J. Biomed. Ther. Sci. 2014, 1(1), 1-33 Article

Journal of Biomedical & Therapeutic Sciences

Phytochemicals in antidiabetic drug discovery

Rambir Singh,[1] Tasleem Arif,[1] Imran Khan[1] and Poonam Sharma[2*]

[1]Department of Biomedical Sciences, Bundelkhand University, Jhansi-284128 UP India. [2]Department of Bioscience, Barkatullah University, Bhopal-462026 MP India.

Received Date: 10-August-2014

ABSTRACT

Management of diabetes mellitus is a challenge for clinicians. Uncontrolled hyperglycemia increases the risk of microvascular and macrovascular complications, damaging the body systems. Although a number of antidiabetic drugs are available for therapeutic intervention, toxicity, loss of efficacy in chronic use and high cost of treatment have necessitated the search for new molecules to manage diabetes. Safety and cost are the main prerequisite for the new antidiabetic molecules. Medicinal plants and their purified phytochemicals have shown promising antidiabetic potential in the past few years. The current review summarizes the antidiabetic activity of alkaloids, phenols, flavonoids, saponins, polysaccharides, terpenoids, glycosides and xanthones isolated from medicinal plants.

Keywords: Diabetes mellitus, Alkaloids, Flavonoids, Medicinal plants, Phenolics, Phytochemicals, Polysaccharides, Saponins, Terpenenoids, Xanthones

INTRODUCTION

Diabetes mellitus (DM) is the world's fastest growing metabolic disorder, characterized by hyperglycemia, altered metabolism of lipids, carbohydrates and proteins.[1,2] DM is a global public health threat and is listed as the third major "killer" of mankind, along with cancer and cardiovascular diseases.[3] Its prevalence among adults aged 20–70 years is expected to rise from 285 million in 2010 to 438 million by the year 2030.[4] Asian countries contribute more than 60% of the world's diabetic population, with China and India sharing the major burden.[5] Recent estimates have shown that 90 million Chinese people are currently living with diabetes and 1.3 million died due to the disease in 2011.[6] Prevalence estimates of DM and impaired glucose tolerance (IGT) are high for all Asian countries and are expected to increase further in the next two decades.[7]

DM is broadly divided into Type1 (T1DM) and Type 2 (T2DM), the latter being the most prevalent form. T1DM is commonly seen in juveniles, and is characterized by failure to produce insulin due to autoimmune destruction of β-cells of the pancreas, while T2DM is usually adult-onset and is associated with insufficient production of insulin and loss of responsiveness by cells to insulin.[8-9]

Effective blood glucose control is the key to preventing or reversing diabetic complications and improving quality-of-life in diabetic patients. Controlled hyperglycemia decreases the risk of developing microvascular and macrovascular complications and better diabetes management .Until the discovery of insulin in the 1920s, nutritional therapy was the only available remedy for treating diabetes. The discovery of insulin revolutionized diabetes care and this hormone is currently the drug of choice for patients with TIDM and T2DM. Apart from insulin, several types of glucose-lowering drugs, including insulin secretagogues (sulfonylureas, meglitinides), insulin sensitizers (biguanides, metformin, thiazolidinediones) and α-glucosidase inhibitors (miglitol, acarbose) have been developed.[10] New peptide analogs, such as exenatide, liraglutide and dipeptidyl peptidase (DPP)-4 inhibitors, increase serum concentration of glucagon-like peptide (GLP-1) and slow down gastric emptying.[11] Most glucose-lowering drugs have side effects, including severe hypoglycemia, lactic acidosis, idiosyncratic liver cell injury, permanent neurological deficit, digestive discomfort, headache and dizziness.

The side effects associated with the prolonged use of present day antidiabetic drugs have necessitated the demand for safe and effective drugs, especially those of herbal origin.[12,13] Different traditional medicinal systems use crude plant extracts or their active constituents for management of diabetes. Herbal

Corresponding Author: Dr. Poonam Sharma
Tel: +91-9415587302
Email: pnm245@yahoo.com

Cite as: *J. Biomed. Ther. Sci., 2014, 1(1), 1-33.*

drugs are generally considered safe compared with synthetic drugs and are relatively cheap and popular.[14] Furthermore, after a recommendation made by the World Health Organization (WHO) on the use of herbs in the management of DM, investigations into antidiabetic agents from medicinal plants have become more important.[15] It is estimated that more than 800 plant species having hypoglycemic activity have been reported across the globe,[16,17] and more than 450 plants have been experimentally tested.[18] A number of papers have been published on the isolation, purification and characterization of active antidiabetic constituents from medicinal plants. A number of reviews on antidiabetic agents from plants have been published in past few years.[19-22] Phytochemicals such as alkaloids, saponins, terpenoids, glycosides, flavonoids, etc., with potential antidiabetic activity have been reported by a number of research groups. The present review discusses different antidiabetic molecules isolated from plants. The structure of reported phytochemicals has been included along with discussion about their potency in antidiabetic therapy.

ANTIDIABETIC PHYTOCHEMICALS

The chemical diversity of natural products is complementary to the diversity found in synthetic libraries. However, natural products are more complex and have a greater diversity due to the long evolutionary selection process. Therefore, strategies to exploit natural sources and to develop methodologies for the preparation of natural products, as with synthetic libraries, by combinatorial biosynthesis and related techniques are possible.[23] As current therapeutic agents are becoming ineffective largely due to indiscriminate use, plant-derived drugs are gaining acceptance across the globe, especially in the western world.[24] The ancient Indian Ayurvedic System of Medicine lists vast resources of herbal drugs. Information on medicinal plants in India, China and the rest of the world has been systematically organized.[25-27]

More than 13,000 secondary metabolites have been isolated from the medicinal plants.[28] The secondary metabolites serve as defense molecules or perform specialized functions in plants. These secondary metabolites possess medicinal properties, including antidiabetic activity. Alkaloids, phenolics, terpenoids, flavonoids, saponins, xanthones, polysaccharides and other compounds have been reported to have antidiabetic activity.

1. ALKALOIDS

Alkaloids are naturally occuring nitrogenous organic molecules with pharmacological effects on humans and other animals. Alkaloids are recognized as a major class of phytochemicals due to their structural diversity and wide variety of biological activities.[29] The first medicinally useful alkaloid was morphine, isolated in 1805 from the poppy plant *Papaver somniferum* Linn.[30] Use of plant alkaloids in the management of diabetes has been reported. Berberine promoted glucose-stimulated insulin secretion in a dose-dependent manner in rats' pancreatic islets, probably via a pathway involving hepatic nuclear factor 4α, which is distinct from sulphonylureas.[31] Details of antidiabetic alkaloids isolated from medicinal plants are given in Table 1 and the structure of some of the compounds is given in Figure 1.

Kinenoside from the methanol extract of whole plant of *Anoectochilus roxburghii* exhibited potential lipid lowering activity in rats at a dose of 15mg/kgbw. Inhibition of α-glucosidase activity by Schulzeines from seeds of *Penares schulzei* and Radicamines form *Lobelia chinensis* possess further scope for potential drug development possibilities.

2. PHENOLICS

Phenolic compounds are known to interact with proteins and inhibit enzymatic activity.[32,33] Food-grade phenols from dietary plant extracts that inhibit α-amylase activity are potentially safe, and therefore may be a preferred alternative for modulation of carbohydrate digestion and control of the glycemic index of food products. Details of phenolics exhibiting antidiabetic activity are given in Table 2 and the structure of some of the compounds is presented in Figure 2.

Increase in glucose uptake by Chlorogenic acid isolated form stem of *Cecropia obtusifolia* in 3T3-L1 adipocytes may be potentially explored for antidiabetic potential, especially in type 2 diabetes. Anacardic acid form *Anacardium occidentale* also enhanced glucose uptake in C_2C1_2 myotubes. Inhibition in α-glucosidase activity also been reported from *Cuscuta reflexa, Hyssopus officinalis* and *Terminalia sericea.*

3. TRITERPENES

A large number of studies have been carried out into the antidiabetic activity of terpenoids of plant origin. A new cycloartane triterpene (23-oxo-3α-hydroxycycloart-24-en-26-oic acid) isolated from an ethanol extract of *Larix laricina* K. Koch (Pinaceae) bark showed strong enhanced adipogenesis in 3T3-L1 cells with an EC_{50} of 7.7 μM and was therefore reported to have putative antidiabetic activity.[34] An acycloartane-type triterpene isolated from the methanol extract of *Krameria pauciflora* roots showed antidiabetic activity in rats at doses of 3, 10, 30, and 100 mg/kgbw.[35] A number of triterpenes exhibiting antidiabetic activity are listed in Table 3, and the structures of some of these compounds are provided in Figure 3.

Palbinone form stem of *Paeonia suffruticosa* Increase glucose uptake and enhance glycogen synthesis by activating AMPK in Hep G2 Cells. Stimulation of insulin secretion as possible mechanism of antidiabetic activity has also been reported from *Scoparia dulcis* and *Stevia rebaudiana.*

4. FLAVONOIDS

The flavonoids are polyphenolic compounds possessing 15 carbon atoms; two benzene rings joined by a linear three-carbon chain. Flavonoids show a wide variety of activities, including anti-hyperglycemic activity.[36-37] Numerous studies on the antidiabetic potential of flavonoids from plants have been published.[38-39] Quercetin regenerated pancreatic islets and increased insulin secretion in streptozotocin (STZ)-induced diabetic rats.40 It has also been found to stimulate insulin release and enhance glucose uptake from isolated islet cells.[41,42]

Table 1. Alkaloids

S no.	Name of plant	Family	Plant part	Name of Extract	Experimental system and Dose	Compound (structure no.)	Mechanism of action	Ref
1	*Angle marmelos*	Rutaceae	Leaves	Methanol	Rats, 100 mg/kgbw	Aegeline (**1**)	Antihyperglycemic activity	50
2	*Syzygium cumini*	Myrtaceae	Seeds	Ethyl acetate Methanol	Rats	Mycaminose (**2**)	Reduction of blood glucose levels	51
3	*Stephania glabra*	Menispermaceae	Tubers	Ethanol	Mice	11-hydroxypalmatine (**3**)	Reduction in blood glucose	52
4	*Anoectochilus roxburghii*	Orchidaceae	Whole plant	Methanol	Rats, 15 mg/kgbw	Kinsenoside	Decreased serum total cholesterol and triglyceride levels and increased high-density lipoprotein cholesterol	53
5	*Murraya koenigii*	Rutaceae	Leaves	Petroleum ether	Rats, 100 mg/kg	Mahanimbine (**4**)	Decrease in blood glucose level, α-amylase inhibitory effect and α-glucosidase inhibitory activity	54
6	*Withania coagulans*	Solanaceae	Fruit	Aqueous	Rats	Withanolide **(5)**	Inhibit post prandial glucose	55
7	*Psacalium peltatum*	Asteraceae	Roots and Rhizomes	Aqueous	Alloxan diabetic mice, 100 mg/kgbw	Ulopyranose	Hypoglycemic activity	56
8	*Penares schulzei*	Ancorinidae	Seed	Methanol	Rat	Schulzeines A (**6**) B (**7**), and C (**8**)	Inhibit α-glucosidase activity	57
9	*Tecoma stans*	Bignoniaceae	Leaves	diethyl ether	Rats	Tecomine (**9**) 5b-hydroxyskitanthine and boschniakine	Increased glucose uptake rate	58
10	*Stephania tetrandra*	Menispermaceae	Whole plant	Aqueous	Rats and mice	Tetrandrine 2'- N-β-oxide **(10)** tetrandrine 2'-N-α-oxide (**11**),tetrandrine 2-N- β-oxide (**12**), fangchinoline 2'-N-α-oxide (**13**), 2'-N-norfangchinoline (**14**), and 2'-N-methyltetrandrinium chloride (**15**)	Increase the blood insulin level and reduction in high blood glucoce	59
11	*Talinum paniculatum*	Portulacaceae	Root	Aqueous ethanol	Mouse	Javaberine A (**16**), Javaberine A hexaacetate **(17)** and Javaberine B hexaacetate (**18**)	Inhibitor of TNF α production	60
12	*Lupinus perennis*	Papilionaceae	Leaves	Aqueous	Rat pancreatic islet cells	Lupanine (**19),** 13-α-OH lupanine (**20**) , 17-oxo-lupanine (**21**)	Enhance glucose-stimulated insulin release and lower blood glucose levels	61
13	*Cryptolepis sanguinolenta*	Apocynaceae	Stem	Ethanol	3T3-L1 cell	Cryptolepine (**22**)	Decrease glucose levels, increase glucose uptake in 3T3-L1 cells	62
14	*Lobelia chinensis*	Campanulaceae	Whole plant	Methanol	Rats	Radicamines A (**23**) and B (**24**)	Inhibit α-glucosidase activity	63
15	*Tinospora cordifolia*	Menispermaceae	Stem	Aqueous	Rats	Berberine (**25**)	Hypoglycaemic activity	64
16	*Catharanthus roseus*	Apocynaceae	Leaves	Rats	500 mg/kgbw	Catharanthine (**26**), vindoline (**27**) ,vindolinine (**28**)	Reduction in blood sugar levels	65

17	*Tribulus terrestris*	Zygophyllaceae	Whole plant	Aqueous	Human islets of Langerhans	β-carbolines harmane, norharmane and pinoline	Increase in insulin secretion	66
18	*Pongamia pinnata*	Fabaceae	Fruit	Ethanol	Rats	Pongamol and karangin	Panigrahihadhyperglycaemic, hyperlipidaemic and hyperinsulinemic activity	67
19	*Ephedra distachya* Linn.	Ephedraceae	Whole plant	Aqueous	Mice	l-ephedrine	Suppression of hyperglycaemia	68
20	*Nelumbo nucifera*	Nelumbonaceae.	Root	Ethanol	Rats pancreatic islets and INS-1E cells	Nuciferine	Stimulate both phases of insulin secretion	69

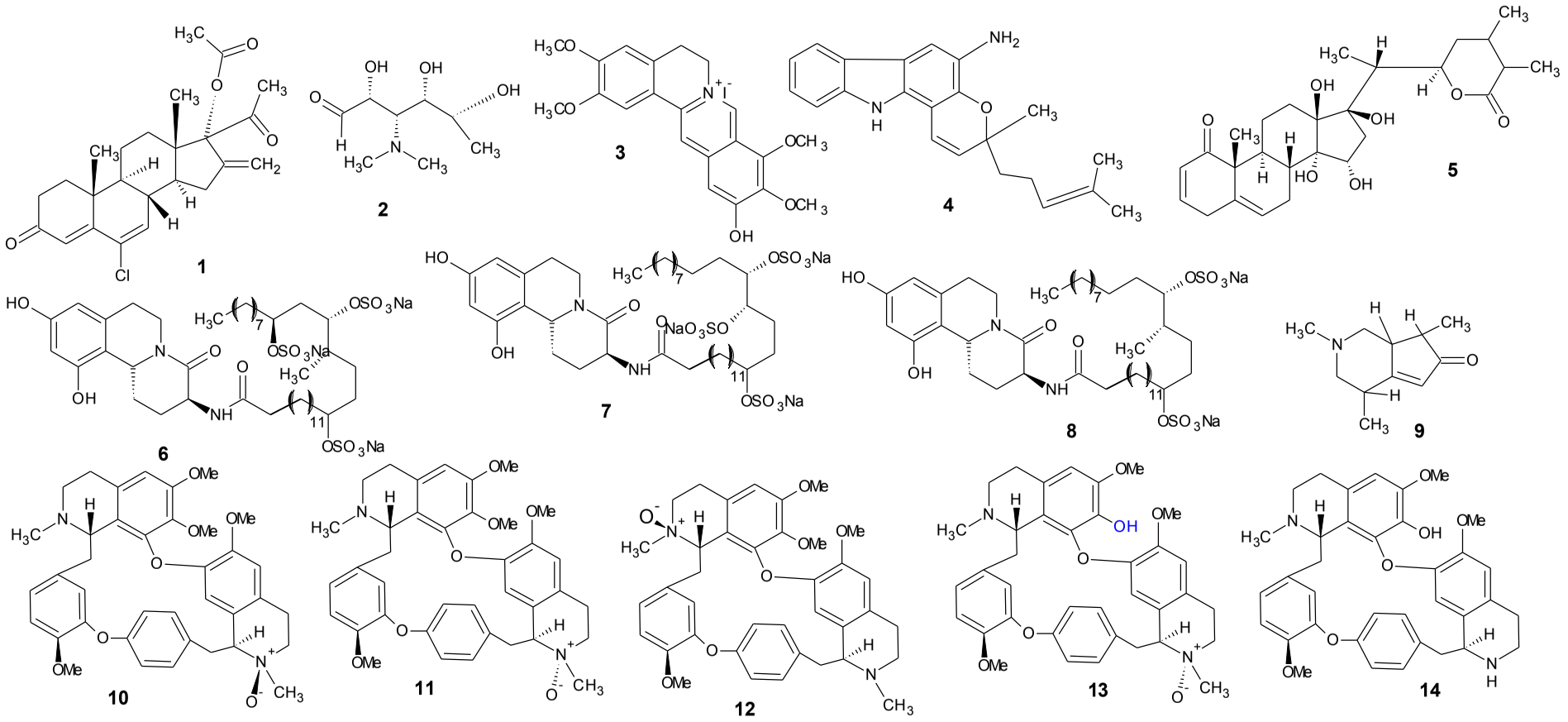

Figure 1a. Structure of Alkaloids

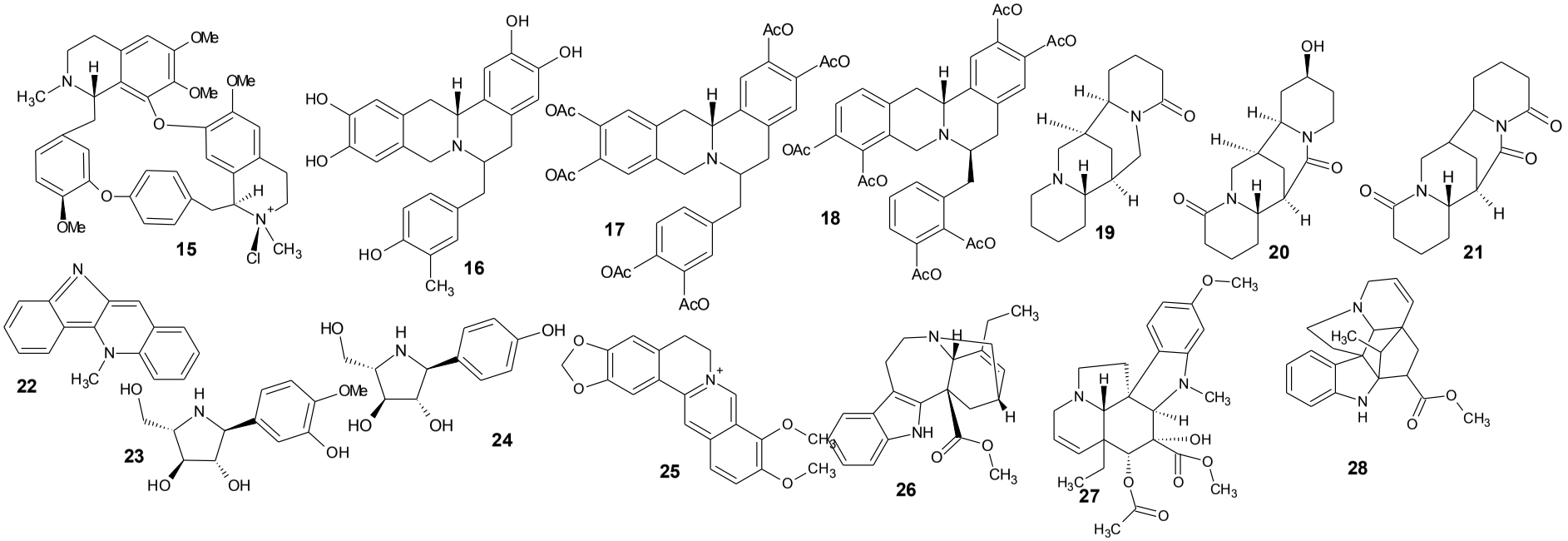

Figure 1b. Structure of Alkaloids

Table 2. Phenols

S. No	Name of plant	Family	Plant part	Name of extract	Experimental system and dose	Compound (structure no.)	Mechanism of action	Ref
1	*Gymnema sylvestre*	Asclepiadaceae	Leaves	Ethanol	Rats	Gymnemic acids	Decrease blood glucose levels	70
2	*Trigonelia foenum-graecum*	Fabaceae	Seeds	Aqueous	Rats, 50 mg/kgbw	Trigonelline (**29**) and nicotinic acid	Antihyperglycaemic activity	71
3	*Terminalia bellerica*	Combretaceae	Fruit	Methanol	Wistar rats	Gallic acid	Reduction in plasma glucose level	72
4	*Oryza glaberrima*	Poaceae	Leaves Seed	Aqueous	Rats	4-hydroxy-3-methoxycinnamic acid (**30**)	Alleviate oxidative stress and attenuate the hyperglycemic response	73
5	*Euterpe oleracea*	Arecaceae	Bark	Pet ether	Albino Wistar rats	3,4-dihydroxybenzoic acid (**31**)	Increase in plasma glucose and glycosylated hemoglobin and decrease in plasma insulin	74
6	*Bougainvillea spectabilis*	Nyctaginaceae	Leaves	Methanol	Rats	Pinitol (**32**)	Antidiabetic activity	75
7	*Hemidemus indicus*	Apocynaceae	Root	Methanol-chloroform	Rats	2-hydroxy 4-methoxy benzoic acid (**33**)	Increase levels of blood glucose and lipid peroxidation in plasma	76

8	*Magnolia officinalis*	Magnoliaceae	Bark	Aqueous	Rats, 100mg/kgbw	Magnolol (**34**)	Control blood glucose levels	77
9	*Otholobium pubescens*	Fabaceae	Leaves	Ethanol	Rats	Piceatannol and scirpusin B (**35**)	Inhibit α-amylase activity	78
10	*Otholobium pubescens*	Moraceae	Stem	Acetone	Rat	Bakuchiol (**36**)	Decrease blood glucose and triglyceride levels	79
11	*Morus alba*	Moraceae	Root	Petroleum ether and water	Mice, 50, 60 and 100 mg/kgbw	Moracin M (**37**), steppogenin-4'-O-β–D-glucosiade (**38**) , mullberroside A (**39**)	Hypoglycaemic effects	80
12	*Morus insignis*	Moraceae	Leaves	Ethyl acetate and n-butanol	Rats	Mulberrofuran U (**40**) , moracin M-3-O- β– d-glucopyranoside (**41**)	Hypoglycaemic activity	81
13	*Cichorium intybus*	Asteraceae	Bark	Aqueous	INS-1E cell line and rat islets of Langerhans	Mono-caffeoyl ester caffeic acid and chlorogenic acid	Insulin-sensitizing and insulin-secreting properties	82
14	*Cecropia obtusifolia*	Urticaceae	Stem	Aqueous	3T3-L1 adipocytes	Chlorogenic acid (**42**)	Stimulation of 2-NBDG uptake	83
15	*Pandanus odorus*	Pandanaceae	Root	Aqueous	Rat, 5 mg/kgbw	4-hydroxybenzoic acid (**43**)	Increases in serum insulin, liver glycogen and hypoglycaemic effect	84
16	*Larrea tridentata*	Zygophyllaceae	Leaves	Ethanol	Mouse models of type 2 diabetes	Nordihydroguaiaretic acid (**44**)	Decrease plasma glucose levels	85
17	*Cuscuta reflexa*	Cuscutaceae	Bark	Water	Rats	Propenamide (**45**), 7'-(4'-hydroxy- 3'-methoxyphenyl)-N-(4-butylphenyl)ethyl] propenamide (**46**), 6,7- dimethoxy-2H-1-benzopyran-2-one (**47**), 3-(3,4-dihydroxyphenyl)- 2-propen-1-ethanoate,6,7,8-trimethoxy-2H-1-benzo pyran-2-one (**48**) , 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 benzopyrane- 4-one (**49**)	Inhibition in α-glucosidase activity	86
18	*Hyssopus officinalis*	Lamiaceae	Leaves	Aqueous methanol	Mice	(7S, 8S)-syringoylglycerol 9-O-β-D-glucopyranoside (**50**) and (7S,8S)-syringoylglycerol-9-O-(6'-O-cinnamoyl)– β-D-glucopyranoside (**51**)	α-glucosidase inhibitory activity	87
19	*Paeonia lactiflora*	Paeoniaceae	Root	Aqueous	Rat	Tetra-penta-O-galloyl-β-D glucose (**52**), paeoniflorin (**53**) and 8-debenzoylpaeoniflorin	Decrease blood sugar and increase glucose utilization	88
20	*Tillandsia usneoides*	Bromeliaceae	Stem	Aqueous	Mice	Ellison (**54**), 3 hydroxy-3-methylglutaric acid (**55**) and allyl propyl disulfide	Hypoglycaemic activity	89
21	*Anacardium occidentale*	Anacardiaceae	Root	Hydro-ethanolic	C_2C1_2 myotubes	Anacardic acid (**56**)	Stimulate glucose transport and elevation in glucose uptake	90
22	*Pterocarpus marsupium*	Fabaceae	Heartwood	Ethanol	Rat	Marsupsin (**57**), pterosupin (**58**) ,pterostilbene (**59**)	Decrease in glycaemia	91
23	*Acrocomia mexicana*	Palmaceae	Root	Methanolic	Mice, 2.5 to 40 mg/kgbw	Coyolosa	Decrease in blood sugar	92
24	*Terminalia sericea*	Combretaceae	Stem bark	Acetone	*In vitro*	Stigma-4-ene-3-one, β-sitosterol-3-acetate, epicatechin-catechin, and gallocatechin-epigallocatechin	α-glucosidase and α-amylase inhibitory activity	93

25	*Solanum torvum* Swartz	Solanaceae	Fruit	Aqueous	Rats, 200–400 mg/kgbw	Rutin, caffeic acid, gallic acid and catechin	Reduce blood glucose level	94

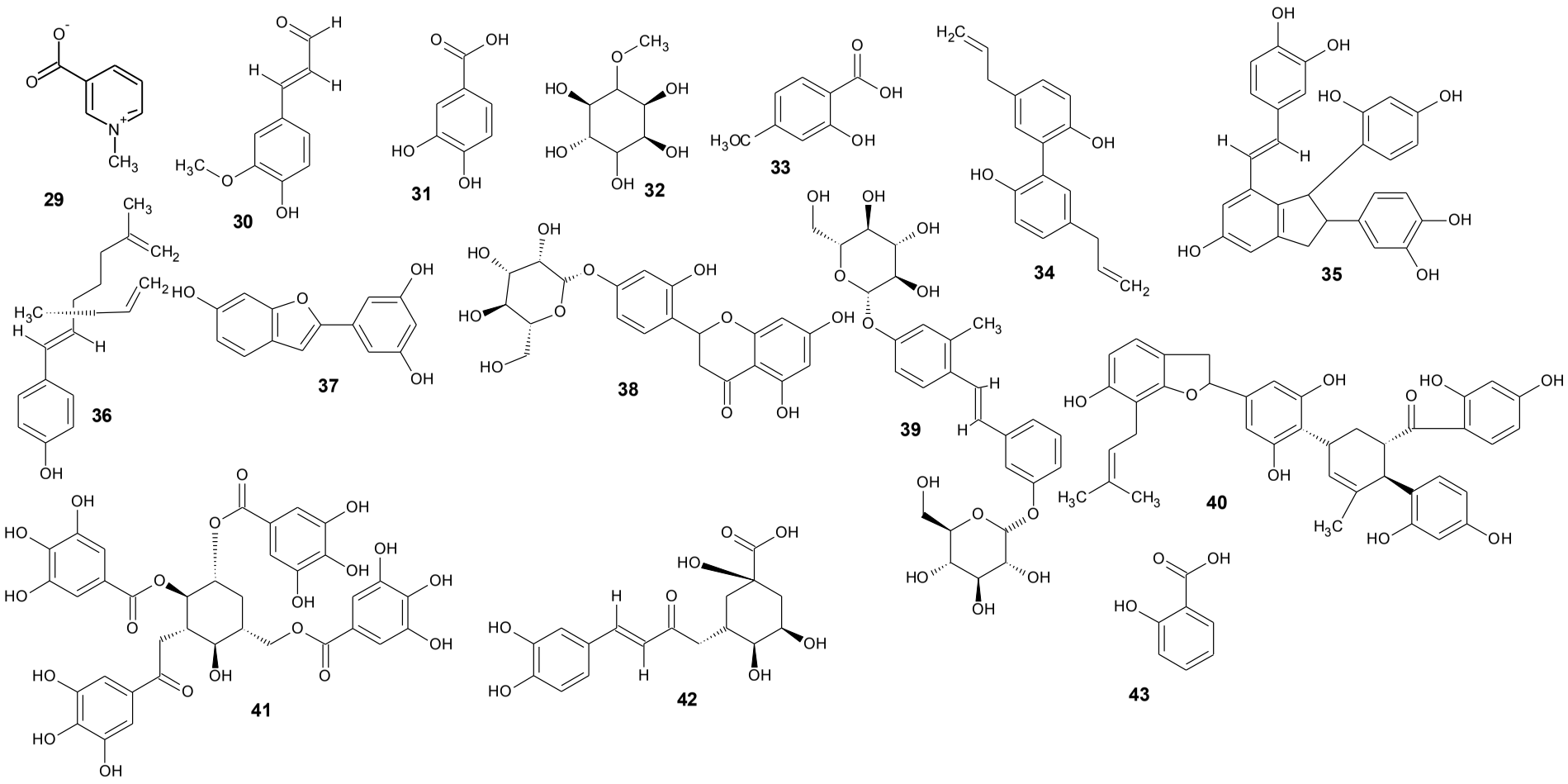

Figure 2(a). Structures of phenols.

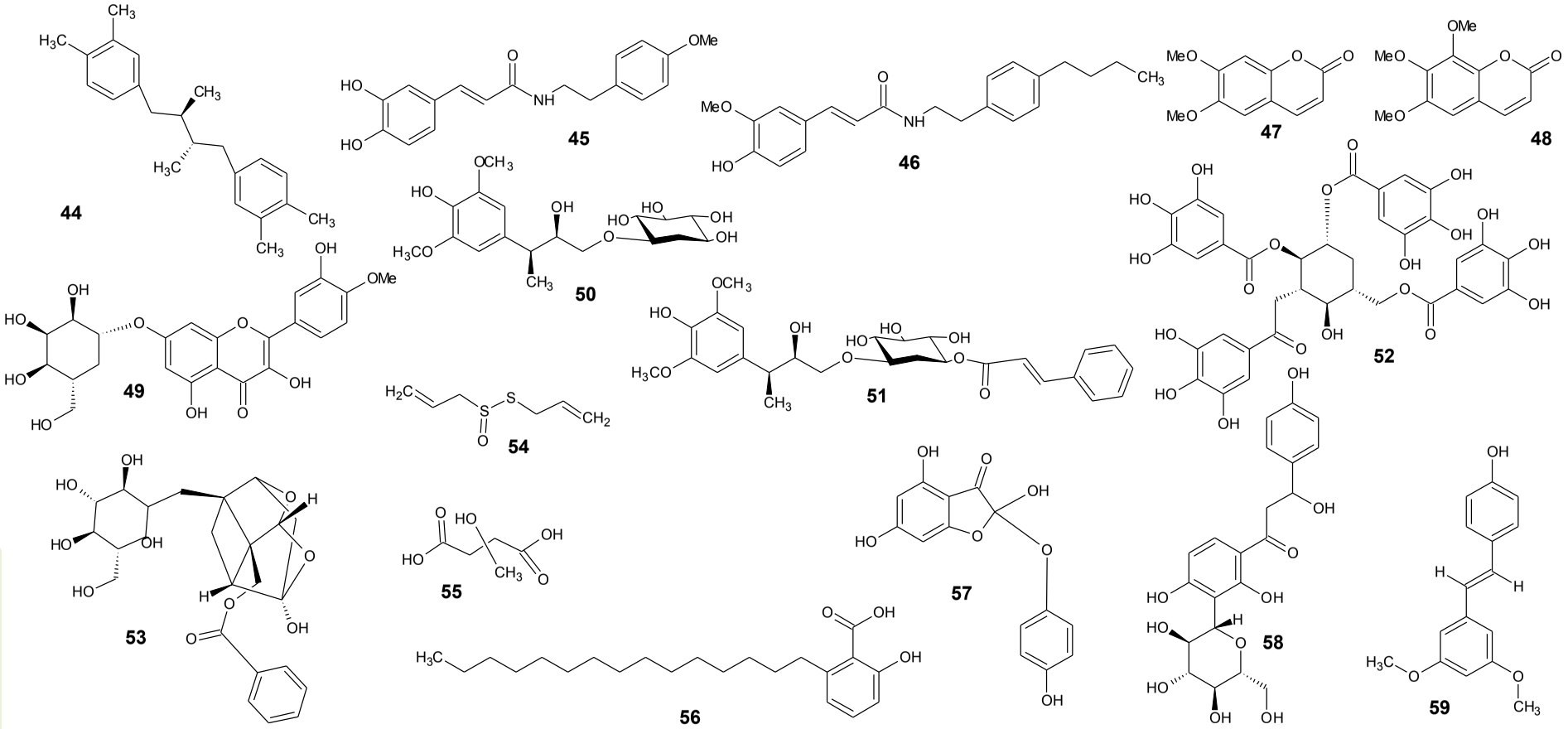

Figure 2(b). Structures of phenols.

Table 3. Triterpenes

S. No	Name of plant	Family	Plant part	Name of extract	Experimental system and dose	Compound (structure no.)	Mechanism of action	Ref
1	*Larix laricina*	Pinaceae	Bark	Ethanol	3T3-L1 cells	23-oxo-3α-hydroxycycloart-24-en-26-oic acid	Enhance adipogenesis	95
2	*Krameria pauciflora*	Krameriaceae	Root	Methanol	Rats, 3, 10, 30 and 100 mg/kgbw	Acycloartane	Antidiabetic activity	96
3	*Paeonia suffruticosa*	Paeoniaceae	Stem	Aqueous	$HepG_2$ cells	Palbinone (**60**)	Increase glucose uptake and enhance glycogen synthesis by activating AMPK	97
4	*Sorbus decora*	Rosaceae	Stem	Ethanol	C_2C1_2 cells	Pentacycle triterpene 23,28-dihydroxylupan-20(29)-ene-	Increase glucose uptake	98

			bark			3β-caffeate (**61**)		
5	*Bacopa monnieri*	Plantaginaceae	Root	Ethyl acetate and ethanol	Rat	Bacosine	Decrease blood glucose level	99
6	*Bixa orellana*	Bixaceae	Leaves	Dichloromethane	Rat, 25, 50, 100 mg/kgbw	Sesquiterpene ishwarane 1 (**62**), phytol 2 (**63**), stigmasterol 4a (**64**) , sitosterol 4b (**65**)	Decrease blood glucose level	100
7	*Bumelia sartorum*	Sapotaceae	Root bark	Ethanol	Rat	Abassic acid	Increase glucose uptake and glycogen synthesis	101
8	*Euclea undulata*	Ebenaceae	Root bark	Acetone	Rat	Betulin (**66**), lupeol (**67**) and epicatechin (**68**)	Decrease blood glucose level and inhibit α-glucosidase activity	102
9	*Lactuca indica*	Asteraceae	Stem	Aqueous	Rats	Lactucain A (**69**), B (**70**) and C (**71**)	Plasma glucose lowering	103
10	*Ferula mongolica*	Umbelliferae	Root	Ethanol	Rats	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 (**72**), (4E, 8E)-1-(2-hydroxy-4-methoxyphenyl)-5,9,13-trimethyltetradeca-4,8,12-trien-1-one (**73**), and (4E, 8E)-1-(2,4- dihydroxyphenyl)-5,9,13-trimethyltetradeca-4,8,12-trien-1- one (**74**)	Inhibit α-glucosidase activity	104
11	*Ficus bengalensis*	Moraceae	Aerial roots	Aqueous	Rats	α-amyrin (**75**)	Plasma glucose lowering	105
12	*Poria cocos*	Polyporaceae	Stem	Chloroform	Rats	Dehydrotrametenolic acid (**76**)	Decrease blood glucose level	106
13	*Lagerstroemia speciosa*	Lythraceae	Leaves	Methanol	Rats	GlucosolTM (**77**)	Glucose transport-stimulating activity and reduce blood glucose levels	107
14	*Acanthopanax senticosus*	Araliaceae	Roots rhizomes	Aqueous	Mice	Senticoside A (**78**)	Lower blood glucose levels	108
15	*Stevia rebaudiana*	Asteraceae	Stem	Pet ether	Pancreatic β-cells	Stevioside (**79**)	Stimulate insulin secretion	109
16	*Croton cajucara*	Euphorbiacea	Bark	Ethanol	Rats	Trans-dehydrocrotonin (**80**)	Hypoglycaemic activity	110
17	*Psacalium decompositum*	Asteraceae	Stem	Water	Mice	3-hydroxycacalolide (**81**), epi-3-hydroxycacalolide, furanoeremophilane (**82**), cacalol (**83**)	Stimulate insulin secretion	111
18	*Scoparia dulcis*	Scrophulariaceae	Leaves	Ethanol	RINm5F cells	Scoparic acid D (**84**)	Stimulation of insulin secretion	112
19	*Senega radix*	Polygalaceae	Root	Aqueous	Rats	Senegin II (**85**)	Hypoglycaemic activity	113
20	*Polygala senega*	Polygalceae	Rhizome	Ethanol	Mice	Desmethoxysenegin II (**86**)	Reduce blood glucose and decrease glucose levels	114
21	*Salacia chinensis*	Celastraceae	Bark	Aqueous methanolic	Rats	Salasones A (**87**), B (**88**), and C (**89**), salaquinone A (**90**), salasol A (**91**), 22-dihydroxyolean-12-en-29-oic acid (**92**), tingenone (**93**), tingenine B (**94**), regeol A (**95**), triptocalline A (**96**)	Inhibit rat lens aldose reductase	115
22	*Centella asiatica*	Apiaceae	Root	Methanol	Rats	Centellasapogenol A (**97**), centellasaponin A (**98**)	Inhibit aldose reductase	116
23	*Salvia miltiorrhiza*	Lamiaceae.	Root rhizome	Ethanol	Rats	Danshenols A (**99**) and B (**100**), danshexinkun A (**101**)	Inhibit activity against the rat lens	117
24	*Tinospora cordifolia*	Menispermaceae	Stem	Ethanol	Mice, 100 mg/kgbw	Tinosporaside (**102**)	Antihyperglycaemic activity	118

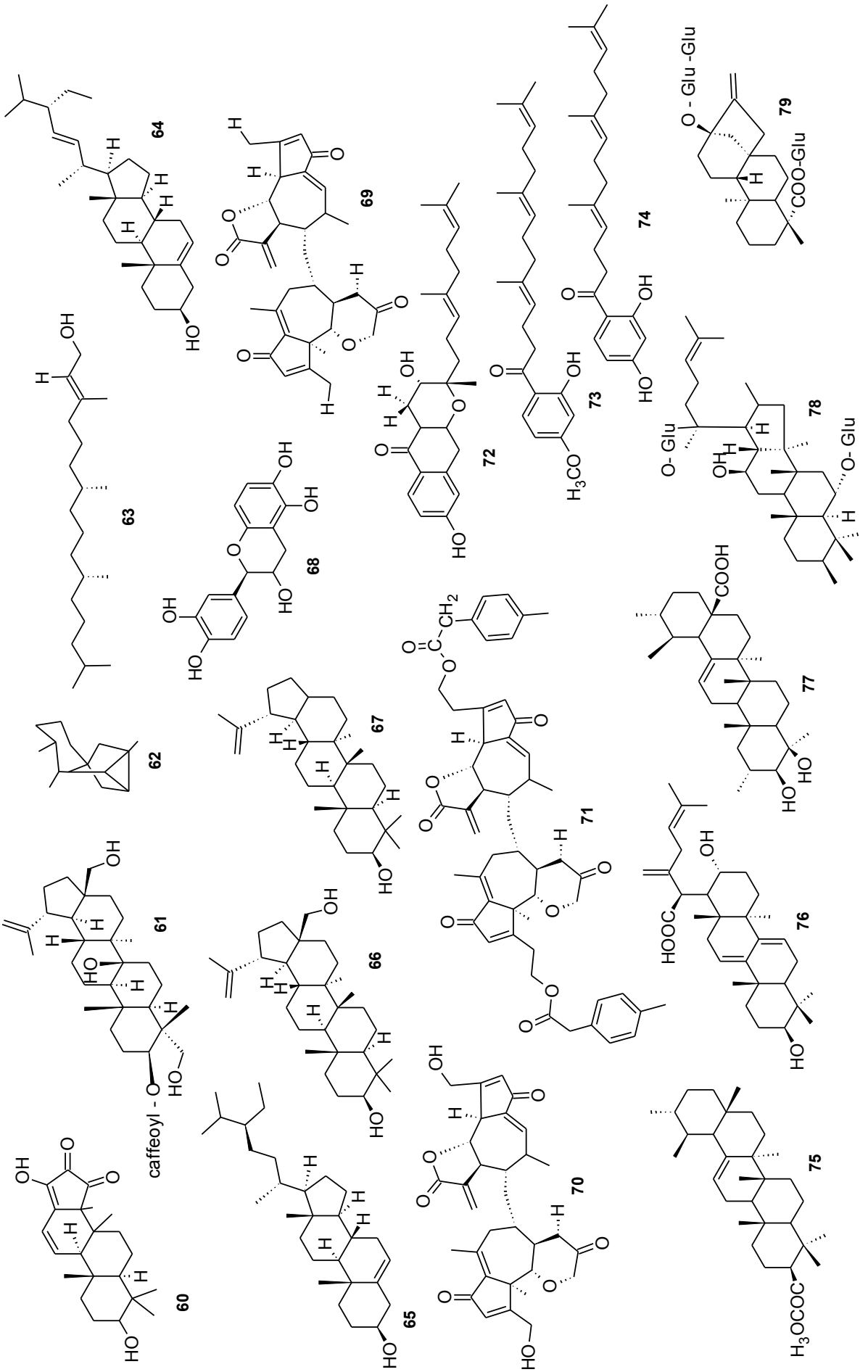

Figure 3(a). Structures of triterpenes

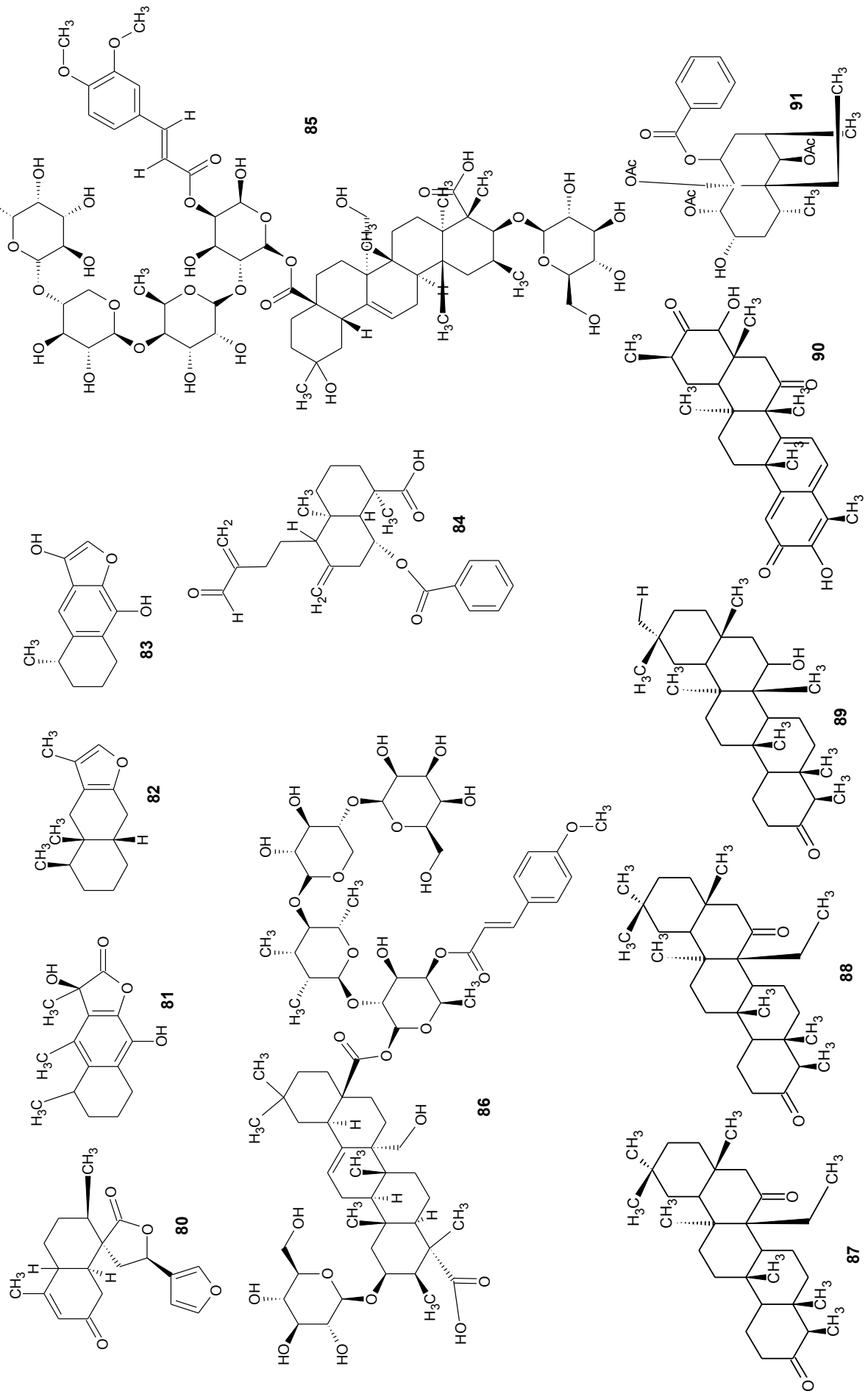

Figure 3(b). Structures of triterpenes

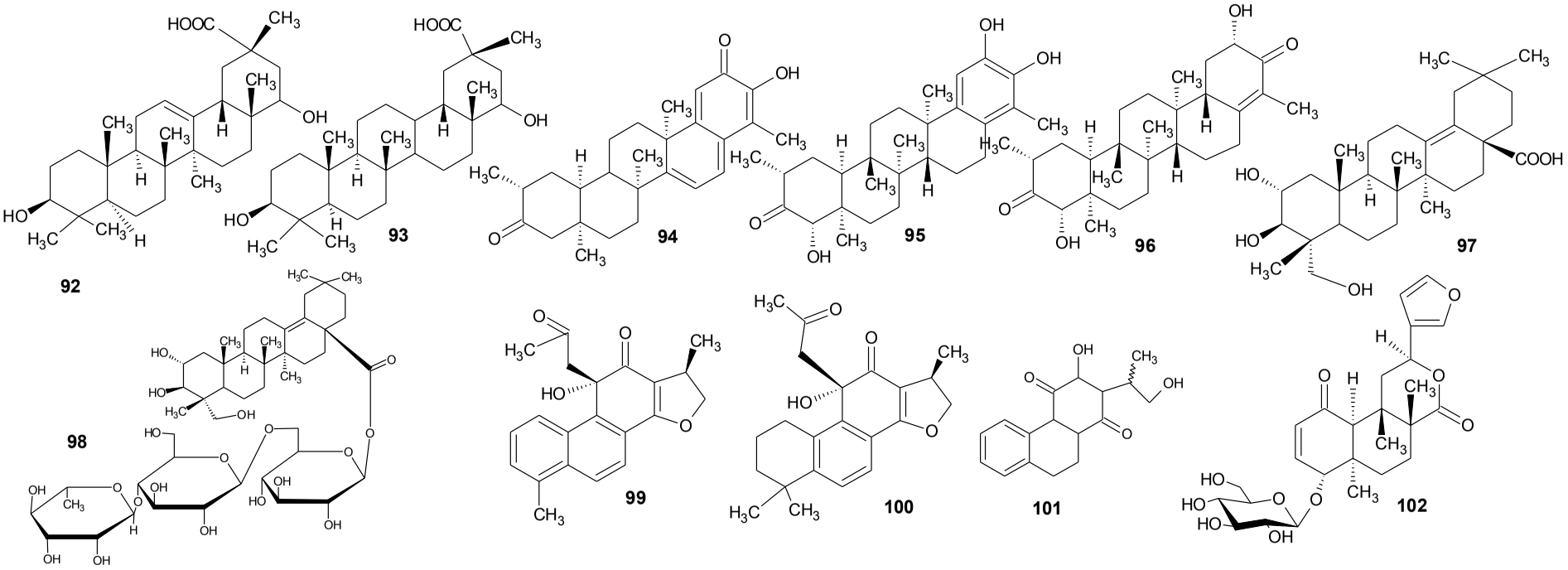

Figure 3(c). Structures of triterpenes

Table 4. Flavonoids

S. No	Name of plant	Family	Plant part	Name of Extract	Experimental system and Dose	Compound (structure number) .	Mechanism of action	Ref
1	*Artocarpus heterophyllus*	Moraceae	Leaves	Ethanol and n-butanol	Rats	Chrysin (**103**) ,silymarin (**104**), isoquercetrin (**105**)	Reduction in levels of serum fasting blood glucose and %HbA1C	119
2	*Beta vulgarisvar*	Chenopodiaceae	Root	Aqueous	Rats	Betavulgarosides I **(106),** II **(107),** III **(108),** IV **(109)**	Oral glucose tolerance test	120
3	*Corni fructus*	Rubiaceae	Stem	Aqueous	Rats	2-butoxybutanedioic acid	Increase in glucose uptake	121
4	*Cinnamomum osmophloeum*	Lauraceae	Leaves	Aqueous	3T3-L1 adipocytes cell line	Kaempferol glycosides CO-1 and CO-2	Insulin -like antidiabetic mechanism	122
5	*Parinari excels*	Chrysobalanaceae	Bark	Aqueous	Mouse	Myricetin (**110**) and quercertin	Induce insulin secretion	123
6	*Origanum majorana*	Labiatae	Leaves	Methanol	Rats	6-hydroxyapigenin (**111**), 6- hydroxyapigenin-7-O-β-D-glucopyranoside(**112**),6-hydroxyluteolin-7-O-β-D-glucopyranoside (**113**), 6-hydroxyapigenin-7- O-(6-O-feruloyl)- β-D-glucopyranoside (**114**), and 6-hydroxyluteolin-7-	α-glucosidase inhibitory activity,	124

						O-(6-O-feruloyl)- β-D-glucopyranoside (**115**), 6-hydroxyluteolin (**116**)		
7	*Scutellaria baicalensis*	Lamiaceae	Root	Ethanol	Rats	Baicalein (**117**)	α-glucosidase activity	125
8	*Garcinia kola*	Clusiaceae	Stem	Aqueous	Rabbits, 100 mg/kgbw	Kolaviron	Reduce blood glucose and decrease glucose levels	126
9	*Tetracera scandens*	Dilleniaceae	Leaves	Ethyl acetate	Rats	3',5'-diprenylgenistein (**118**), 6,8-diprenylgenistein (**119**), derrone (1**20**) , alpinumisoflavone (**121**)	Uptake of glucose increased and induced GLUT4 and GLUT1 mRNA expression levels	127
10	*Eucommia ulmoides*	Eucommiaceae	Leaves	Aqueous	Rats	Quercetin 3-O-α-Larabinopyranosyl-(1, 2)- β-D-glucopyranoside (**122**) , kaempferol 3-O-β-D-glucopyranoside **(123**) , quercetin 3-O-β-d-glucopyranoside (**124**)	Glycation inhibitory activity, lower plasma levels of triglyceride, total cholesterol, LDL-cholesterol, non HDL-cholesterol, and free fatty acid	128
11	*Cecropia obtusifolia*	Urticaceae	Root bark	Water and n-butanol	Rats	Isoorientin (**125**)	Reduction of glucose and HbA1c	129
12	*Dorstenia psilurus*	Moraceae	Root	Aqueous	Mice	Dorsilurins F-K (1**26-131**)	α-glucosidase and β-glucosidase inhibitory activity	130
13	*Hintonia latiflora*	Rubiaceae	Bark	Aqueous	Wistar rats	Coutareagenin	Reduce blood glucose and decrease glucose levels	131
14	*Bauhinia forficate*	Fabaceae	Stem	n-butanol	Rats	Kaempferol-3,7-*O*-(α)-dirhamnopyranoside (**132**)	β-glucosidase inhibitory activity	132
15	*Bauhinia forficate*	Fabaceae	Root	Aqueous	Rats	Kaempferol-3-neohesperidoside	Induce insulin secretion	133
16	*Phyllostachys nigra*	Poaceae	Leaves	Metanol	Rats	Luteolin 6-*C*-(6″-*O*-*trans*-caffeoylglucoside) (**133**)	Inhibitory effect against advanced glycation	134
17	*Actinidia arguta*	Actinidiaceae	Root	Methanol	Rats	6-(2-pyrrolidinone-5-yl)-(−)-epicatechin (**134**) ,8-(2-pyrrolidinone-5-yl)-(−)-epicatechin (**135**)	*In vitro* inhibitory activity by formation of advanced glycation	135
18	*Euphorbia leucophylla*	Euphorbiaceae	Root	Alcoholic	Rats	4',5-dihyroxy-6,7-dimethoxyflavone-3-*O*-β- D-xylopyranoside (**136**)	Reduce blood glucose levels and increase serum insulin levels	136
19	*Eysenhardtia platycarpa*	Fabaceae	Leaves	Aqueous	Rats	Flavone [1″(*R*)-5,4′,1″-trihydroxy-6,7-(3″,3″-dimethylchromano)flavone, **137** and flavanone [(2*S*)-4′-*O*-methyl-6-methyl-8-prenylnaringenin, (**138**)	Reduce blood glucose levels	137
20	*Erigeron annuus*	Asteraceae	Flowers	Methanol	Mice	Erigeroflavanone (**139**)	Inhibitory activity against advanced glycation formation	138
21	*Brickelia veronicaefolia*	Asteraceae	Leaf	Chloroform	Mice, 10, 20 and 50 mg/kgbw	5, 7, 3'-trihydroxy-3, 6, 4'-trimethoxyflavone (**140**)	Reduce blood glucose levels	139
22	*Bombax ceiba*	Malvaceae	Leaves	Methanol	Sprague-Dawley rats	Shamimin (2-(2, 4, 5-trihydroxyphenyl)-3,5,7-trihydroxy-6-C- glucopyranosyloxy-4H-1-benzopyran-4-one **141**)	Reduction in glycaemia	140
23	*Averrhoa carambola*	Oxalidaceae	Leaves	Ethanol	Rats	Apigenin-6-C-(2"-O-α-L-rhamnopyranosyl)-β-L-fucopyranoside	Blood glucose-lowering effects,, stimulate glucose-induced insulin secretion	141
24	*Pueraria lobata*	Fabaceae	Root	Chloroform	Mice	Kakonein (**142**)	Lower blood glucose levels	142
25	*Pueraria*	Faboideae	Flowers	Ethanol	Rats	Tectorigenin (**143**) , kaikasaponin III (**144**)	Up-regulating or down-	143

	thunbergiana						regulating antioxidant mechanisms	
26	*Psidium guajava*	Myrtaceae	Leaves	Aqueous	Rats	strictinin (**145**) and isostrictinin and pedunculagin	Decrease in blood glucose levels	144

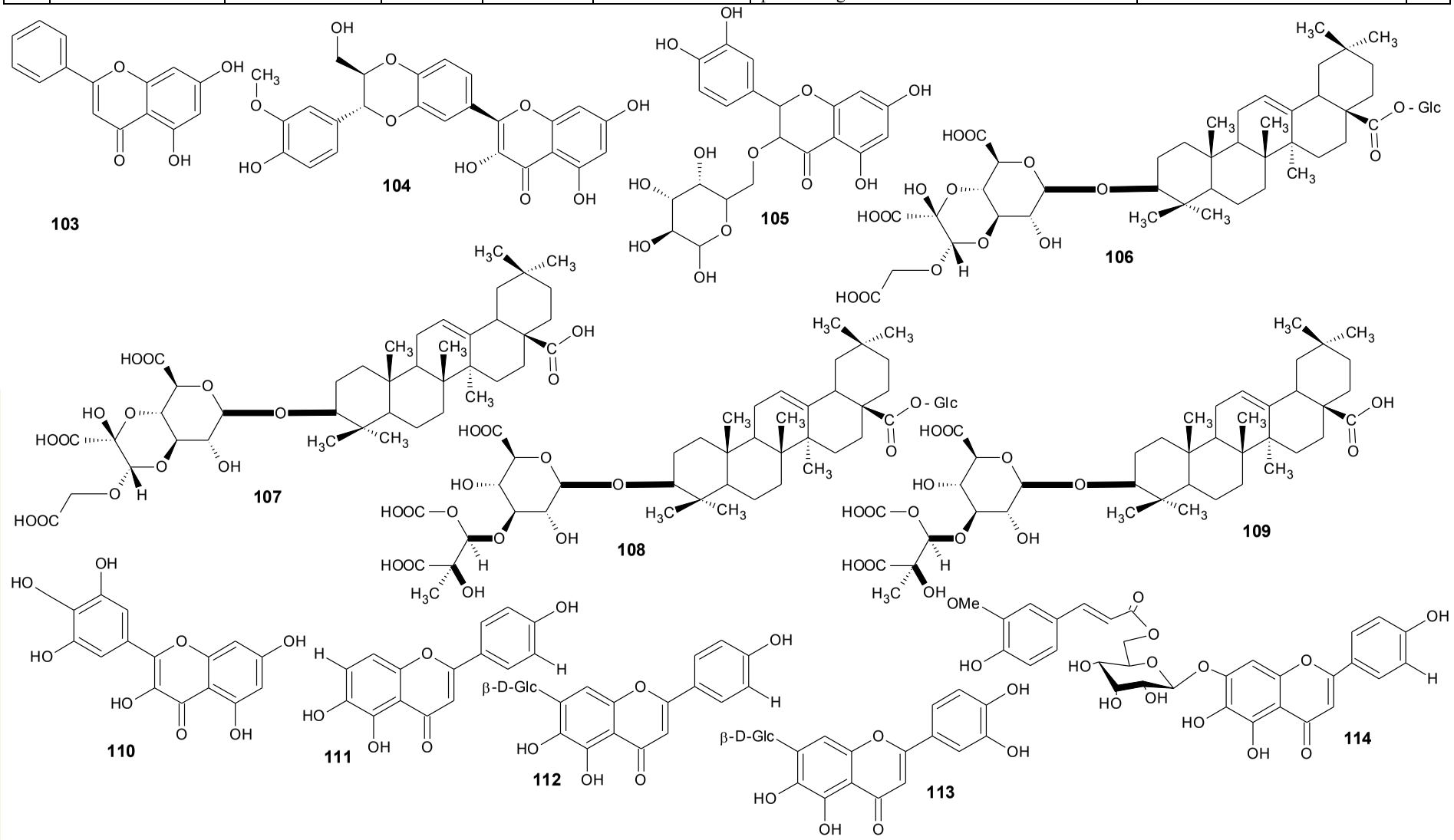

Figure 4(a). Structures of flavonoids

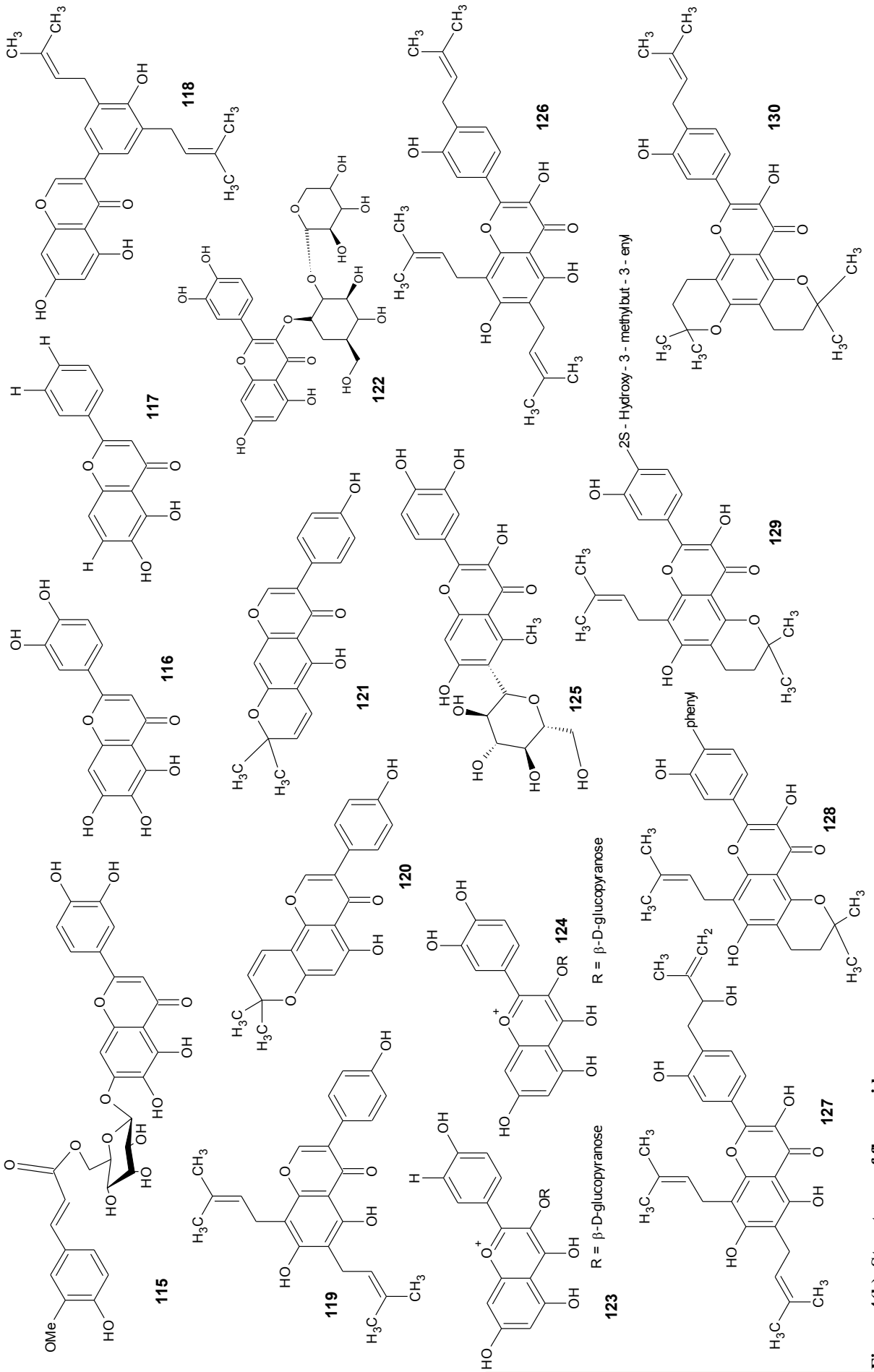

Figure 4(b). Structures of flavonoids

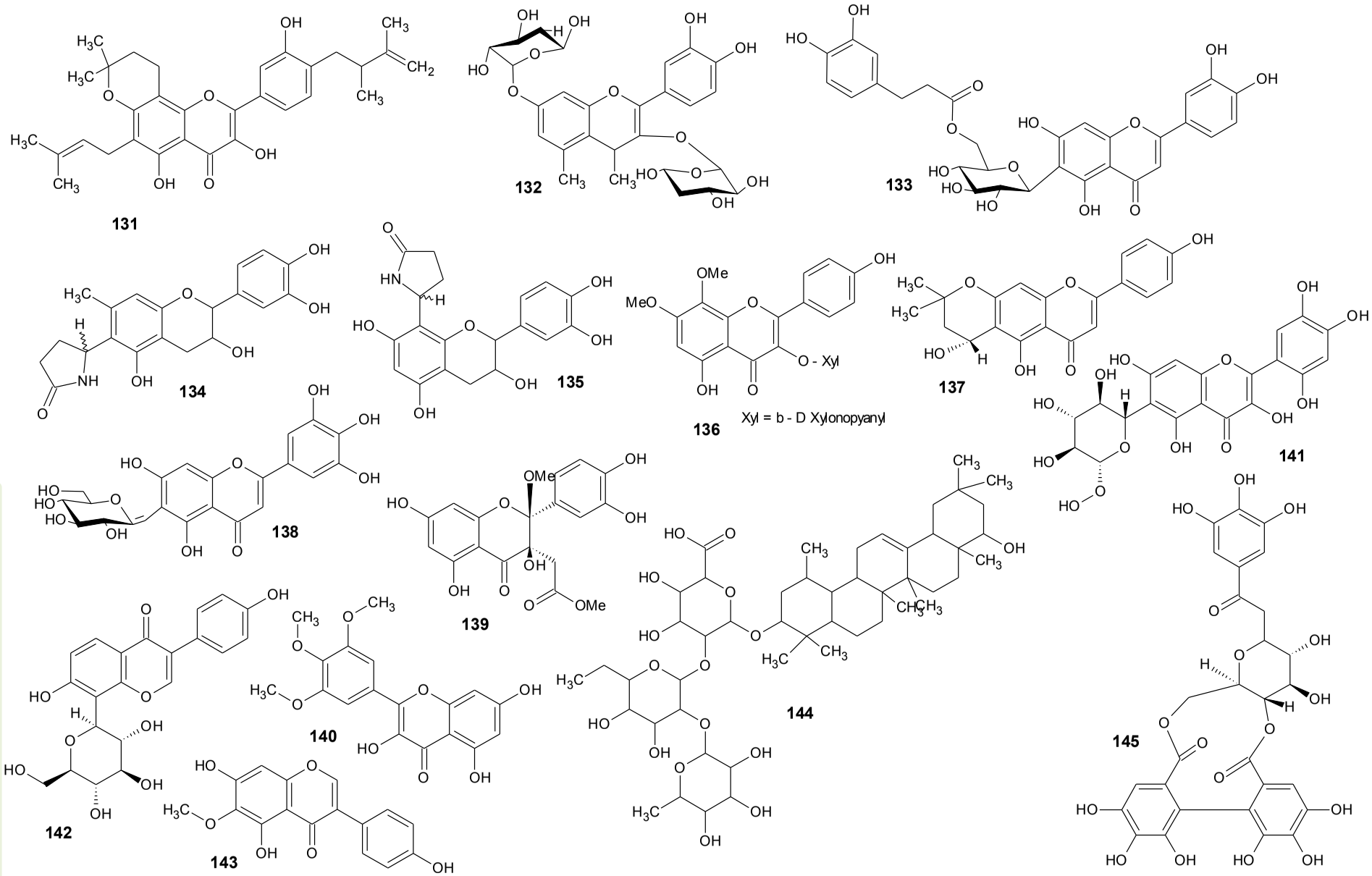

Figure 4(c). Structures of flavonoids

Table 5: Saponins

S. No	Name of plant	Family	Plant part	Name of Extract	Experimental system and Dose	Compound (structure number	Mechanism of action	Ref
1	*Anemarrhena asphodeloides*	Asparagaceae	Rhizomes	Hot water	Rats	Timosaponin A (**146**) , sarsasapogenin (**147**)	Reduce blood glucose levels	145
2	*Polygala senega*	Polygalaceae	Root	Methanol	Rats	Z-senegins II (**148**) and III, IV, Esenegasaponin C and Z-senegasaponin C	Reduce blood glucose levels	146
3	*Gymnema sylvestre*	Asclepiadaceae	Leaves	Acetone	Mice	Dihydroxy gymnemic triacetate (**149**) , Gymnemosides A (**150**), B (**151**) , gymnemic acid V (**152**), gymnemic acids I-IV and gymnemasaponin V (**153**)	Enhance endogenous insulin release, inhibit α-glycosidase activity	147
4	*Gynostemma pentaphyllum*	Cucurbitaceae	Root	Ethanol	Pancreatic islets	Gypenoside (**154**)	*In vitro* insulin release, enhance plasma insulin levels and improve glucose tolerance levels	148
5	*Aralia elata*	Araliaceae	Stem	Butanol	Hepg2 cells	Elatosides E (**155**)	Increase of glycogen levels	149
6	*Kochia scoparia*	Amaranthaceae	Furit	Methanol	Rats	Momordin Ic (**156**) and 2'-O-β-D-glucopyranoside	Inhibit glucose and ethanol absorption	150
7	*Elephantopus scaber*	Asteraceae	Leaves	Acetone	Rats	28 Nor-22(R)Witha 2,6,23-trienolide	Elevation of blood glucose levels and restoration of insulin levels	151
8	*Panax ginseng*	Aralioideae	Roots and rhizomes	Ethanol	Rats	Ginsenoside Rg1 (**157**)	Regulate blood glucose levels and reduction in serum insulin levels	152

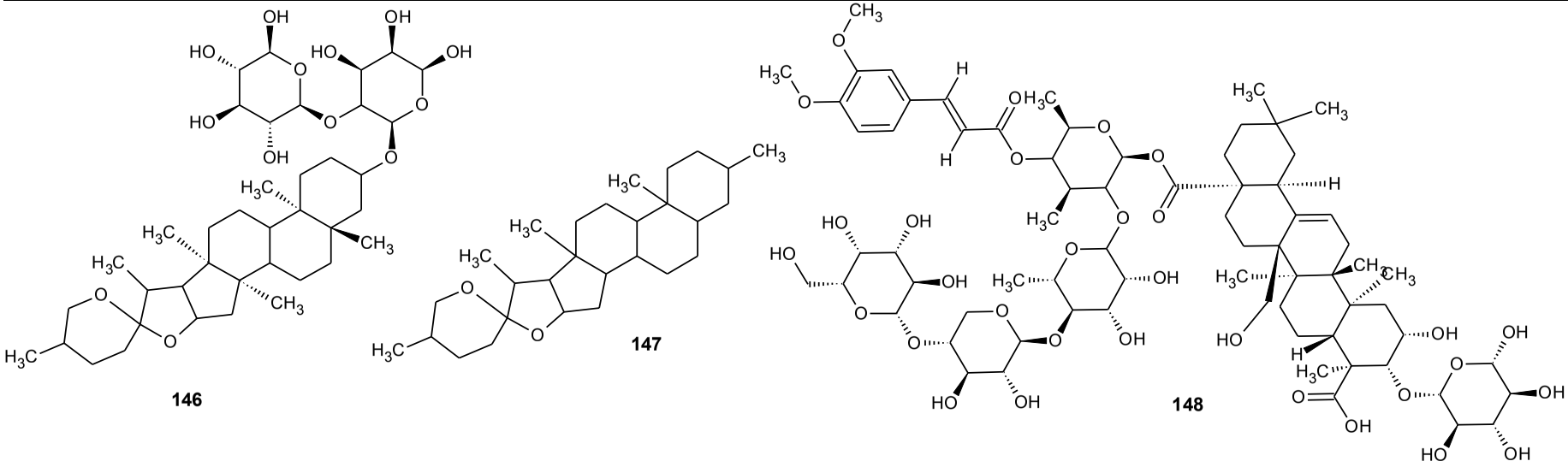

Figure 5(a). Structures of Saponins

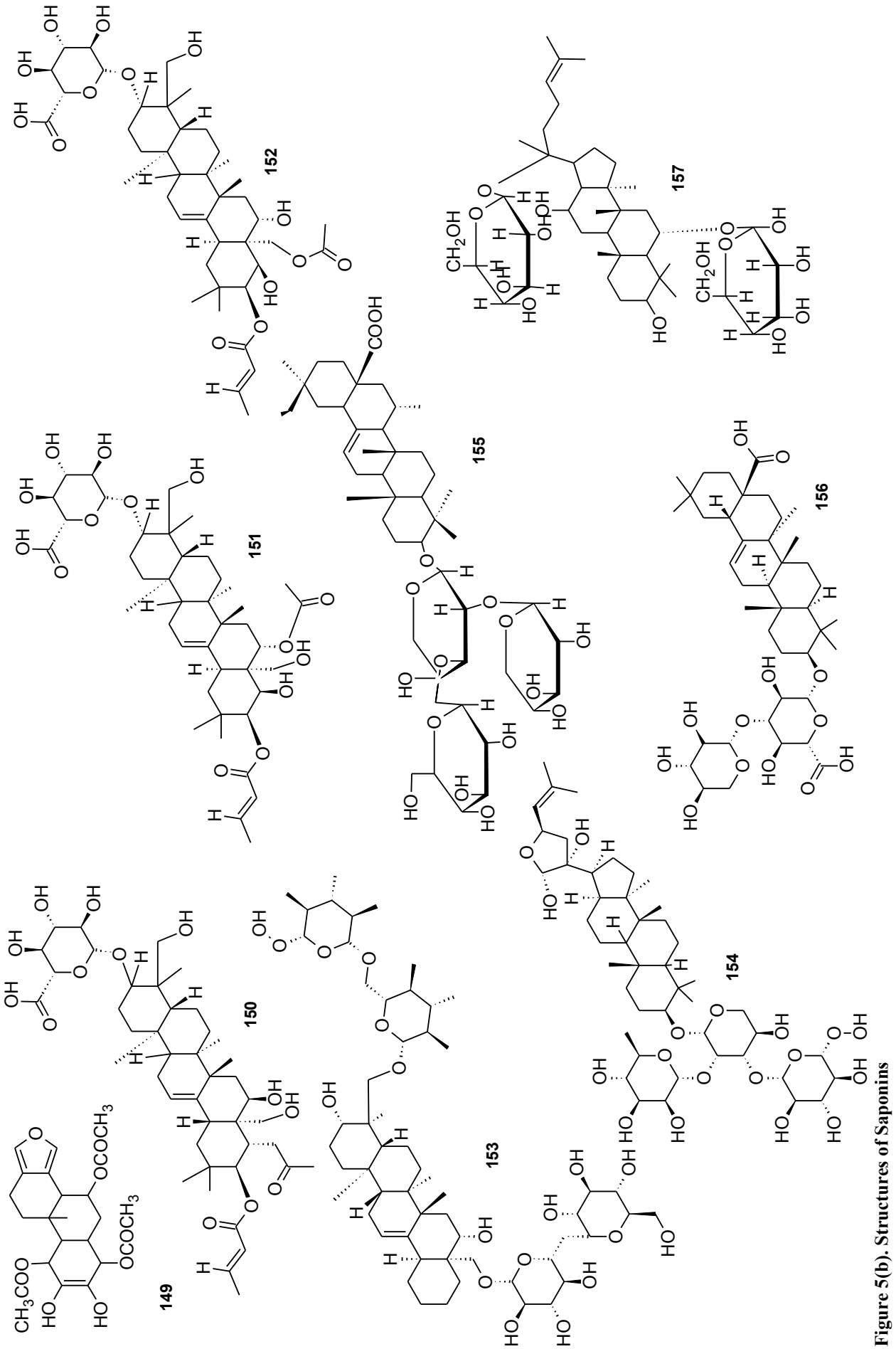

Figure 5(b). Structures of Saponins

Table 6. Glycosides

S. No	Name of plant	Family	Plant part	Name of Extract	Experimental system and Dose	Compound Name and Number	Mechanism of action	Ref
1	*Lantana camara*	Verbenaceae	Leaves		Rat	urs-12-en-3β-ol-28-oic acid 3β-D-glucopyranosyl-4'-octadecanoate	Reduction in blood glucose levels	153
2	*Vaccinium arctostaphylos*	Ericaceae	Berries	methanol :glacial acetic acid :water	Rats	Anthocyanin (**158**) , malvidin-3-O–β–glucoside (**159**)	Inhibitory effects on pancreatic α-amylase activity	154
3	*Scoparia dulcis*	Plantaginaceae	Leaves and stems	Aqueous and chloroform	Rat	Ammelin	Reduce blood glucose levels	155
4	*Ficus bengalensis*	Moraceae	Bark	Juice	Rat, 100 mg/kgbw	Leucopelargonidin (**160**), 3, 7 dimethoxy ether of leucopelargonidin-3- O-α-L rhamnoside (**161**), leucodelphinidin (**162**)	Serum insulin-enhancing effects, serum insulin-raising actions	156
5	*Syzygium malaccense*	Myrtaceae	Root	Methanol	Mice	Casuarine 6-O-α-glucoside	Inhibit α-glucosidase activity	157
6	*Salacia reticulatea*	Celastraceae	Leaves	Methanol	Mice	Salacinol **(163)**	α–glucosidase inhibitory activity	158
7	*Bidens pilosa*	Asteraceae	Whole plant	Methanol and n-butanol	Non-obese diabetic mice	Cytopiloyne (**164**) and 2-β-D-glucopyranosyloxy-1-hydroxy-5(E)-tridecene-7,9,11-triyne and 3-β–D-glucopyranosyloxy-1-hydroxy-6(E)-tetradecene-8,10,12-triyne	Glucose-lowering and insulin-releasing activities, suppres differentiation of Th0 cells into Th1 cells, decreases in blood glucose	159
8	*Acosmium panamense*	Faboideae	Bark	Methanol	Rat/ 20-200 mg/kgbw	β- D-Oglucoside (**165**) and β– D-O-di (1-6) glucoside (**166**)	Decrease in plasma glucose levels	160
9	*Rehmannia glutinosa*	Phrymaceae	Root	Acetone	Rats	rehmannioside A (**167**) ,D (**168**) , leucosceptoside A (**169**), purpureaside C (**170**)	Decrease in plasma glucose levels	161
10	*Trichosanthes kirilowii*	Cucurbitaceae	Root	Aqueous	Mice	Trichosans A, B, C, D and E	Reduce plasma glucose levels	162
	Gycine max	Fabaceae	Leaves	Methanol	Mice	Kaempferol 3-O-β-D-glucopyranosyl(1→2)-O-[α-L-rhamnopyranosyl(1→6)]-β-D-galactopyranoside, kaempferol 3-O-β-D-glucopyranosyl(1→2)-O-[α-L-rhamnopyranosyl(1→6)]-β-D-glucopyranoside,	Decrease in Hb1Ac level, oral glucose tolerance test,triglyceride level and fatty acid synthase activity	163

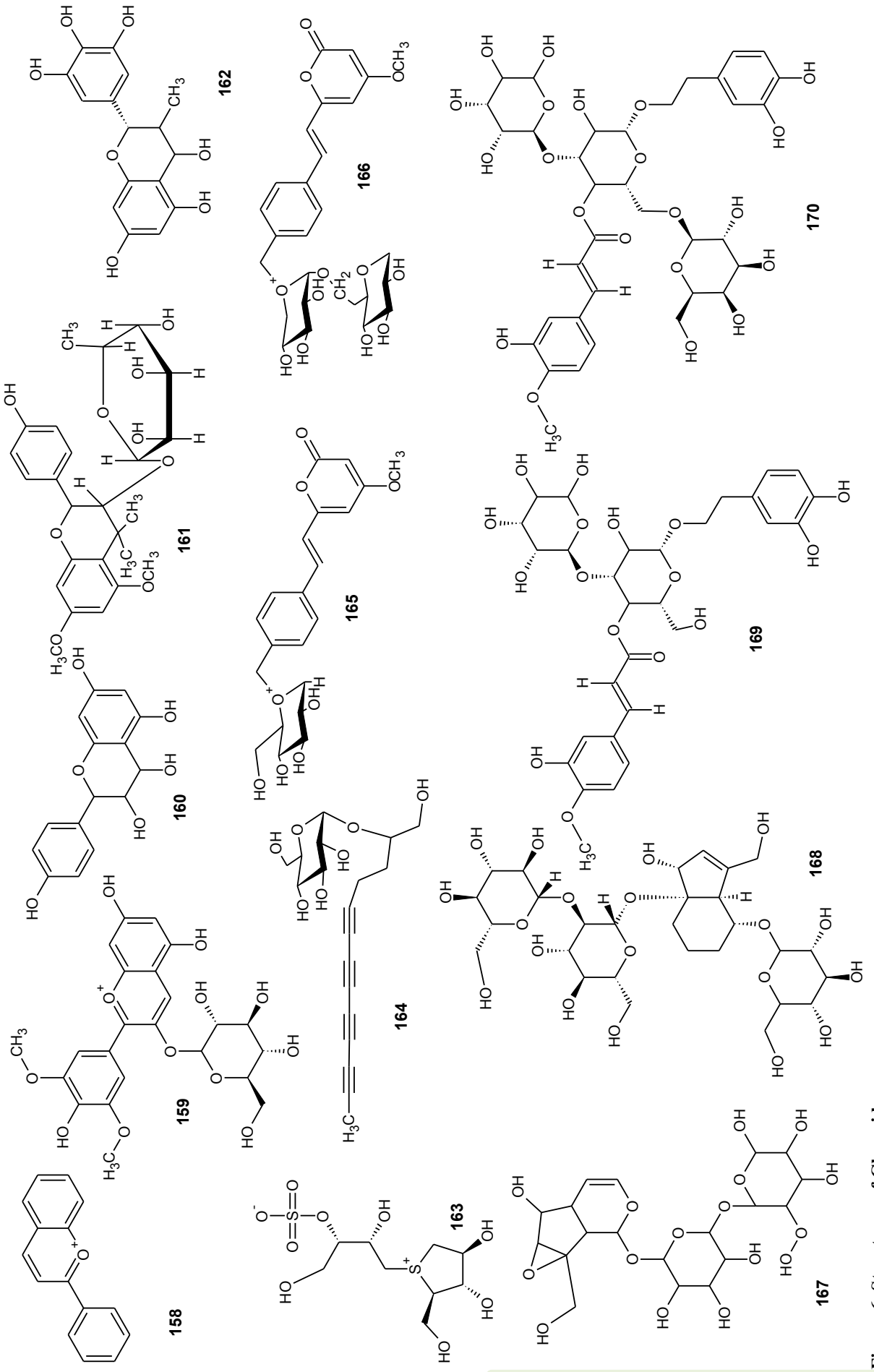

Figure 6. Structures of Glycosides

Table 7: Xanthone

S. No	Name of plant	Family	Plant part	Name of Extract	Experimental system and Dose	Compound Name and Number .	Mechanism of action	Ref
1	*Ilex paraguariensis*	Aquifoliaceae	Leaves	Chloroform, ethylaccetate and n-butonal	Rat	Methyl xanthone	Lower blood glucose levels	164
2	*Swertia Punicea*	Gentianaceae	Whole plant	Ethyl acetate and ethanol	Mice	Methylswertianin (**171**) and bellidifolin (**172**)	Reduce fasting blood glucose, enhance insulin signalling	165
3	*Anemarrhena asphodeloides*	Asparagaceae	Rhizome, Arial part	Aqueous	Mice	Mangiferin (**173**) , mangiferin-7-O-β-d glucoside (**174**)	Decrease blood glucose level and increase insulin sensitivity	166
4	*Mangifera indica*	Anacardiaceae	Stem leaves, heartwood, roots and fruit	Decoction with polar solvent	KK-Ay mice	C-glucosylxanthone mangiferin	Hyperinsulinemia and, on insulin tolerance test, reduced blood glucose levels	167
5	*Swertia chirayita*	Gentianaceae	Whole plant	Hexane	Islets of Langerhans	Swerchirin (**175**)	Lowers blood glucose level by stimulating insulin release	168

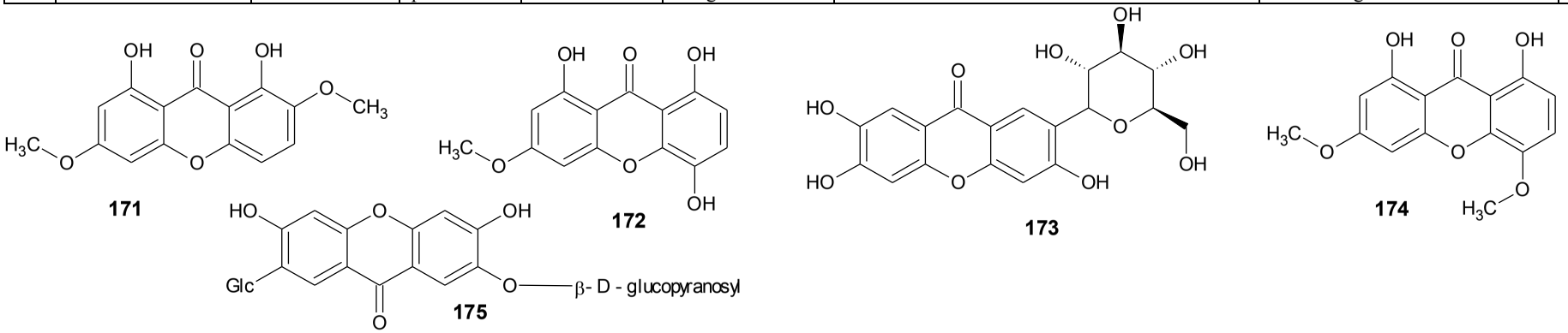

Figure 7(a). Structures of Xanthones

Table 8: Polysaccharides

S. No	Name of Plant	Family	Part Used	Name of extract	Experimental system and dose	Compound (structure number)	Mechanism of action	Ref
1	*Gynura divaricata*	Asteraceae	Aerial part	Water	Rats	β–D-fructofuranose, sucrose, 1-kestose, nystose, and 1(F)-β–fructofuranosylnystose	Hypoglycaemic activity	169
2	*Curcuma longa*	Zingiberaceae .	Rhizomes	Water	Mice	Turmerin	Inhibition in α-amylase and α-glucosidase activities (IC_{50} values of 31 and 192 µg/ml)	170
3	*Ophiopogon japonicus*	Asparagaceae	Roots	hot water	STZ-induced diabetic rats	Water -soluble polysaccharide	Reduce blood glucose level, increased insulin level and remediate destruction of pancreatic islets	171

4	*Cucurbita moschata*	Cucurbitaceae .	Fruits	Methanol and aqueous	Rats	Polysaccharide	Showed α-glucosidase inhibitory effect	. 172
5	*Cucurbita moschata*	Cucurbitaceae	Fruits	95% ethanol	STZ and high-fat-diet-induced diabetic mice	Tetrasaccharide glyceroglycolipids	Significantly decreased glucose level	173
6	*Cucurbita moschata*	Cucurbitaceae	Fruits	water	Alloxan induced diabetic rats at a dose of 1000 mg/kgbw	Protein-bound polysaccharide	Hypoglycemic activity and increased serum insulin levels	174
7	*Sonneratia Alba*	Sonneratiaceae	Leafs	Water	Mice	Complex polysaccharide	Significantly high attenuating activity for blood glucose	175
8	*Opuntia ficus-indica*	Cactaceae	Fresh cladodes	Juice	Alloxan diabetic mice at a dose of 500 mg/kgbw	Polysaccharide (POLOF and POLOS)	Hypoglycemic effects	176
10	*Portulaca oleracea*	Portulacaceae	Fresh whole plant	Chloroform-methanol	Alloxan-induced diabetic mice at a dose of 400 mg/kgbw	Polysaccharide (POP)	Significant decrease in the concentration of fasting blood glucose , total cholesterol triglyceride and significant increased in the concentration of HDL cholesterol and serum insulin level	177
11	*Momordica charantia*	Cucurbitaceae	Fruit	Juice	Rats	Momordicosides	Hypoglycemic activity	178
12	*Ganoderma lucidum*	Ganodermataceae	Fruit pulp	Hot water	Rat	(1, 4)-β-D-mannoxylan or (1,3)–β-D-glucan	Reduce serum glucose levels	179
13	*Camellia sinensis*	Theaceae	Leaves	Water	Rats	L-arabinose, D-ribose, D-xylose, D-glucose, D-galatose, D-mammose and glucuronic acid	Reduce blood glucose, blood triglycerides and antihyperglycemic activity	180
14	*Lycium barbarum Linn*	Solanaceae	Fruits	Water decoction	Alloxan-induced diabetic rabbits	Crude polysaccharide	Hypoglycemic and hypolipidemic activity	181
15	*Psacalium decompositum*	Asteraceae	Root	Water , methanol, and hexane	Mice	Polysaccharide	Significantly reduction in fasting glycemia	182
16	*Physalis alkekengi Linn.*	Solanaceae	Fruit	Ethanol and hot water	Mice	Rha, Ara, Gal, Glc and GalA	Hypoglycemic activity	183
17	*Astragalus membranaceus*	Astragalus	Root	Water and ethanol	Diabetic rats and mice	Astragalus polysaccharides	Significantly lowered the level of blood glucose, triglyceride levels	184
18	*Rehmannia glutinosa*	Scrophulariaceae	Rhizome	Water	Normal and STZ induced diabetic mice	Pectin-like polysaccharide	Hypoglycemic activity, stimulated secretion of insulin and reduced the glycogen content in the liver	185
19	*Panax ginseng Linn.*	Araliaceae.	Root	Water	Rats at doses of 50-200 mg/kgbw	Ginseng polypeptides	Antihyperglycemic effect	186
20	*Panax quinquefolium Linn.*	Araliaceae.	Roots and rhizomes	Ethanol	Normal and alloxan induced hyperglycemic mice	Quinquefolans A, B, and C	Hypoglycemic effect	187

21	*Malva verticillata*	Malvaceae	Seeds	-	Mice	Polysaccharides and peptidoglycans	Hypoglycemic activity	188
22	*Coix lacryma-jobi*	Poaceae	Seeds	Water	Normal rats	Coixans A, B and C polysaccharides	Decrease in blood glucose and increased serum insulin levels	189
23	*Cordyceps sinensis*	Ophiocordyciptaceae	Whole plant	Hot water	Alloxan- and STZ-induced diabetic rats	Polysaccharide CS-F10, CS-F30, CHWp	Significantly lower plasma glucose	190
24	*Ganoderma lucidum*	Ganodermataceae	Seed	Ethanol	Normal rats	Polysaccharides Ganoderans A and B	Hypoglycemic activity	191
25	*Psidium guajava*	Myrtaceae	Leaves	Aqueous	Rats	Glycoprotein	Antidiabetic activity	192
26	*Rhodiola sachalinensis*	Crassulaceae	Root	Water	Rats at doses of 200 and 400 mg/kgbw	Polysaccharide	Significant hypoglycemic activity via lowering of blood glucose level	193
27	*Liriope spicata var*	Asparagaceae	Root	Aqueous Ethanol	Rat	Polysaccharide β-(1>2)-fructosyl	Hypoglycemic and hypolipidemic activity	194
28	*Triticum aestivum*	Gramineae	Whole plant	Water and ethanol	RIN-5F cell line, dose of 0.1 to 2 mg/ml	Polysaccharide	Significant increase in glucose-induced 45Ca2+ uptake and proinsulin mRNA expression in rat islets and stimulating effect on insulin secretion, production in pancreatic β-cells via K+ channel closure and calcium influx	195
29	*Amorphophallus rivieri*	Araceae	Tuber	Water	Animals	Konjack oligosaccharides and galactomannan	Decrease blood glucose in animals	196

Table 9: Other compounds

S. No	Name of Plant	Family	Part Used	Name of extract	Experimental system and Dose	Compound (Structure number)	Mechanism of action	Ref
1	*Acer rubrum*	Aceraceae	Stem	Methanol		Maplexins A–E	α-glucosidase inhibitory activity	197
2	*Syzygium aromaticum*	Myrtaceae	Flower Bud	Ethanol	Mice	Dehydrodieugenol and Dehydrodieugenol B	PPAR binding activities and decrease blood glucose levels	198
3	*Glycyrrhiza inflata*	Fabaceae	Roots	Water	Mice	Lico E aretrochalcone	Lower blood glucose levels and serum triglyceride levels	199
4	*Lippia nodiflora*	Verbenaceae	Whole plant	Methanol	Rats	γ-sitosterol (**176**)	Antidiabetic activity	200
5	*Trigonella foenum-graecum*	Fabaceae	Seeds	Water	Islets of rats and human	4-hydroxyisoleucine (**177**)	Induce insulin release, activation of insulin signaling	201
6	*Lithospermum erythrorhizon*	Boraginaceae	Root	Aqueous	Skeletal muscle cells and Rats	Shikonin (**178**)	Increases in glucose uptake and enhanced insulin sensitivity	202
7	*Acer pycnanthum*	Aceraceae	Leaves	Hot water	ddY male mice	Pycnalin (**179**), ginnalins A (**180**), B, C, and 3, 6-di-O-galloyl-1,5-anhydro-D-glucitol (**181**)	Inhibit α-glucosidase activity	203
8	*Casearia esculenta*	Samydaceae	Root	Benzene and alcoholic	Type 2 DM Rats	3-hydroxymethyl xylitol (**182**)	α-Glucosidase inhibitory activity	204
9	*Potentilla chinesis*	Rosaceae	Flower	Ethanol	Mice and rats	Trans-tiliroside (**183**)	Antihyperglycaemic and antihyperlipidaemic activity	205

10	*Laminaria japonica*	Laminariacea e	Root	Aqueous	Mice	Butyl-isobutyl-phthalate (**184**)	Inhibit α-glucosidase activity	206
11	*Ligusticum porter*	Apiaceae	Root		Rats, 56.2 mg/kgbw	(Z)-6,6',7,3'α-diligustilide (**185**), (Z)-ligustilide (**186**) ,3-(Z)-butylidenephthalide (**187**)	inbhit α-glucosidase activity	207
12	*Lagerstroemia speciosa*	Lythraceae	Leaves	Hot water	Rats	Lagerstroemin (**188**)	Increase glucose uptake and decrease isoproterenol-induced glycerol release	208
13	*Olea europaea*	Oleaceae	Leaves	Methanol and water	Rats, 8 and 16 mg/kgbw	Oleuropein (**189**) ,hydroxytyrosol (**190**)	Increase in lipid peroxidation	209
14	*Cinnamonum zeylanicum*	Lauraceae	Dried barks	Aqueous	Male Wistar rats	Cinnamaldehyde (**191**)	Glucose and lipid lowering effect	210
15	*Peucedani Radix*	Umbelliferae	Root bark	Ethanol	Rats	Myo-inositol (**192**) and peucedanol 7-O-β-D-glucopyranoside	Inhibit postprandial hyperglycaemia	211 222
16	*Achyrocline satureioides*	Asteraceae	Whole part	Aqueous ethanol	Mice, 20 mg/kgbw	Achyrofuran (**193**)	Decrease blood glucose level	212
17	*Xanthocercis zambesiaca*	Fabaceae	Leaves and root	Aqueous methanol	Mice and pancreas islets	Fagomine (**194**), 4-O-β-D-glucopyranosylfagomine (**195**), 3-O-β-D-glucopyranosylfagomine (**196**), 3-epifagomine (**197**), 2,5-dideoxy-2,5-imino-D-mannitol (**198**), castanospermine (**199**), α-homonojirimycin (**200**) , 1-deoxynojirimycin (**201**)	Glucose-induced insulin release	213
18	*Citrullus colocynthis*	Cucurbitaceae	Seeds	Aqueous alcoholic	Rat pancreas and Rat islets	β-pyrazol-1-ylalanine (**202**)	Induce insulin secretion *in vitro*	214
19	*Caesalpinia sappan*	Fabaceae	Whole plant	water, alcohol	Rat	Caesalpin P (**203**), sappanchalcone (**204**), 3-deoxysappanone, brazilin (**205**), protosappanin (**206**)	Aldose reductase inhibitory activity	215
20	*Allium sativum*	Amaryllidace ous	Bulb	Water	Rats and Rabbit	*S*-allyl cysteine sulfoxide (**207**)	Blood sugar lowering activity	216
21	*Artemisia dracunculus*	Asteraceae	Fresh herb	Ethanol	Rats	Davidigenin, sakuranetin, 2',4'-dihydroxy-4-methoxydihydrochalcone, 4,5-di-O-caffeoylquinic acid, 5-O-caffeoylquinic acid, and 6-demethoxycapillarisin	Inhibitory effects towards the enzyme aldose reductase	217
22	*Magnolia dealbata*	Magnoliaceae	Seeds	Ethanol	Rats	Honokiol and magnolol	2-NBDG uptake	218
23	*Tectona grandis*	Lamiaceae	Leaves, Bark	Chloroform n-butanol	Rats/ 100 mg/kgbw	3,8-dihydroxy-2-methyl anthraquinone)	Reduction in blood glucose	219
24	*Allium cepa*	Amaryllidace ae	Bulb			Allyl propyldisulfide and *S*-methyl cysteine sulfoxide	Reduction in fasting blood glucose levels	220
25	*Aconitum carmichaelii*	Ranunculacea e	Root		Rats	Aconitians A, B, C, and D	Blood glucose lowering	221

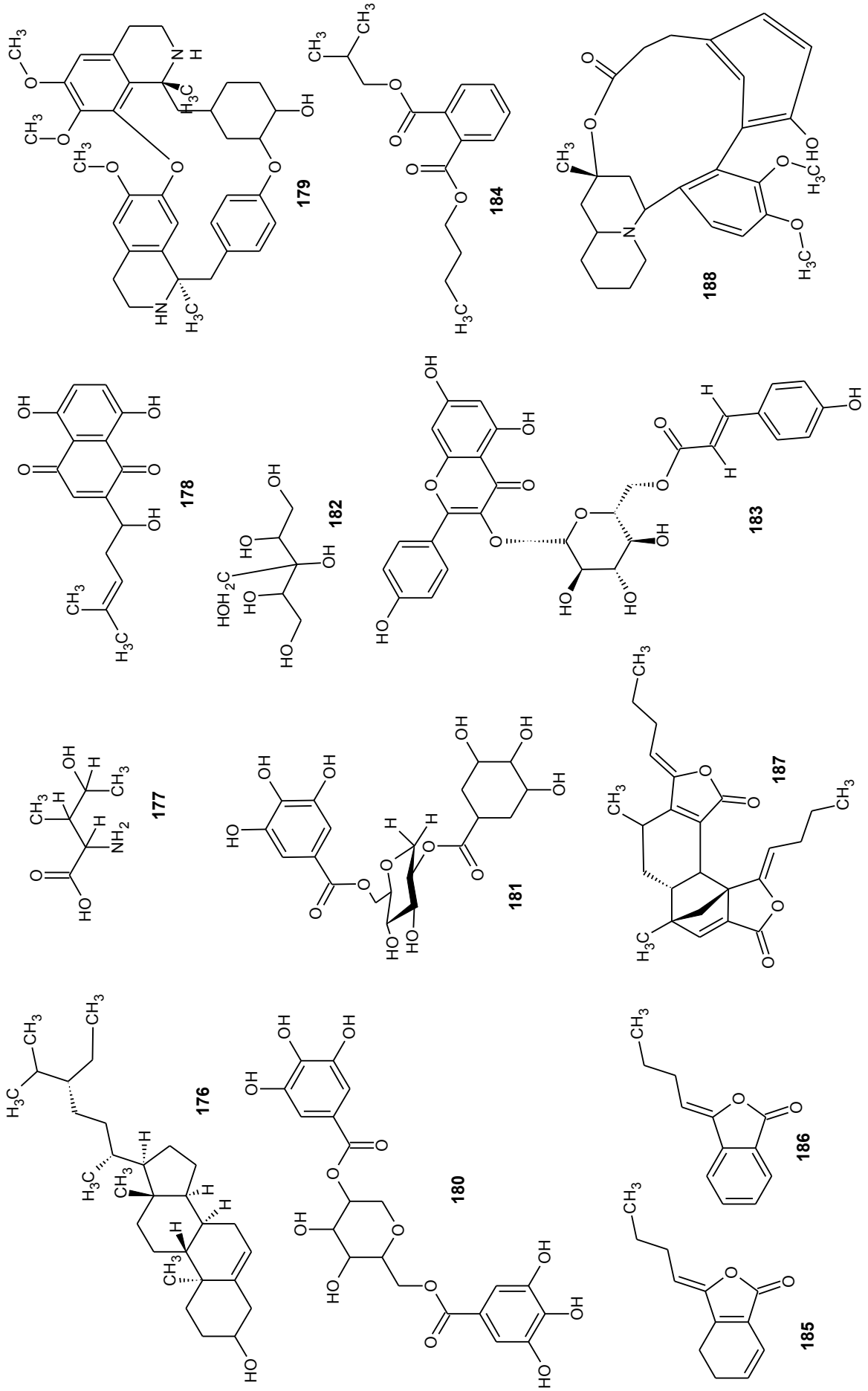

Figure 8(a). Structures of other compounds

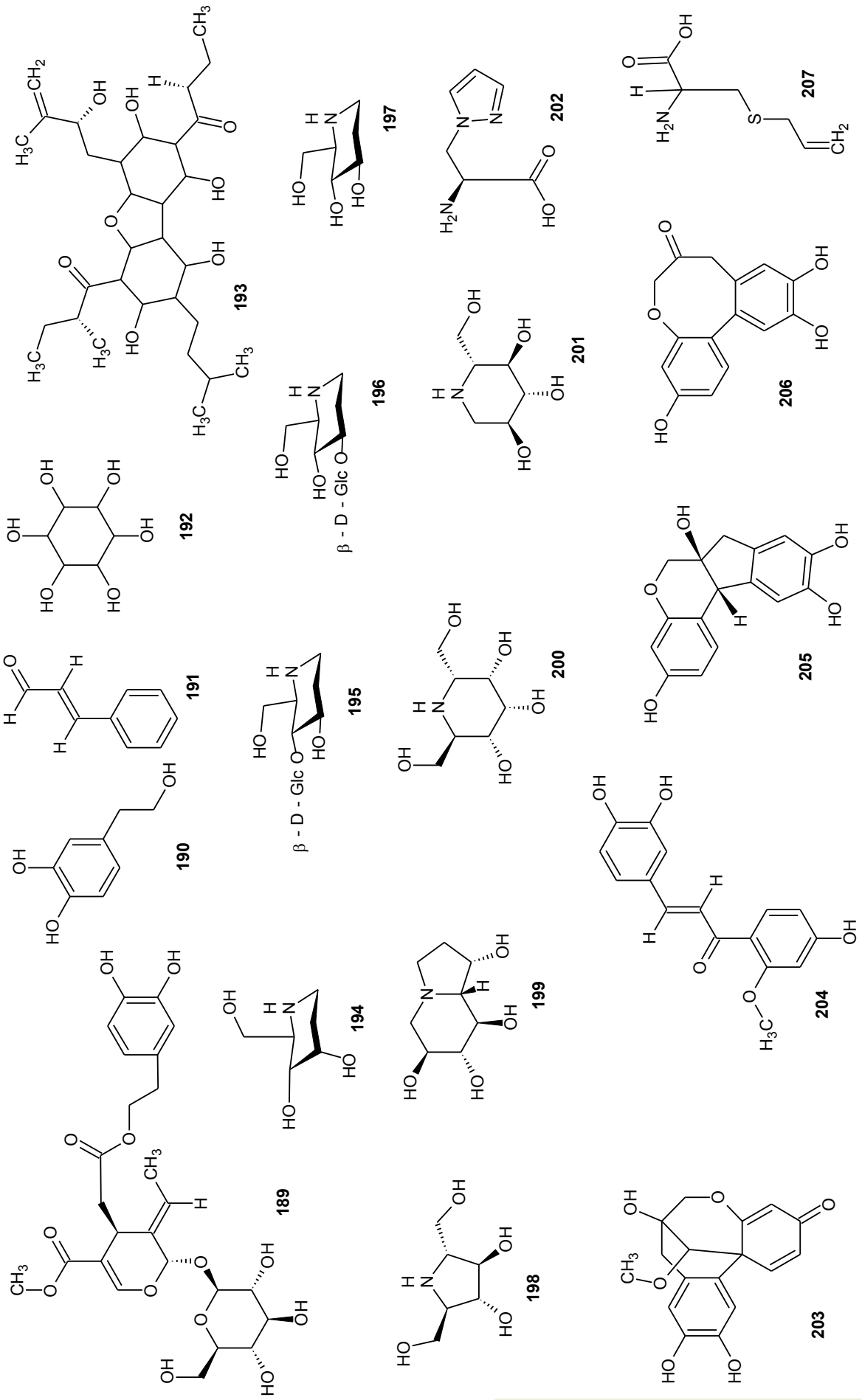

Figure 8(b). Structures of other compounds

Intraperitoneal administration of prunin (naringenin 7-*O*-β-D-glucoside) produced significant hypoglycemic effects in diabetic rats.[43] Details of flavonoids exhibiting antidiabetic activity are provided in Table 4 and the structure of some of the compounds is presented in Figure 4.

Kaempferol glycosides from *Cinnamomum osmophloeum* exhibited insulin like properties and stimulated glucose uptake in 3T3-L1 adipocytes cell line. Phytochemicals from *Tetracera scandens* increased and induced GLUT4 and GLUT1 mRNA expression levels and enhanced uptake of glucose.

5. Saponins

Saponins are glycosylated compounds widely distributed in the plant kingdom and can be divided into three major groups; triterpenoid, steroid, or a steroidal glycoalkaloid. Saponins isolated from leaves of *Acanthopanax senticosus* (Rupr. and Maxim) decreased hyperglycemia induced by adrenaline, glucose and alloxan. A number of saponins exhibiting antidiabetic activity are listed in Table 5, along with the structures of some of these compounds (Figure 5).

Increase in insulin secretion has been reported from saponins or plant extracts enriched with saponins. Plants with potential insulin secretary activities are *Gymnema sylvestre, Gynostemma pentaphyllum* and *Panax ginseng*.

6. Glycosides

Plant glycosides are molecules in which a sugar is bound to a non-carbohydrate moiety. Glycosides play various important roles in living organisms. Many plants store chemicals in the form of inactive glycosides that undergo enzyme hydrolysis to yield a non-sugar moiety available for physiological action.[44] Many such plant glycosides possess medicinal properties, including antidiabetic activity. A new stearoyl glucoside of ursolic acid, urs-12-en-3β-ol-28-oic acid 3β-D-glucopyranosyl-4'-octadecanoate, isolated from the leaves of *Lantana camara* L. showed significant reduction in blood glucose levels in STZ-induced diabetic rats.[45] Details of antidiabetic glycosides isolated from medicinal plants are given in Table 6 and the structures of some of the compounds are given in Figure 6).

Casuarine 6-O-α-glucoside from *Syzygium malaccense* and Salacinol from *Salacia reticulatea* showed α-glucosidase inhibitory activity in animal models.

7. Xanthones

Xanthones are polyphenol compounds, biosynthetically related to the flavonoids. The xanthone backbone consists of two benzene rings attached through a carbonyl group. The unique backbone along with type and position of the attached chemical groups defines the specific properties of xanthones. Xanthones are reported to have numerous bioactive properties, including antidiabetic activity. Methyl xanthenes isolated from chloroform, ethylaccetate and n-butonal extracts of *Ilex paraguariensis* have been reported to have anti-hyperglycemic potential, be able to improve diabetic status and are probably a source of multiple hypoglycemic compounds.[46] Xanthones with potential antidiabetic activity are listed in Table 7 and their structures are given in Figure 7a.

8. Polysaccharides

Polysaccharides are the most abundant natural products produced by plants. Polysaccharides are well recognized for their importance in our food. Polysaccharides reduce the level of blood cholesterol, regulate flow through the body and reduce uptake of glucose from intestines. Some of the polysaccharides showing antidiabetic activity are listed in Table 8.

Although no mechanism of hypoglycemic activity of polyschhrides has been reported, possibly the intake of complex polyscahhrides compared to simpler ones is known to show glucose lowering effect.

9. Other compounds

Some phytochemicals (Figure 8), which could not be covered in above classification have been reported to possess antidiabetic activity. Five new gallotannins, maplexins A–E, isolated from *Acer rubrum* (red maple) stems showed 20-fold greater α-glucosidase inhibitory activity than acarbose.[47] Dehydrodieugenol and dehydrodieugenol B isolated from flower bud ethanol extracts of *Syzygium aromaticum* were reported to have potent peroxisome proliferator-activated receptor (PPAR)-γ ligand-binding activities and significantly suppressed the increase in blood glucose level in type 2 diabetic KK-A(y) mice.[48] Licochalcone E aretrochalcone isolated from the root of *Glycyrrhiza inflata* lowered blood glucose levels and serum triglyceride levels in diabetic mice and showed weak but significant PPARγ ligand-binding activity.[49] Details of these compounds are provided in Table 9.

Conclusion

In order to check the prevalence of this alarming health problem, there is the utmost need for potential antidiabetic drug leads. Therapies developed along the principles of allopathic medicines are often limited in efficacy, carry the risk of adverse effects and are too costly during long treatment regimens. Therefore, discovering novel antidiabetic molecules of herbal origin with low cost, easy accessibility and high safety indexes is an exciting area of research.

The medicinal plant, *Galega officinalis* provided the first lead antidiabetic compound that led to the development of metformin, one of the widely prescribed antidiabetic drugs. Large numbers of articles are published every year on plant-based medicines. NCBI's 'Pub Med' literature survey showed that 317 articles were published on the antidiabetic activity of medicinal plants in 2011, advocating use of herbs in the management of diabetes. The current review compiled data regarding the antidiabetic plants and their active phytochemicals. *Opuntia streptacantha* Lem, *Trigonella foenum graecum* Linn, *Momordica charantia* Linn, *Ficus bengalensis* Linn, *Polygala senega* Linn, *Gymnema sylvestre* R and *Pterocarpus marsupium* Roxburgh plants are reported to possess potential hypoglycemic/antidiabetic activity. A number of phytochemicals have been isolated from the medicinal plants exhibiting antidiabetic activity. Many of these phytochemicals have shown hypoglycemic/antidiabetic activity equal and sometimes even more potent than currently used drugs. In this

review an attempt has been made to categorize these antidiabetic phytochemicals into alkaloids, terpenoids, saponins, flavonoids, phenolics, glycosides, xanthones and polysaccharides. *In vitro* and *in vivo* activity of these phytochemicals along with effective concentration/dose and possible mechanism of action have been documented in the review. The literature showed that antidiabetic compounds have been reported from a variety of chemical groups. Alkaloids (11-hydroxypalmatine, kinsenoside, pongamol) phenolics (protocatechuic acid, mullberroside A), terpenoids (betulin, lupeol, epicatechin), flavonoids (6-hydroxy-flavonoids, 6-hydroxyapigenin), saponins (phanoside, momordicin), polysacchrides (anthocyanin), and other compounds such as γ-sitosterol, cinnamaldehyde, and achyrofuran have been identified as the proming antidiabetic molecules.

Therefore, considering the promising potential of phytochemicals in antidiabetic drug development, large-scale clinical trials are required for efficacy and safety evaluation of these compounds. The antidiabetic phytochemicals may also be used in combination with existing drugs. The combination therapy may reduce the dose of synthetic antidiabetic drugs and help in addressing the toxicity and cost-related issues in chronic use during the management of diabetes.

REFERENCES

1. D.K. Patel, R. Kumar, S.K. Prasad, K. Sairam, S. Hemalatha. Anti-diabetic and in vitro antioxidant potential of *Hybanthus enneaspermus* (Linn) F. Muell in streptozotocin-induced diabetic rats. *Asian Pac J Trop Biomed*. **2011**, 1(4), 316–22.
2. S.L. Warjeet. Traditional medicinal plant of Manipur as anti-diabetics. *J Med Plants Res.* **2011,** 5(5), 677–87.
3. Chauhan, P.K Sharma, P. Srivastava, N. Kumar, R. Dudhe, Plants having potential anti-diabetic activity: A review. *Der Pharmacia Lettre*. **2010**, 2(3), 369–87.
4. N. Unwin, D. Whiting, D. Gan, O. Jacqmain, G. Ghyoot, editors. *IDF* Diabetes Atlas. 4th ed. Brussels: *International Diabetes Federation*, 2009.
5. Ramachandran, C Snehalatha, AS. Shetty, A. Nanditha. Trends in prevalence of diabetes in Asian countries. *World J Diabetes.* **2012,** 3(6), 110–7.
6. T. Scully, Diabetes in numbers. *Nature* **2012,** 485. S 2
7. N. Unwin, D. Whiting, D. Gan, O. Jacqmain, G. Ghyoot, editors. *IDF* Diabetes Atlas. 4th ed. Brussels: *International Diabetes Federation*, 2009.
8. Z. Ferreira, A. Ayeleso, E. Mukwevho . Control of carbohydrate and lipid metabolism by NRF-1 and sirtuins: Implications on type 2 diabetes and obesity. *Chem. Biol. Lett.* **2014**, 1(2), 66-76.
9. RS. Yallow, H. Black, M. Villazan, S. Berson. A comparison of plasma insulin levels following administration of tolbutamide a.nd glucose. *Diabetes.* **1960,** (9), 356–62.
10. JG. Eurich, FA. McAlis ter, DF. Blackburn, SR. Majumdar, RT. Tsuyuki, J. Varney, J. A. Johnson. BMJ *Clin res ed.* **2007,** P. 335,497.
11. P.H. Geelhoed-Duijvestijn, Incretins: A new treatment option for type 2 diabetes. *Neth J Med.* **2007,** 65, 60–4.
12. P.J. Watkins. ABC of Diabetes, cardiovascular diseases hypertension and lipids. *Brit Med J.* **2003,** 10, 82–4.
13. J.K. Grover, S. Yadav, V. Vats. Medicinal plants of India with antidiabetic potential. *J Ethnopharmacol.* **2002,** 81, 81–100.
14. Momin. *Role of indigenous medicine in primary healthcare* In: Proceedings of first international seminar on Unani medicine. New Delhi, India, 1987; vol. 54.
15. World Health Organization. Expert Committee on Diabetes mellitus Technical report series. *World Health Organization*, Geneva, 1980.
16. B. Oliver-Bever. Oral hypoglycemic action of medicinal plants in tropical West Africa. *Cambridge University Press*, London, 1986; p. 245–67.
17. M.K. Rai. A review on some antidiabetic plants of India. *Ancient Sciences of Life.* **1995,** 14, 42–54.
18. F.J. Alarcon-Aguilara, R. Roman-Ramos, S. Perez-Gutierrez, A. Aguilar-Contreras, C.C. Contreras-Weber, J.L. Flores-Saenz. Study of the anti-hyperglycemic effect of plants used as antidiabetic. *J Ethnopharmacol.* **1998,** 61, 101–10.
19. M. Jung, M. Park, H.C. Lee, Y.H. Kang, E.S. Kang S.K. Kim. Antidiabetic agents from medicinal plants. *Curr Med Chem.* **2006,** 13, 1203–18.
20. R.M. Perez, M.A.Zavala, S. Perez, C. Perez. Antidiabetic effect of compounds isolated from plants. *Phytomed.* **1998,** 555–75.
21. R.M. Perez, M.A.Zavala, S. Perez, C. Perez. Antidiabetic effect of compound isolated from plants. *Phytomed.* **2011,** 4520–9.
22. W.H. Lewis, M.P. Elvin-Lewis. Medicinal plants as sources of new therapeutics. *Ann Mo Bot Gard.* **1995,** 82, 16–24.
23. R.E. Schultes. The kingdom of plants in Medicines from the Earth edited by WAR Thomson, McGraw-Hill Book Co: New York, **1978.**
24. K.R. Kirtikar B.D. Basu. *In: Indian Medicinal Plants.* 2nd edn. Blatter E, Caius JF.editors. Lalit Mohan Basu; Allahabad, 1975.
25. P.R. Ram, B.N. Malhotra. *Indian Medicinal Plants.* Central Drug Research Institute Lucknow Council for Scientific and Industrial Research, Delhi, 1989. vol. 4.
26. N. Arulrayan, S. Rangasamy, F. James, D. Pitchai. A database for medicinal plants used in the treatment of diabetes and its secondary complications. *Bioinform.* **2007,** 2, 22–3.
27. G.V. Satyavati, A.K. Gupta. *Medicinal Plants of India*. Indian Council of Medical Research, New Delhi, 1987.vol. 2.
28. O.C. Rubio, A.C. Cuellar, N. Rojas, H.V. Castro, L. Rastrelli, R.A. Aquino. A polyisoprenylated benzophenone from *Cuban propolis*. *J Nat Prod.* **1999,** 62, 1013–5.
29. G.A. Cordell, M.L. Quinn-Beattie, N.R. Farnsworth. The potential of alkaloids in drug discovery. *Phytother Res.* **2001,** 15, 183–205.
30. P.J. Facchini, A.G. Johnson, J. Poupart, V. de Luca. Uncoupled defense gene expression and antimicrobial alkaloid accumulation in elicited opium poppy cell cultures. *Plant Physiol.* **1996,** 111, 687–97.
31. Z.Q. Wang, F.E. Lu, S.H. Leng, X.S. Fang, G. Chen, Z.S. Wang, et al. Facilitating effects of berberine on rat pancreatic islets through modulating hepatic nuclear factor 4 α expression and glucokinase activity. *World J Gastroenterol.* **2008,** 14(39), 6004–11.
32. R.K. Dawra, H.P. Makkar, B. Singh. Protein-binding capacity of microquantities of tannins. *Anal Biochem.* **1988,** 170, 50–3.
33. P. Suryanarayana, P.A. Kumar, M. Saraswat, J.M. Petrash, G.B. Reddy. Inhibition of aldose reductase by tannoid principles of *Emblica officinalis*: Implications for the prevention of sugar cataract. *Mol Vision.* **2004,** 10, 148–54.
34. N. Shang, J.A. Guerrero-Analco, L. Musallam, A. Saleem, A. Muhammad, B. Walshe-Roussel, et al. Adipogenic constituents from the bark of *Larix laricina* du Roi (K. Koch; Pinaceae), an important medicinal plant used traditionally by the Cree of Eeyou Istchee (Quebec, Canada) for the treatment of type 2 diabetes symptoms. *J Ethnopharmacol.* **2012,** 141(3), 1051–7.
35. M.A. Ramírez-Cisneros, M.Y. Rios, M. Deciga-Campos, A.B. Aguilar-Guadarrama. Phytochemical study and anti-inflammatory, antidiabetic and free radical scavenger evaluations of *Krameria pauciflora* methanol extract. *Molecules.* **2012,** 17(1), 861–72.
36. U.J. Jung, M.K. Lee, K.S. Jeong, M.S. Choi. The hypoglycemic effects of hesperidin and naringin are partly mediated by hepatic glucose-regulating enzymes in C57BL/KsJ-db/db mice. *J Nutr.* **2004,** 134, 2499–503.
37. G. Brahmachari. *In Natural Products*: Chemistry Biochemistry and Pharmacology. G Brahmachari Ed Narosa Publishing House Pvt Ltd, New Delhi, 2009.

38. T. Matsui, I.Q. Ogunwande, K.J.M. Abesundara, K. Matsumoto. Antihyperglycemic potential of natural products. *Med Chem.* **2006,** 6, 109–20.
39. L.W. Qi, L. H. Liu, C. Chu, Y.B. Peng, H.X. Cai, P. Li. Anti-diabetic agents from natural products-an update from 2004 to 2009. *Curr Top Med Chem.* **2010,** 10, 434–57.
40. M. Vessal, M. Hemmati, M. Vasei. Antidiabetic effects of quercetin in streptozocin-induced diabetic rats. *Comp Biochem Physiol.* **2003,** 135, 357–64.
41. C.S. Hif, S.L. Howell. Effects of epicatechin on rat islets of langerhans. *Diabetes.* **1984,** 33, 291–6.
42. C.S. Hif, S.L. Howell. Effects of flavonoids on insulin 45+2 secretion and Cahandling in rat islets of langerhans. *J Endocrinol.* **1985,** 107, 1–8.
43. J.S. Choi, T. Yokozawa, H. Oura. Improvement of hyperglycemia and hyperlipemia in streptozotocin-diabetic rats by a methanolic extract of *Prunus davidiana* stems and its main component pruning. *Planta Med.* **1991,** 57, 208–11.
44. Brito-Arias. Synthesis and characterization of glycosides. Springer. ISBN 978-0-387:26251-2.
45. Kazmi, M. Rahman, M. Afzal, G. Gupta, S. Saleem, O. Afzal, et al. Anti-diabetic potential of ursolic acid stearoyl glucoside: A new triterpenic gycosidic ester from *Lantana camara*. *Fitoterapia.* **2012,** 83(1), 142–6.
46. D.F. Pereira, V.D. Kappel, L.H. Cazarolli, A.A. Boligon, M.L. Athayde, S.M. Guesser, et al. Influence of the traditional Brazilian drink *Ilex paraguariensis* tea on glucose homeostasis. *Phytomedicine.* **2012,** 19(10), 868–77.
47. C. Wan, T. Yuan, L. Li, V. Kandhi, N.B. Cech, M .Xie, et al. Maplexins, new α-glucosidase inhibitors from red maple (*Acer rubrum*) stems. *Bioorg Med Chem Lett.* **2012,** 22(1), 597–600.
48. M. Kuroda, Y. Mimaki, T. Ohtomo, J. Yamada, T. Nishiyama, T. Mae, et al. Hypoglycemic effects of clove (*Syzygium aromaticum* flower buds) on genetically diabetic KK-Ay mice and identification of the active ingredients. *J Nat Med.* **2012,** 66(2), 394–9.
49. H.G. Park, E.J. Bak, G.H. Woo, J.M. Kim, Z. Quan, J.M. Kim, et ak. Licochalcone E has an antidiabetic effect. *J Nutr Biochem.* **2012,** 23(7), 759–67.
50. T. Narender, S. Shweta, P. Tiwari, K. Papi Reddy, T. Khaliq, et al. Antihyperglycemic and antidyslipidemic agent from *Aegle marmelos*. *Bioorg Med Chem Lett.* **2007,** 17, 1808–11.
51. Kumar, R. Ilavarasan, T. Jayachandran, M. Deecaraman, P. Aravindan, N. Padmanabhan, et al. Anti-diabetic activity of *Syzygium cumini* and its isolated compound against streptozotocin-induced diabetic rats. *J Med Plants Res.* **2008,** 2, 246–9.
52. D.K. Semwal, U. Rawat, R. Semwal, R. Singh, G.H. Singh. Anti-hyperglycemic effect of 11-hydroxypalmatine a palmatine derivative from *Stephania glabra* tubers. *J Asian Nat Prod Res.* **2010,** 12, 99–105.
53. Y. Zhang, J. Cai, H. Ruan, H. Pi, J. Wu. Antihyperglycemic activity of kinsenoside a high yielding constituent from *Anoectochilus roxburghii* in streptozotocin diabetic rats. *J Ethnopharmacol.* **2007,** 114, 141–520.
54. B. Dineshkumar, I.G. Tamil , M. Nandhakumar , M. Senthilkumar , A. Mitra . In vitro study on α-amylase inhibitory activity of an Indian medicinal plant, Phyllanthus amarus. *Indian J Pharmacol.* **2010,** 42(5):280-2.
55. R. Maurya, V. Wazir, A. Tyagi, R.S. Kapil. Clerodane diterpenoids from *Tinospora cordifolia*. *Phytochem.* **2008,** 38, 659–61.
56. C. Contreras, R. Roman, C. Perez, F. Alarcón, M. Zavala, S. Perez. Hypoglycemic activity of a new carbohydrate isolated from the roots of *Psacalium peltatum*. *Chem Pharm Bull.* **2005,** 53, 1408–10.
57. K. Takada, T. Uehara, Y. Nakao, S. Matsunaga, W.M. Van Soest, N. Fusetani. A.C. Schulzeines. New α-glucosidase inhibitors from the marine sponge *Penares schulzei*. *J Am Chem Soc.* **2004,** 126:187.
58. L. Costantino, L. Raimondi, R. Pirisino, T. Brunetti, P. F. Pessotto Giannessi, et al. Isolation and pharmacological activities of the Tecoma stans alkaloids. *Farmaco.* **2003,** 58, 781–85.
59. T. Tsutsumi, S. Kobayashi, Y.Y. Liu, H. Kontani. Anti-hyperglycemic effect of fangchinoline isolated from *Stephania tetrandra* radix in streptozotocin-diabetic mice. *Biol Pharm Bull*. **2003,** 26, 313–7.
60. K. Yuzo, S. Hiroshi, N. Norinaga, N. Kiyofumi, Y. Masayuki. *Jpn Kokai yokkyo koho.* **2003,** 56:14–20.
61. P.M. Lopez, P.G. Mora, W. Wysocka, B. Maiztegui, M.E. Alzugaray, H.D. Zoto, et al. Quinolizidine alkaloids isolated from Lupinus species enhances insulin secretion. *Eur J Pharmacol.* **2004,** 504, 139–42.
62. J. Luo, D.M. Fort, T.J. Carlson, B.K. Noamesi, D. Nii-Amon-Kotei, S.R. King, et al. *Cryptolepis sanguinolenta*: An ethnobotanical approach to drug discovery and the isolation of a potentially useful new antihyperglycaemic agent. *Diabet Med.* **1998,** 15, 367–74.
63. M. Shibano, D. Tsukamoto, A. Masuda, Y. Tanaka, G. Kusano. Two new pyrrolidine alkaloids radicamines A and B as inhibitors of α-glucosidase from *Lobelia chinensis* LOUR. *Chem Pharm Bull.* **2001;** 49, 1362.
64. S.S. Singh, S.C. Pandey, S. Srivastava, V.S. Gupta, B. Patro, A.C. Ghosh. Chemistry and medicinal properties of *Tinospora cordifolia* (Guduchi). *Indian J Pharmacol.* **2003,** 35,83–91.
65. R.R. Chattopadhyay. A comparative evaluation of some blood sugar lowering agents of plant origin. *J Ethnopharmacol.* **1999,** 67(3),367–72.
66. E.J. Cooper, A.L. Hudson, C.A. Parker, A.G. Morgan. Effects of the beta-carbolines harmane and pinoline on insulin. *Eur J Pharmacol.* **2003**, 482,189–96.
67. A.K. Tamrakar, P.P. Yadav, P. Tiwari, R. Maurya, A.K. Srivastava. Identification of pongamol and karanjin as lead compounds with antihyperglycemic activity from *Pongamia pinnata* fruits. *J Ethnopharmacol.* **2008,** 118,435–9.
68. L.M. Xiu, A.B. Miura, K. Yamamoto, T. Kobayashi, Q.H. Song, H. Kitamura, et al. Pancreatic islet regeneration by ephedrine in mice with STZ-induced diabetes. *Am J Chinese Med.* **2001,** 29,493–500.
69. K.H. Nguyen, T.N. Ta. Pham TH, Nguyen QT, Pham HD, Mishra S, et al. Nuciferine stimulates insulin secretion from beta cells-an *in vitro* comparison with glibenclamide. *J Ethnopharmacol.* **2012,** 142(2),488–95.
70. M.H. Kang, M.S. Lee, M.K. Choi, K.S. Min, T. Shibamoto. Hypoglycemic activity of *Gymnema sylvestre* extracts on oxidative stress and antioxidant status in diabetic rats. *J Agric Food Chem.* **2012,** 60(10), 2517–24.
71. R. Rawat, M. Kumar, N. Rahuja, D.S. Lal Srivastava, R. Moorthy, K.M. Prabhu, et al. Anti-hyperglycemic compound (GII) from fenugreek (*Trigonella foenum*-graecum Linn) seeds its purification and effect in diabetes mellitus. *Indian J Exp Biol.* **2010,** 48, 1111–8.
72. R.C. Latha, P. Daisy. Insulin-secretagogue antihyperlipidemic and other protective effects of gallic acid isolated from *Terminalia bellerica* Roxb in streptozotocin-induced diabetic rats. *Chem Biol Interact.* **2011,** 189, 112–8.
73. M. Ohnishi, T. Matuo, T. Tsuno, A. Hosoda, E. Nomura, H. Taniguchi, et al. Antioxidant activity and hypoglycemic effect of ferulic acid in STZ-induced diabetic mice and KK-Ay mice. *Bio Factors.* **2004,** 21, 315–9.
74. R. Harini, K.V. Pugalendi. Antihyperglycemic effect of protocatechuic acid on streptozotocin-diabetic rats. *J Basic Clin Physiol Pharmacol.* **2010,** 21, 79–91.
75. G. Gayathri, K. Kannabiran. Antidiabetic activity of 2-hydroxy 4-methoxy benzoic acid isolated from the roots of *Hemidesmus indicus* on streptozotocin-induced diabetic rats. *Int J Diabetes Metabol.* **2009,** 17, 53–7.
76. G. Gayathri, K. Kannabiran. Antidiabetic activity of 2-hydroxy 4-methoxy benzoic acid isolated from the roots of *Hemidesmus indicus* on streptozotocin-induced diabetic rats. *Int J Diabetes Metabol.* **2009,** 17, 53–7.

77. E.J. Sohn, C.S. Kim, Y.S. Kim, D.H. Jung, D.S. Jang, Y.M. Lee, et al. Effects of magnolol (55'-diallyl-22'-dihydroxybiphenyl) on diabetic nephropathy in type 2 diabetic Goto-Kakizaki rats. *Life Sci*. **2007,** 80, 468–75.
78. K. Kobayashi, T. Ishihara, E. Khono, T. Miyase, F. Yoshizaki. Constituents of stem bark of *Callistemon rigidus* showing inhibitory effects on mouse alpha-amylase activity. *Biol Pharm Bull.* **2006,** 29, 1275–7.
79. J.M. Krenisky, J. Luo, M.J. Reed, J.R. Carney. Isolation and antihyperglycemic activity of bakuchiol from *Otholobium pubescens* (Fabaceae) a Peruvian medicinal plant used for the treatment of diabetes. *Biol Pharm Bull.* **1999,** 22, 1137–40.
80. M.C. Zhang, M. Zhang, H. Qing, S. Shi, Xia. Bing, W.F. Hua. *In vivo* hypoglycemic effect of phenolics from the root bark of Morus alba. *Fitoterapia.* **2007,** 80(8), 475–7.
81. P. Basnet, S. Kadota, S. Terashima, M. Shimizu, T. Namba. Screening of traditional medicines for their hypoglycemic activity in streptozotocin (STZ)-induced diabetic rats and a detailed study on *Psidium guajava*. *Chem Pharm Bull.* **1993,** 41, 1238–43.
82. D. Tousch, A.D. Lajoix, E. Hosy, J. Azay-Milhau, K. Ferrare, C. Jahannault, et al. Chicoric acid a new compound able to enhance insulin release and glucose uptake. *Biochem Biophy Res Com.* **2008,** 377, 131–5.
83. A.J. Alonso-Castro, R. Zapata-Bustos, F. Domínguez, A. García-Carrancá, L.A. Salazar-Olivo. *Magnolia dealbata* Zucc and its active principles honokiol and magnolol stimulate glucose uptake in murine and human adipocytes using the insulin-signaling pathway. *Phytomedicine*. **2011,** 18(11), 926–33.
84. P. Peungvicha, R. Temsiririrkkul, J.K. Prasain, Y. Tezuka, S. Kadota, S.S. Thirawarapan, et al. 4-Hydroxybenzoic acid: a hypoglycemic constituent of aqueous extract of *Pandanus odorus* root. *J Ethnopharmacol.* **1998,** 62, 79–84.
85. J. Luo, T. Chuang, J. Cheung, J. Quan, J. Tsai, C. Sullivan, et al. Masoprocol (nordihydroguaiaretic acid): A new antihyperglycemic agent isolated from the creosote bush (*Larrea tridentata*) *Eur J Pharmacol.* **1998,** 346, 77–9.
86. H. Andrade-Cetto, H. Wiedenfeld. Hypoglycemic effect of *Acosmium panamense* on streptozotocin diabetic rats. *J Ethnopharmacol.* **2004,** 90, 217–26.
87. H. Sawad, M. Hamatake, A. Hara, M. T. Nakagawa. Nakayama Inhibition of human placenta aldose reductase by tannic acid. *Chem Pharma Bull.* 1989; 37, 1662–4.
88. Kaoru, T. Masato, S. Hideo, O. Toshimasa, Hiroshi S. The existence of aldose reductase inhibitors in some Kampo medicines (Oriental herb prescriptions). *Planta Med.* **1989,** 55**,** 22–6
89. G.M. Konig, A.D. Wrigh, W.J. Keller, R.L. Judd, S. Bates, C. Day. Hypoglycaemic activity of an HMG-containing flavonoid glucoside chamaemeloside from *Chamaemelum nobile*. *Planta Med.* **1998,** 64, 612–4.
90. L. Tedong, P. Madiraju, L.C. Martineau, D. Vallerand, J.T. Arnason, D.D. Desire, et al. Hydro-ethanolic extract of cashew tree (*Anacardium occidentale*) nut and its principal compound anacardic acid stimulate glucose uptake in C2C12 muscle cells. *Mol Nutr Food Res.* **2010,** 54, 1753–62.
91. M. Manickam, M. Ramanathan, M.A. Jahromi, J.P. Chansouria, A.B. Ray. Antihyperglycemic activity of phenolics from *Pterocarpus marsupium* . *J Nat Prod.* **1997,** 60, 609–10.
92. S. Perez, R.M. Perez, C. Perez, M.A. Zavala, R. Vargas. Coyolosa a new hypoglycemic from *Acrocomia mexicana*. *Pharm Acta Helv.* **1997,** 72, 105–11.
93. N. Nkobole, P.J. Houghton, A. Hussein, N. Lall. Antidiabetic activity of *Terminalia sericea* constituents. *Nat Prod Commun.* **2011,** (11), 1585–8.
94. G.R. Gandhi, S. Ignacimuthu, M.G. Paulraj. *Solanum torvum* Swartz. fruit containing phenolic compounds shows antidiabetic and antioxidant effects in streptozotocin induced diabetic rats. *Food Chem Toxicol.* **2011,** 49(11), 2725–33.
95. N. Shang , J.A. Guerrero-Analco , L. Musallam , A. Saleem , A. Muhammad , B. Walshe-Roussel , et.al Adipogenic constituents from the bark of Larix laricina du Roi (K. Koch; Pinaceae), an important medicinal plant used traditionally by the Cree of Eeyou Istchee (Quebec, Canada) for the treatment of type 2 diabetes symptoms. *J Ethnopharmacol*. **2012,** 141(3), 1051-7.
96. M.Á. Ramírez-Cisneros , M.Y. Rios , M. Déciga-Campos , A.B. Aguilar-Guadarrama. Phytochemical study and anti-inflammatory, antidiabetic and free radical scavenger evaluations of Krameria pauciflora methanol extract.Molecules. **2012,** 17(1), 861-72.
97. T. Ha do, D.T. Tuan, N.B. Thu, N.X. Nhiem, T.M. Ngoc, N. Yim, et al. Palbinone and triterpenes from Moutan Cortex (*Paeonia suffruticosa* Paeoniaceae) stimulate glucose uptake and glycogen synthesis via activation of AMPK in insulin-resistant human HepG2 Cells. *Bioorg Med Chem Lett.* **2009,** 19, 5556–9.
98. J.A. Guerrero-Analco, L. Martineau, A. Saleem, P. Madiraju, A. Muhammad, T. Durst, et al. Bioassay-guided isolation of the antidiabetic principle from *Sorbus decora* (Rosaceae) used traditionally by the Eeyou Istchee Cree First Nations. *J Nat Prod.* **2010,** 73, 1519–23.
99. T. Ghosh, T.K. Maity, J. Singh. Antihyperglycemic activity of bacosine a triterpene from *Bacopa monnieri* in alloxan-induced diabetic rats. *Planta Med*. **2011,** 77, 804–8.
100. D.D. Raga, R.A. Espiritu , C.C. Shen , C.Y. Ragasa. A bioactive sesquiterpene from Bixa orellana. *J Nat Med.* **2011,** 65(1), 206.
101. S.R. Naik, J.M. Barbosa Filho, J.N. Dhuley, V. Deshmukh. Probable mechanism of mechanism of hypoglycaemic activity of bassic acid a natural product isolated from *Bumelia sartorum*. *J Ethnopharmacol.* **1991,** 33, 37–44.
102. M.S. Deutschländer, N. Lall, M. Van de Venter, A. Hussein. A Hypoglycemic evaluation of a new triterpene and other compounds isolated from *Euclea undulata* Thunb var myrtina (Ebenaceae) root bark. *J Ethnopharmacol.* **2011,** 133:1091–5.
103. C.C. Hou, S.J. Lin, J.T. Cheng, F.L. Hsu. Antidiaetic dimeric guianolides and a lignan glycoside from *Lactuca indica*. *J Nat Prod.* **2003,** 66, 625–9.
104. I.M. Choudhary, L. Baig, M. Nure-Alam, S. Shahzad-ui- Hussan, P. ondognii, Bunderya M, et al. New α-Glucosidase inhibitors from the Mongolian medicinal plant *Ferula mongolica. Helvetica Chimica Acta.* **2002,** 84, 2409–2416.
105. A.B. Singh, D.K. Yadav, R. Maurya, A.K. Srivastava. Antihyperglycaemic activity of α-amyrin acetate in rats and db/db mice. *Nat Prod Res.* **2009,** 23, 876–82.
106. M. Sato, T. Tai, Y. Nunoura, Y. Yajima, S. Kawashima, K. Tanaka. Dehydrotrametenolic acid induces preadipocyte differentiation and sensitizes animal models of noninsulin-dependent diabetes mellitus to insulin. *Bio Pharm Bull.* **2002,** 210, 27–30.
107. W.V. Judy, S.P. Hari, W.W. Stogsdill, J.S. Judy, Y.M.A. Naguib, R.J. Passwater. Antidiabetic activity of a standardized extract (Glucosol and unknown) from *Lagerstroemia speciosa* leaves in Type II diabetics - A dose-dependence study. *J Ethanopharmacol.* **2003,** 87, 115–7.
108. P.B. Jeppesen, S. Gregersen, K.K. Alstrup, K. Hermansen. Stevioside induces antihyperglycaemic insulinotropic and glucagonostatic effects in vivo: studies in the diabetic Goto-Kakizaki (GK) rats. *Phytomed*. **2002**, 9, 9–14.
109. W.L. Li, H.C. Zheng, J. Bukuru, N. De Kimpe. Natural medicines used in the traditional Chinese medical system for therapy of diabetes mellitus. *J Ethnopharmacol.* **2004,** 92, 1–21.
110. R.A. Farias, V.S. Rao, G.S. Viana, E.R. Silveira, M.A. Maciel, A.C. Pinto. Hypoglycemic effect of trans-dehydrocrotonin a nor-clerodane diterpene from *Croton cajucara*. *Planta Med*. **1997**, 63, 558–60.
111. W.D. Inman, J. Luo, S.D. Jolad, S.R. King, R. Cooper. Antihyperglycemic sesquiterpenes from *Psacalium decompositum J Nat Prod.* **1999,** 62, 1088–92.
112. M. Latha, L. Pari, K.M. Ramkumar, P. Rajaguru, T. Suresh, T. Dhanabal, et al. Antidiabetic effects of scoparic acid D isolated from

Scoparia dulcis in rats with streptozotocin induced diabetes. *Nat Prod Res.* **2009,** 23, 1528–40.
113. M. Yoshikawa, S. Yoshizumi, T. Ueno, H. Matsuda, T. Murakami, J. Yamahara, et al. Hypoglycemic constituents from a garnish foodstuff "taranome" the young shoot of *Aralia elata* SEEM:elatosides G H I J and K. *Chem Pharm Bul.l* **1995,** 43, 1878–82.
114. M. Kako, T. Miura, Y. Nishiyama, M. Ichimaru, M. Moriyasu, A. Kato. Hypoglycaemic activity of some triterpenoid glycosides. *J Nat Prod.* **1997,** *60*, 604–5.
115. T. Morikawa, A. Kishi, Y. Pongpiriyadacha, H. Matsuda, M. Yoshikawa. Structures of new friedelane-type triterpenes and eudesmane-type esquiterpene and aldose reductase inhibitors from *Salacia chinensis*. *J Nat Prod.* **2003,** *66*, 1191–6.
116. H. Matsuda, T. Morikawa, H. Ueda, M. Yoshikawa. Medicinal foodstuffs xxvii1) saponin constituents of gotu kola (2): Structures of new ursane- and oleanane-type triterpene oligoglycosides centellasaponins B C and D from *Centella asiatica* cultivated in Sri Lanka. *Chem Pharm Bull.* **2001,** 491, 368–73.
117. De. La. Angel, J. Fuente, S. Manzanaro. Aldose reductase inhibitors from natural sources. *Nat Prod Rep.* **2003,** 20, 243–51.
118. R. Maurya, V. Wazir, A. TyagI, R.S. Kapil. Clerodane diterpenoids from *Tinospora cordifolia*. *Phytochem.* **1995,** 38, 659–61.
119. H.S. Omar, H.A. El-Beshbishy, Z. Moussa, K.F. Taha, A.N. Singab. Antioxidant activity of *Artocarpus heterophyllus* Lam (Jack Fruit) leaf extracts: remarkable attenuations of hyperglycemia and hyperlipidemia in streptozotocin-diabetic rats. *Scientific World J.* **2011,** 11, 788–800.
120. M. Yoshikawa , T. Murakami , M. Kadoya , H. Matsuda , O. Muraoka , J. Yamahara , N. Murakami .et al. Medicinal foodstuff. III. Sugar beet. (1): Hypoglycemic oleanolic acid oligoglycosides, betavulgarosides I, II, III, and IV, from the root of *Beta vulgaris* L. (Chenopodiaceae). *Chem Pharm Bull*. **1996**, 44(6), 1212-7.
121. M.H. Lin, H.K. Liu, W.J. Huang, C.C. Huang, T.H. Wu, F.L. Hsu. Evaluation of the potential hypoglycemic and β-cell protective constituents isolated from *Corni fructus* to tackle insulin-dependent diabetes mellitus. *J Agric Food Chem.* **2011,** 59, 7743–51.
122. M.J. Lee, Y.K. Rao, K. Chen, Y.C. Lee, Y.M. Tzeng. Effect of flavonol glycosides from *Cinnamomum osmophloeum* leaves on adiponectin secretion and phosphorylation of insulin receptor β in 3T3-L1 adipocytes. *J Ethnopharmacol.* **2009,** 126, 79–85.
123. O.A. Adaramoye, E.O. Adeyemi. Hypoglycaemic and hypolipidaemic effects of fractions from kolaviron a biflavonoid complex from *Garcinia kola* in streptozotocin-induced diabetes mellitus rats. *J Pharm Pharmacol.* **2006,** 58, 121–8.
124. J. Kawabata, K. Mizuhata, E. Sato, T. Nishioka, Y. Aoyama, T. Kasai. 6-Hydroxyflavonoid as α-glucosidase inhibitors from marjoram (*Origanum majorana*) leaves. *Biosci Biotechnol Biochem.* **2003,** 67, 445–7.
125. T. Nishioka, J. Kawabata, Y. Aoyama. Baicalein an α-glucosidase inhibitor from *Scutellaria baicalensis*. *J Nat Prod*. **1998,** 61, 1413–5
126. M.M. Lwu, O.A. Igboko, C.O. Okunji, M.S. Tempesta. Antidiabetic and aldose reductase activities of biflavones of *Garcinia kola*. *J Pharm Pharmacol.* **1990,** 42, 290–2.
127. M.S. Lee, C.H. Kim, D.M. Hoang, B.Y. Kim, C.B. Sohn, M.R. Kim, J.S. Ahn. Genistein-derivatives from *Tetracera scandens* stimulate glucose-uptake in L6 myotubes. *Biol Pharm Bull.* **2009,** 32, 504–8.
128. H.Y. Kim, B.H. Moon, H. J. Lee, D.H. Choi. Flavonol glycosides from the leaves of *Eucommia ulmoides* O with glycation inhibitory activity. *J Ethnopharmacol.* **2004,** 93, 227–30.
129. M.C. Revilla-Monsalve , A. Andrade-Cetto , M.A. Palomino-Garibay , H. Wiedenfeld, S. Islas-Andrade . Hypoglycemic effect of Cecropia obtusifolia Bertol aqueous extracts on type 2 diabetic patients. *J Ethnopharmacol.* **2007,** 111(3), 636-40.
130. T.K. Tabopda, J. Ngoupayo, P.K. Awoussong, A.C. Mitaine-Offer, M.S. Ali, B.T. Ngadjui, et al. Triprenylated flavonoids from *Dorstenia psilurus* and their α-glucosidase inhibition properties. *J Nat Prod.* **2008,** 71, 2068–72.
131. R. Korec, M. Korecova, K.H. Sensch, T. Zoukas. Antidiabetic effect of neoflavonoides coutareagenin in STZ diabetic rats and diabetic menopausal women. *Diabetes Res Clin Prac.* **2000,** 50, 42.
132. E. De Sousa, L. Zanatta, I. Seifriz, T.B. Creczynski-Pasa, M.G. Pizzolatti, B. Szpoganicz, et al. Hypoglycemic effect and antioxidant potential of kaempferoI-37-O-(α)-dirhamnoside from *Bauhinia foificata* leaves. *J Nat Prod.* ***2004,*** 67, 829–32.
133. L.H. Cazarolli, L. Zanatta, A.P. Jorge, H. Horst, E. De Sousa, V.M. Woehl, et al. Mechanism of action of the stimulatory effect of apigenin-6-C-(2"-O-alpha-l-rhamnopyranosyl)-beta-L-fucopyranoside on 14C-glucose uptake. *Chem Biol Interact.* **2006,** 163, 177–91.
134. S.H. Jung, J.M. Lee, H.J. Lee, C.Y. Kim, E.H. Lee, E.H. Um. Aldose reductase and advanced glycation end products inhibitory effect of *Phyllostachys nigra*. *Biol Pharm Bull.* **2007,** 30, 1569–72.
135. D.S. Jang, G.Y. Lee, Y.M. Lee, Y.S. Kim, H. Sun, D.H. Kim, et al. Flavan-3-ols having a lactam from the roots of *Actinidia arguta* inhibit the formation of advanced glycation end products *in vitro*. *Chem Pharm Bull*. **2009,** 57, 397–400.
136. T. Satyanarayana, K.B. Katyayani, E. Hema Latha, A.A. Mathews, M. Chinna Eswaraiah. Hypoglycemic and antihyperglycemic effect of alcoholic extract of *Euphorbia leucophylla* and its fractions in normal and in alloxan induced diabetic rats. *Pharmacog Magaz.* **2006,** 2, 244–53.
137. J. M. Narvez-Mastache, M.L. Garduo-Ramrez, L. Alvarez, G. Delgado. Antihyperglycemic activity and chemical constituents of *Eysenhardtia platycarpa*. *J Nat Prod.* **2006,** 69, 1687–91.
138. N.H. Yoo, D.S. Jang, J.L. Yoo, Y.M. Lee, Y.S. Kim, J.H. Cho, et al. Erigeroflavanone a flavanone derivative from the flowers of *Erigeron annuus* with protein glycation and aldose reductase inhibitory activity. *J Nat Prod.* **2008,** 71, 713–5.
139. R.M. Perez, H. Cervantes, M.A. Zavala. Isolation and hypoglycaemic activity of 5 7 3'-trihydroxy-3 6 4'-trimethoxyflavone from *Brickellia veronicaefolia*. *Phytomed.* **2000,** 7, 25–9.
140. R. Saleem, M. Ahmad, S.A. Hussain, A.M. Qazi, S.I. Ahmad, M.H. Qazi, et al. Hypotensive hypoglycaemic and toxicological studies on the flavonol C-glycoside shamimin from *Bombax ceiba*. *Planta Med.* **1999,** 65, 331–4.
141. L.H. Cazarolli, P. Folador, H.H. Moresco, I.M. Brighente, M.G. Pizzolatti, F.R. Silva. Mechanism of action of the stimulatory effect of apigenin-6-C-(2"-O-alpha-l-rhamnopyranosyl)-beta-L-fucopyranoside on 14C-glucose uptake. *Chem Biol Interact.* **2009,** 179, 407–12.
142. Z.F. Shen, M.Z. Xie. The anti-hyperglycemic effect of kakonein and aspirin. *Acta Pharmaceutica Sinica.* **1985,** 20, 863–5.
143. K.T. Lee, I.C. Sohn, D.H. Kim, J.W. Choi, S.H. Kwon, H.J. Park. Hypoglycemic and hypolipidemic effects of tectorigenin and kaikasaponin III in the STZ-induced diabetic rat and their antioxidant activity *in vitro*. *Arch Pharmacol Res.* **2000,** 23, 461–6.
144. Y. Deguchi, K. Osada, K. Uchida, H. Kimura, M. Yoshikawa, T. Kudo, et al. Effects of extract of guava leaves on the development of diabetes in the db/db mouse and on the postprandial blood glucose of human subjects. *Nippon Nogei Kagaku Kaishi.* **1998,** 72, 923–31.
145. B. Lee, K. Jung, D.H. Kim. Timosaponin AIII, a saponin isolated from *Anemarrhena asphodeloides*, ameliorates learning and memory deficits in mice. *Pharmacology Biochem Behav.* **2009,** 93(2), 121–7.
146. M. Yoshikawa, T. Murakami, T. Ueno, M. Kadoya, H. Matsuda, J. Yamahara, et al. E-senegasaponins A and B, Z-senegasaponins A and B, Z-senegins II and III, new type inhibitors of ethanol absorption in rats from senegae radix, the roots of *Polygala senega* L. var latifolia Torrey et Gray. *Chem Pharm Bull (Tokyo).* **1995,** 43(2), 350–2.
147. P. Daisy, J. Eliza, K. Abdul, M.M. Farook. A novel dihydroxy gymnemic triacetate isolated from *Gymnema sylvestre* possessing normoglycemic and hypolipidemic activity on STZ-induced diabetic rats. *J Ethnopharmacol.* **2009,** 126, 339–44.

148. N.K. Hoa, A. Norberg, R. Sillard, D. Van Phan, N.D. Thuan, D.T. Dzung, et al. The possible mechanisms by which phanoside stimulates insulin secretion from rat islets. *J Endocrinol*. **2007,** 192, 389–94.
149. M. Yoshikawa , S. Yoshizumi , T. Ueno , H. Matsuda , T. Murakami , J. Yamahara , N. Murakami .Medicinal foodstuffs. I. Hypoglycemic constituents from a garnish foodstuff "taranome," the young shoot of Araliaelata SEEM.: elatosides G, H, I, J, and K. *Chem Pharm Bull (Tokyo)*. **1995,** 43(11), 1878-82.
150. M. Yoshikawa, H. Shimada, T. Morikawa, S. Yoshizumi, N. Matsumura, T. Murakami, et al. Medicinal foodstuffs VII On the saponin constituents with glucose and alcohol absorption-inhibitory activity from a food garnish "Tonburi" the fruit of Japanese *Kochia scoparia* (L) Schrad:structures of scoparianosides A B and C. *Chem Pharm Bull.* **1997,** 45, 1300–5.
151. P. Daisy, R. Jasmine, S. Ignacimuthu, E. Murugan. A novel steroid from *Elephantopus scaber* L an ethnomedicinal plant with antidiabetic activity. *Phytomed* **2009,** 16, 252–57.
152. A.S. Attele, Y.P. Zhou, J.T. Xie, J.A. Wu, L. Zhang, L. Dey, et al. Antidiabetic effects of *Panax* ginseng berry extract and the identification of an effective component. *Diabetes.* **2002,** 51, 1851–8.
153. Kazmi, M. Rahman, M. Afzal, G. Gupta, S. Saleem, O. Afzal, et al. Anti-diabetic potential of ursolic acid stearoyl glucoside: A new triterpenic gycosidic ester from *Lantana camara*. *Fitoterapia.* **2012,** 83(1), 142–6.
154. B. Nickavar, G. Amin. Bioassay-guided separation of an α-amylase inhibitor anthocyanin from *Vaccinium arctostaphylos* berries. *Z Naturforsch.* **2010,** 65, 567–70.
155. M.C. Nath. Investigations on the new antidiabetic principle (amellin) occurring in nature Part I Studies on some of its biochemical properties. *Annals Biochem Exp Med*.**1943,** 3, 55–62.
156. B.S. Geetha, B.S. Mathew, B.T. Augusti. Hypoglycaemic effects of leucodelphinidin derivative isolated from *Ficus bengalensis* (Linn). *Ind J Physiol Pharmacol.* **1994,** 38, 220–2.
157. T. Kiyoteru, T. Shinichi, K. Junichi, Y. Shunivhi, L. Kazuo, W. Kinzo, et al. Antidiabetic Agents from Medicinal Plants. *Jpn Kokai yokkyo koho*. **2005,** p. 12.
158. S. Nakamura, K. Takahira, G. Tanabe, T. Morikawa, M. Sakano, K. Ninomiya, et al. Docking and SAR studies of salacinol derivatives as alpha-glucosidase inhibitors. *Bioorg Med Chem Lett.* **2010,** 204, 420–3.
159. S.C. Chien, P.H. Young, Y.J. Hsu, C.H. Chen, Y.J. Tien, S.Y. Shiu, et al. Anti-diabetic properties of three common *Bidens pilosa* variants in Taiwan. *Phytochem.* **2009,** 70, 1246–54.
160. Andrade-Cetto , H. Wiedenfeld. Hypoglycemic effect of Acosmium panamense bark on streptozotocin diabetic rats. *J Ethnopharmacol.* **2004,** 90(2-3), 217-20.
161. H. Nishimura, T. Ogino, T. Morota, S. Sasaki. Extraction of monocyclic sesquiterpenes and their glycosides from *Rehmannia glutinosa* and *Rehmannia rupestris* as aldose reductase inhibitors. *Japan Kokai Tokkyo Koho (Patent) Patent number*: JP 03163035; 1991. p. 9.
162. H. Hikino, M. Yoshizawa, Y. Suzuki, Y. Oshima, C. Konno. Isolation and hypoglycemic activity of trichosans A B C D and E: glycans of *Trichosanthes kirilowii* roots. *Planta Med*. **1989**, 55, 349–50.
163. Y. Zang, H. Sato, K. Igarashi. Anti-diabetic effects of a kaempferol glycoside-rich fraction from unripe soybean (Edamame, Glycine max L. Merrill. 'Jindai') leaves on KK-A(y) mice. *Biosci Biotechnol Biochem.* **2011,** 75(9), 1677–84.
164. D.F. Pereira V.D. Kappel , L.H. Cazarolli, A.A. Boligon, M.L. Athayde , S.M. Guesser , E.L. Da Silva , F.R. Silva . Influence of the traditional Brazilian drink Ilex paraguariensis tea on glucose homeostasis. *Phytomedicine.* **2012,** 19(10), 868-77.
165. L.Y. Tian, X. Bai, X.H. Chen, J.B. Fang, S.H. Liu, J.C. Chen. Anti-diabetic effect of methylswertianin and bellidifolin from *Swertia punicea* Hemsl and its potential mechanism. *Phytomed.* **2010,** 17, 533–9.
166. T. Miura, H. Ichiki, I. Hashimoto, N. Iwamoto, M. Kato, M. Kubo, et al. Antidiabetic activity of a xanthone compound mangiferin. *Phytomed.* **2001,** 8, 85–7.
167. S. Muruganandan, K. Scrinivasan, S. Gupta, P.K. Gupta, J. Lal. Effect of mangiferin on hyperglycemia and atherogenicity in streptozotocin diabetic rats. *J Ethnopharmacol.* **2005,** 97, 497–501.
168. A.M. Saxena, M.B. Bajpai, S.K. Mukherjee. Swerchirin induced blood sugar lowering of streptozotocin treated hyperglycemic rats. *Ind J Exp Biol.* **1991,** 29, 674–5.
169. S.C. Chou, L.M. Chuang, S.S. Lee. Hypoglycemic constituents of *Gynura divaricata* subsp. formosana. *Nat Prod Commun.* **2012**, 7(2), 221–2.
170. P.C. Lekshmi, R. Arimboor, K.G. Raghu, A. N. Menon. Turmerin, the antioxidant protein from turmeric (*Curcuma longa*) exhibits antihyperglycaemic effects. *Nat Prod Res.* **2012,** 26(17), 1654–8.
171. X. Chena, J. Jin, J. Tanga, Z. Wangb, J. Wanga, L. Jin, et al. Extraction purification characterization and hypoglycemic activity of a polysaccharide isolated from the root of *Ophiopogon japonicas. Carbohydrate Polymers.* **2011,** 83, 749–54.
172. Yi. Song, Y. Zhang, T. Zhou, H. Zhang, H.U. Xiaosong, Li. Quanhong. A preliminary study of monosaccharide composition and a-glucosidase inhibitory effect of polysaccharides from pumpkin (*Cucurbita moschata*) fruit. *Int J Food Sci Tech.* **2012,** 47, 357–61.
173. Z. Jiang, Q. Du. Glucose-lowering activity of novel tetrasaccharide glyceroglycolipids from the fruits of *Cucurbita moschata*. *Bioorg Med Chem Lett.* **2011,** 21, 1001–3.
174. L. Quanhong, F. Caili, R. Yukui. Effects of protein-bound polysaccharide isolated from pumpkin on insulin in diabetic rats. *Plant Foods for Human Nut.* **2005,** 60, 13–6.
175. N.J. Morada, E.B. Metillo, M.M. Uy, J.M. Oclarit. *Conference on Asia Agriculture and Animal.* 2011, 13.
176. F.J. Alarcon-Aguilar, A. Valdes-Arzate, S. Xolalpa-Molina, T. Banderas-Dorantes, M. Jimenez-Estrada, E. Hernandez-Galicia, et al. Hypoglycemic activity of two polysaccharides isolated from *Opuntia ficus-indica* and *O streptacantha*. *Proc West Pharmacol Soc.* **2003,** 46, 139–42.
177. Li. Fenglin, Li. Qingwang, D. Gao, Y. Peng, C. Feng. Preparation and antidiabetic activity of polysaccharide from *Portulaca oleracea* L. *African J of Biotech.* **2009,** 8, 569–73.
178. L.S. McWhorter. Biological complementary therapies: A focus on botanical products in diabetes. *Diabetes Spectrum.* **2001,** 14, 199–208.
179. L.S. Lee, D.H. Yang. Rheological properties of the hot-water extracted polysaccharides in Ling-Zhi (*Ganoderma lucidum*). *Food Hydrocolloids.* **2007,** 21, 739–46.
180. H. Zhou, D. Wang, P. Sun, P. Bucheli, L. Li, Y. Hou, et al. Effects of soluble tea polysaccharides on hyperglycemia in alloxan-diabetic mice. *J Agr Food Chem.* **2007,** 55, 5523–8.
181. Q. Luoa, Y. Caib, J. Yana, M. Sunc, H. Corkeb. Hypoglycemic and hypolipidemic effects and antioxidant activity of fruit extracts from *Lycium barbarum*. *Life Sci.* **2004,** 76, 137–49.
182. F.J. Alarcon-Aguilar, M. Jimenez-Estrada, R. Reyes-Chilpa, B. Gonzalez-Paredes, C.C. Contreras-Weber, R. Roman-Ramos. Hypoglycemic activity of root water decoction, sesquiterpenoids and one polysaccharide fraction from *Psacalium decompostum* in mice. *J Ethnopharmacol*. **2000,** 69, 207–15.
183. H. Tong, Z. Liang, G. Wang. Structural characterization and hypoglycemic activity of a polysaccharide isolated from the fruit of *Physalis alkekengi* L. *Carbohydr Polym.* **2008,** 71, 316–23.
184. Z.Y. Zhang, H.Y. Ye, M.H. Yu, L. You, Y.Q. Yan, X.F. Yang. Effects of astragalus polysaccharide on the myocardial ultrastructure of diabetic rats. *J of Fudan Uni.* **2001,** 28, 476–8.
185. R.X. Zhang, G.M. Gu, X.Y. Zhang. The effect of oligosaccharides from *Rehmannia glutinosa* Libosch to regulate the metabolism of glucose of experimental diabetic rat. *Pharm and Clinic of Chinese Trad Med*. **1996,** 14.

186. B.X. Wang , M. Yang , Y.L. Jin , Z.Y. Cui, Y. Wang . Studies on the hypoglycemic effect of ginseng polypeptide**,** Yao Xue Xue Bao.**1990,** 25(6), 401-5.
187. Y. Oshima, K. Sato, H. Hikino. Isolation and hypoglycemic activity of quinquefolans A B and C glycans of *Panax quinquefolium* roots. *J Nat Prod.* **1987,** 50, 188–90.
188. M. Tomoda, N. Shimizu, R. Gonda, M. Kanari, H. Yamada, H. Hikino. Anticomplementary and hypoglycaemic activities of the glycans from the seeds of *Malva verticillata*. *Planta Med.* **1990,** 56, 168–70.
189. Z.H. Xu, S.W. Zhou, L.Q. Huang. Protective effect of coixan on pancreatic islet cell injury by alloxan in rats. *Chinese Pharma Bul.* **2000,** 16, 639–42.
190. Y.M. Kwon, S.M. Cho, J.H. Kim, J.H. Lee, Y.A. Lee, S.J. Lee, et al. Hypoglycemic effect of *Cordyceps militaris. Saengyak Hakhoechi.* **2001,** 32, 327–9.
191. H. Hikino, T. Mizuno, Y. Oshima, C. Konno. Isolation and hypoglycemic activity of Morans A a glycoprotein of *Morus alba* root barks. *Planta Medica*.**1985,** 51, 159–60.
192. P. Basnet, S. Kadota, R.R. Pandey T. Takahashi, Y. Kojima, M. Shimizu, et al. Screening of traditional medicines for their hypoglycemic activity in streptozotocin (STZ)-induced diabetic rats and a detailed study on *Psidium guajava*. *Wakan Iyakugaku Zasshi.* **1995,** 12, 109–17.
193. D. Gao, Q. Li, Z. Liu, J. Feng, J. Li, Z. Han, et al. Antidiabetic potential of *Rhodiola sachalinensis* root extract in streptozotocin-induced diabetic rats. *Methods Find Exp Clin Pharmacol.* **2009,** 31, 375–81.
194. S.C. Chien, P.H. Young, Y.J. Hsu, C.H. Chen, Y.J. Tien, S.Y. Shiu, et al. Anti-diabetic properties of three common *Bidens pilosa* variants in Taiwan. *Phytochem.* **2009,** 701, 246–54.
195. S.W.H. Lee, S.W. Lim, Y.M. Lee, H.S. Lee, D.K. Kim. Polysaccharide isolated from *Triticum aestivum* stimulates insulin release from pancreatic cells via the ATP-sensitive K+ channel. *Int J Mol Med.* **2012,** 29:913–9.
196. Y.Y. Yang, S. Gao, H.P. Wang, S. Chen, L.X. Ma. Studies on the effect of konjak oligosaccharides on blood sugar and serum cholesterol in the diabetic mice. *J Hubei University.* **2001,** 23, 277–9.
197. C. Wan , T. Yuan , L. Li , V. Kandhi , N.B. Cech , M. Xie , N.P. Seeram . Maplexins, new α-glucosidase inhibitors from red maple (Acer rubrum) stems. *Bioorg Med Chem Lett.* **2012,** 22(1), 597-600.
198. M. Kuroda , Y. Mimaki , T. Ohtomo , J. Yamada , T. Nishiyama , T. Mae , H. Kishida , T. Kawada. Hypoglycemic effects of clove (Syzygium aromaticum flower buds) on genetically diabetic KK-Ay mice and identification of the active ingredients**.** *J Nat Med.* **2012,** 66(2), 394-9.
199. H.G. Park , E.J. Bak , G.H. Woo , J.M. Kim , Z. Quan , J.M. Kim, H.K. Yoon, S.H. Cheon , G. Yoon , Y.J. Yoo , Y. Na , J.H. Cha . Licochalcone E has an antidiabetic effect**.** *J Nutr Biochem.* **2012,** 23(7), 759-67.
200. R. Balamurugan, V. Duraipandiyan, S. Ignacimuthu. Antidiabetic activity of γ-sitosterol isolated from *Lippia nodiflora* L in streptozotocin induced diabetic rats. *Eur J Pharmacol.* **2011,** 667, 410–8.
201. Y. Sauvaire, P. Petit, C. Broca, M. Manteghetti, Y. Baissac, J. Fernandez-Alvarez, et al. 4-Hydroxyisoleucine: A novel amino acid potentiator of insulin secretion. *Diabetes.* **1998,** 47, 206–10.
202. A.I. Oberg, K. Yassin, R.I. Csikasz, N. Dehvari, I.G. Shabalina, H.S. Hutchinson, et al. Shikonin increases glucose uptake in skeletal muscle cells and improves plasma glucose levels in diabetic Goto-Kakizaki rats. *PLoS One.* **2011,** 6, 22510.
203. Ogawa, Y. Miyamae, A. Honma, T. Koyama, K. Yazawa, H. Shigemori. Pycnalin a new α-glucosidase inhibitor from *Acer pycnanthum*. *Chem Pharm Bull.* ***2011*,** 59, 672–5.
204. Govindasamy, K.S. Al-Numair, M.A. Alsaif, K.P. Viswanathan. Influence of 3-hydroxymethyl xylitol a novel antidiabetic compound isolated from *Casearia esculenta* (Roxb) root on glycoprotein components in streptozotocin-diabetic rats. *J Asian Nat Prod Res.* **2011,** 13, 700–6.
205. W. Qiao, C. Zhao, N. Qin, H.Y. Zhai, H.Q. Duan. Identification of trans-tiliroside as active principle with anti-hyperglycemic anti-hyperlipidemic and antioxidant effects from *Potentilla chinesis*. *J Ethnopharmacol.* **2011,** 135, 515–21.
206. T. Bu, M. Liu, L. Zheng, Y. Guo, X. Lin. α-Glucosidase inhibition and the *in vivo* hypoglycemic effect of butyl-isobutyl-phthalate derived from the *Laminaria japonica* rhizoid. *Phytother Res.* **2010,** 24, 1588–91.
207. F. Brindis, R. Rodríguez, R. Bye, A. M. González, R. Mata. (Z)-3-butylidenephthalide from *Ligusticum porteri* an α-glucosidase inhibitor. *J Nat Prod.* **2011,** 74, 314–20.
208. K. Hattori, N. Sukenobu, T. Sasaki, S. Takasuga, T. Hayashi, R. Kasai, et al. Activation of insulin receptors by lagerstroemin. *J Pharmacol Sci.* **2003,** 93, 69–73.
209. H. Jemai, A. El Feki, S. Sayadi. Antidiabetic and antioxidant effects of hydroxytyrosol and oleuropein from olive leaves in alloxan-diabetic rats. *J Agric Food Chem.* **2009,** 57, 8798–804.
210. P.S. Babu, S. Prabuseenivasan, S. Ignacimuthu. Cinnamaldehyde—A potential antidiabetic agent. *Phytomed.* **2007,** 14, 15–22.
211. S.O. Lee, S.Z. Choi, J.H. Lee, S.H. Chung, S.H. Park, H.C. Kang, et al. Antidiabetic coumarin and cyclitol compounds from *Peucedanum japonicum*. *Arch Pharm Res.* **2004,** 27, 1207–10.
212. J.R. Carney, J.M. Krenisky, R.T. Williamson, J. Luo. Achyrofuran a new antihyperglycemic dibenzofuran from the South American medicinal plant *Achyrocline satureioides*. *J Nat Prod.* **2002**, 65, 203–5.
213. H. Nojima, I. Kimura, F.J. Chen, Y. Sugihara, M. Haruno, A. Kato, et al. Antihyperglycemic effects of N-containing sugars from *Xanthocercis zambesiaca Morus bombycis Aglaonema treubii* and *Castanospermum australe* in streptozotocin-diabetic mice. *J Nat Prod.* **1998,** 61, 397–400.
214. Nmila R, Gross R, Rchid H, M. Roye, M. Manteghetti, P. Petit, et.al. Insulinotropic effect of *Citrullus colocynthis* fruits extract. *Planta Med.* **2000,** 66, 418–23.
215. T. Morota, H. Takeda, H. Sasaki, S. Sato. Aldose reductase inhibitors containing phenols of *Caesalpinia sappan*. *Patent number: JP* 02264718. 1990; 7.
216. R. Dong, Y.Q. Duan, X.Y. Wang, Y. Liu, G.L. Gao. Effect of garlic on peroxidation in rats with diabetes. *Chinese J Public Hygiene.* **2000,** 16, 605–6.
217. S.W. Eisenman, A. Poulev, L. Struwe, I. Raskin, D.M. Ribnicky. Qualitative variation of anti-diabetic compounds in different tarragon (*Artemisia dracunculus* L.) cytotypes. *Fitoterapia*. **2011,** 82(7), 1062–74.
218. A.J. Alonso-Castro, A.C. Miranda-Torres, M.M. González-Chávez, L.A. Salazar-Olivo. *Cecropia obtusifolia* Bertol and its active compound chlorogenic acid stimulate 2-NBD glucose uptake in both insulin-sensitive and insulin-resistant 3T3 adipocytes. *J Ethnopharmacol.* **2008,** 120, 458–64.
219. N. Shukla, M. Kumar, G. Akanksha, N. Ahmad, A.B. Rahuja, A.K. Singh, et al. Tectone a new antihyperglycemic anthraquinone from *Tectona grandis* leaves. *Nat Prod Commun.* **2010,** 5, 427–30.
220. K. Kumari, B.C. Mathew, K.T. Augusti. Antidiabetic and hypolipidemic effects of S-methyl cysteine sulfoxide isolated from *Allium cepa* Linn. *Ind J of Biochem & Biophy.* **1995,** 32, 49–54.
221. C. Konno, M. Murayama, K. Sugiyama, A. Arai, M. Murakami, M. Takahashi, et al. Isolation and hypoglycemic activity of acontians A B C and D glycans of *Aconitum carmichaeli* roots. *Planta Med.* **1985,** 51, 160–1.
222. N. Hatae, S. Yamauchi, T. Saeki, I. Suzuki, T. Choshi, S. Hibino, C. Okada, Y. Watanabe, E. Toyota. Effects of 1,3-di-O-substituted-myo-inositol derivatives on the antiproliferation and caspase-3 activity of HCT-116 and HL-60 cells. *Chem. Biol. Lett*., **2014**, 1(2), 40-43.