Anti-Diabetic Agents from Natural Products—An Update from 2004 to 2009

Lian-Wen Qi†, E-Hu Liu†, Chu Chu, Yong-Bo Peng, Hai-Xia Cai and Ping Li*

Key Laboratory of Modern Chinese Medicines, China Pharmaceutical University, Ministry of Education, Nanjing 210009, China

Abstract: Diabetes mellitus (DM), the third killer of the mankind health along with cancer, cardiovascular and cerebrovascular diseases, is one of the most challenging diseases facing health care professionals today. The World Health Organization (WHO) has declared that a DM epidemic is underway. Primary DM and its complications are costly to manage, not only for affected individuals, but also for healthcare systems around the world. Screening of anti-diabetic agents has been extensively investigated in the past decades. Natural products (NPs) have served as a major source of drugs for centuries, and about half of the pharmaceuticals in use today are derived from natural substances. Many natural products especially plants-derived medicines have been recommended for the treatment of DM. The present paper reviews NPs appeared in the literature with potential for DM and also identifies the research needs in this area. It mainly covers the time period from January 2004 to June 2009. The current review is divided into three major sections based on classification of the natural materials involved. The first part focuses on known and some new chemical entities isolated mainly from medicinal plants possessing anti-diabetic properties, including saponins, flavonoids, alkaloids, anthraquinones, terpenes, coumarins, phenolics, polysaccharides, and some other compounds. The second part summarizes crude extract of medicinal plants which are commonly used in the traditional Chinese medical system and have been demonstrated experimental or/and clinical anti-diabetic effectiveness, mainly including Leguminosae, Cucurbitaceae, Araliaceae, Liliaceae, Chenopodiaceae, Solanaceae, Compositae, Campanulaceae, Cornaceae, Rhamnaceae, Scrophulariaceae, Euphorbiaceae, Ginkgoceae, Gramineae, Myrtaceae, Sterculiaceae, Annonaceae, Labiatae, Crassulaceae, and Miscellaneous. The third part lists some compound formulae consisting of extracts of several plants that have been reported as beneficial for the treatment of DM, major involving Xiaokeling tablet, Huang-Lian-Jie-Du-Decoction, Ba-Wei-Di-Huang-Wan and Formula 1.

Keywords: Anti-diabetic agents, chemical entities, compound formulae, diabetes mellitus, herbal medicines, hypoglycemic, medicinal plants, natural products, review.

1. INTRODUCTION

Diabetes mellitus (DM) is a hereditary, chronic, potentially debilitating and often fatal endocritic disorder disease, characterized by hyperglycaemia and eventual glycosuria. It is caused by the inability of tissues to carry out normal metabolism of carbohydrate, lipid and protein. Two forms of DM are usually described: insulin dependent DM (type 1) and non-insulin dependent DM (type 2). Type 1 DM is characterized by an absolute deficiency of insulin secretion, associated with auto-immune destruction of pancreatic β-cells, and this disease is more likely to occur in relatives of an affected person. Type 2 DM, which accounts for more than 90% of cases and largely results from excess body weight and physical inactivity, is caused by a combination of resistance to insulin action and impaired insulin secretion. The long-term durative hyperglycemia usually leads to serious damage to many of the body's systems, especially the nerves, blood vessels, heart, eyes, and kidneys, and thus concurs serious macrovascular and microangiopathy complications, including retinopathy, nephropathy, and peripheral neuropathy [1].

Due to population growth, aging, urbanization, lifestyle alterations, and increasing prevalence of obesity and physical inactivity [2], the past two decades have seen an explosive worldwide increase in the number of people that are diagnosed with DM. An estimated 30 million people worldwide had DM in 1985. The latest data from International Diabetes Federation (IDF) and World Health Organization (WHO) indicate that DM now affects a staggering 246 million people worldwide, with 46% of all those affected in the 40-59 age group during their economically most productive years, and this is likely to increase to at least 380 million by 2025 [3]. A DM epidemic is undoubtedly underway. Figure **1** shows top 10 countries in prevalence of DM and number of people with DM (20-79 age group) in 2007, the prevalence of DM in Nauru is the highest in the world and India has the largest DM population with an estimated 41 million people. DM is becoming the third "killer" of the health of mankind along with cancer, cardiovascular and cerebrovascular diseases because of its high prevalence, morbidity and mortality. The excess global mortality attributable to DM in the year 2000 was estimated to be 2.9 million deaths, equivalent to 5.2% of all deaths. An even greater number die from cardiovascular disease that is made worse by DM-

*Address correspondence to this author at Key Laboratory of Modern Chinese Medicines, China Pharmaceutical University, Ministry of Education, No. 24, Tongjia Lane, Nanjing 210009, China; Tel: +86-25-8532-2256; Fax: +86-25-8532-2747; E-mail: liping2004@126.com; fleude@126.com

†The first two authors contributed equally to this work.

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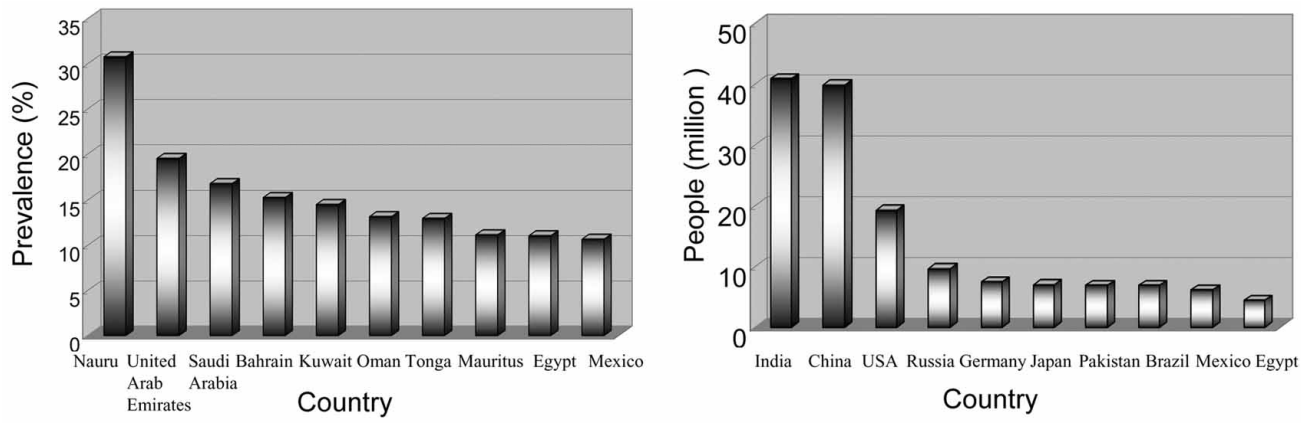


Fig. (1). Top 10 countries in prevalence of diabetes and number of people with diabetes (20-79 age group) in 2007.

related lipid disorders and hypertension [4]. Primary DM and its complications are costly to manage, not only for affected individuals, but also for healthcare systems around the world. According to the IDF, DM already accounts for 5-10% of the total healthcare budget in many countries. November 14 was marked as World Diabetes Day by the United Nations in 2007 to raise awareness of the growing threat of DM.

Although, oral hypoglycemic agents/insulin are the mainstay of treatment of DM and are effective in controlling hyperglycemia, the treatment of DM using these chemical drugs is complicated by several factors inherent to the disease process, typically insulin resistance, hyperinsulinemia, hypertension, impaired insulin secretion and cholesterol abnormalities. Most of them have prominent side effects and fail to significantly alter the course of diabetic complications. As the presently available oral hypoglycemic agents and insulin therapy have limitations with regard to systemic efficacy, patient compliance and adverse effects, it has promoted a tremendous effort worldwide in searching for alternative therapeutic approaches for this metabolic disease.

The multifactorial pathogenicity of DM demands a multimodal therapeutic approach. Future therapeutic strategies might require the combination of various types of anti-diabetic agents [5], including a strategy to use multi-component-based natural products (NPs). The use of natural substances particularly plants to cure diseases is a centuries old practice. Many medicinal plants remain important in modern medicine, not only because they continue to be applied as crude drug preparations and formulas, but also because the serve as the abundant sources of important pure chemicals that have become mainstays of modern therapy. Noteworthy, about 50% of the drugs on the market are from vegetal origin [6]. For example, metformin was a biguanide derivative of guanide, originated from the plant Goat's Rue (*Galega officinalis*) as a structure-modified natural product to vastly improve its efficacy. In recent years, a great number of NPs, including chemical entities, medicinal plants and compound formulae consisting of multiple plants, have been reported to possess hypoglycemic activity with candidates for new anti-diabetic agents.

The aim of this article was to review these studies that have been appeared in the literature for DM and also to identify the research needs in this area. It mainly covers the time period between January 2004 and June 2009. Because of space citation limitations, the references included represent only a fraction of the total number published. Books and book chapters are not included. Nature products from microbial and marine sources are not involved. The current review is divided into three major sections based on classification of the materials employed. These are know and some novel chemical entities from natural substances, crude plant extracts from Chinese herbal medicines, and compound formulae consisiting of extracts of several plants. Additionally, the major sections are subdivided in terms of specific classification.

2. ANTI-DIABETIC CHEMICAL ENTITIES FROM NPS

With the scientific and technological development on chemical and pharmacological research, numerous bioactive compounds have been isolated, purified and identified from NPs especially from medicinal plants for DM. Jung *et al.* reported new NPs from 2001 to 2004 with anti-diabetic potential. This part reviews known some new chemical entities with diverse structures for their therapeutic activities against DM reported from 2005 to present. These compounds are categorized into saponins, flavonoids, alkaloids, anthraquinones, terpenes, coumarins, phenolics, polysaccharides, and other compounds according to their structures. Their structures are shown in Fig. **2**.

2.1. Saponins

Saponins are a group of secondary metabolites which are widely distributed in great number of plant species and in some marine organisms. They consist of non-sugar aglycone and sugar chain units, and can be divided into steroidal and triterpene groups according to the nature of the aglycone. The sugars can be attached to the aglycone either as one, two or three side chains. Both triterpene and steroidal aglycones have a number of different substituents (-H, -COOH, $-CH_3$). A number of saponins isolated mainly from medicinal plant have been shown anti-diabetic activities by decreasing the

level of blood glucose, adjusting blood fat and improving the level of insulin and the tolerance to glucose.

Five new cucurbitane glycosides, momordicosides Q (**1**), R (**2**), S (**3**), T (**4**), and karaviloside XI (**5**) were isolated from bitter melon (*Momordica charantia*) which is a popular medicinal vegetable with reported hypoglycemic effects, and absolute configurations of these compounds were established [7]. These compounds and their aglycones exhibited a strong efficacy (EC_{50}: ~1 nM) comparable to insulin (100 nM) in stimulating glucose transporter 4 (GLUT4) translocation to the cell membrane in both L6 myotubes and 3T3-L1 adipocytes. Further study revealed that these compounds activate AMP-activated protein kinase (AMPK), the protein responsible for regulating fuel metabolism and enabling glucose uptake. *In vivo* studies in insulin resistant high fat fed mice showed that compound **4** (10 mg/kg, intraperitoneal, i.p.) significantly improved glucose tolerance.

Five phytosterols named lophenol (**6**), 24-methyl-lophenol (**7**), 24-ethyl-lophenol (**8**), cycloartanol (**9**) and 24-methylene-cycloartanol (**10**) were isolated from *Aloe barbadensis* Miller [8]. Their anti-hyperglycemic effects were evaluated in type 2 diabetic db/db mice. In comparison with the hemoglobin A1c levels of vehicle-treated mice, statistically significant decreases of 15% to 18% in hemoglobin A1c levels were observed in mice treated with 1 μg of the five phytosterols singly. After administration of **6**-**10** separately for 28 d, fasting blood glucose (FBG) levels decreased to approximately 64%, 28%, 47%, 51%, and 55% of control levels, respectively. Subsequent studies revealed that administration of **6** or **9** could reduce visceral fat mass and improve hyperlipidemia and hyperglycemia in Zucker diabetic fatty rats [9].

Phanoside (**11**), a new dammarane-type saponin isolated from the plant *Gynostemma Pentaphyllum* Thunb Makino, was found to stimulate insulin release from isolated rat pancreatic islets [10]. Phanoside at 500 μM stimulated insulin release *in vitro* 10-fold at 3.3 mM glucose and potentiates the release almost 4-fold at 16.7 mM glucose. At these glucose levels, 2 μM glibenclamide stimulated insulin release only 2-fold. Also when given orally to rats, phanoside (40 and 80 mg/ml) improved glucose tolerance and enhanced plasma insulin levels at hyperglycemia. The effect seems to be exerted distal to K-ATP channels and L-type Ca^{2+} channels, which is on the exocytotic machinery of the β-cells [11].

A new anti-diabetic compound named corosolic acid (**12**) was isolated from *Lagerstroemia speciosa* [12]. The anti-diabetic effects were investigated in KK-Ay mice, an animal model of type 2 DM. Compound **12** (2 mg/kg) reduced the blood glucose levels after a single oral dose and also significantly decreased insulin resistance.

A new steroid, 28Nor-22(R)Witha 2,6,23-trienolide (**13**), was isolated from acetone extract of *Elephantopus scaber* [13]. This compound has been demonstrated to reduce the blood glucose levels and restore the insulin levels in streptozotocin (STZ)-induced diabetic rats through stimulation of pancreatic β-cells and subsequent secretion of insulin.

Ginsenoside Re (**14**) and ginsenoside Rh_2 (**15**) are active saponins derived from *Panax ginseng*, an herb widely used to treat DM. They showed marked effects on blood glucose and lipid levels. Zhang *et al.* revealed that activation of insulin signaling by ginsenoside Re is initiated at IR substrate-1 and further passes on through phosphatidylinositol 3-kinase and downstream signaling cascades. Moreover, ginsenoside Re demonstrates an impressive suppression of c-Jun and NF-kappaB activation and inhibitor of NF-kappaB degradation [14]. While Lai *et al.* indicated that the mechanism of lowering plasma glucose of ginsenoside Rh2 is based on an increase in β-endorphin secretion that activates opioid mu-receptors thereby resulting in an increased expression of glucose transporter subtype 4 [15].

A new tetracyclic triterpenoid, 3b,19a-dihydroxyurs-12,20(21)-diene-28-oic acid (**16**), together with other two known hypoglycemic ingredients oleanolic acid (**17**) and ursolic acid (**18**), were isolated from the chloroform extract of the leaves of *Astianthus viminalis* [16]. Oleanolic acid (**17**) and oleuropein (**19**), were also isolated from *Olea europeaea* and *Ligustrum Japonicum*, two traditional anti-diabetic and antihypertensive herbal drugs [17]. Studies showed that oleanolic acid lowered serum glucose and insulin levels in mice fed with a high fat diet and it enhanced glucose tolerance. Oleanolic acid is an agonist for TGR5, a member of G-protein coupled receptor activated by bile acids and which mediates some of their various cellular and physiological effect, demonstrating the potential role of TGR5 agonists to improve metabolic disorders [18].

Astragaloside IV (**20**) and astragaloside I (**21**), are two active cycloartane-type triterpenoid saponins with high content isolated from *Astragalus membranaceus* (Fisch.) Bge. var. *mongholicus* (Bge.) Hsiao or *A. membranaceus* (Fisch.) Bge. [19]. Researches indicated that they exhibited protective effects on early stage of diabetic nephropathy in rats [20].

2.2. Flavonoids

Flavonoids, one of the largest groups of low molecular weight secondary metabolites presenting a common benzo-γ-pyrone structure, are naturally occurring phenolic compounds. Due to the presence of aromatic hydroxyl groups, flavonoids have strong antioxidant properties. Many of the biological action of flavonoids have been attributed to their powerful antioxidant properties. Since the beginning of 1980s, the beneficial effects of flavonoids have been studied in DM. Flavonoids with antioxidant properties and free radical scavengers in particular prevent autopoly (ADP-ribosyl)-ation of poly synthetase polymerase and by stabilizing Reg gene transcriptional complex, result in the regeneration of β-cells and protect pancreatic islets. Recently, many biologically active flavonoids for treating DM and its complications have been found.

Quercetin (**22**), (-)-epicatechin (**23**) and rutin (**24**), three of the most widely distributed flavonoids in plants, can improve the antioxidant status, inhibit hyperglycemia and β-cell destruction in the rat pancreas as well as block NO production and inhibition of insulin release from the isolated islets [21-23].

Two new flavonoids, quercetin 3-*O*-α-(2″-galloyl) rhamnoside (**25**) and kaempferol 3-*O*-α-(2″-galloyl) rhamnoside

(**26**), were isolated from the methanol extract of *Bauhinia megalandra* fresh leaves, and their anti-diabetic activities were evaluated by rat liver microsomal glucose-6-phosphatase bioassay. Results demonstrated that **25** and **26** showed high inhibitory effect on the disrupted microsomal glucose-6-phosphatase with 50% inhibiting concentration (IC_{50}) values at about 30 μM, and strongly inhibited the neoglucogenic capacity of rat liver slices [24].

Puerariafuran (**27**), a new 2-arylbenzofuran, as well as a known compound coumestrol (**28**), were isolated from a methanol extract of the roots of *Pueraria lobata* [25]. They showed a significant *in vitro* inhibitory effect on advanced glycation end products (AGEPs) with IC_{50} values at 0.53 and 0.19 μM. Another novel 2,3-dioxygenated flavanone, erigeroflavanone (**29**) was isolated from an ethyl acetate extract of the flowers of *Erigeron annuus*, and showed inhibitory activity against AGEPs formation and rat lens aldose reductase (AR) [26].

Butein (**30**) and sulfuretin (**31**) were isolated from an ethyl acetate fraction from *Rhus verniciflua via* bioactivity guided fractionation and isolation and tested for their effects on recombinant human AR and AGEPs. They were found to possess strong both forms of AR and AGEPs inhibition. The inhibitory activity of butein against a recombinant human AR (IC_{50} value: 0.5 μM) was 2.6 times more potent than that of epalrestat as a positive control (IC_{50} value: 1.3 μM). The inhibitory potency of sulfuretin (IC_{50} value: 124.7 μM) on AGEPs was about 10 times more potent than that of aminoguani-dine as a positive control (IC_{50} value: 1231.0 μM) [27].

Two dihydroflavonol glycosides, engeletin (**32**) and astilbin (**33**), were isolated from an acetic ether extract of the leaves of *Stelechocarpus cauliflorus*. They only differ in the number of hydroxyl groups in their aglycones, but exhibited different activities against aldose mand and AGEPs formation. The inhibitory activity of engeletin against a recombinant human AR (IC_{50} value = 1.16 μM) was 23 times greater than that of astilbin (26.7 μM). Astilbin was about as potent as the positive control, quercetin, in its inhibition of AGEPs formation [28].

Two chalcones, 4-hydroxyderricin (**34**) and xanthoangelol (**35**) isolated from the ethanol extract of *Angelica keiskei* showed strong insulin-like activities *via* a pathway independent of the peroxisome proliferator-activated receptor (PPARγ) -gamma activation. Compound **34** especially showed the preventive effects on the progression of DM in genetically diabetic KK-Ay mice [29].

Myricetin (**36**), an active principle of *Abelmoschus moschatus* (Malvaceae), was tested for treating insulin resistance with obese Zucker rats. Rsults indicated that myricetin improves insulin sensitivity through increased post-receptor insulin signaling mediated by enhancements in IRS-1-associated PI3-kinase and GLUT 4 activity in muscles [30].

The effect of chronic administration of genistein (**37**) was studied on aortic reactivity of STZ-reduced diabetic rats. Results showed that chronic treatment of diabetic rats with genistein could prevent the abnormal functional changes in vascular reactivity in diabetic rats through NO- and prostaglandin-dependent pathways and *via* attenuating oxidative stress in the wall of aortic tissue [31]. In addition, the hypoglycemic effects of genistein as well as hesperidin (**38**), naringin (**39**), and daidzein (**40**) were revealed and partly mediated by hepatic glucose-regulating enzymes in C57BL/KsJ-db/db mice [32].

Many other flavonoids have also been shown anti-diabetic activities through the mechanism of anti-oxidation, inhibiting α-glucosidas, parainsulin, antiinflammatory, inhibiting AR and glycosylation, including scutellarin (**41**) from *Erigeron multiradiatus* [33], eupatilin (**42**) from *Artemisia princeps* Pampanini [34], isoginkgetin (**43**) from *Gingko biloba* L. [35], and saponarin (**44**) from *Tinospora cordifolia* [36].

2.3. Alkaloids

Alkaloids are naturally occurring chemical compounds containing basic nitrogen atoms. Alkaloids are usually classified by their common molecular precursors, based on the metabolic pathway used to construct the molecule. A few alkaloids were isolated from plants for DM.

Berberine (**45**), an isoquinoline alkaloid isolated from a variety of plants, such as *Coptis chinensis*, *Berberis aquifoliu*, and *Berberis ariatata*, represents one of the most studied among the naturally occurring protoberberine alkaloids. In China in the 1980s, a hypoglycemic effect was accidentally found when berberine was administered to diabetic patients with diarrhea. Since then berberine has often been used as an antihyperglycemic agent by many physicians in China. In recent years, there have been substantial amounts of clinical, *in vitro* and *in vivo* experimental reports showing that berberine has potentially beneficial effects in the treatment of DM and obesity. Lee *et al.* revealed that berberine can reduce body weight and cause a significant improvement in glucose tolerance in db/db mice and high-fat-fed Wistar rats [37]; Ko and his team demonstrated that berberine may increase glucose-stimulated insulin secretion and proliferation in Min6 cells [38]; Pan *et al.* showed that berberine could inhibit α-glucosidase activities and reduce glucose absorption in Caco-2 cell [39]; Zhou *et al.* revealed that berberine promoted glucose uptake in HepG2 and T3-L1 cells independent of insulin action and improved glucose metabolism *via* glycolysis [40]; Cheng *et al.* demonstrated that berberine stimulated glucose uptake in L6 myotubes [41]; Zhou *et al.* demonstrated that berberine modulated Cdk9 and cyclin T1 protein expression in diabetic myocardium which may contributed to ameliorate myocardium damage [42]. Several clinical investigations of berberine in the treatment of DM were also reported. Li's group performed a randomized, double-blind, placebo controlled trial in four centers to evaluate the efficacy and safety of berberine in the treatment of DM and dyslipidemia, demonstrating that berberine is effective and safe in the treatment of type 2 DM and dyslipidemia [43].

Seven alkaloids including berberine (**45**), palmatine (**46**), jateorrhizine (**47**), epiberberine (**48**), coptisine (**49**), groenlandicine (**50**) and magnoflorine (**51**) were isolated from the rhizome of *Coptis chinensis* Franch. The anti-diabetic complications capacities of these alkaloids were evaluated via rat lens aldose reductase and human

recombinant aldose reductase inhibitory assays. Different from the study before, Jung and his group pointed out, the two major components, compound **45** and **46** exhibited no aldose reductase inhibitory effects at a higher concentration of 50 μg/ml in their study. Conversely, compound 48-50 exhibited moderate inhibitory effects with IC_{50} values of 100.1, 118.4, 140.1 μM for rat lens AR and 168.1, 187.3, 154.2 μM for human recombinant AR [44].

Lupanine (**52**), 13-α-OH lupanine (**53**) and 17-oxo-lupanine (**54**), three quinolizidine alkaloids isolated from *Lupinus* species, have been proven promoting glucose-induced insulin release from isolated rat pancreatic islet cells [45]. However, their effect on insulin secretion was dependent on the glucose concentration in the incubation media. The three alkaloids only showed efficacy at high concentrations of glucose, while 2-thionosparteine, a synthetic derivative, enhanced insulin secretion at all glucose concentrations. In a subsequent study, Dworacka's team further investigated the hypoglycemic effects of lupanine and 2-thionosparteine in non-diabetic and in STZ-induced diabetic rats. Results demonstrated that 2-thionosparteine showed similar hypoglycemic effects to glibenclamide and sparteine, but did not result in a significant increase in plasma insulin levels. While lupanine did not exert hypoglycemic potency or significantly increase plasma insulin concentration independent of the group examined [46].

Tetramethylpyrazine (**55**), one of the active components in Qing Huo Yi Hao, displayed strong antioxidant and endothelial protective effects, which can be comparable as Qing Huo Yi Hao. The result indicated that some therapeutic potential of Qing Huo Yi Hao and tetramethylpyrazine for vascular complications of diabetes [47].

Rhetsinine (**56**) was isolated from the hot water extract from the *Evodia rutaecarpa* by gel filtration chromatography. It inhibited AR with IC_{50} values of 24.1 μM. Furthermore, rhetsinine inhibited sorbitol accumulation by 79.3% at 100 μM [48]. This compound could be potentially useful in the treatment of diabetic complications.

2.4. Anthraquinones

Two anthraquinones, emodin (**57**) and chrysophanol (**58**), and one stilbene, desoxyrhapontigenin (**59**) were isolated from the the 80% EtOH extracts obtained from cultivated *Rheum undulatum* [49]. They inhibited postprandial hyperglycemia by 29.5%, 42.3%, and 35.8%, respectively on ICR mice by oral glucose tolerance test determined by the glucose oxidase method.

Aurantio-obtusin (**60**), chryso-obtusin-2-*O*-β-D-glucoside (**61**), emodin (**62**), and obtusifolin (**63**), isolated from acetic ether extract of the seeds of *Cassia tora*, were subjected to *in vitro* bioassays to evaluate their inhibitory activity against AGEPs formation and rat lens AR. Compounds **62** and **63** exhibited a significant inhibitory activity on AGEPs formation with observed IC_{50} values of 118 and 28.9 μM, respectively, in an AGEPs-bovine serum albumin (BSA) assay by specific fluorescence. Furthermore they inhibited AGEPs-BSA formation more effectively than aminoguanidine, an AGEPs inhibitor, by indirect AGEPs-ELISA. In addition, compounds **60, 61,** and **62** showed a significant inhibitory activity on rat lens AR with IC_{50} values at 13.6, 8.8, and 15.9 μM, respectively [50].

Damnacanthol-3-*O*-β-D-primeveroside (**64**) and lucidin 3-*O*-β-D-primeveroside (**65**), two anthraquimounes with no subsititents in one aromatic ring, were isolated from n-butanol soluble phase of the methanol extract of *Morinda citrifolia* roots [51]. The two anthraquinones showed a significant reduction of the blood glucose levels at 5 h after oral administration (100 mg/kg). Other compounds isolated from this plant such as iridoids did not show a hypoglycemic effect.

2.5. Terpenes

A novel sesquiterpene glycoside, nerolidol-3-*O*-α-L-rhamnopyranosyl (1→4)-α-L-rhamnopyranosyl (1→2)-[α-L-rhamnopyranosyl (1→6)]-β-D-glucopyranoside (**66**) was isolated from dried leaves of loquat [*Eriobotrya japonica* (Thunb.) Lindl., Rosaceae]. The dose of 25 and 75 mg/kg of compound 66 exhibited a significant (p<0.05) hypoglycemic effect in alloxan-induced diabetic rats [52].

Costunolide (**67**) is a benefit compound isolated from *Costus speciosus* (Koen ex.Retz.). It significantly (p<0.05) reduced plasma glucose in a dose dependent manner. In addition, oral administration of costunolide (20 mg/kg) significantly decreased glycosylated hemoglobin**,** serum total cholesterol, triglyceride, low density lipoprotein (LDL) cholesterol and at the same time markedly increased plasma insulin, tissue glycogen, high density lipoprotein (HDL) cholesterol and serum protein. Costunolide might have stimulated the β islets to secrete insulin by inhibiting the expression of NO [53].

Mmorroniside (**68**) is an active compound isolated from Corni Fructus (*Cornus officinalis*). Yokozawa *et al.* investigated the effects of morroniside on renal damage in STZ-treated diabetic rats. Oral administration of morroniside at a dose of 20 mg/kg 20 d to diabetic rats resulted in significant decreases in serum glucose and urinary protein levels, inhibition of oxidative stress [54].

2.6. Coumarins and Lignans

A coumarin named peucedanol 7-*O*-β-D-glucopyranoside (**69**) and a cyclitol named *myo*-inositol (**70**) were isolated from 80% ethanol extracts from Peucedani Radix (*Peucedanum japonicum*, Umbelliferae). Compound **69** showed 39% inhibition of postprandial hyperglycemia at 5.8 mg/kg dose, and compound **70** also significantly inhibited postprandial hyperglycemia by 34%. Overexpression of glucose transporter-4 in skeletal muscle and amelioration of insulin resistance were found to be responsible for plasma glucose lowering activity [55].

Laserpitin (**71**) is a characteristic coumarin, from the *Angelica keiskei* extract. The effect of dietary laserpitin was investigated on blood pressure and lipid metabolism in stroke-prone spontaneously hypertensive rats. Results showed that dietary laserpitin produces increases in serum HDL levels, especially apolipoprotein E-HDL, and decreases in the hepatic triglyceride content [56].

Umbelliferone (7-hydroxycoumarin) (**72**) is present in the edible fruits such as golden apple (*Aegle marmelos* Correa) and bitter orange (*Citrus aurantium*) [57]. A number of researches by Pugalendi and co-workers indicated that umbelliferone could reduce blood glucose and lipid profiles, decrease lipid peroxidation markers and enhance antioxidants' status, and protect membrane fatty acid composition of liver and kidney [58]. All of these observations demonstrated that umbelliferone has anti-diabetic and antihyperlipidemic effects.

Three lignans, isotaxiresinol (**73**), secoisolariciresinol (**74**) and taxiresinol (**75**), were isolated from water extracf of the wood of *Taxus yunnanensis*. At a dose of 100 mg/kg (i.p.), they reduced the FBG level of diabetic rats by 34.5%, 33.4%, and 20.9%, respectively, compared with 24.0% by the mixture of tolbutamide (200 mg/kg) and buformin (1 mg/kg) [59].

2.7. Phenolics

Resveratrol (**76**), has demonstrated a wide variety of biological activities which make it a good candidate for the treatment of diabetes mellitus. It is found in a diversity of plants, notably berry fruit, giant knotweed rhizome *etc*.. It is reported that compound **76** could modulate adenine nucleotide hydrolysis and attenuate the activities of some key enzymes of carbohydrate metabolism such as hexokinase, pyruvate kinase, lactate dehydrogenase and glucose-6-phosphatase and other enzymes such as AChE. Thus, it is important in the control of the platelet coagulant status in diabetes, and it can modulate cholinergic neurotransmission and consequently improve cognition. The antihyperglycemic nature of resveratrol is also evidenced from the improvement in the levels of plasma insulin and hemoglobin. Furthermore, the results are comparable with glyclazide, an oral standard drug. All of above afford a promise for widespread use for treatment of diabetes in the future [60-63].

7-*O*-galloyl-D-sedoheptulose (**77**), isolated from *Cornus officinalis* Sieb. et Zucc., was investigated the effect against diabetic oxidative stress and AGE formation. After 20 d of orally treatment with compound **77** to STZ-induced rats, the changes in serum glucose levels, as well as those of body weight were evaluated. It demonstrated that compound **77** had beneficial effects on hypoglycemic and renal metabolic abnormalities, including renal glucose, oxidative stress, and AGE formation [64].

A new compound 2,5-dihydroxy-4,3′-di-(*β*-D-glucopyranosyloxy)-*trans*-stilbene (**78**) was isolated from *Morus bombycis* Koidzumi. At doses of 200-800 mg/kg, this compound improved hyperglycemia in STZ-induced diabetic rats, and the hypoglycemic effect of **78** was comparable to that of tolbutamide [65].

Caffeic acid phenethyl ester (**79**) is a naturally occurring phenolic compound as the derivative of caffeic acid. It has been demonstrated to markedly ameliorate oxidative stress in hepatic tissue [66] and cardiac tissue [67], reduce the activities of antioxidant enzymes such as superoxide dismutase and catalase in STZ-induced diabetic rats. The results demonstrated that lipid peroxidation may be one of the molecular mechanism involed in STZ-induced diabetic damage.

Caffeic acid (**80**) and chlorogenic acid (**81**) from *Cichorium* and *Lonicera*,, have been described as potential anti-diabetic agents. They increased glucose uptake in L6 muscular cells and stimulate insulin secretion from the INS-1E insulin-secreting cell line and rat islets of Langerhans [68].

2.8. Polysaccharides

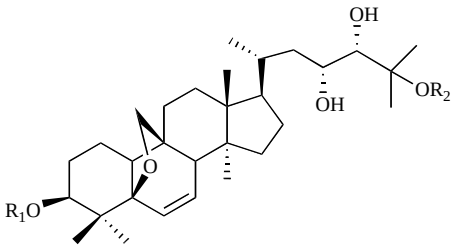
Polysaccharides belong to a structurally diverse and complex class of macromolecules, in which many monosaccharides joined together by glycosidic linkages. They are abound in nature products, especially in plant medicines. They are commonly extracted from NPs by hot water, and can be further purified using a combination of techniques, such as ethanol precipitation, fractional precipitation, and acidic precipitation with acetic acid, ion-exchange chromatography, gel filtration, and affinity chromatography. Over 100 poly-saccharides from plants have been reported for hypogly-cemic activity. Some botanical polysaccharides are consi-dered as important bioactive components responsible for hypoglycemic effect.

Tong *et al.* isolated an acid heteropolysaccharide with molecular weight of 2.7×10^5 Da consisting of Ara, Gal, Glc and GalA in ratio of 2.6: 3.6: 2: 1 and α-configuration from the fruit of *Physalis alkekengi* L. [69]. This polysaccharide has a backbone composed of (1→5)-linked Ara, (1→6)-linked Gal with three branches attached to *O*-3 of (1→6)-linked Gal and terminated with either Gal or Gal and Glc, and all of Glc and the majority of GalA are distributed in branches. Investigations showed this polysaccharide administered orally can significantly reduce blood glucose levels and water intake, and increase the body weight of diabetic mice compared with alloxan-induced diabetic control group.

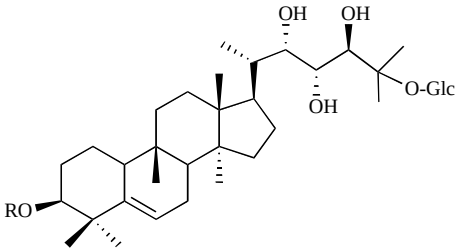
Using anti-oxidation activity-guided fractionation, a polysaccharide of molecular weight ～210 kDa was isolated from cultured *Cordyceps* mycelia by ion-exchange and sizing chromatography [70]. The isolated polysaccharide, contains glucose, mannose and galactose in a ratio of 1: 0.6: 0.75. When administered at a dose of higher than 200 mg/kg body weight daily for 7 days, it produced a significant drop in blood glucose level, increased the insulin levels ($p<0.05$) in both STZ-induced diabetic rats and alloxan-induced diabetic mice.

A new polysaccharide with molecular weight of approximately 150 kDa was isolated from the stem *Dendrobium chrysotoxum*, and its antioxidative, hypoglycemic and immune stimulating effects were evaluated using various *in vitro* and *in vivo* assay systems [71]. Results showed that it has potent antioxidant, immune stimulating, and hyperglycemic properties that highlights the potential use of this compound as a therapeutic agent for diabetic patients.

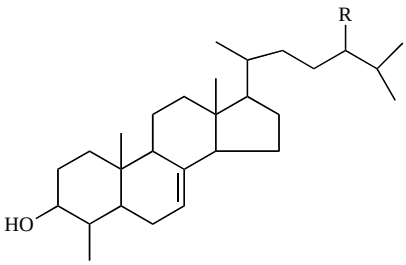
Although the extraction, isolation process and anti-diabetic activity of polysaccharides have been extensively investigated from NPs in the past three decades, the structural characterization and relationship with the anti-diabetic



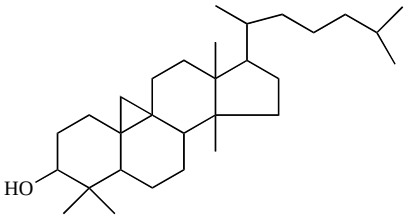
	R_1	R_2
1	Glc	H
2	All	Glc
5	All	H



	R
3	Glc (1→6)-Glc
4	Xyl (1→4)-[Glc (1→6)]-Glc



	R
6	H
7	CH_3
8	CH_2—CH_3



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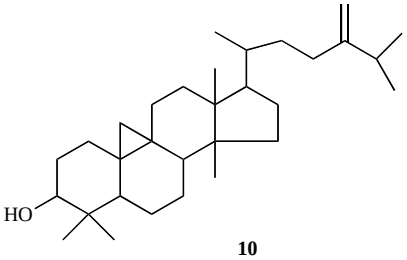

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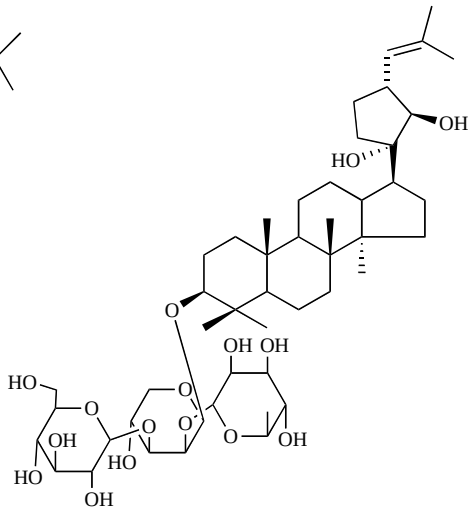

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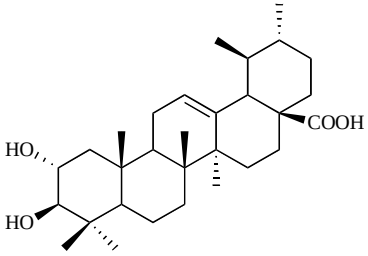

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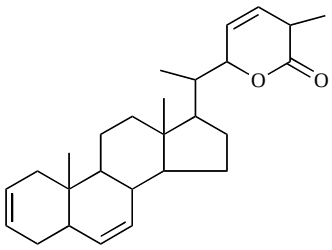

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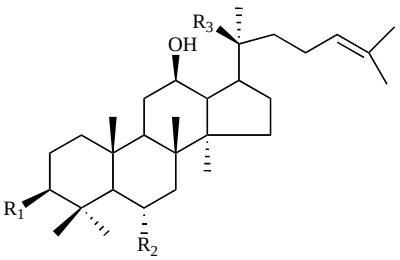
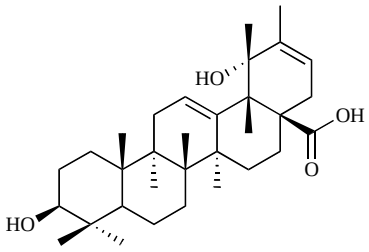


	R_1	R_2	R_3
14	OH	O-Glc(2→1)-Rha	O-Glc
15	Glc	H	OH



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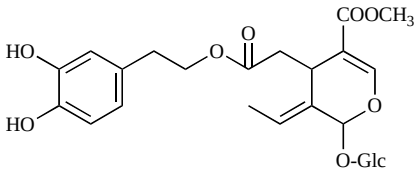

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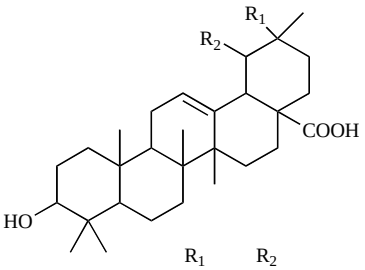
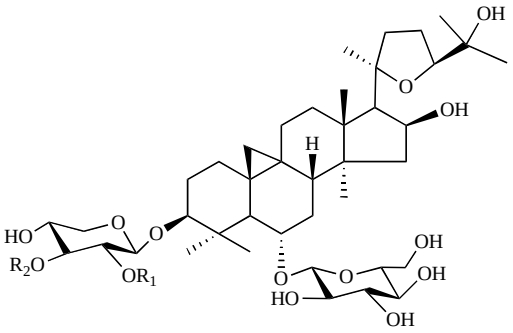
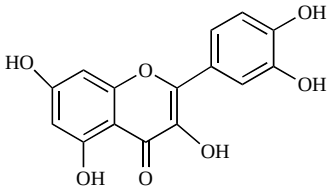


	R_1	R_2
17	CH_3	H
18	H	CH_3



	R_1	R_2
20	H	H
21	Ac	Ac



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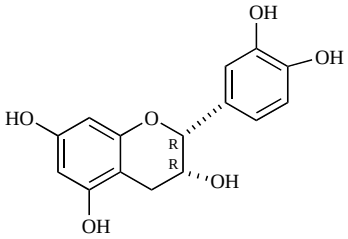

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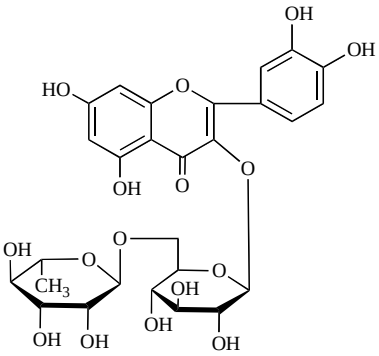

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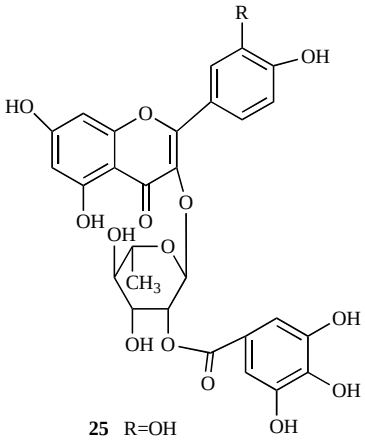
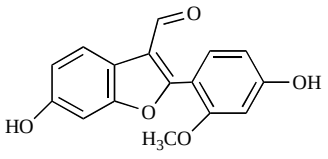


25 R=OH
26 R=H



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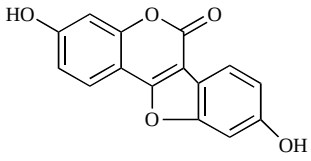

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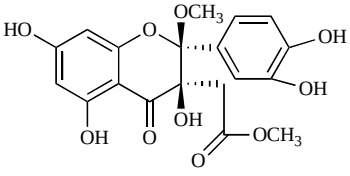

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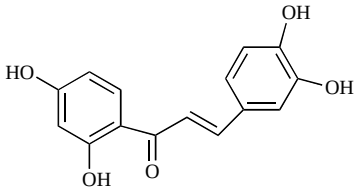

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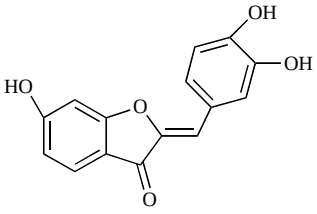

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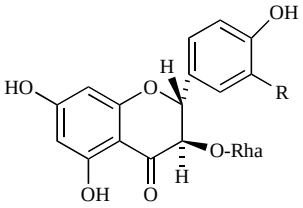
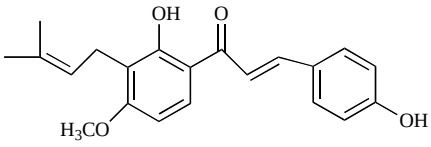


32 R=H
33 R=OH



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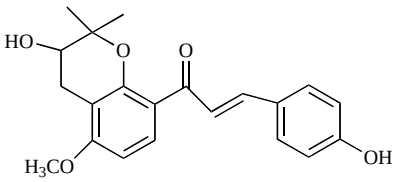

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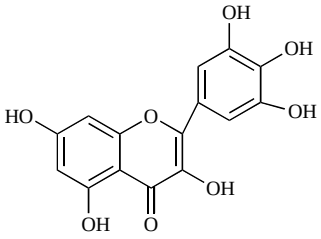

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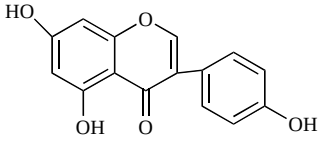

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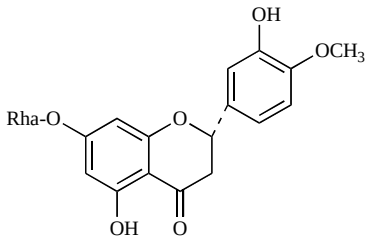

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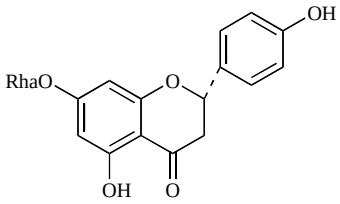

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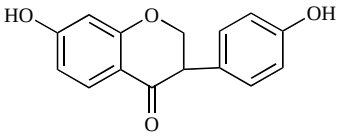

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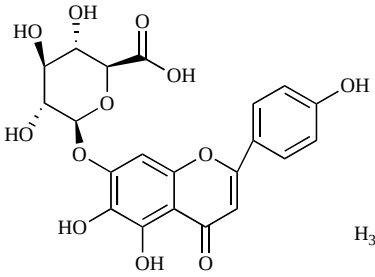

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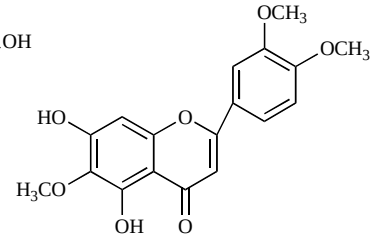

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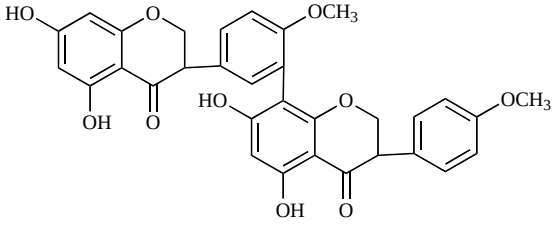

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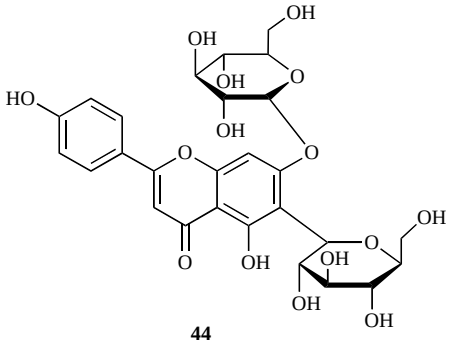

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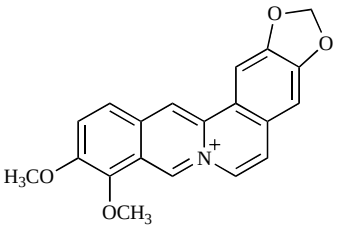

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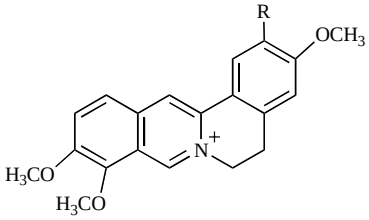
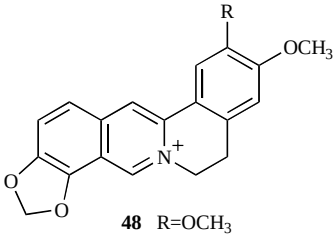


46 R=OCH_3
47 R=OH



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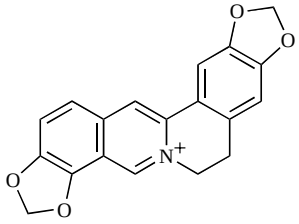
50 R=OH



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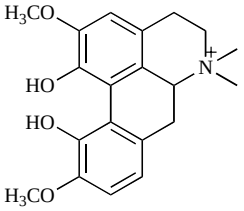

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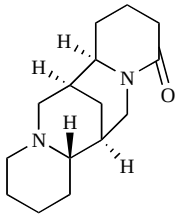

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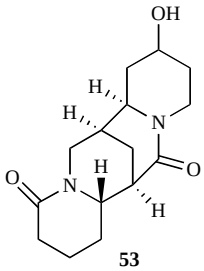

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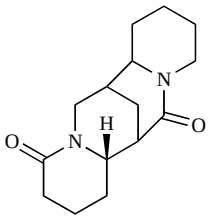

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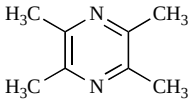

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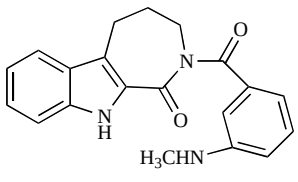

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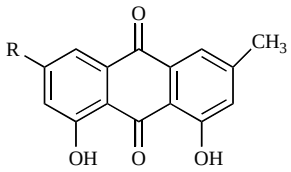
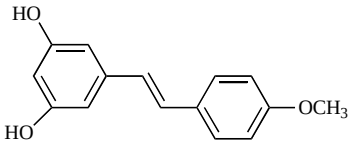


57 R=OH
58 R=H



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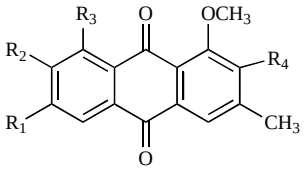
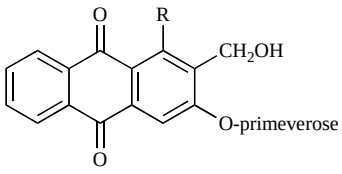
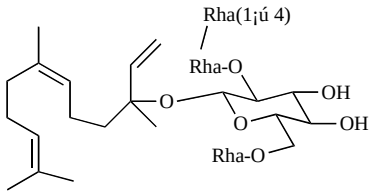


	R_1	R_2	R_2	R_4
60	OH	OCH_3	OCH_3	OH
61	OCH_3	OH	OCH_3	O-Glc
62	OH	H	OH	H
63	H	H	OH	OH



64 R=OCH_3
65 R=OH



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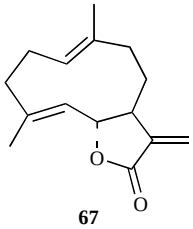

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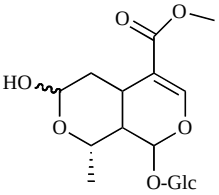

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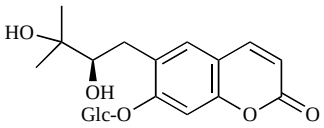

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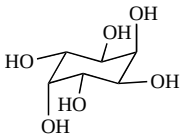

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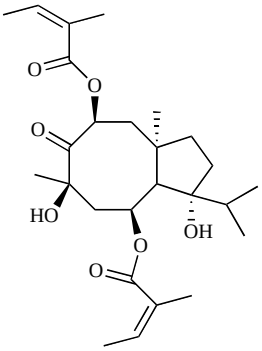

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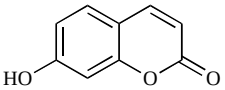

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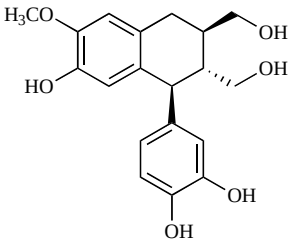

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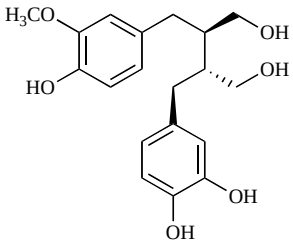

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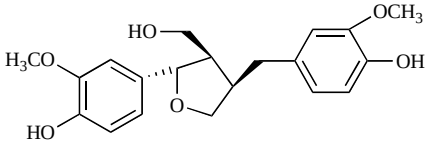

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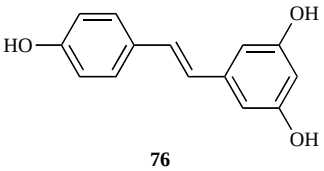

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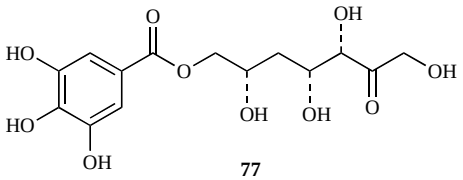

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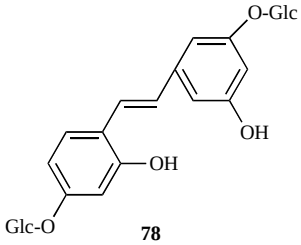

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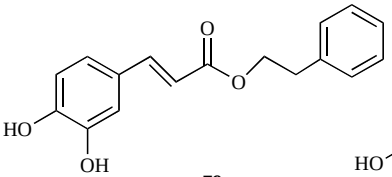

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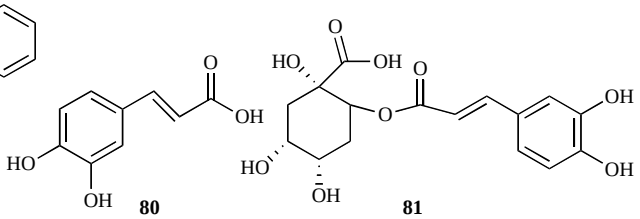

80 **81**

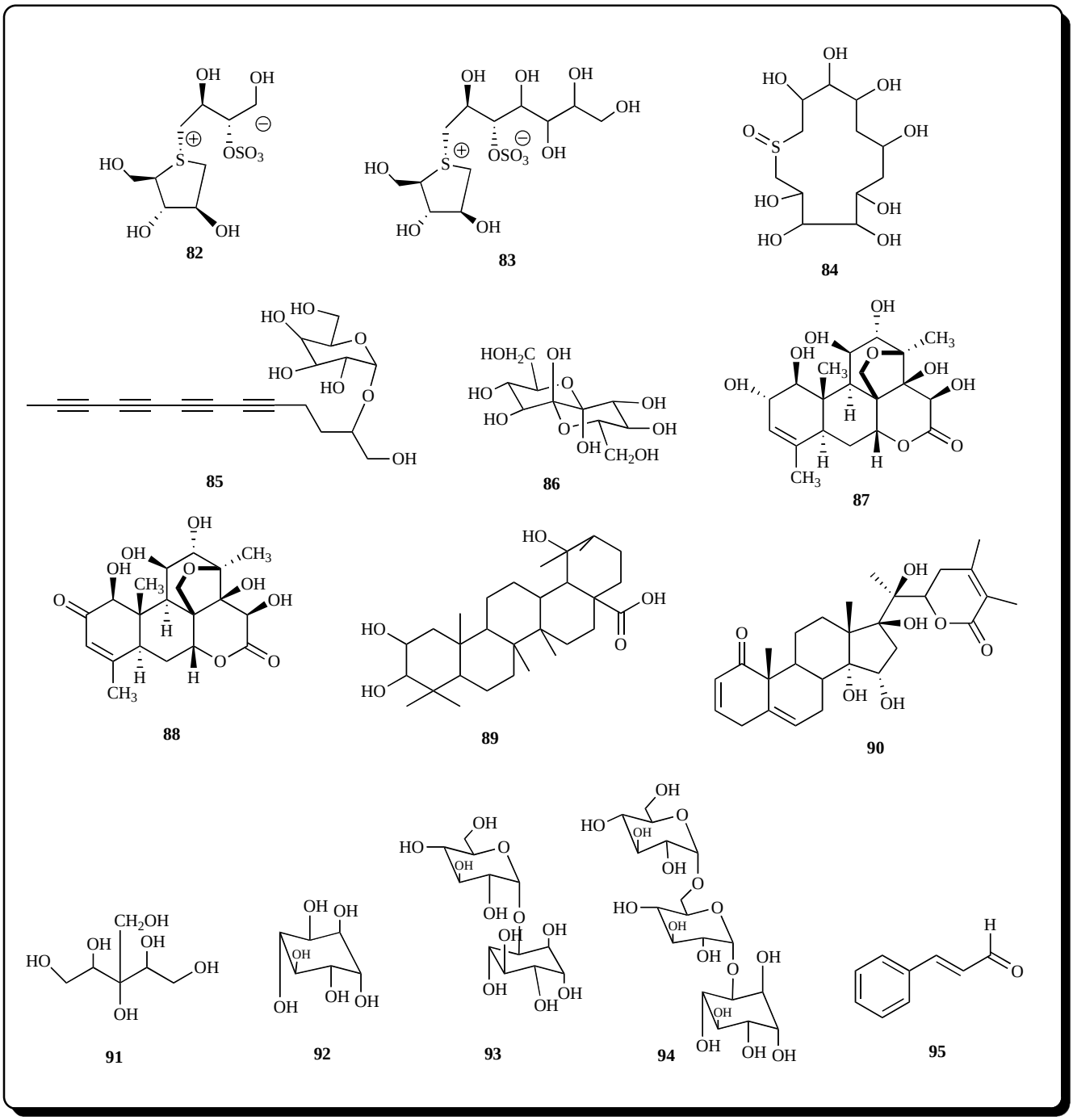

Fig. (2). Chemical structures of anti-diabetic entities from natural products.

activity are still not well established. These studies are still in progress in many laboratories. The future challenge is to define the 3-dimensional structure of polysaccharides and the structure function relationship. This presents a good opportunity for scientists to elucidate the biological roles of polysaccharides and design high potential anti-diabetic drugs based on the 3-dimensional structures [72].

2.9. Other Compounds

Salacinol (**82**) and kotalanol (**83**), with an internal salt of spiro-like configuration, as well as a novel 13-membered ring thiocyclitol (**84**) were isolated from an aqueous extract of *Salacia reticulate* [73]. Yoshikawa *et al*. investigated the effect of these compounds on postprandial glucose levels in maltose- and sucrose-loaded rats. It was found that **84** showed more potent α-glucosidase inhibitory activities (IC_{50}: maltase, 0.23 μM; sucrase, 0.19 μM) than those of **82** (IC_{50}: maltase, 9.6 μM; sucrase, 2.5 μM) [74].

Cytopiloyne (**85**), a novel polyacetylenic glucoside from the plant *Bidens pilosa*, has been reported to prevent type 1 DM mainly via T cell regulation [75]. It inhibits $CD4^+$ T cell proliferation and suppresses the differentiation of type 1 Th.

Also, long-term application of cytopiloyne significantly decreases the level of $CD4^+$ T cells inside pancreatic lymph nodes and spleens.

A new carbohydrate (**86**) isolated from aqueous extract of roots and rhizomas of *Psacalium peltatum* has been determined to have hypoglycemic activity at doses of 100 mg/kg, comparable to that of tolbutamide and insulin in alloxan-induced diabetic mice [76].

Bruceines E (**87**) and Bruceines D (**88**), obtained from the seeds of *Brucea javanica* (L.), have been found to reduce blood glucose concentration of mice and rats. Normoglycemic mice administered with 1mg/kg of compound **87** and **88** exhibited significant blood glucose concentration reduction of 40.07+/-11.45% and 48.82+/-13.34%, respectively. STZ induced diabetic rats administered with compound 86 and 87 also exhibited significant blood glucose concentration reduction of 73.57+/-13.64% and 87.99+/-2.91%, respectively. These two compounds might act as an insulin secretagogue [77].

Euscaphic acid (**89**), a natural product from Folium Eriobotryae, was investigated on the hypoglycemic effect in normoglycemic and alloxan-diabetic mice. Compound **89** exerted a significant ($P < 0.05$) hypoglycemic effect in alloxan-diabetic mice after oral administration with the dosage of 50 mg/kg [78].

Coagulanolide (**90**), a withanolide from *Withania coagulans* fruits, showed significant inhibition on postprandial rise in hyperglycemia post-sucrose load in normoglycemic rats as well as STZ-induced diabetic rats. It also showed significant fall on FBG profile and improved the glucose tolerance of db/db mice. The median effective dose of the compound **90** was determined to be around 25 mg/kg in STZ-induced diabetic rats, which is comparable to the standard anti-diabetic drug metformin [79].

The long-term effect of 3-hydroxymethyl xylitol (**91**), a novel compound isolated from *Casearia esculenta* (Roxb.) root, has been investigated on type 2 diabetic rats. Compound **76** at 40 mg dose markedly reduced hyperglycemia in STZ-diabetic rats due to increased insulin secretion and inhibition of gluconeogenesis with similar effects as glibenclamide [80].

Three novel cyclitols, D-chiro-inositol (**92**), and its two galacto-derivatives (**93** and **94**), were isolated from *Mucuna pruriens* which is prescribed in traditional Indian medicine and has been studied for its hypoglycemic and anti-hyperglycemic activity. They showed a significant hypoglycemic effect responsible for anti-diabetic properties of this medicinal plant [81].

Cinnamaldehyde (**95**) is an active compound from *Cinnamonum zeylanicum* (cinnamon). Ignacimuthu *et al*. found that oral administration of cinnamaldehyde significantly decreased plasma glucose concentration ($p<0.05$) in a dose-dependent manner, lowered both total cholesterol and triglyceride levels and, at the same time, increased HDL-cholesterol in STZ-induced diabetic rats [82].

3. ANTI-DIABETIC PLANT EXTRACT FROM CHINESE HERBAL MEDICINES

Plants are particularly interesting since they not only can be used as complementary and alternative medicines to prevent metabolic diseases, but also serve as an interesting source of drug candidates for the pharmaceutical industrial research. More than 1200 plants have been used traditionally for the treatment of DM in China medicinal system and in other ancient systems of the world, although evidence for their effects is limited. Such plants crude extracts have been prepared and their usefulness was evaluated in experimental diabetes in animals. Several papers have reviewed the medicinal plants with anti-diabetic potential in India [83,84], Morocco [85], Lebanon [86], South Western Nigeria [87], Jordan [88], Mexico [89] and Senegal [90].

The ethnobotanical information reports many Chinese herbal medicines that may possess anti-diabetic properties. Among the medicinal plants used in Traditional Chinese Medicine (TCM) for their anti-diabetic action, some of these have been thoroughly investigated. The present review circumscribes crude plant extract from Chinese herbal medicines that have been pharmacologically tested and shown to be of some value in DM published between 2004 and 2009. These were reviewed to identify multiple references to a particular species or genus. These findings are discussed below, where species have been grouped by family.

3.1. Leguminosae

Radix Astragali (Huangqi in Chinese), derived from the dried roots of *Astragalus membranaceus* (Fisch.) Bge. var. *mongholicus* (Bge.) Hsiao or *A. membranaceus* (Fisch.) Bge. belonging to Fabaceae (China Pharmacopoeia, 2005 edition), is one of the oldest and most frequently used herbal medicines for oriental medicine in China, Korea, Japan and other Asian countries. Astraglycan is one of an aqueous extract from Radix Astragali. It is believed to be helpful in the treatment of early diabetic nephropathy with an effect on mRNA expressions of NF-kappaB and IkappaB in renal cortex of streptozotoxin-induced diabetic rats [91]. Li *et al.* [92] investigated the therapeutic effects of astraglycan on hyperglycemia, and elucidated the immunotherapeutic molecular mechanisms of how astraglycan attenuated the development of type 1 DM induced by multiple low dose STZ. Downregulated blood glucose level, upregulated serum insulin concentration, increased β-cell mass, decreased apoptotic β-cell percentage, downregulation of Th_1/Th_2 cytokine ratio and upregulation of PPARγ gamma gene expression in spleens were significantly time- and dose-dependent on astraglycan treatment, when compared to saline controls.

Ko *et al.* [93] examined the anti-diabetic effect and mechanism of raw and roasted *Glycyrrhiza uralensis* extracts and their major respective components, glycyrrhizin and glycyrrhetinic acid. In partial pancreatectomized diabetic mice, both raw and roasted ones improved glucose tolerance, but only roasted *G. uralensis* extracts enhanced glucose-stimulated insulin secretion as much as exendin-4. Both raw

and roasted extracts enhanced insulin-stimulated glucose uptake through peroxisome PPARγ-gamma activation in 3T3-L1 adipocytes. Consistent with the results of the mice study, only roasted *G. uralensis* extracts and glycyrrhetinic acid enhanced glucose-stimulated insulin secretion in isolated islets. In addition, they induced mRNA levels of insulin receptor substrate-2, pancreas duodenum homeobox-1, and glucokinase in the islets, which contributed to improving β-cell viability [93].

Other plants from family Leguminosae, which have been described to have anti-diabetic effect include: *Tephrosia purpurea* [94], *Bauhinia forficate* [95].

3.2. Cucurbitaceae

Momordica charantia, also known as bitter melon, bitter gourd, and orbalsam pear, is widely cultivated as a vegetable and medicinal herb in many Asian countries and has been shown to exert hypoglycemic effects inanimal models andhumans. It contains biologically active chemicals that include glycosides, saponins, alkaloids, fixed oils, triterpenes, proteins and steroids. Acetone extract of whole fruit powder of *M. charantia* in doses 25, 50, and 75 mg/100 g body weight lowered the blood glucose from 13.30 to 50% after 8 to 30 days treatment in alloxan diabetic albino rats. Histological observations with acetone extract showed different phases of recovery of β-cells of the islets of Langerhans of pancreas. The presence of small scattered islets among the acinar tissue was also observed, which reflect neoformation of islets from pre-existing islet cells [96]. In another study, aqueous extract of this plant was found to have significant repairing effects on HIT-T15 Hamster Pancreatic β-cells against superoxide anion radicals [97]. The toxicological studies of this plant indicated that it had beneficial effects on blood glucose level as well as improving kidney, liver function and hyperlipidaemia due to DM [98].

Qi *et al.* [99] evaluated the supplementation of a mogrosides extractfrom fruits of *Siraitia grosvenori* on reducing oxidative stress, hyperglycemia, and hyperlipidemia in alloxan-induced diabetic mice. The study seem to demonstrate that the extract have capacity to inhibiting hyperglycemia induced by DM, and the data suggest that administration of the extract may be helpful in the prevention of diabetic complications associated with oxidative stress and hyperlipidemia.

Coccinia cordifolia extract [100], *Cucurbita ficifolia* fruit extract [101], Monoglycerides and fatty acids from *Ibervillea sonorae* root [102], the seed extract of *Benincasa hispida* Cogniaux [103] were also reported to have hypoglycemic activities.

3.3. Araliaceae

In an attempt to develop new substances for handling insulin resistance, an aqueous extract of the root of *Acanthopanax senticosus* was used to screen the effect on insulin resistance induced by fructose-rich chow in rats [104]. An increase in insulin sensitivity following the administration of this herb was further identified using the plasma glucose-lowering action of exogenous insulin in STZ-diabetic rats. Oral administration of the aqueous extract of *A. senticosus* root at a dose of 150.0 mg/kg three times daily to STZ-diabetic rats increased the responses to exogenous insulin 10 days later. The results obtained suggest that oral administration of the aqueous extract from *A. senticosus* root has the ability to improve insulin sensitivity and delay the development of insulin resistance in rats and, thus, may be used as an adjuvant therapy for patients with insulin resistance.

Ginseng is a well-known invigorator that can effectively strengthen the systemic regulatory network in response to interior and exterior stimuli. Ginseng extract was also reported to have protective effect on cytokine-induced apoptosis in pancreatic β-cells [105] and diabetic renal damage [106]. The principal components believed to be responsible for inducing the hypoglycemic activity are triterpenoid saponins glycosides, commonly referred to as ginsenosides or panaxosides.

3.4. Liliaceae

Rhizoma Anemarrhenae (Zhimu in Chinese), is the dried rhizome of *Anemarrhena asphodeloides* Bunge from family Liliaceae. The aqueous extract of the rhizome (90 mg/kg) reduced the blood glucose level after oral administration and also tended to reduce serum insulin levels in KK-Ay mice [107]. The extract-treated KK-Ay mice had significantly reduced blood glucose levels in an insulin tolerance test. The anti-diabetic mechanism of this plant extract may be due to decreased insulin resistance and its active components were confirmed to be mangiferin and its glucoside (mangiferin-7-*O*-β-D-glucopyranose).

The anti-diabetic effect of garlic ethanolic extract (*Allium sativum* L.) was investigated in normal and STZ-induced diabetic rats [108]. Oral administrations of the garlic extract significantly decreased serum glucose, total cholesterol, triglycerides, urea, uric acid, creatinine, aspartate amino transferase and alanine amino transferase levels, while increased serum insulin in diabetic rats but not in normal rats ($p<0.05$). A comparison was also made between the action of garlic extract and glibenclamide (600 μg/kg), the known anti-diabetic drug. It was found that the anti-diabetic effect of the extract was more effective than that observed with glibenclamide. Ashraf *et al.* [109] conducted a trial to evaluate the effects of garlic (*Allium Sativum*) on patients with type 2 DM. Garlic significantly reduced serum total cholesterol and LDL cholesterol and moderately raised HDL cholesterol as compared to placebo. The study suggested that possible small short term benefits of garlic on dyslipidemia in type 2 diabetic patients.

Water extract and crude polysaccharides obtained from the tuberous root of *Liriope spicata* (Thund.) var. prolifera Y. T. Ma were investigated for their hypoglycemic potential. Water extract and crude polysaccharides were administered orally at different doses (200 and 100 mg/kg body weight) to normal and STZ-induced type 2 diabetic male BABL/c mice, respectively. Both doses caused a marked decrease of FBG and a significant improvement on glucose tolerance and insulin resistance in STZ-induced type 2 diabetic mice. In addition, Water extract and crude polysaccharides elevated the relative HDL cholesterol level (HDL/TC) in serum. Compared to water extract, the hypoglycemic and hypolipi-

demic effects of crude polysaccharides were more marked [110].

Other plants from family Liliaceae including Onion [111], *Asparagus adscendens* (Shweta musali) [112], were also reported to possess anti-diabetic potential.

3.5. Chenopodiaceae

The fresh fruit of *Kochia scoparia* from family Chenopodiaceae has been used as a food garnish from ancient times, and may prevent metabolic syndromes such as hyperlipidemia, hypertension, obesity and atherosclerosis. Han *et al.* [113] performed a study to clarify whether an ethanol extract of *K. scoparia* fruit prevented obesity induced in mice by a high-fat diet for 9 weeks. In their study, the ethanol extract (250 mg/kg) and total saponins (100 mg/kg) of *K. scoparia* was found to inhibit the elevation of the plasma triacylglyccerol level 2 or 3 h after the oral administration of the lipid emulsion. Total saponins, momordin Ic, 2'-*O*-β-D-glucopyranosyl momordin Ic and 2'-*O*-β-D-glucopyranosyl momordin IIc isolated from *K. scoparia* fruit inhibited the pancreatic lipase activity (*in vitro*). These findings suggest that the anti-obesity actions of *K. scoparia* extract in mice fed a high-fat diet may be partly mediated through delaying the intestinal absorption of dietary fat by inhibiting pancreatic lipase activity [113].

The extract of Chard (*Beta vulgaris* L. var cicla) was also reported to reduce blood glucose and have protective effect on the liver in DM [114].

3.6. Solanaceae.

The fruit of *Lycium barbarum* L. from family Solanaceae is well-known in traditional Chinese herbal medicine. *L. barbarum* polysaccharide has been identified as one of the active ingredients responsible for its biological activities. Li's team evaluated the potential antioxidative activity of *L. barbarum* polysaccharide in the STZ-induced diabetic rats. The results show that *L. B.* polysaccharides is effective in the protection of liver and kidney tissue from the damage of STZ-induced diabetic rats and *L. B.* polysaccharide may be of use as an antihyperglycemia agent [115]. Gao *et al.* [116] investigated the effects of *Cortex Lycii* Radicis on alloxan-induced diabetic mice and its mechanisms. The results indicated that *C. Lycii* alleviates the blood glucose and lipid increases associated with DM and improves the abnormal glucose metabolism and increases insulin secretion by restoring impaired pancrease β-cells in alloxan-induced diabetic mice.

The data obtained from a recent study suggest that 2% dietary red chilli (*Capsicum frutescens* L.) is insulinotropic rather than hypoglycemic at least in type 2 DM model of rats [117]. Eggplant (*Solanum melongena*) [118], Tomatoes [119], *Solanum xanthocarpum* Schrad & Wendl [120] were also proved to have hypoglycemic activity or inhibit key enzymes relevant for type 2 DM.

3.7. Compositae

Pushparaj *et al.* [121] investigated the hypoglycemic and hypolipidemic properties of an ethanolic extract of *Cichorium intybus* (CIE), a member of the Compositae family. Administration of CIE produced a significant reduction in serum glucose, triglycerides and total cholesterol in STZ-induced diabetic rats without any effects on insulin secretion.

In the study by Huseini *et al.* [122], the effects of the herbal medicine, *Silybum marianum* seed extract (silymarin) on the glycemic profile in diabetic patients were evaluated. A 4-month randomized double-blind clinical trial was conducted in 51 type 2 diabetic patients in two well-matched groups. One group (n = 25) received a silymarin (200 mg) tablet 3 times a day plus conventional therapy, while the other group (n = 26) received the same therapy but a placebo tablet instead of silymarin. The results showed a significant decrease in hemoglobin A1c, FBS, total cholesterol, LDL, triglyceride serum glutamic-oxaloacetic transaminase and serum glutamic-pyruvic transaminase levels in silymarin treated patients compared with placebo as well as with values at the beginning of the study in each group.

The total lignan from the plant *Fructus Arctii* [123], the aerial part of the *Matricaria chamomilla* L. ethanolic extract [124], *Artemisia sphaerocephala* Krasch seed polysaccharide [125], the ethanolic extract of *Artemisia dracunculus* L. [126], water extract of *Bidens pilosa* and *Inula viscosa* L. [127, 128] were also reported to have antihyperglycemic activity in diabetic rats.

3.8. Campanulaceae

The root of *Platycodon grandiflorum* (Jacq.) A. DC has been reported to have a wide range of health benefits in oriental food. Zheng J, *et al.* [129] examined the hypoglycemic effects of *P. grandiflorum* aqueous-ethanol extract in STZ-induced diabetic ICR mice. A significant decrease in blood glucose levels was observed after single administration of this plant extract. Furthermore, Glibenclamide and the extract significantly suppressed the rise in blood glucose after 30 min in the acute glucose tolerance test. Treatment with glibenclamide and the extract resulted in a reduction in blood glucose levels from the second week, and this reduction was maintained until the fourth week of treatment. Plasma insulin levels were increased with glibenclamide treatment in STZ diabetic mice, whereas such effect was not observed with the extract, indicating that *P. grandiflorum* aqueous-ethanol extract could induce hypoglycemic effects without stimulating insulin secretion.

3.9. Cornaceae

Corni Fructus could ameliorate glucose-associated metabolic disorders, and its mechanisms were intimately related to the formation of AGEPs [130]. Yamabe *et al.* [131] prepared active fractions of *C. Fructus* and evaluated their activities in STZ-induced diabetic rats. Iridoid glycosides and low molecular weight polyphenol fractions could reduce the pathogenesis of diabetic renal damage, each having different mechanisms, *i.e.*, iridoid glycosides successfully decreased the hyperglycemic state and affected renal AGEPs accumulation, such as *N*-(carboxyethyl) lysine and *N*-(carboxymethyl) lysine, while low molecular weight polyphenol fractions could reduce renal lipid peroxidation, the receptor for AGEPs, and inducible NO synthase.

3.10. Rhamnaceae

Abdel-Zaher *et al.* [132] investigated the anti-diabetic activity and toxicity of the butanol extract of *Zizyphus spina*-christi leaves and its major saponin glycoside, christinin-A, in non-diabetic control, type 1 and type 2 diabetic rats. Treatment either with 100 mg/kg butanol extract or christinin-A reduced the serum glucose level and increased the serum insulin level of non-diabetic control and type 2 diabetic rats but not of type 1 diabetic rats. The hyperglycemic and hypoinsulinemic effects of diazoxide in non-diabetic control and type 2 diabetic rats were inhibited and antagonized, respectively by pretreatment with the butanol extract or christinin-A. Treatment of rats with 100 mg/kg butanol extract for 3 months produced no functional or structural disturbances in liver and kidney and no haematological changes. The acute toxicity tests also indicated that butanol extract of *Z. spina*-christi leaves was a safe alternative to lower blood glucose. The authors suggested that the insulinotropic and subsequent hypoglycemic effects of *Z. spina*-christi leaves may be due to blockade of K-ATP channels in pancreatic β-cell membranes.

3.11. Scrophulariaceae

The hypoglycemic and anti-diabetic effect of *Rehmannia glutinosa* oligosaccharide in glucose-induced hyperglycemic and alloxan-induced diabetic rats and its mechanism was investigated [133]. It was found that pretreatment of *R. glutinosa* oligosaccharide in normal rats at the dose of 100 mg/kg × 3 days, i.p., caused a partial prevention of hyperglycemia induced by glucose (2 g/kg, i.p.). In alloxan-induced diabetic rats, *R. glutinosa* oligosaccharide (100 mg/kg × 15 days, i.p.) showed a significant decrease in blood glucose level. These results suggested that *R. glutinosa* oligosaccharide is a new active principle from this plant with hypoglycemic effect. It was thought that the regulatory mechanism of *R. glutinosa* oligosaccharide on glucose metabolism may be mediated through the interaction between insulin and glucocorticoids. Aqueous extract of Radix Rehmanniae was investigated for its wound healing effects in a diabetic foot ulcer rat model and its detailed mechanism of actions. The ulcer healing effect of Radix Rehmanniae extract was supported by the reduction of the wound area, better developed scars and epithelialization as well as good formation of capillaries with enhanced VEGF expression. The results demonstrated that Radix Rehmanniae was effective in promoting diabetic foot ulcer healing in rats through the processes of tissue regeneration, angiogenesis and inflammation control [134].

Pari *et al.* reported the anti-diabetic, antioxidant, and antiperoxidative effect of *Scoparia dulcis* in plasma and tissues [135], and then evaluated the effects of aqueous extract of *S. dulcis* on the blood glucose and plasma insulin levels and serum and tissue lipids in STZ-induced diabetic rats [136]. Oral administration of this crude extract (200 mg/kg of body weight) to diabetic rats for 6 weeks resulted in a significant reduction in blood glucose, serum and tissue cholesterol, triglycerides, free fatty acids, phospholipids, 3-hydroxy-3-methylglutaryl-CoA reductase activity, and LDL cholesterol levels.

3.12. Euphorbiaceae

The plant *Phyllanthus reticulates* was claimed to have anti-diabetic activity in tribal area. To validate the tribal claim, the petroleum ether and ethanolic extracts of leaves of the *P. reticulatus* were orally tested at 500 and 1000 mg/kg for hypoglycemic effect in alloxan-induced diabetic mice [137]. It shows anti-diabetic activity at the dose of 1000 mg/kg and the phytochemical screening of the residues revealed the presence of terpenoids glycosides, protein, carbohydrates and absence of alkaloids and steroids.

Suryanarayana *et al.* [138] reported that the aqueous extract of *Emblica officinalis* and its constituent tannoids inhibited AR *in vitro* which is a drug target because of its involvement in the development of secondary complications of DM including cataract, and prevented hyperglycemia-induced lens opacification in organ culture. The results also pointed out that *E. officinalis* and its tannoids might counter the polyol pathway-induced oxidative stress as there was a reversal of changes with respect to lipid peroxidation, protein carbonyl content, and activities of antioxidant enzymes.

3.13. Ginkgoceae

Ginkgo biloba, the best-selling herbal remedy in the world, is derived from the leaves of the maidenhair tree, family Ginkgoceae. Active isolates of ginkgo fall into two classes: flavonoids and terpenoids. Three studies have tested the anti-diabetic effect of the extract of Ginkgo biloba (EGb). It was believed that the EGb could repair and protect β islet cell, reduce blood glucose, increase insulin serection, as well as to adjust blood lipids metabolism [139-141].

3.14. Gramineae

The style of *Zea mays* L. (Gramineae) is commonly known as corn silk and has been used in folk medicine as a decoction for diuretic treatment. Suzuki *et al.* [142] investigated the effect of water extract from the style of Zea mays on diabetic nephropathy. STZ-induced diabetic rats were used to evaluate the therapeutic effect of the style. From their study, it was learned that the style of *Z. mays* prevented glomerular hyperfiltration. The findings indicated that the water extract of the title material suppressed the progression of diabetic glomerular sclerosis in STZ-induced diabetic rat.

3.15. Myrtaceae

The hypoglycemic and hypolipidemic effects of flavonoid rich extract obtained from seeds of *Eugenia jambolana* was analyzed in STZ-induced diabetic rats [143]. Hypoglycemic activity was assessed by reduction in FBG and peak blood glucose level within 60 min of glucose tolerance test (GTT) in mild and severe diabetic (MD and SD respectively) rats. The data obtained from that study indicated that the flavonoid rich fraction of *E. jambolana* seed contains some bioactive molecules which may have beneficial effects as both hypoglycemic, anti-hyperglycemic and anti-hyperlidemic agents. However, the exact mechanism of action of EJ needs further detailed studies.

3.16. Sterculiaceae

Guazuma ulmifolia L., is a plant widely distributed throughout the Neotropical region whose bark is used as infusions by the Mexican traditional medicine for the treatment of type 2 DM. *G. ulmifolia* aqueous extracts exerts anti-diabetic properties by stimulating glucose uptake in both insulin-sensitive and insulin-resistant adipocytes without inducing adipogenesis. The ability of *G. ulmifolia* aqueous extracts to induce glucose uptake in insulin-resistant adipocytes, in addition to its lack of pro-adipogenic or anti-adipogenic effects, suggests that it could be very useful in the treatment of type 2 DM [144].

3.17. Annonaceae

Annona squamosa L., commonly known as custard apple, is a native of West Indies and is now widely used in TCM. Anti-diabetic activity of aqueous extract of *A. squamosa* has been reported in STZ-nicotinamide type 2 diabetic rats [145]. Nutritional and hypoglycemic effect of fruit pulp of *A. squamosa* in normal healthy and alloxan-induced diabetic rabbits was also reported in another study [146]. Recently, Gupta *et al*. [147] evaluated the effect of aqueous exctract of *A. squamosa* on antioxidant enzymes and lipid profile type 2 diabetic models. The results clearly suggest that the water extract of *Annona squamosa* leaves possessed antioxidant activity as shown by increased activities of scavenging enzymes, catalase, superoxide dismutase, reduced glutathione, glutathione reductase and glutathione-s-transferase and decrease in malondialdehyde levels present in various tissues. Administration of the extract also improved the lipid profile of the treated groups indicating thereby that the high levels of triglyceride and total cholesterol associated with DM can also be significantly managed with the extract.

3.18. Labiatae

Prunella vulgaris L. has been reported to have a wide range of health benefits in oriental medicine. Zheng *et al*. [148] examined the antihyperglycemic effects of *P. vulgaris* in STZ-induced diabetic ICR mice. The effects of aqueous-ethanol extract of *P. vulgaris*on on blood glucose, exogenous insulin sensitivity and plasma insulin levels were investigated. A significant decrease in blood glucose levels was observed after treatment of this extract in diabetic mice. A combination of the extract and glibenclamide produced a greater effect in blood glucose level than using them alone. The data from their results showed that aqueous-ethanol extract of *P. vulgaris*on enhances the antihyperglycemic effects of exogenous insulin without stimulating insulin secretion, indicating that insulin sensitivity is increased in STZ diabetic mice.

Scutellaria baicalensis [149], Hsian-tsao (*Mesona procumbens* Hemsl.) [150] from family Labiatae were also described to either have antihyperglycemic activity or protect myocardium in STZ-induced diabetic rats.

3.19. Crassulaceae

Sinocrassula indica is a biennial plant distributed on the mountain areas in China (*e.g.*, Yunnan, Guangxi, Sichuan, Guizhou, and Hunan provinces). This plant also has been used as a vegetable and an herbal tea in Chinese local areas such as Guangxi province. Studies showed that the methanol extract of this whole plant inhibited the increase in serum glucose levels in both sucrose and glucose-loaded rats at a dose of 250 mg/kg (oral administration). From the methanolic extract, four new acylated flavonol glycosides were isolated [151].

3.20. Miscellaneous

Other plant extracts from Chinese herbal medicines which were reported to have anti-diabetic potentials include: Turmeric [152], Ginger [153, 154] from family Zingiberaceae, *Aconitum* [155] from family Ranunculaceae, *Dioscorea opposita* Thunb. [156] from family Dioscoreaceae, *Alisma orientalis* (Sam.) Juzep. [157] from family Alismataceae, Ganoderma lucidum and Poria [158] from family Polyporaceae, Eriobotrya japonica [159], Folium Eriobotryae [160, 161], Hawthorn [162], and Plum [163] from family Rosaceae, Citrus sinensis and Punica granatum from family Rutaceae [164], *Dendrobium chrysotoxum* Lindl. [165] and *Anoectochilus roxburghii* [166] from family Orchidaceae, *Amaranthus spinosus* Linn. [167] from family Amaranthaceae, and Cinnamon [168] from family Lauraceae, *Berberis aristata* DC from family Berberidaceae [169], *Angelica hirsutiflora* Liu Chao & Chuang from family Umbelliferae [170], *Morus alba* from family Moraceae [171] and Hibiscus sabdariffa from family Malvaceae [172].

More than 70 articles on the anti-diabetic activity of the plants from 29 families used in Chinese herbal medicine have been reviewed. The anti-diabetic profiles of the plant extracts discussed within this systematic review look encouraging at the experimental animals studies. Of these, the most promising, at the present time, are the species *Momordica charantia*, *Panax ginseng*, *Allium sativum* L. However, of the published studies, we were still uncertain which plant extract was potentially the most efficacious. Despite the great interest in the development of new drugs to prevent and treat DM and the raised interest in the scientific community to evaluate either raw or isolated NPs in experimental studies, of the plant extracts reviewed the majority has been performed in animals and relatively few have had their efficacy confirmed in humans. In fact, only three extracts have been tested in a human clinical trial and they seem to generally support findings in animals. This is clearly one area that needs further investigation as findings in animals need to be translated to humans in order for a natural extract to be recommended for traditional use as an anti-diabetic agent. The design of trials also needs some attention. Some extracts may appear to be potentially interesting, but it must be pointed out that not all trials have been designed in the same manner. Some may be criticized for lacking a placebo control group or comparison with a known anti-diabetic agent. There was also some variation in the duration and doses used, which again makes comparisons between trials difficult. A further issue that needs to be addressed is whether some of these extracts are safe for human consumption when taken alone or with other foods or drugs.

4. ANTI-DIABETIC COMPOUND FORMULAE OF TCM

The principles of treatment for DM in TCM are to nourish the yin and clear away the heat using preparations tailored to the symptoms and clinical characteristics of individual patients. The compound formulae of TCM, containing several medicinal plants that have evolved through years of clinical practice, are still routinely used today by medical practitioners in an attempt to improve the overall therapeutic efficacy and reduce side effects. It appeared that the selection of herbal ingredients in many of these multi-component herbal formulae is proven to have a sound scientific basis through modern research and evaluation. The difference between a single-herb formula and a multi-herb compound formula is not merely the addition of more herbs, but also the interaction between the components of mixtures of herbs. A system of synergistic interactions among herbal drugs is formed in a compound formula which is believed to take a multi-targeted therapeutic approach in the treatment. The proprietary herbal medicines were formulated in capsules, tablets, pills, powders, and granules, whereas the recipes were prepared in decoctions and composed of 3 to 24 herbs. The most frequently prescribed 10 herbs used in compound formulae and their major constituents for the clinical treatment of DM are summarized in Table **1**. To date, a great number of TCM formulae have been reported to have been used for the treatment of DM. These include: Xiaokeling tablets [173], Huang-Lian-Jie-Du-Decoction [174], Ba-Wei-Di-Huang-Wan [175], Formula 1 [176, 177], Gui-zhi-fu-ling-wan [178], Die-huang-wan [179], and Danggui-Buxue-Tang [180].

A Xiaokeling tablet is an anti-diabetic complex formulae embodied in the 2005 Chinese Pharmacopeia, edition I. The formula which is widely used by TCM practitioners for the treatment of diabetic conditions consists of 10 medicinal herbs, *i.e.*, *Rehmannia glutinosa*, *Schisandra chinensis*, *Ophiopogon japonicuc*, *Paeonia suffruticosa*, *Astragalus membranaceus*, *Coptis chinensis*, *Poria cocos*, *Panax ginseng*, *Trichosanthes kirilowii*, and *Lycium barbarum*. Among them, *Rehmannia glutinosa* and *Ophiopogon japonicuc*, with the major ingredients being polysaccharides, are regarded as key components that exert the main therapeutic effect of the whole formula [173].

Huang-Lian-Jie-Du-Decoction, a well-known Chinese herbal formula, has been used for diabetic treatment. It is prepared with Rhizoma coptidis 30 g, Radix scutellariae 20 g, Cortex phellodendri 20 g and Fructus gardeniae 30 g. It was found that 5-week this formula treatment attenuated alteration of glucose level and insulin level in plasma and tissues of STZ-induced diabetic rats, accompanied by improvement of diabetic syndrome. Also, 5-week this formula treatment increased GLP-1 (7-36) amide level in portal vein plasma and distal ileum. Furthermore, 5-week this formula treatment increased the mRNA level of proglucagon gene in distal ileum, promoted pancreatic beta cell and intestinal L cell proliferation in a dose-dependent manner [174].

The herbal prescription Hachimi-jio-gan (Ba-Wei-Di-Huang-Wan) has been used for the treatment of patients with DM since the late middle ages. The composition of this formula is as follows: Rehmanniae radix (6 g), Corni fructus (3 g), Dioscoreae rhizoma (3 g), Alismatis rhizoma (3 g), Hoelen (3 g), Moutan cortex (2.5 g), Cinnamomi cortex (1 g), and Aconiti tuber (0.5 g). Ba-Wei-Di-Huang-Wan markedly suppressed hyperglycemia in STZ-induced diabetic rats at three and four weeks after oral administration. It did not increase the number of pancreatic β-cells, but increased insulin production and release by residual pancreatic β-cells and significantly suppressed the expression of hepatic glucose transporter 2 protein, which is involved in glucose uptake and release in the liver. Ba-Wei-Di-Huang-Wan also increased amylase secretion by the liver and had favorable effects on pancreatic secretion. Because this compound formula appears to be involved in hepatic glucose release as well as in suppressing hyperglycemia by increasing insulin secretion from residual pancreatic cells, long-term administration to diabetics may aid therapy [175].

Table 1. The Most Frequently Used 10 Herbs for the Treatment of Diabetes Mellitus or its Complications

Chinese Names	Medicinal Position Names	Family	Major Constituents
Huangqi	Radix Astragali	Leguminosae	Flavonoids, saponin, polysaccharides
Shanyao	Rhizoma Dioscoreae	Ranunculaceae	Monoterpene glycosides, galloyl glucosides
Dihuang	Radix Rehmanniae	Scrophulariaceae	Polysaccharides, iridoid glucosides
Dansheng	Radix Salviae Miltiorrhizae	Labiatae	Phenolic and diterpenoid compounds
Gegen	Radix Puerariae	Leguminosae	Flavonoids
Huangliang	Rhizoma Coptidis	Ranunculaceae	Alkaloids
Gouqi	Fructys Lycii	Solanaceae	Polysaccharides, alkaloids
Fuling	Poria	Fungi	Polysaccharides, saponins
Zexie	Rhizoma Alismatis	Alismataceae	Saponins
Shanzhuyu	Fructus Corni	Cornaceae	Polysaccharides, iridoid glucosides

Formula 1, the 'Herbal drink to strengthen muscle and control swelling', is a Chinese herbal medicine formula consists of six medicinal plants, including Radix Astragali, Radix Rehmanniae, Rhizoma Atractylodis Macrocephalae, Radix Polygoni Multiflori Preparata, Rhizoma Smilacis Chinensis, and Radix Stephania Tetrandrae. It has been shown to effectively promote the healing of diabetic foot ulcers [176]. Lau *et al.* [177] used an interdisciplinary approach to test the hypothesis that Formula 1 and its components influence tissue and systemic glucose homeostasis. The results of *in vitro* studies indicated that all herbal extracts can modify cellular glucose homeostasis. Formula 1 and Rhizoma Smilacis Chinensis extracts demonstrated potent effects on modifying glucose homeostasis in multiple tissues *in vitro*. However, the anti-diabetic activities *in vivo* showed that Formula 1 and Rhizoma Smilacis Chinensis extracts did not significantly improve oral glucose tolerance or basal glycaemia in diabetic rats.

Combination herbal formulae and combination photochemical compounds derived from traditional formulae with a holistic therapeutic approach may hold the potential to become the therapeutics of choice in the future, due to the synergistic effect and dynamic adjustment achieved by the multiple ingredients that inhibit the causative factors at different stages, strengthen the impaired immune system and improve the overall symptoms and the patient's quality of life. Owing to the different pharmacological roles of those herbs in formula, the hypoglycemic mechanism of drug products containing a mixture of those extracts becomes complicated. Tao *et al.* [181] speculated that polysaccharide-containing agents in formula restored the functions of pancreatic tissues and caused an increase in insulin output by the functional β-cells. Others attributed the hypoglycemic effect of many products to their ability to inhibit the intestinal absorption of glucose, to the increased availability of insulin, or to the facilitation of metabolites in insulin-dependent processes. Unfortunately, research regarding the efficacy of compound formulae to treat DM is limited, and none of the investigators was capable of providing conclusive evidence to ascertain the actual hypoglycemic mechanisms of herbal drugs developed in China. In addition, well-performed clinical trials on their therapeutic value in the treatment of DM are very rare and the side effect of herbal drugs remains uncharted, since its use is largely uncontrolled. Future efforts will have to implement extensive methodological improvements to separate the real therapeutic value of these agents from unfounded hopes and mysteries associated with them.

5. CONCLUDING REMARKS AND FUTURE PERSPECTIVES

For thousands of years NPs have been closely linked with medicines through the use of traditional medicines. Clinical, pharmacological, and chemical studies of these traditional medicines, which were derived predominantly from plants, were the basis of most early and modern medicines. Numerous reviews have described the importance of natural compounds to treat human diseases [182-184]. The continuing and overwhelming contribution of NPs to the expansion of anti-diabetic agents is clearly evident. As estimated that only 6% of 10-100 million species or organisms living on earth has been investigated for biological activities and 15% for their chemical constituents, it looks increasingly like we have only scratched the surface of this world's wonderful resource [185]. In addition, only a tiny fraction of the microbial and marine world has been explored. Nature's "treasure trove of small molecules" remains to be explored. There are several theoretical advantages to the screening of NPs for discovery of anti-diabetic medicines. They provide markedly chemical diversity with structural complexity and biological potency [186]. Researches on NPs will certainly lead to the discovery of novel chemical entities for DM [187, 188]. Meanwhile, the use of NPs as templates for combinatorial chemistry enables the generation of libraries of NPs' analogs, which might have enhanced drug-like properties (*e.g.*, pharmacokinetics, solubility). Consequently, exploring new chemical entitles from NPs will remain the predominant way to provide the leads and scaffolds for elaboration into efficacious anti-diabetic medicines.

However, in order for drug discovery from NPs to continue to be successful, new and innovative approaches are required to increase the current efficiency. The past few years have witnessed major developments in extract preparation, purification, structure elucidation and bioassay-guided fractionation of NPs, thus enabling much faster access to sufficient amounts of pure compounds [189]. The recent development in the hyphenated techniques such as ultra-fast high-performance liquid chromatography with mass spectrometry or nuclear magnetic resonance [190-192], holistic approaches and integrated evaluation models to directly and simultaneously screen multiple bioactive candidates from a mixture [193,194], and metabonomics [195] have had a substantial impact in shortening the time line for dereplication, isolation and structure elucidation of the NPs present in the crude extracts. After identifying genuine natural product leads, applying new organic synthetic methodologies, biotransformation and combinatorial biosynthesis for the modification of these leads would generate a large number of novel, structurally diverse analogs for improved properties or new anti- diabetic activities.

On the other hand, this review also included a great number of plant extract and compound formulae that have gained gratifying results at the experimental animal models and clinic studies in treatment of DM. Unlike the single chemical entity aimed at a specific single target, plant extract and compound formulae represent integrated effects of multi-components upon multi-target sites and dynamic adjustments that will restore the balance of an imbalanced body caused by DM [193,196]. They are a set of multi-component parts self-organized into an interactive and indivisible whole. Screening of bioactive chemical entities through isolation and pharmacological test one by one, or bioassay-guided fractionation might become in vain. The idea of combination therapy has been practiced in Chinese herbal medicine for thousands of years, and has been gaining ever-increasing acceptance in the world. Important information came from the US Food and Drug Administration and the European Parliament and the Council claimed the approval of herbal mixtures with unknown ingredients, if convincing evidence for their safety and efficacy [197]. This raised the interest of many pharmaceutical companies on herbal medicines all over the world. There is no doubt that

plant extracts and compound formulae should be viewed as a potential complementary treatment for DM. However, most of them are being used in the management of DM with a relatively insufficient knowledge of their mechanism of action as well as adverse effects and safety profiles. No experience of drug interactions was reported by the researchers. The mechanism of action of most of these anti-diabetic compound formulae is still unknown, although a multi-targeted approach through a synergistic interaction *in vivo* is generally assumed in the treatment. Despite extensive use, the lack of regulatory scrutiny of these herbal medicines contributes to the paucity of reliable clinical data assessing their efficacy and safety. Furthermore, due to chemical complexity and instability, there is limited knowledge about the chemical compositions, pharmacokinetics, pharmacodynamics and metabolomics of herbal medicines, and the data about authentication, efficacy, safety and quality control are far from sufficient to meet the criteria needed to support their use worldwide. There is an undoubted need for further research into the treatment of DM by herbal medicines. Only rigorous scientific testing along the principles of evidence-based medicine will help herbal medicines to become more than a fashionable trend.

In conclusion, it is promising to discover new chemical entities of NPs for DM, was well as standard extracts and validated compound formulae. We now look to the future with eager anticipation and great expectations.

ABBREVIATIONS

AChE	=	Acetylcholinesterase
AGEPs	=	Advanced glycation end products
AMPK	=	AMP-activated protein kinase
AR	=	Aldose reductase
BSA	=	Bovine serum albumin
DM	=	Diabetes mellitus
EC_{50}	=	50% effective concentration
FBG	=	Fasting blood glucose
GLUT4	=	Glucose transporter 4
HDL	=	High density lipoprotein
IC_{50}	=	50% inhibiting concentration
IDF	=	International Diabetes Federation
i.p.	=	Intraperitoneal
LDL	=	Low density lipoprotein
NPs	=	Natural products
PPARγ	=	Peroxisome proliferator-activated receptor
STZ	=	Streptozotocin
TCM	=	Traditional Chinese Medicine
WHO	=	World Health Organization

ACKNOWLEDGEMENTS

The authors greatly appreciate financial support from the National Science and Technology Major Project 'Creation of Major New Drugs' from China (No. 2009ZX09502-020). We would also like to thank Dr. J. F. Cheng for the fruitful advices and revision on the original mansucrpt.

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Received: February 1, 2009 Revised: June 22, 2009