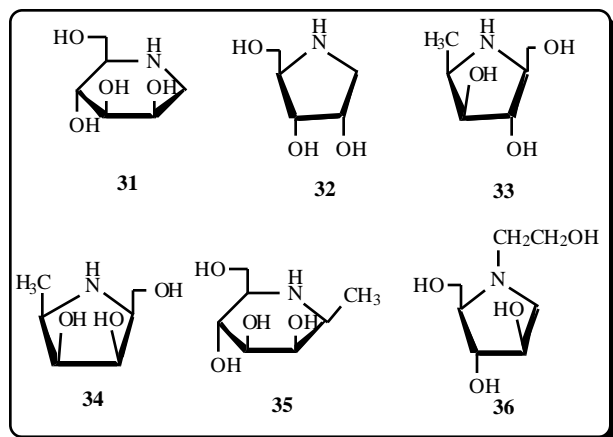
New polyhydroxylated alkaloids—(2*R*,3*R*,4*R*)-2-hydroxymethyl-3,4-dihydroxy-pyrrolidine-*N*-propionamide (**22**) from the root bark of *Morus alba* L. (Moraceae), and 4-*O*-*R*-*D*-galactopyranosyl-calystegine B2 (**23**), 3 β ,6 β -dihydroxynortropine (**24**), and known 1,4-dideoxy-1,4-imino-*D*-arabinitol (**25**) from the fruits—were isolated by column chromatography using a variety of ion-exchange resins. (**24**) showed no inhibitory activity against any glycosidases tested. 1,4-Dideoxy-1,4-imino-*D*-arabinitol (**25**) is a potent inhibitor of yeast α -glucosidase and mammalian isomaltase. (**25**) is also an inhibitor of mammalian α -mannosidase and porcine kidney trehalase. Its *N*-propionamide derivative (**22**) significantly decreased its inhibition against all glycosidases. It is known that the *N*-alkylation of (**25**) markedly lowers or abolishes its inhibition of all glycosidases. Calystegine B2 is a potent inhibitor of α -glucosidases and α -galactosidases. The first glycoside of a calystegine was isolated from *Nicandra physalodes* L. (Solanaceae) fruits, and the structure was determined to be 3-*O*- α -*D*-glucopyranosyl-calystegine B1 (**25**). This α -glucoside was a potent inhibitor ($IC_{50}=1.9$ μ M) of rice α -glucosidase, although calystegine B1 showed no inhibitory activity toward the enzyme. The introduction of the α -glucosyl residue to calystegine B1 and of the β -glucosyl or β -galactosyl residue to calystegine B2 resulted in the significant decrease of glycosidase inhibitory activity. 4-*O*-*R*-*D*-Galactopyranosyl-calystegine B2 (**23**) showed a similar result. α -Glucosidase inhibitors have potential for the treatment of diabetes because they reduce diet-induced hyperglycemia and endogenous insulin secretion by inhibiting intestinal α -glucosidases [22].





Five isoquinoline alkaloids, berberine chloride (**26**), berberine sulfate (**27**), berberine iodide (**28**), palmatine sulfate (**29**), and palmatine chloride (**30**), have been isolated from the root of *Coptis japonica* makino var. *dissecta* nakai (Ranunculaceae), and their inhibitory activity against lens aldose reductase was measured. The IC_{50} values of berberine chloride (**26**), berberine sulfate (**27**), and berberine iodide (**28**) are 13.98, 13.45, and 32.84 nM, respectively. The IC_{50} values of palmatine sulfate (**29**) and palmatine iodide (**30**) are 51.78 and 68.0 nM, respectively [23].

The isomers of 2,5-imino-1,2,5-trideoxy-D-mannitol, (**33**) and (**34**), were very specific inhibitors of R-L-fucosidase with no significant inhibitory activity toward other glycosidases. 1,4-dideoxy-1,4-imino-D-arabinitol is known to be a potent inhibitor of yeast R-glucosidase and mammalian isomaltase. Recently, 1,4-dideoxy-1,4-imino-D-arabinitol has been found to be a potent inhibitor of glycogen phosphorylase both *in vitro* and *in vivo*. The *N*-methyl derivative of 1,4-dideoxy-1,4-imino-D-arabinitol was isolated from the bark, while *N*-hydroxyethyl-DAB (**36**) was found in the pods. The *N*-hydroxyethyl derivative of 1-deoxynojirimycin (DNJ), miglitol, is commercially available for the treatment of diabetes in several countries [24].

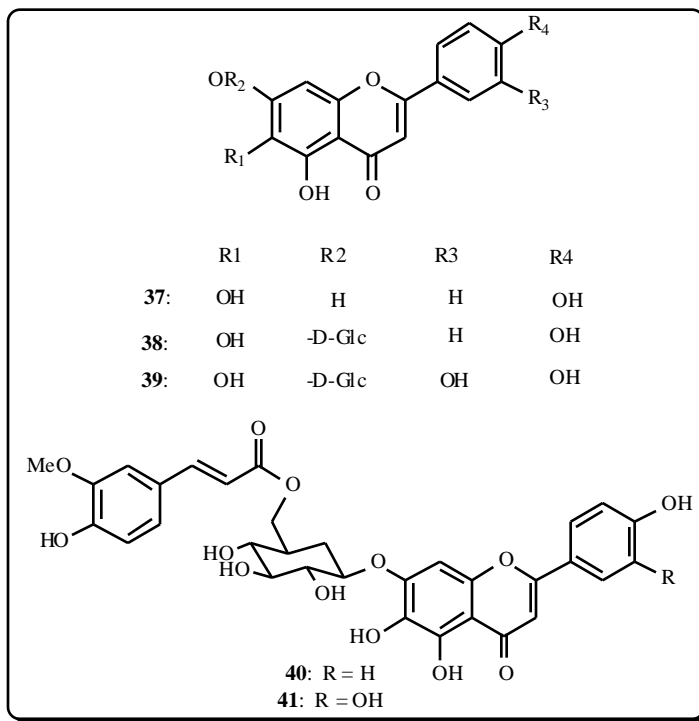


Six sugar-mimic alkaloids, 1-deoxymannojirimycin (**31**), 1,4-dideoxy-1,4-imino-D-ribitol (**32**), 2,5-imino-1,2,5-trideoxy-L-glucitol (**33**), 2,5-dideoxy-2,5-imino-D-fucitol (**34**), β -homofuconojirimycin (**35**), and 1,4-dideoxy-1,4-imino-(hydroxyethyliminiumyl)-D-arabinitol (**36**), were isolated from the pod extract of *Angylocalyx pynaertii* De Wild. (Leguminosae), which inhibits various α -L-fucosidases. Among these alkaloids, (**33**) and (**35**) were very potent inhibitors of bovine epididymis α -L-fucosidase, with IC_{50} values of 1 and 0.01 μ M, respectively. Although 2,5-imino-1,2,5-trideoxy-D-mannitol has been reported to be a weak inhibitor of snail β -mannosidase, 1,4-dideoxy-1,4-imino-D-ribitol (**32**) was a better inhibitor of lysosomal β -mannosidase than was 2,5-imino-1,2,5-trideoxy-D-mannitol.

FLAVONOIDS

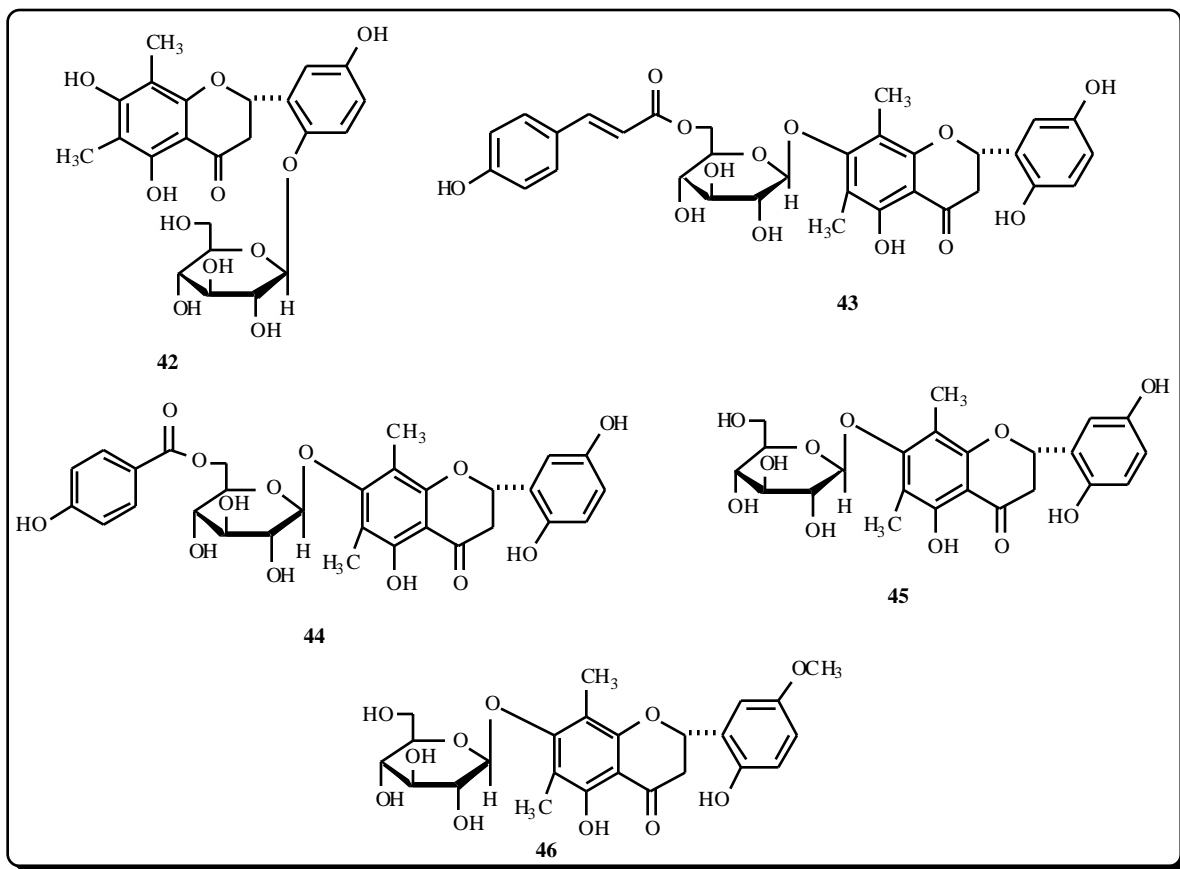
Five 6-hydroxy-flavonoids, 6-hydroxyapigenin (**37**), 6-hydroxyapigenin-7-O- β -D-glucopyranoside (**38**), 6-hydroxyuteolin-7-O- β -D-glucopyranoside (**39**), 6-hydroxyapigenin-7-O-(6-O-feruloyl)- β -D-glucopyranoside (**40**), and 6-hydroxyuteolin-7-O-(6-O-feruloyl)- β -D-glucopyranoside (**41**), were isolated from the methanol extract of *Origanum majorana* L. (Lamiaceae) leaves. All have shown rat intestinal α -glucosidase inhibitory activity. The two feruloylglucosides, (**40**) and (**41**), are novel compounds. The IC_{50} values for (**37**), (**38**), (**39**), (**40**), and (**41**), are 12, >500, >300, >500, and >500 μ M, respectively [25].

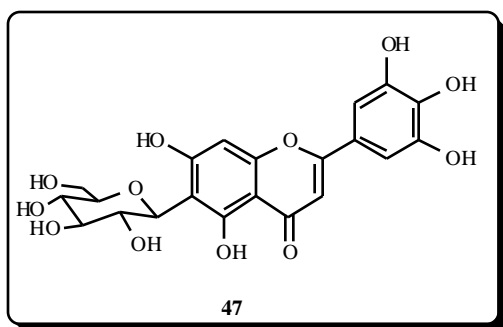
The three new flavonoid compounds, myrciacitrin III (**42**), IV (**43**), and V (**44**), and two previously known flavonoids, myrciacitrin I (**45**) and II (**46**), have been isolated from the leaves of *Myrcia multiflora* DC. (Myrtaceae). All five have shown rat lens aldose reductase inhibitory activity. The IC_{50} values of myrciacitrin III (**42**), IV (**43**), V (**44**), I (**45**), and II (**46**), are 4.6×10^{-5} , 7.9×10^{-7} , 1.6×10^{-5} , 3.2×10^{-6} , and 1.5×10^{-5} M, respectively. Among these, myrciacitrin IV (**43**) showed the most potent activity, although it had less activity than epalrestat, a commercial synthetic aldose reductase inhibitor [26].



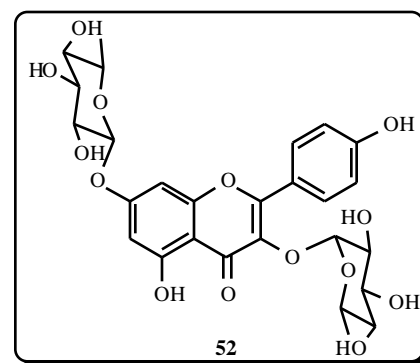
Isoaffineyin (5,7,3',4,5'-pentahydroxyflavone-6-C-glucoside) (**47**) was isolated from *Manikara indica* Lamk. (Sapotaceae). Isoaffineyin (**47**) showed potent inhibition with an IC₅₀ of 4.6 μM against porcine lens aldose reductase. Epalrestat, a clinically developed aldose reductase inhibitor, exhibited 50% inhibition at 0.87 μM [27].

A new flavonol glycoside, quercetin 3-O- -L-arabinopyranosyl-(1 2)- -D-glucopyranoside (**48**), and the known flavonols kaempferol 3-O- -D-glucopyranoside (astragalins) (**49**) and quercetin 3-O- -d-glucopyranoside (isoquercitrin) (**50**) were isolated from *Eucommia ulmoides* D. Oliver (Eucommiaceae) leaves as glycation inhibitors.

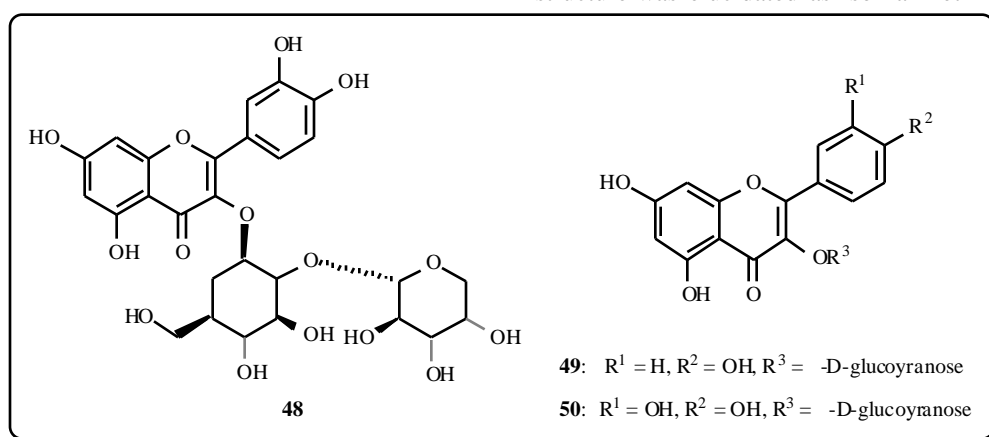




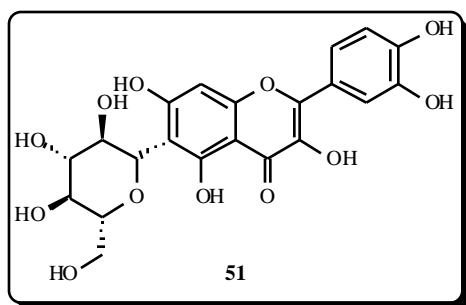
These compounds exhibited glycation inhibitory activity comparable to that of aminoguanidine, a known glycation inhibitor. The IC_{50} values for (48), (49), and (50) and aminoguanidine are 2.95×10^{-7} , 4.86×10^{-7} , 3.20×10^{-7} , and 5.45×10^{-7} , respectively [28].



The EtOAc fraction from *Salicornia herbacea* L. (Chenopodiaceae) was found to exhibit a potent RLAR inhibition ($IC_{50}=0.75 \mu\text{g/ml}$), from which an active principle as a potent AR inhibitor was isolated. Its chemical structure was elucidated as isorhamnetin-3-O- β -D-glucoside

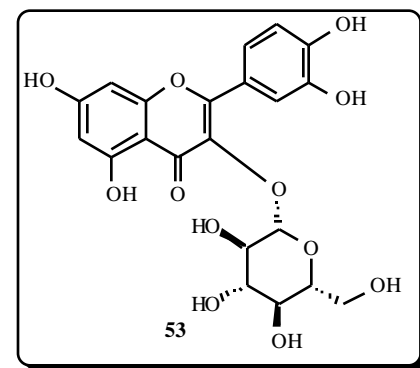


Isoorientin (51) was isolated from the water and butanolic extracts of *Cecropia obtusifolia* Bertol. (Cecropiaceae), which exhibited significant hypoglycemic effect comparable to that of glibenclamide at a dose of 3 mg/kg bw in diabetic rats [29].

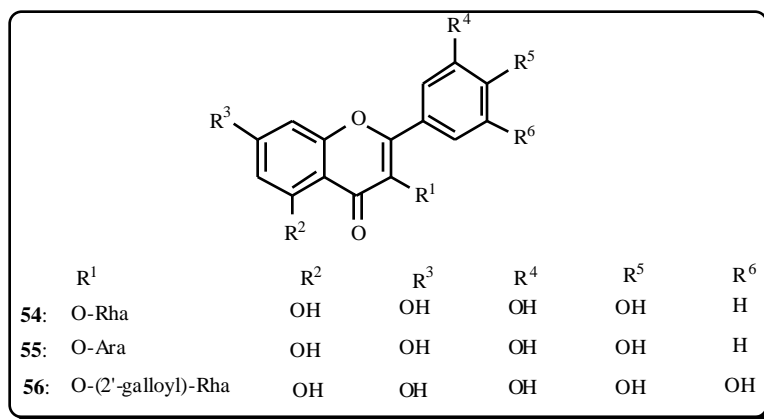


Kaempferol-3, 7-O-(R)-dirhamnoside (kaempferitrin) (52) was isolated from the *n*-butanol fraction of the leaves of *Bauhinia forficata* Link (Leguminosae). Oral administration of kaempferitrin led to a significant hypoglycemic effect in normal and alloxan-induced diabetic rats. In normal rats, blood glucose decrease was observed only with the higher dose of kaempferitrin (200 mg/kg) at 1 h after treatment. However, the hypoglycemic effect of kaempferitrin in diabetic rats was evident at all doses tested (50, 100, and 200 mg/kg), and this profile was maintained throughout the period studied for both higher doses. Additionally, in glucose-fed hyperglycemic normal rats, kaempferitrin failed to decrease blood glucose levels [30].

(53) by spectral analysis. Compound (53) exhibited a significant RLAR inhibition *in vitro* with an IC_{50} of 1.4 mM, which is similar to that of tetramethylene glutaric acid (TMG, 1.7 mM) [31]. Compound (53), when administered orally at 25 mg/kg in STZ-induced diabetic rats, caused not only a significant inhibition of serum glucose concentration but also sorbitol accumulation in the lenses, red blood cells, and sciatic nerves.



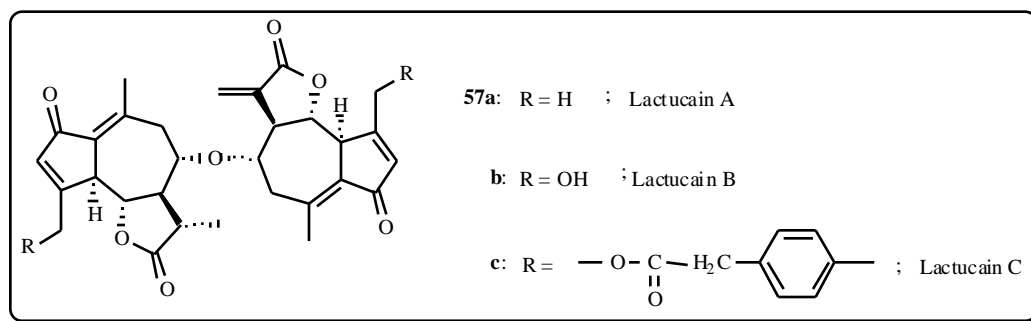
Three known flavonoid glycosides, quercitrin (54), ($IC_{50}=0.15 \mu\text{M}$ [25]) guajaverin (55) ($0.18 \mu\text{M}$ [26]), and desmanthin-1 (56), ($0.082 \mu\text{M}$ [32]), isolated from methanolic extracts from *Myrcia multiflora* DC. (Myrtaceae) (leaves) showed the most potent activity against rat lens aldose reductase. The activity of (56) was equivalent to that of a commercial synthetic aldose reductase inhibitor, epalrestat ($0.072 \mu\text{M}$) [32].



TERPENES

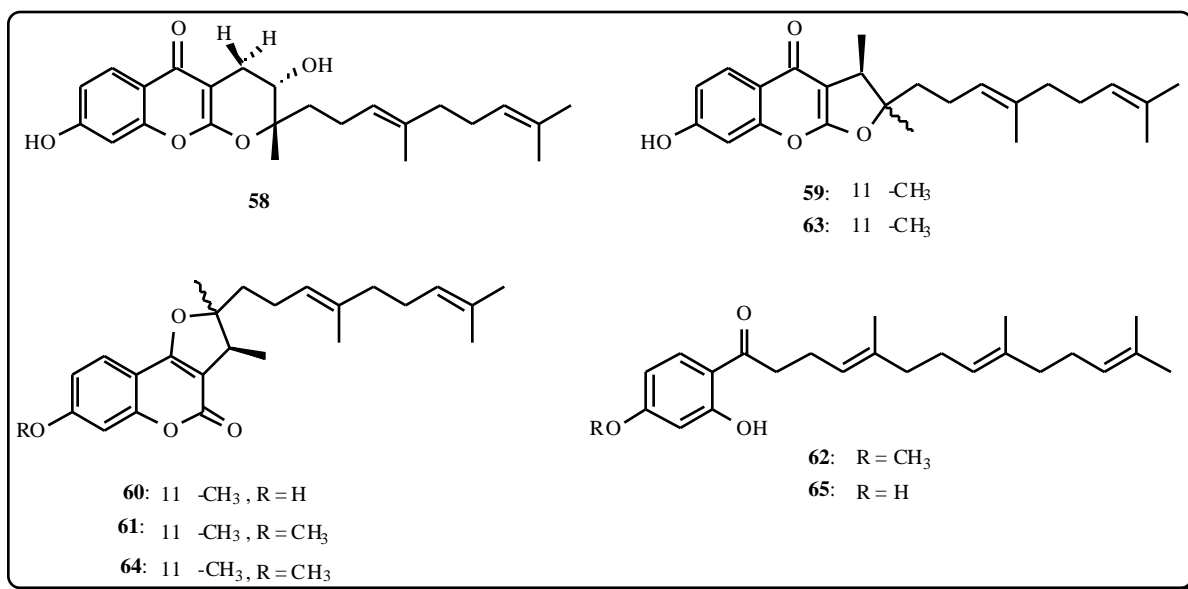
Three novel sesquiterpene lactones, lactucain A (**57a**) and B (**57b**) and C (**57c**), and a new furofuran lignan, lactucaside, were isolated from *Lactuca indica* L. (Compositae) along with nine known compounds. Lactucain C (-22.74±12.53%) (**57c**) showed moderate lowering of plasma glucose at a dose of 1 mM/kg *in vivo* using STZ-diabetic rats [33].

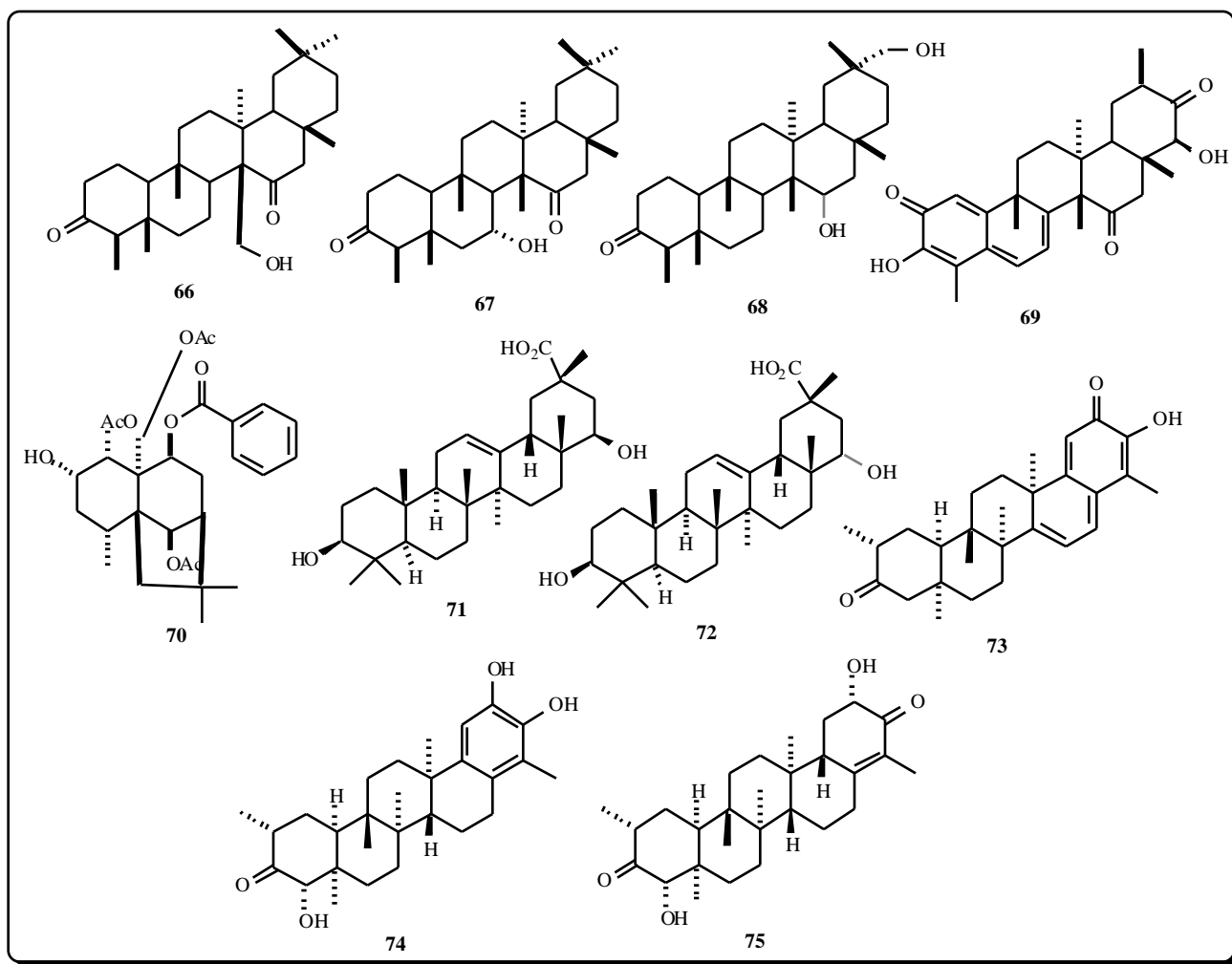
-glucosidase inhibitors. The structures of these compounds were determined by spectroscopic methods and found to be rel-(2R,3R)-2-[(3E)-4,8-dimethylnona-3,7-dienyl]-3,4-dihydro-3,8-dihydroxy-2-methyl-2H,5H-pyrano[2,3-b][1]benzo pyran-5-one (**58**), rel-(2R,3R)-2-[(3E)-4,8-dimethylnona-3,7-dienyl]-2,3-dihydro-7-hydroxy-2,3-dimethyl-4H-furo[2,3-b][1]benzopyran-4-one (**59**), rel-(2R,3R)-2-[(3E)-4,8-dimethylnona-3,7-dienyl]-2,3-dihydro-7-hydroxy-2,3-dimethyl-4H-furo[3,2-c][1]benzopyran-4-one (**60**), rel-(2R,3R)-2-[(3E)-4,8-dimethyl-



The four new and four known sesquiterpenoid derivatives (**58–61**) and (**62–65**), respectively, were isolated from the air-dried roots of *Ferula mongolica* Seud. (Umbelliferae) as

nona-3,7-dienyl]-2,3-dihydro-7-methoxy-2,3-dimethyl-4H-furo[3,2-c][1]benzopyran-4-one(**61**), (4E,8E)-1-(2-hydroxy-4-methoxyphenyl)-5,9,13-trimethyltetradeca-4,8,12-trien-1-one

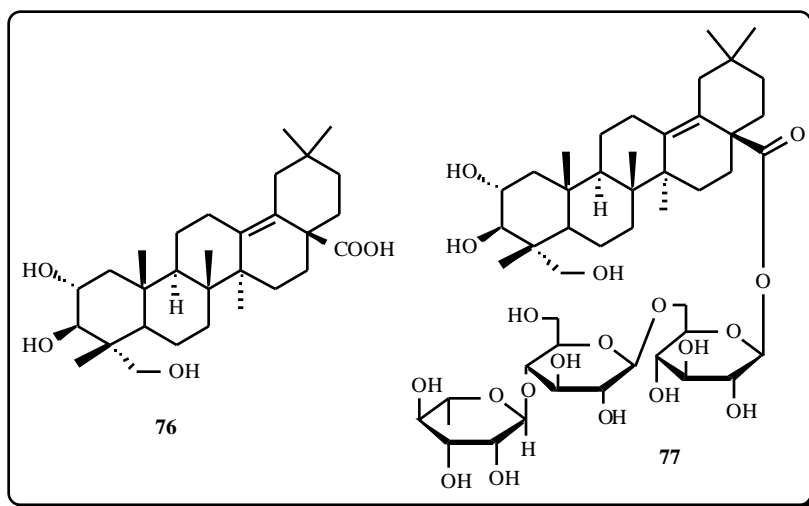


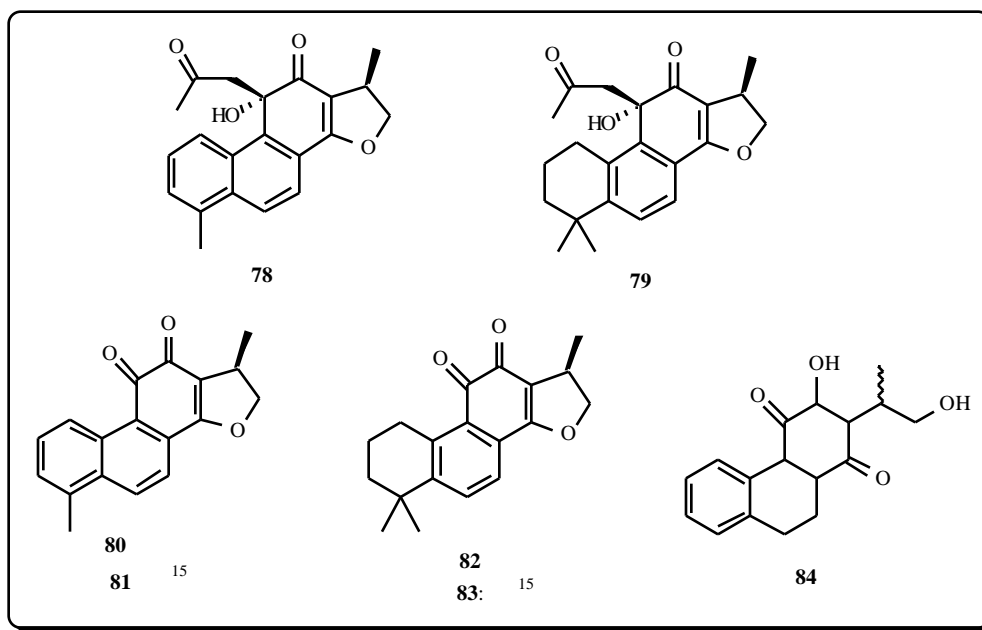


(**62**), the *rel*-(2*R*,3*S*) diastereoisomer (**63**) of (**59**), the *rel*-(2*R*,3*S*) diastereoisomer (**64**) of (**61**), and (4*E*,8*E*)-1-(2,4-dihydroxyphenyl)-5,9,13-trimethyltetradeca-4,8,12-trien-1-one (**65**). The IC_{50} values (**58–65**) are 56.06, 32.21, 63.68, 79.87, 82.41, 20.50, and 9.31 μ M, respectively [34].

Three new friedelane-type triterpenes named salasones A (**66**), B (**67**), and C (**68**), a new norfriedelane-type triterpene,

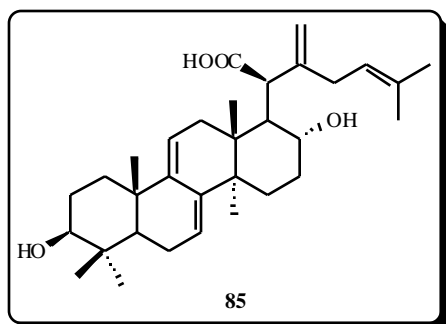
salaquinone A (**69**), and a new acylated eudesmane-type sesquiterpene, salasol A (**70**), were isolated from the 80% aqueous methanolic extract of the stems of *Salacia chinensis* L. (Celastraceae) collected in Thailand. Their stereostructures were elucidated on the basis of chemical and physicochemical evidence. Because the stems of *Salacia chinensis* L. (Celastraceae) have been used for the treatment of diabetes, 25 constituents from the stems of *Salacia*





chinensis L. (Celastraceae) were examined on rat lens for aldose reductase inhibitory activity. Among them, six constituents, 3 β ,22 β -dihydroxyolean-12-en-29-oic acid (**71**), tingenone (**72**), tingenine B (**73**), regeol A (**74**), triptocalline A (**75**), and mangiferin were found to show an inhibitory effect on rat lens aldose reductase. The IC₅₀ values (**71**–**75**) and mangiferin are 26, 72, 13, 7.0, 30, and 3.2 μ M, respectively [35,36].

The new olean-13-ene-type triterpene, centellasapogenol A (**76**) and its oligoglycoside, centellasaponin A (**77**) were isolated from the methanolic extract of *Centella asiatica* L. (Apiaceae) as rat lens aldose reductase inhibitors. The structure of centellasapogenol A (**76**) was found to be 2,3,23-trihydroxyolean-13(18)-en-28-oic acid. The structure of centellasaponin A (**77**) was determined to be centellasapogenol A 28-O- β -D-rhamnopyranosyl- β -D-glucopyranosyl- β -D-glucopyranoside. MeOH extract of the plant inhibited aldose reductase with an IC₅₀ value of 0.80 μ g/mL [37-39].

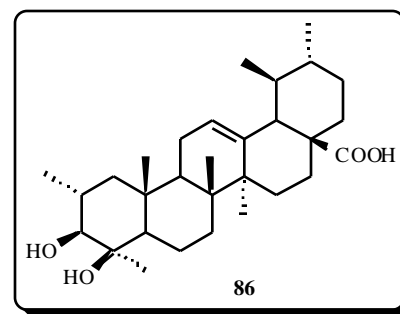


Seven abietane-type diterpenoids, danshenols A and B (**78**, **79**), dihydrotanshinone I (**80**), tanshinone I (**81**), cryptotanshinone (**82**), tanshinone IIA (**83**), and (-)-danshexinkun A (**84**), were isolated from "Danshen," the dried root and rhizome of *Salvia miltiorrhiza* Bunge (Labiatae). This plant is officially listed in the Chinese Pharmacopoeia and is widely used for treatment of hematological abnormalities, heart diseases, menstrual

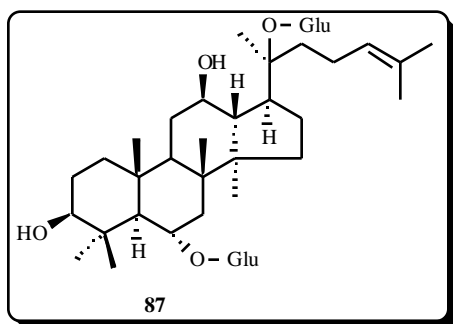
disorder, miscarriage, hepatitis, and swelling. All of these compounds showed inhibitory activity against rat lens ALR2 with danshenol A (**78**) being the strongest inhibitor of the group [40].

The triterpene dehydrotrametenolic acid (**85**) isolated from dried sclerotia of *Poria cocos* Wolf. (Polyporaceae) was shown to have an anti-hyperglycemic effect in a mouse model of non-insulin-dependent diabetes mellitus as an insulin sensitizer [41]. This natural product is a promising candidate for a new type of insulin-sensitizing drug.

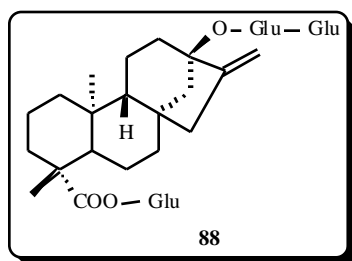
Corosolic acid (Glucosol™) (**86**), isolated from the leaves of *Lagerstroemia speciosa* L. (Lythraceae), showed a significant glucose transport-stimulating activity at a concentration of 1 μ M. Glucosol™ at daily dosages of 32 and 48 mg/Kg for 2 weeks elicited a significant reduction in blood glucose levels. Glucosol™ in a soft-gel capsule formulation brought about a 30% decrease in blood glucose levels compared to a 20% drop seen with the dry-powder-filled, hard-gelatin capsule formulation ($P < 0.001$), suggesting that the soft-gel formulation results in better bioavailability than the dry-powder formulation [42].



Senticoside A (**87**) was isolated from the roots or rhizomes of *Acanthopanax senticosus* (Rupr. et Maxim.) Harms family Araliaceae. Doses of 10 and 200 mg/kg of senticoside A (**87**) were effective in lowering the blood glucose of diabetic mice or rats induced by glucose, alloxan, and adrenaline [43].



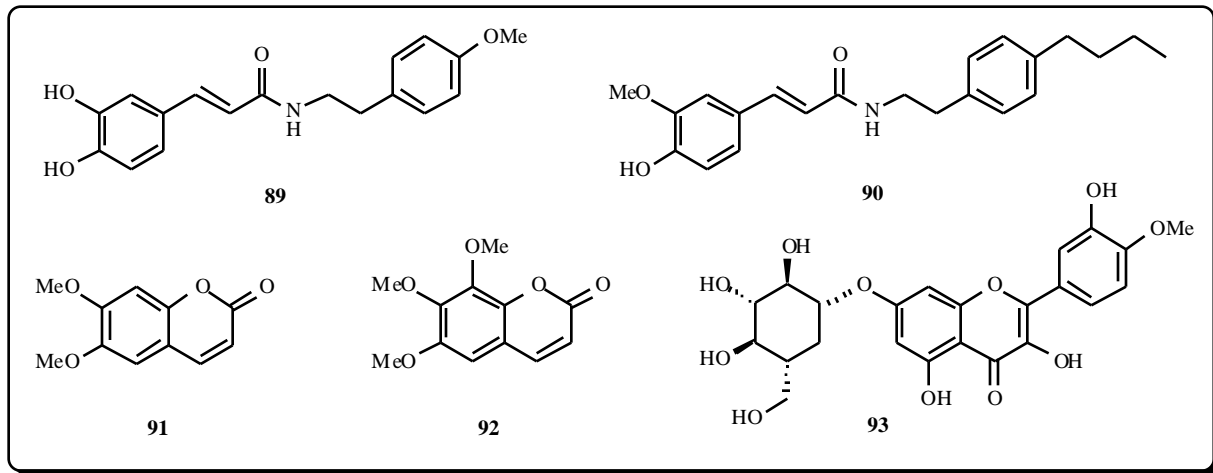
The natural sweetener stevioside (**88**), which is found in the plant *Stevia rebaudiana* Bertoni (Asteraceae), has been used in the treatment of diabetes for many years in many parts of the world. Stevioside, with a mechanism for stimulating insulin secretion *via* direct action on the β -cells of pancreatic islets, is considered to have the potential of becoming a new antidiabetic drug for use in treatment of type 2 diabetes [1,44].



using 1-deoxynojirimycin as control ($IC_{50}=0.3$ mM). Compounds (**89**) and (**90**) showed strong inhibitory activity ($IC_{50}=103.58$ and 45.67 μ M, respectively) while compounds (**91**) and (**93**) showed moderate activity. Compound (**92**) was inactive. None of these compounds showed activity against thrombin and α -glucuronidase [45].

Ellagic acid and its two derivatives, 4-O-methylellagic acid and 4-(β -rhamnopyranosyl)ellagic acid (**94**), were isolated as inhibitors of aldose reductase (AR) from *Myrciaria dubia* McVaugh (Myrtaceae). Compound (**94**) showed the strongest inhibition against human recombinant aldose reductase (HRAR) and rat lens aldose reductase (RLAR). Inhibitory activity of (**94**) against HRAR (IC_{50} value= 4.1×10^{-8} M) was 60 times more than that of quercetin (2.5×10^{-6} M) [46].

Two new desmethylyangonine derivatives, β -D-O-glucoside (**95**) and β -D-O-di (1-6)glucoside (**96**), and one previously known desmethylyangonine, (6[(E)-2-(4-hydroxyphenyl) vinyl]-4-methoxy-2H-pyron-2-one), were isolated as the active constituents from the extract of the bark of *Acosmium panamense* (Benth.) Yacolev. (Fabaceae) against the hypoglycemic effect in diabetic rats (STZ-induced). Oral application of water extracts at doses of 20 and 200 mg/kg and of butanol extracts at doses of 20 and 100 mg/kg significantly lowered the plasma glucose levels in diabetic rats within 3 h. Glibenclamide was used as reference and the extracts showed similar hypoglycemic effect. The mixture of (**95**) and (**96**) showed a similar activity ($P<0.01$) at 120 min lasting to 180 min.

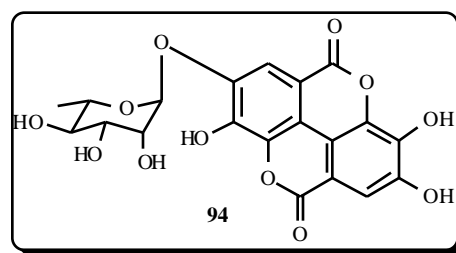


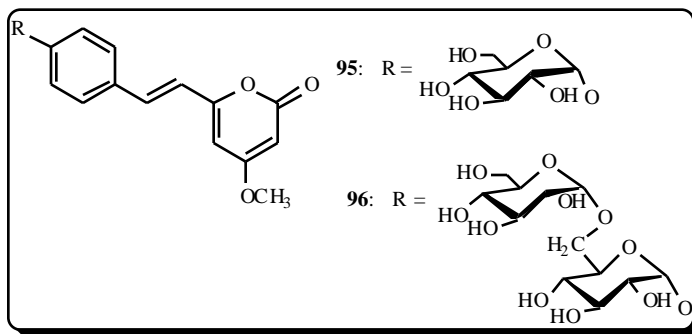
PHENOLICS

Two new compounds, 7'-(3',4'-dihydroxyphenyl)-N-[(4-methoxyphenyl) ethyl]propanamide (**89**) and 7'-(4'-hydroxy-3'-methoxyphenyl)-N-[(4-butylphenyl)ethyl]propanamide (**90**), have been isolated from *Cuscuta reflexa* Roxb. (Convolvaceae) along with three known compounds: 6,7-dimethoxy-2H-1-benzopyran-2-one (**91**), 3-(3,4-dihydroxyphenyl)-2-propen-1-ethanoate, 6,7,8-trimethoxy-2H-1-benzopyran-2-one (**92**), and 3-(4-O- β -D-glucopyranoside-3,5-dimethoxyphenyl)-2-propen-1-ol, 2-(3-hydroxy-4-methoxyphenyl)-3,5-dihydroxy-7-O- β -D-glucopyranoside-4H-1 benzopyran-4-one (**93**). All of the isolated compounds were subjected to enzyme inhibition studies against α -glucosidase type VI

Glibenclamide (3 mg/kg) produced a significant decrease ($P<0.05$) at 120 min lasting to 180 min ($P<0.01$) [47].

Two compounds, (7S,8S)-syringoylglycerol 9-O- β -D-glucopyranoside (**97**) and (7S,8S)-syringoylglycerol-9-O-(6'-

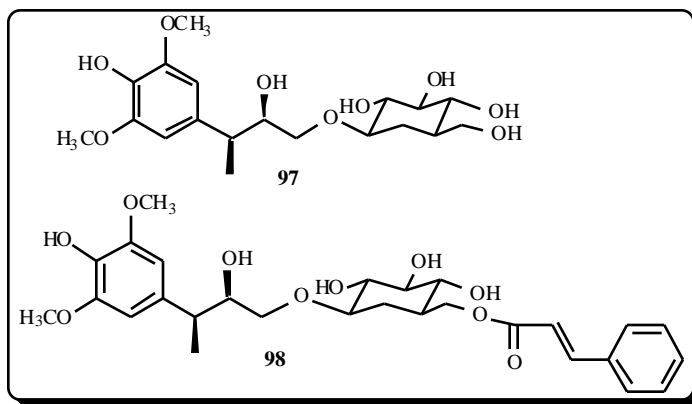




O-cinnamoyl)- α -D-glucopyranoside (**98**), were isolated for α -glucosidase inhibitory activity from the aqueous methanol extracts of dried *Hyssopus officinalis* L. (Lamiaceae) leaves. The inhibitory activity of (**97**) and (**98**) were compared with 1-deoxynojirimycin. Compounds (**97**) and (**98**) exhibited 53% and 54% inhibitory activity at a concentration of 3×10^{-7}

DC. (Nymphaeaceae), respectively. Compounds (**99**) and (**100**) were found to inhibit human placenta ALR2 with IC_{50} values of 0.8 and 0.07 μ M, respectively [40,48].

Magnesium lithospermate B (**101**) isolated from the 80% MeOH extract of the dried roots of *Salviae multiorrhizae* Bunge (Labiatae) shows strong *in vitro* inhibition

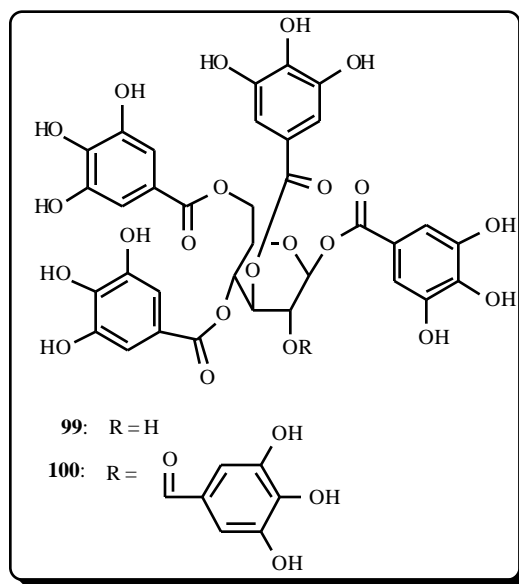


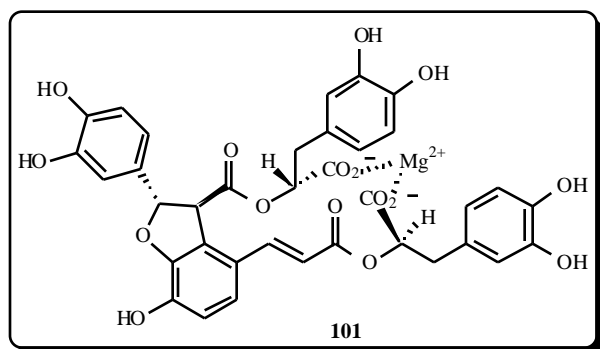
3×10^{-7} M, respectively, but 1-deoxynojirimycin exhibited 58% inhibitory activity at 3×10^{-7} M [48].

Two allotannins, 1,3,4,6-tetragalloylglucose (**99**) and 1,2,3,4,6-pentagalloyl glucose (**100**), were isolated from *Caesalpinia brevifolia* (Fabaceae) and *Nuphar japonicum*

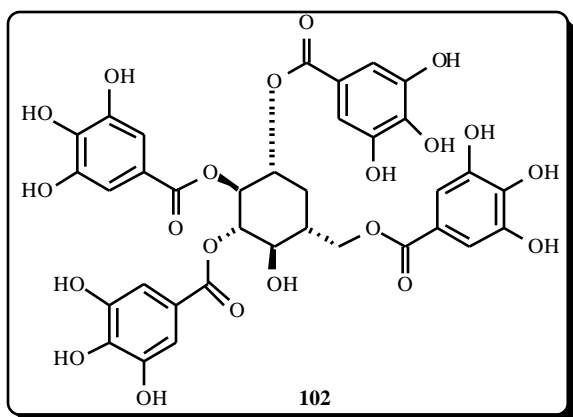
($IC_{50}=0.04$ mM) of aldose reductase, 2.5 times that of clinically used epalrestat ($IC_{50}=0.1$ mM), and accumulation of fibronectin dose dependently [49].

The constituents of *Glycyrrhizae uralensis* FISCH. et DC. (Leguminosae) and *Paeonia lactiflora* Pall





(Ranunculaceae), used in Kampo medicines for the treatment of diabetic neuropathy, showed potent aldose reductase inhibitory activities. Tetra- (**102**) and penta-*O*-galloyl- β -D-glucose, isolated from *Paeonia lactiflora* Pall (Ranunculaceae), inhibited RLAR by 77.6% and 61.0%, respectively. The IC_{50} of (**102**) on RLAR was $6.3 \times 10^{-7} M$. Paeoniflorin and 8-debenzoylpaeoniflorin were isolated from the dried roots of *Paeonia lactiflora* Pall (Ranunculaceae), which produced significantly lowered blood sugar and increase glucose utilization in STZ-treated rats [50].

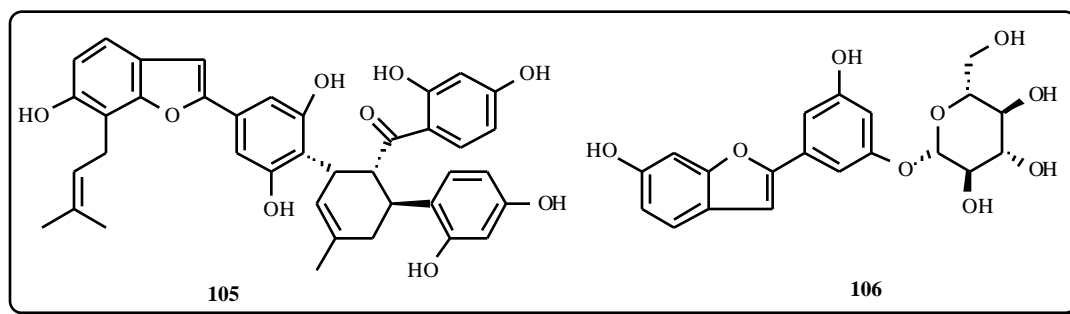
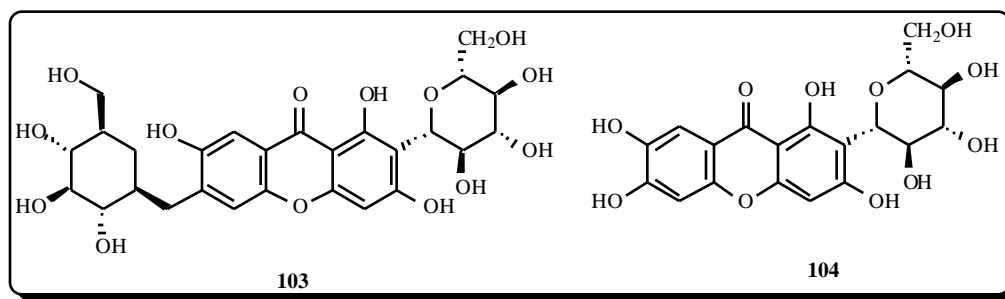


The water extract of the rhizoma (90 mg/kg) of *Anemarrhena asphodeloides* Bunge., family *Liliaceae*, reduced blood glucose level after oral administration and also tended to reduce serum insulin levels in KK-Ay mice. The active components were confirmed to be mangiferin (**104**) and its glucoside (**103**) (mangiferin-7-*O*- β -D-glucoside). It was inferred that mangiferin and its glucosides exert an antidiabetic activity by increasing insulin sensitivity [51].

The ethyl acetate and n-butanol fractions of the leaves of *Morus insignis* Bureau (Moraceae) showed a significant antihypoglycemic activity in STZ-induced hyperglycemic rats. From the fractions with antihypoglycemic activity, two new compounds, mulberrofuran U (**105**) and moracin M-3-*O*- β -D-glucopyranoside (**106**), were obtained along with six known compounds: β -sitosterol, β -sitosterol-3-*O*- β -D-glucopyranoside, moracin M, kaempferol-3-*O*- β -D-glucopyranoside, ursolic acid, and quercetin-3-*O*- β -D-glucopyranoside [52].

MECHANISM AND PRESENT DRUGS FOR THERAPY OF DIABETES MELLITUS

The present treatment of diabetes is focused on controlling and lowering blood glucose to a normal level. The mechanisms that form the basis of both Western approaches and the traditional medicine approaches to lower blood glucose are (1) to stimulate pancreatic islet β -cell release of insulin; (2) to inhibit hormones that increase blood glucose; (3) to increase the number, affinity, or sensitivity of the insulin receptor to insulin; (4) to decrease the release of glycogen; (5) to enhance the use of glucose in the tissues and organs; (6) to clear away free radicals, resist lipid peroxidation, and correct the lipid and protein metabolic disorder; and (7) to improve microcirculation in the body. Based on the above-mentioned targets, the drugs clinically used to treat diabetes can be mainly divided into



insulin, insulin secretagogues, insulin sensitivity improvement factors, insulin-like growth factor, aldose reductase inhibitor, α -glucosidase inhibitors, and protein glycation inhibitor, almost all of which are chemical and biochemical drugs. Use of these drugs targets lowering the level of blood glucose. Moreover, in most cases, side effects such as hypoglycemia, lactic acid intoxication, and gastrointestinal upset occur [1]. Many type 2 diabetic patients have normal levels of insulin in the blood. Thus, the diabetes is not caused by the destruction of beta cells in the pancreas but by other mechanisms, such as insulin resistance related to downregulation of insulin receptors, and other changes to the glucose transporter system [53].

CONCLUSION

In this review, natural products classified into terpenoids, alkaloids, flavonoids, phenolics, and some other categories have shown antidiabetic potential. Schulzeines A (8), B (9), and C (10), radicamines A (14) and B (15), 2,5-Imino-1,2,5-trideoxy-L-glucitol (33), β -homofuconojirimycin (35), myrciacitrin IV (43), dehydrotrametenolic acid (85), corosolic acid (Glucosol™) (86), 4-(α -rhamnopyranosyl)ellagic acid (94), and 1,2,3,4,6-pentagalloylglucose (100) showed significant antidiabetic potential. Additionally, some flavonoids and polyphenols, as well as sugar derivatives, are found to be effective against the inhibitory activities of α -glucosidase and aldose reductase [54].

Treatment with *Momordica charantia* L. (Cucurbitaceae), *Eugenia jambolana* L. (Myrtaceae), *Mucuna pruriens* Bak. (Leguminosae), and *Tinospora cordifolia* W. (Menispermaceae) prevented polyuria in comparison with diabetic controls. Administration of plant extracts (notably *Momordica charantia* and *Eugenia jambolana*) to diabetic mice prevented an increase in urine volume, UAE excretion, and renal hypertrophy, as well as causing a marginal reduction in plasma glucose levels. Most of the plant extracts exhibited hypoglycemic, hypolipidemic, and antioxidant effects in animals as well as in humans, which may be helpful in approaches to treating diabetes and associated complications. Because many medicinal plants constitute a rich source of bioactive chemicals that are largely free from adverse effects and have excellent pharmacological actions, they could lead to the development of new classes of possibly safer antidiabetic agents. Therefore, much effort should be focused on assessing natural products and herbal plants for the discovery of potentially useful α -glucosidase inhibitors and aldose reductase inhibitors or other treatment approaches to diabetes.

ACKNOWLEDGEMENT

This study was supported by a research grant from the Ministry of Health and Welfare (Project No. HMP-0405-OD00-0815-0013), the Republic of Korea.

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