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Diabetic Complications: A Natural Product Perspective

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Abstract: Diabetes is a chronic disease that affects over 400 million people globally. With 5.5% increase in diabetes related deaths in 2010, as compared to the 2007 and World Health Organisation's projection of diabetes as the 7th leading cause of death by 2030, has dazed the current drug discovery fraternity. The major focus of drug discovery has been towards the control of hyperglycemia while the severe complications arising due to it have been overlooked. Plant based natural products (pure phytochemicals or in the form of crude extracts) have been the mainstay of drug discovery program for treatment of numerous human diseases. In addition, indigenous systems of medicines like *Ayurveda* and Traditional Chinese Medicine (TCM) possess a rich plethora of knowledge about clinically used medicinal plants for controlling the diabetic complications. With India becoming the capital of diabetes and its associated complications, the present natural products perspective is more evident and highlights the current natural products based research that has been done for the last five years in tackling diabetic complications.

Keywords: Cardiovascular disease, diabetes, diabetic complications, natural products, nephropathy, neuropathy, retinopathy.

INTRODUCTION

Diabetes is defined as "a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces" [1]. Hyperglycaemia, or raised blood sugar, is a common effect of uncontrolled diabetes and with time, this leads to serious damage to many of the body systems, especially the nerves and blood vessels. Globally, 382 million people were detected with diabetes in 2013, and the number is expected to project to 592 million by 2035. The severity of diabetes is more in low and middle income countries with 80% of the population contributing to the global statistics [2]. Close to four million deaths in the age group of 20-79 were recorded due to diabetes in 2010, accounting for 6.8% of global all-cause mortality in this age group. There has been a 5.5% increase in diabetic deaths in 2010, as compared to the 2007 statistics [3]. Another problem associated with diabetes is that the increase in blood glucose level may lead to severe complications that affect various systems of the body. These complications are divided into two types. Microvascular complications include eye disease or "retinopathy", kidney disease termed "nephropathy", and neural damage or "neuropathy". The major macrovascular complication includes accelerated cardiovascular disease resulting in myocardial infarction and cerebrovascular disease manifesting as strokes [4]. Diabetic retinopathy and cardiovascular disease are one among the leading causes of blindness and deaths, respectively.

Medicinal plants have been an integral part of human healthcare systems for centuries. They have been used either in the form of pure phytochemicals (e.g. taxol, artemisinin etc.) or crude extracts (single or combinations) for the treatment of various diseases. Also there has been an increasing importance in the utilization of plant based natural products, commercially due to their lower side effects as compared to the synthetic drugs. The contribution of plant based therapeutics for treatment of diabetes has been very valuable and the vast plethora of research articles being published makes it more evident. With India becoming the diabetic capital of the world and with still a lot of uncertainty over the other subclass of diabetes like Type 1.5 (Latent Autoimmune Diabetes in Adults, LADA), it became imperative to discover and develop newer, safer and effective antidiabetic therapeutics which will not only control diabetes but also its associated complications. The present review discusses about the various natural products that have been investigated for their potential to prevent or ameliorate various diabetic complications during the last five years. This review is an attempt to channelize the available research data to add value to natural products in the area of diabetic complications.

DIABETIC EYE DISEASES

Diabetic eye diseases include cataract (where the eye lens is clouded), glaucoma (where the fluid pressure inside the eye increases leading to optic nerve damage) and diabetic retinopathy (where the blood vessels of the retina are damaged) [5]. Diabetic retinopathy is the most common disease among all the diabetic complications and is characterized by a spectrum of lesions within the retina. The first stage (Mild Nonproliferative Retinopathy) starts with the occurrence of microaneurysms, small outpouchings from retinal capillaries, and dot intraretinal haemorrhages. As the disease progresses to the second stage (Moderate Nonproliferative Retinopathy), there is an increase in the number and size of intraretinal haemorrhages. This increase may be accompanied by

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cotton-wool spots which indicate regional failure of the retinal microvascular circulation resulting in ischemia. Further progression of the disease leads to Severe Proliferative Diabetic Retinopathy where the retina sends signals to the brain for the development of new blood vessels. This leads to the final stage (Proliferative Retinopathy) which involves the formation of new blood vessels that develop from the retinal circulation [5, 6]. These new vessels can extend into the vitreous cavity of the eye and can lead to haemorrhages into the vitreous, resulting in vision loss. Another important change that can occur is the diabetic macular oedema, which involves the breakdown of the blood–retinal barrier, with leakage of plasma from small blood vessels in the macula, the central portion of the retina that is responsible for the major part of visual function. This causes swelling of the retina [6]. It is the leading cause of blindness among adults aged 20–74 years.

Hence prevention of diabetic eye diseases by targeting different pathways and enzymes via strategies like inhibiting the production of Advanced Glycation End products (AGEs), down regulation of inflammatory mediators, Interleukins (ILs), Cyclooxygenase-2 (COX-2), Vascular Endothelial Growth Factor (VEGF), prevention of oxidative stress through anti-oxidant activity, and inhibition of certain enzymes like Aldose reductase (AR) are needed. Various pure natural products and plant extracts have been reported to prevent or delay the progression of diabetic eye diseases and are summarized below.

Pure Compounds

Various pure phytochemicals have been tested in different cell cultures, *in vitro* and *in vivo* studies for their potential in treatment of diabetic retinopathy (See Fig. **1**) and are described below.

Epigallocatechin-3-gallate (EGCG) **(1):** EGCG is one of the major polyphenols isolated from *Camellia sinensis* (L.) Kuntze. (Theaceae). It was found by Ye *et al.* to exhibit protective effect against high glucose-induced apoptosis in Human lens epithelial B-3 cells by decreasing the expression of Bcl-2/Bax (B-cell lymphoma 2/Bcl-2 associated X), c-fos (A murine *fos* proto-oncogene), c-myc (A cellular homolog gene of the v-myc oncogene) and p53 (A tumour suppressor protein), when the cells were pre-incubated with EGCG at concentrations of 25-50 μM, thus proving beneficial in prevention of diabetic cataract formation [7].

Astragaloside IV **(2):** It is a bioactive principle mainly found in the genus *Astragalus* (Fabaceae). Hao *et al.* found that the compound exhibited a protective effect on retinal ganglion cells-5 against high-glucose induced damage by elevation of mitochondrial membrane potential and alleviation of mitochondrial swelling. The cell survival rates were found to be 81.6%, 80.0% at concentrations of 100, 200 mg/L of astragaloside IV respectively [8].

Resveratrol **(3):** It is a phytoalexin found in wine grapes infected by the fungus *Botrytis cinerea* De Bary. Whetzel. (Sclerotiniaceae). Spontaneously arising retinal pigment epithelial (ARPE-19) cells incubated with 33 mM glucose in the presence of 0-10 μM *trans*-resveratrol was found by Losso *et al.* to dose dependently inhibit VEGF, transforming growth factor (TGF)-β1, COX-2, IL-6, IL-8 accumulation, Protein kinase C (PKC)-β activation, Connexion 43 degradation and enhanced Gap junction intercellular communication [9]. In another study it was found by Srivastava *et al.* that resveratrol regulated Forkhead box O (FOXO) transcription factors at concentrations ranging from 10-20 μM determined through luciferase assay and suggested to be useful in treatment of diabetic retinopathy [10].

Ginsenoside Rb2 **(4):** It is a steroidal constituent isolated from genus *Panax* (Araliaceae). Park *et al.* found that Ginsenoside Rb2 exhibited its protective effect against diabetic retinopathy by prevention of high glucose-induced apoptosis through decreasing Bcl-2 expression, lipid peroxide (LPO) and COX-2 expression, and increasing Bax expression in ARPE-19 cells at a concentration of 1 μg/mL [11].

3,5-Di-O-caffeoyl-epi-quinic Acid **(5):** It is isolated from the leaves and stems of *Erigeron annuus* L. Pers. (Compositae). It was found by Jang *et al.* to inhibit the formation of AGEs and rat lens aldose reductase (RLAR) with IC_{50} values of 6.06 μM and 0.44 μM respectively, along with AGEs-bovine serum albumin cross-linking to collagen and prevented opacification of rat lenses [12].

Puerariafuran **(6):** It is a 2-arylbenzofuran isolated from the roots of *Pueraria lobata* Ohwi. (Fabaceae). Kim *et al.* found that Puerariafuran potently inhibited RLAR with an IC_{50} value of 22.34 μM. The xylose induced opacity of lenses was significantly improved, and there was a significant increase in the reduced glutathione (GSH)/oxidized glutathione (GSSG) ratio, superoxide dismutase (SOD) and catalase (CAT) activity in rat lenses on treatment with puerariafuran (3 -15 μM) **[**13].

Scopoletin **(7)** ***and Tiliroside*** **(8):** Scopoletin is a coumarin, while Tiliroside is a phenolic compound. Both the compounds were isolated from the flower buds of *Magnolia fargesii* Cheng. (Magnoliaceae) and investigated for their RLAR and AGEs inhibitory activity by Lee *et al.* Scopoletin inhibited AGEs formation with IC_{50} value of 2.93 μM and showed a significant RLAR inhibition with IC_{50} value of 22.5 μM. Scopoletin significantly inhibited cataractogenesis of rat lenses induced with xylose in *ex vivo* experiments in dose dependent manner. Tiliroside exhibited potent inhibitory activity against RLAR with an IC_{50} of 14.9 μM [14].

β-Glucogallin **(9):** It is 1-*O*-galloyl-*β*-D-glucose found in *Phyllanthus emblica* L. (Phyllanthaceae). Puppala *et al.* found potent inhibition of AR *in vitro* (IC_{50} value of 17 μM) and sorbitol accumulation by 73% at 30 μM under hyperglycemic conditions in an *ex-vivo* organ culture model of lenses excised from transgenic mice over expressing human AR [15].

Arctiin **(10):** It is isolated from dry seeds of *Arctium lappa* L. (Asteraceae). Treatment of Streptozotocin (STZ) induced diabetic male Sprague-Dawley (SD) rats with arctiin (30, 90 or 270 mg/kg body weight (b.w)/day p.o. for sixteen weeks) was found by Lu *et al.* to ameliorate retinal oedema, detachment of the retina, and VEGF expression in the retina. Increase in the viability of retinal microvascular endothelial cells *in vitro* at concentrations ranging from 10 μg/mL to 100 mg/mL was also found using MTT assay signifying the importance of this compound as an inhibitor of diabetic retinopathy [16].

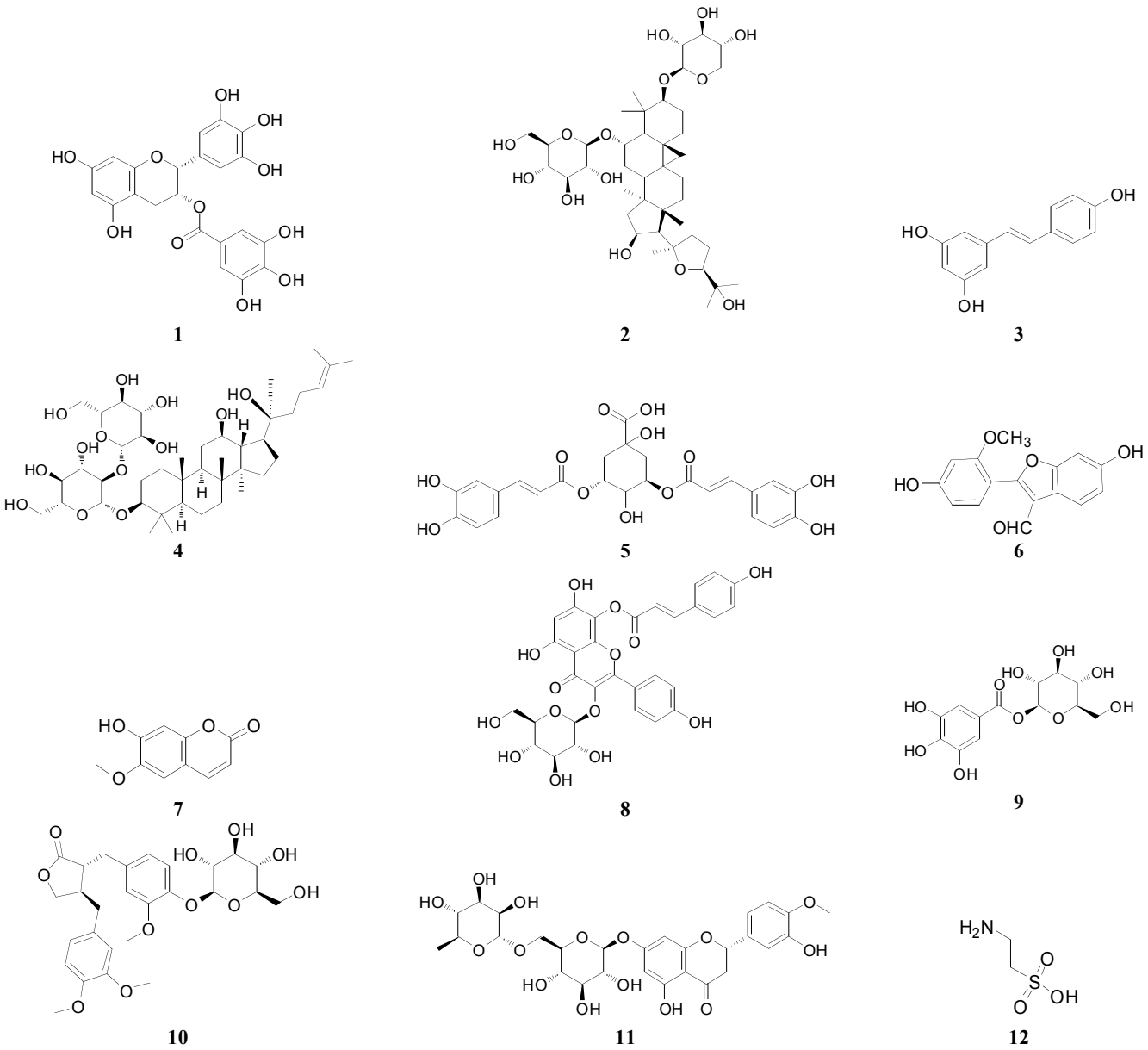

Fig. (1). Structures of phytochemicals (1-12) active against diabetic retinopathy.

Hesperidin **(11):** It is a flavonone glycoside abundantly found in citrus fruits. Administration of hesperidin (100, 200 mg/kg b.w/day i.g.) for 12 weeks to STZ induced male SD rats was found by Shi *et al.* to suppress blood-retina breakdown and increased retinal thickness. It also reduced AR activity, retinal tumour necrosis factor (TNF)-α, Intercellular adhesion molecule (ICAM)-1, VEGF and IL-1β. It significantly reduced the plasma malondialdehyde (MDA) levels and increased the SOD activity [17].

Extracts

Table **1** summarizes list of plants and their extracts reported to have protective effect in diabetic eye diseases.

Miscellaneous

Lycium barbarum, Taurine **(12)** ***and Chrysanthemum morifolium:*** Song *et al.* found that the fruit of *Lycium barbarum* L. (Solanaceae) and Taurine prevented diabetic retinopathy progression by enhanced expression of Peroxisome proliferator activated receptor (PPAR γ) mRNA and protein. It dose-dependently (0.1, 0.5 and 1 mg/mL) enhanced PPARγ luciferase activity in human embryonic kidney-293 cell line transfected with PPAR-γ reporter gene. It also dose dependently (0.1 mg/mL, 0.5 mg/mL and 0.75 mg/mL) down-regulated mRNA of pro-inflammatory mediators encoding matrix metalloproteinase (MMP)-9, Fibronectin (FN) and the protein expression of COX-2 and inducible nitric oxide synthase (iNOS) proteins in an inflammation exposing ARPE-19 cells to high glucose [28]. In another study by Hu *et al.* on STZ induced male SD rats, aqueous decoction of dried fruits of *L. barbarum* and *Chrysanthemum morifolium* Ramat. (Asteraceae) were administered alone and in combination (5 g/kg b.w/day p.o.) for eight weeks. In *Lycium* treated rats, reduction of electroretinogram b-wave was reversed after diabetic induction and was suggested to be due

Table 1. Plants and their extracts reported to have protective effect in diabetic eye diseases.

Plant Name (Family)	Plant Parts and Extracts	Study Models	Dose, Duration, Route of Administration/ Concentration	Effects	Ref.
Camellia sinensis (L.) Kuntze. (Theaceae)	Aqueous decoction of green leaves	ARPE-19 cells	1, 10, and 100 μg/mL	Decrease in Excitatory Amino Acid 1 transporter expression and reduced reactive oxygen species (ROS)	[18]
		Spontaneously hypertensive and Wistar-Kyoto STZ male rats	100 mL/d p.o. (equivalent to 5.7 g/kgb.w/day) for 12 weeks	Restoration of the glutamate transporter, glutamate receptor and glutamate metabolizing enzyme	[18]
	MeOH: water (1:1) leaf extract	STZ induced male wistar albino rats	200 mg/kg b.w/day p.o. for a period of 16 weeks	Restoration of retinal GSH levels, SOD and CAT enzymatic activities and significant inhibition of TNF-α and VEGF	[19]
Salvia miltiorrhiza Bunge. (Labiatae)	Aqueous extract of rhizome	Alloxan induced diabetic mice of natural incidence type	0.06, 0.6 and 1.4 mL/kg b.w/day for 10 weeks	Improvement in the blood oxygen transport in the retinal hypoxia-ischemia tissues	[20]
Zingiber officinalis Roscoe. (Zingiberaceae)	Dried rhizome powder	STZ induced male wistar rats	0.5 or 3% via diet for a period of two months	Delayed cataract progression through dose dependent normalization of AR and sorbitol dehydrogenase activities	[21]
Cleistocalyx operculatus Roxb. Merr and Perry. (Myrtaceae)	Aqueous extract of flower buds	STZ induced male wistar rats	500 mg/kg b.w/day p.o. for nine weeks	Reduction in the LPO level in the lens, partial regeneration/proliferation of the pancreatic β-cells	[22]
Morus alba L. (Moraceae)	Aqueous extract of leaves	STZ induced mother rats	100 mg/kg b.w/day for six weeks	Amelioration in the retinal cell death, reduction of low density lipoprotein and creatine phosphokinase (CPK)	[23]
Moringa oleifera Lam. (Moringaceae)	Aqueous extract of leaves	STZ induced wistar albino rats of either sex	100 mg/kg b.w/day p.o. for 24 weeks	Inhibition of retinal TNF-α, IL-1β, VEGF and PKC-β, prevention in the dilatation of retinal vessels	[24]
Chromolaena odorata L. (Asteraceae)	Ethanolic extract of leaves	STZ induced female wistar rats	200 and 400 mg/kgb.w/day p.o. for eight weeks	Protective against cataract through improved high density lipoprotein cholesterol and glucose tolerance	[25]
Panax quinquefolius L. (Araliaceae)	Alcoholic root extract	STZ induced type 1 and type 2 male C57BL/6 mice	200mg/kg b.w/day p.o. for two to four months	Increase in the SOD and GSH, upregulation in FN, VEGF and endothelin (ET)-1	[26]
Vitis vinifera L. (Vitaceae)	Proanthocyanidin rich seed extract	STZ induced male wistar rats	250 mg/kg b.w/day i.g. for 24 weeks	Decrease in neovascularization through regulation of α-B-crystalline, α-A-crystalline, Vimentin, Tubulin α, Tubulin β2 and Ubiquitin carboxy-terminal hydrolase L1	[27]

to anti-apoptotic effects on neurons and retinal ganglion cells respectively. *Chrysanthemum* treatment did not prevent decrease of a-wave amplitude after diabetes induction indicating its ineffectiveness; however treatment with a mixture of *Lycium* and *Chrysanthemum* showed a significant protective effect and prevention of the a-wave amplitude loss similar to that achieved by insulin treatment [29].

CARDIOVASCULAR DISEASES

Cardiovascular diseases include a spectrum of complications which arise from endothelial dysfunction, oxidation, inflammation, and vascular remodelling, leading to atherogenesis. This might progress into a coronary blockade, ultimately resulting into diabetic heart disease. Diabetic heart disease may also arise due to high glucose induced hypertension or due to a direct effect of diabetes on myocardium, termed as diabetic cardiomyopathy. Altered metabolism in diabetes leads to reduced glucose and pyruvate utilisation, increased free fatty acid oxidation, accumulation of non-chain acyl carnitines, and reduced glucose transporter type 4 (Glut-4) expression. These features when combined, result in impaired oxidative phosphorylation and myocardial oxygen demand. As a result, it leads to reduced myocardial performance, morphological changes and apoptosis. The morphological changes in the myocardium include increased fibrosis due to increase in angiotensin (Ang) II and its receptors, which induces myocyte fibrosis. Activation of PKC results

in the binding of the AGEs to their receptors leading to induction of nuclear factor, proinflammatory cytokines, inflammation, growth factor release, and fibrosis [30].

In an attempt of preventing or reducing the diabetic cardiovascular complications, many phytochemicals and crude plant extracts have been screened for their potential which are summarized below.

Pure Compounds

Various pure phytochemicals (Fig. **2**) tested in different cell culture and *in vivo* studies for their potential in treatment of diabetic cardiovascular disease are described below.

EGCG (**1**): In a study conducted by Yang *et al.*, EGCG (10, 30, and 50 μM) was found to suppress the high glucose induced proliferation of vascular smooth muscle cells (VSMC) as determined by MTT assay. EGCG inhibited PKC and extracellular signal-regulated kinase (ERK) 1/2 signalings, which resulted in an attenuation of its downstream transcription factor, Elk-1 (ETS domain-containing protein) phosphorylation [31]. In another study by Yu *et al.*, EGCG (40 μM) was found to attenuate the down regulation of the cardiac gap junction in rat cardiomyocytes induced by high glucose through activation of time dependent phosphorylated ERK, c-Jun-N-terminal kinase (JNK) and p38 mitogen activated protein kinase (MAPK) pathways [32].

Astragaloside IV (**2**): Yuan *et al.* found that the compound inhibited the proliferation of VSMC induced apoptosis by 11.1 and 14.0% respectively at concentrations of 5 and 50 μg/mL under high glucose conditions (25 mM) accompanied with typical morphological alterations and loss of mitochondrial membrane potential. It also increased the expression of α-smooth muscle actin (α-SMA) [33].

5-hydroxymethylfurfural (**13**): It has been isolated from processed *Cornus officinalis* Torr. ex Dur. (Cornaceae) by Cao *et al.*, where they found that in concentrations of 100, 200, and 400 μM it prevented high glucose-induced oxidative stress and expression of JNK1 and JNK2/3 in human umbilical vein endothelial cells (HUVECs). It also inhibited high glucose-induced activation of IL-8 [34].

Oleanolic Acid (**14**): It is an active constituent of *Syzygium aromaticum* L. Merrill & Perry. (Myrtaceae). Mapanga *et al.* found that it dulled the hyperglycemia induced contractile dysfunction, attenuated the high glucose induced oxidative stress and apoptosis at 20 and 50 μM concentrations in H9C2 cardiac myoblasts. It also decreased hexosamine biosynthetic pathway flux and proteasomal activity following ischemic reperfusion. It decreased SOD activity in simulated acute hyperglycemic hearts following an ischemic insult. Two week treatment with 0.45 mg/kg b.w/day i.v. also improved heart function in STZ induced male wistar rats [35].

Icariin (**15**): It is a flavonoid isolated from *Epimedium grandiflorum* C. Morren. (Berberidaceae). Bao *et al.* found that administration of Icariin (30 and 120 mL/kg b.w/day i.g.) for eight weeks to female SD rats was found to reduce mitochondrial oxidative stress injury in diabetic hearts. It also reduced the ratio of ventricular weight and body weight, increased the left ventricular systolic pressure and left ventricular end diastolic pressure in diabetic rats. Reduction in the myocardial collagen and the level of cardiac mitochondrial ROS along with decrease in the mitochondrial MDA level and increased SOD activity was also found [36].

Genistein (**16**): It is an isoflavone, majorly found in *Glycine max* L. (Fabaceae). It was investigated by Palanisamy *et al.* that genistein lowered blood pressure (BP), restored Angiotensin converting enzyme (ACE) and endothelial nitric oxide synthase (eNOS) expression through activation of PKC-βII in fructose fed hypertensive male wistar rats administered with 1 mg/kg b.w/day of genistein [37].

Breviscapine (**17**): It is a flavonoid extracted from *Erigeron breviscapus* Vant. Hand-Mazz. (Compositae). Wang *et al.* found that administration of *Breviscapine* twice a day (10 and 25 mg/kg b.w/day i.g.) for six weeks in STZ induced male SD rats ameliorated cardiac dysfunction and regulated the myocardial Ca^{2+}-cycling proteins. It decreased the expression and activity of PKC-α and PKC-β2 by inhibiting the over-expression of PKC. It also decreased the expression of phospholamban in diabetic rats and increased the expression of protein phosphatase inhibitor-1, sarco/endoplasmic reticulum Ca^{2+}-ATPase and Ryanodine receptor [38].

Phlorizin (**18**): It is a compound isolated from genus *Malus* (Rosaceae) commonly called as apples. Lin *et al.* found that the administration of Phlorizin (20 mg/kg b.w/day i.g.) to male C57BLKS/J db/db and db/m mice for 10 weeks ameliorated vascular complications. It blocked the intestinal glucose absorption through inhibition of the sodium-glucose symporters (SGLT) located in the proximal renal tubule (SGLT2) and mucosa of the small intestine (SGLT1), which reduced plasma glucose levels. The vascular wall of the untreated diabetic group was found to be thickened with impaired intima and a narrowed lumen. Also the migration of VSMC into the elastic laminar, and an increase of heterochromatin was found. With phlorizin treatment, these micro- and ultra-structure changes were less severe [39].

Rosmarinic acid (**19**): It is natural phenolic acid found in *Rosmarinus officinalis* L. (Lamiaceae). Sotnikova *et al.* found that administration of rosmarinic acid (50 mg/kg b.w/day p.o.) to STZ induced male wistar rats attenuated diabetes induced vascular dysfunction of the rat aorta. Aortic dysfunction due to structural alterations of endothelium and decreased endothelium dependent relaxation accompanied by overexpression of IL-1β, TNF-α, preproendothelin-1 and endothelin converting enzyme-1 antioxidant and anti-inflammatory effects was found to be ameliorated [40].

Extracts

Table **2** summarizes list of plants and their extracts reported to have protective effect in diabetic cardiovascular disease as investigated through various cell culture and *in vivo* studies

Miscellaneous

Kalpaamrutha: It is a modified indigenous *Siddha* preparation found to be anti-inflammatory on myocardium of STZ induced male SD rats by Raja *et al.,* where they have investigated reduction in Plasma C- reactive protein (CRP), iNOS, COX-2, IL-1β and IL-6, TNF-α NF-kB and expressions of MMP-2 and MMP-9; increase in eNOS and nucleotide

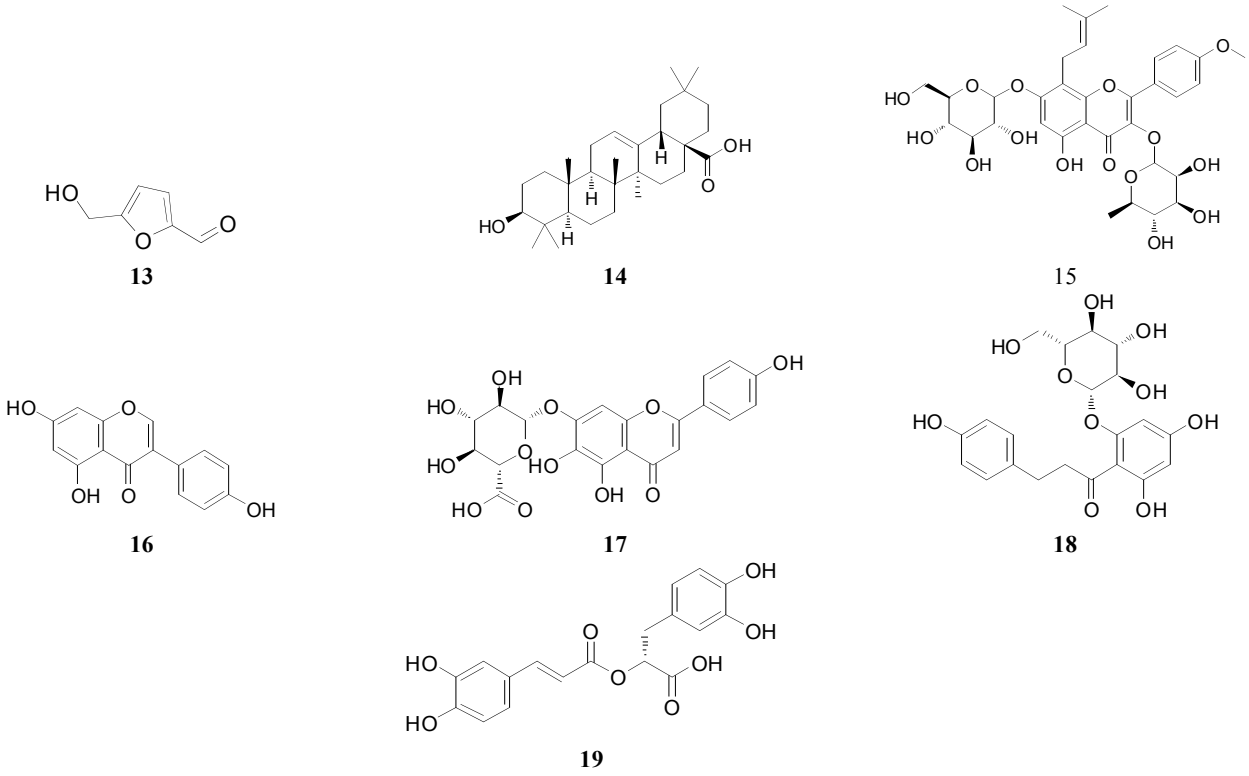

Fig. (2). Structures of phytochemicals (13-19) active against diabetic cardiovascular disease.

Table 2. Plants and their extracts reported to have protective effect in diabetic cardiovascular disease.

Plant Name (Family)	Plant Parts and Extracts	Study Models	Dose, Duration, Route of Administration/ Concentration	Effects	Ref.
Benincasa hispida Cogniaux. (Cucurbitaceae)	Aqueous whole plant extract	High glucose induced HUVECs	1-20 µg/mL	Inhibition of high glucose induced cell adhesion molecules (CAMs) and mRNA expression level of monocyte chemoattractant protein-1 (MCP-1), reduced adhesion of U937 monocytes	[41]
Buddleja officinalis Maxim. (Scrophulariaceae)	Ethanolic extract	Primary cultured Human Aortic Smooth Muscle Cells	—	Suppression of VSMC proliferation through inhibition of p38, JNK, nuclear factor-kappaB (NF-kB) and MMP signal pathways	[42]
Salvia miltiorrhiza Bunge. (Labiatae)	Hydrophilic extract of roots	Human Microvascular Endothelial Cells-1	10 µg/mL	Significant decrease of VEGF mRNA and ROS	[43]
	Alcohol precipitated root aqueous extract	STZ induced male SD rats	100 mg/kg b.w/day i.p. for four weeks	Protection of myocardium through prevention of upregulation of Thrombospondin (TSP)-1 and TGF-β1 protein levels.	[44]
Astragalus mongholicus Bunge. (Fabaceae)	Aqueous extract of the roots	STZ induced male hamsters	40 mg/kg b.w/day i.p. for three days	Improvement in myocardial glycolipid metabolic disorder by decrease in CPK and its isoenzyme	[45]
Astragalus membranaceus Bunge. (Fabaceae)	Polysaccharide rich extract	STZ induced male hamsters	2 g/kg b.w/day p.o. for 10 weeks	Significant decrease in heart Ang II levels	[46]
			1 g/kg b.w/day for 10 weeks	Significant reduction in the gene expression and enzyme activities of local myocardial chymase	[47]

(Table 2) contd….

Plant Name (Family)	Plant Parts and Extracts	Study Models	Dose, Duration, Route of Administration/ Concentration	Effects	Ref.
Aloe vera L. Burm.f. (Asphodelaceae)	30% gel in distilled water from leaves	STZ induced male wistar albino rats	100, 200 mg/kg b.w/day i.v. for 20 days	Reduction of the thiobarbituric acid reactive substances (TBARS) and increase in the reduced GSH	[48]
Aegle marmelos L. Corr. Serr. (Rutaceae)	Ethanolic leaf extract	STZ induced wistar rats of either sex	100, 200, 400 mg/kg b.w/day for 14 days	Dose dependent decrease in TBARS, Lactate dehydrogenase (LDH) and creatine kinase, increase in GSH and CAT	[49]
Prosopis glandulosa Torr. (Fabaceae)	Dried and ground pod powder	Diet induced obesity (DIO) and High fat diet (HFD) male wistar rats, and Cardiac-specific insulin recep-tor knock-out (CIRKO) C57Bl6 mice	100 mg/kg b.w/day p.o. for eight weeks	Elicitation in the infarct-sparing effect in the CIRKO mice, lowered ratio of phosphorylated to total protein of protein kinase B (PKB/Akt) in hearts of the DIO animals and reduction in the expression of the p85 subunit of phosphoinositide-3-kinase	[50]
Bauhinia thoningii Schum. (Fabaceae)	Aqueous extract of fresh leaves	Alloxan induced wistar albino rats of either sex	500 mg/kg b.w/day p.o. for seven days	Coronary risk index lowering effects through inhibitory effect on glucose absorption and reduced hepatic gluconeogenesis	[51]
Panax quinquefolius L. (Araliaceae)	Alcoholic root extract	STZ induced type 1 and type 2 maleC57BL/6 mice	200 mg/kg b.w/day p.o. for two to four months	Induction of the transcription of Cu-Zn SOD gene, upregulation of TGF-β1 and down regulation of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP)	[26]
Mesona procumbens Hemsl. (Lamiaceae)	Aqueous extracts of leaves	STZ induced male SD rats	1.5 g/kg b.w/day i.g. for four weeks	Reduction in disordered myofibrils and modification of diabetic cardiomyocytes nuclei and heterochromatin accumulation	[52]
Aralia elata Miq. Seem (Araliaceae)	Total aralosides rich extract	STZ induced male wistar rats	4.9, 9.8 and 19.6 mg/kg b.w/day p.o. for eight weeks	Regulation of L-type calcium channel current, and inhibition of the upregulation of connective tissue growth factor (CTGF)	[53]
Morus rubra L. (Moraceae)	Aqueous extracts of leaves	STZ induced male wistar albino rats	100, 200, 400 mg/kg b.w/day p.o. for 30 days	Modulation of soluble vascular cell adhesion molecule (sVCAM-1), Fibrinogen, apolipoprotein A and apolipoprotein B	[54]
Salacia oblonga Wall. (Celastraceae)	Aqueous root extract	Male zucker diabetic fatty rats	100 mg/kg b.w/day p.o. for seven weeks	Suppression of over expressed ANP, BNP and Ang II type 1 (AT1) mRNAs and AT1 protein as found in H9C2 cells	[55]
Gynostemma penta-phyllum Makino. (Cu-curbitaceae)	Gypenosides rich extract	STZ induced SD rats of either sex	100 mg/kg b.w/day p.o. for six weeks	Increase in left ventricular systolic pressure, decrease in left ventricular end diastolic pressure, but no alterations in titin and nebulin	[56]
Hippophae rhamnoides L. (Elaeagnaceae)	Total flavones from seed residues	Chronic sucrose fed male SD rats	50, 100, 150 mg/kg b.w/day i.g. for six weeks	Suppression of hypertension through increased Ang II levels	[57]
Psidium guajava L. (Myrtaceae)	Ethyl acetate leaf extract	STZ induced female SD rats	25, 50 mg/kg b.w/day i.g. for one month	Decrease in the α-2 macroglobulin of liver	[58]
Pinus pinaster Aiton. (Pinaceae)	Pycnogenol (Standard bark extract)	STZ induced male albino wistar rats	5mg/kg b.w/day i.g. for eight weeks	Significant reduction in plasma TXB_2 concentrations	[59]

adenine diphosphate (NADPH) oxidase mRNA expressions when administered with 200 mg/kg b.w/day p.o. for four weeks [60, 61].

Shengmai powder and Danshen decoction: Jie *et al.* assessed the protective effect of *Shengmai San* alone [62] as well as a mixture (7.125 g/kg b.w/day p.o.) of *Shengmai* powder and *Danshen* Decoction [63] in STZ induced male SD rats in two different studies conducted for 12 weeks and nine weeks respectively. They found a decrease in the expression levels of TSP-1 mRNA, Tribbles homolog (TRB)-3 mRNA, chymase, Active and Latent-TGF-β1 protein in both the studies.

DIABETIC NEUROPATHY

Diabetic neuropathy is a microvascular complication which is linked to the autonomous nervous system but spinal cord and central nervous system may also be involved, which might result in impairment in wound healing, erectile dysfunction, and cardiovascular dysfunction. Symptoms such as vascular abnormalities and improved nerve conduction velocities are proposed to be a result of increase in neuronal blood flow. In the advanced stages, nerve fibre deterioration may take place through apoptosis which results in altered sensitivities to vibrations and thermal thresholds, gradually leading to loss of sensory perception [4].

Pure Compounds

Various pure phytochemicals have been tested in different *in vitro*, cell culture and *in vivo* studies for their potential in treatment of diabetic neuropathy (See Fig. **3**) and are described below.

EGCG (**1**): Romeo *et al.* found that EGCG at doses of 10-200 μM induced heme oxygenase (HO-1) in rat neurons (H 19-7) and acted as a cytoprotective agent against oxidative stress damage in immortalized rat neurons. Activation of the transcription factor Nrf2 was proposed to be the mechanism for the induction [64].

Tanshinone IIA (**20**): It is a major component of *Salvia miltiorrhiza* Bunge. (Lamiaceae). Liu *et al.* investigated its neuroprotective effect by administering 20, 50 and 100 mg/kg b.w/day i.p. to STZ induced male SD albino rats for four weeks. Parameters like thermal and mechanical nociceptive threshold, motor nerve conducting velocity (MNCV), levels of SOD, CAT and MDA in sciatic nerve were alleviated [65].

Naringin (**21**): It is a flavonone glycoside found majorly in *Citrus paradisi* Macfad. (Rutaceae). It was evaluated by Kandhare *et al.* for its neuroprotective effect in STZ induced male wistar rats. Dose dependent attenuation of nociceptive threshold, endogenous antioxidant and membrane bound inorganic phosphate enzyme and decrease in neural cell apoptosis were found with treatment of naringin (40 and 80 mg/kg b.w/day p.o.) for four weeks [66].

Extracts

Table **3** summarizes list of plants and their extracts reported to have protective effect in diabetic neuropathy.

Miscellaneous

Coffee: Hong *et al.* investigated the effect of coffee, trigonelline (**22**), and caffeine (**23**) on auditory neuropathy, a hearing disorder characterized by abnormal auditory brainstem response in which coffee (35, 100, or 300 mg/kg b.w/day p.o.), trigonelline (10 mg/kg b.w/day p.o.) or caffeine (10 mg/kg b.w/day p.o.) was administered to different groups of STZ induced male ICR mice. Amelioration in the hearing threshold shift and delayed latency of the auditory evoked potential was found [78].

Baimai-San prescription: A famous Chinese minority complex prescription used for curing neuropathy was administered at doses of 0.1, 0.3, and 0.9 mg/kg b.w/day i.g. for 75 days to STZ induced male wistar rats by Liu *et al.* to evaluate its beneficial effects on peripheral neuropathy. Picroside II (**24**), ellagic acid (**25**), borneol (**26**), verbascose (**27**) and taurine (**12**) were found to be the effective compounds present in *Baimai San* through the use of high throughput screening. Reductions in the MNCV of sciatic nerve, sensory nerve conduction velocity and response speed to pain in the sciatic nerve fibre were determined. Increased neuronal survival rates, decreased LDH release, alleviation in the loss of neurite length through experiments from primary cortical neuronal cultures was found [79].

Nigella sativa oil and Thymoquinone (**28**): *Nigella sativa* L. (Ranunculaceae) and its active constituent Thymoquinone, a quinone derivative, were found by Hamdy *et al.* to attenuate oxidative stress in the heart and brain of STZ induced male wistar albino rats administered with 1 mL/kg b.w/day p.o. of oil or 10 mg/kg b.w/day p.o. of thymoquinone. Significant decrease in heart and brain NO and MDA concentrations, significant increase in Glutathione-S-transferase (GST), GSH and CAT, and restoration of Serum creatine kinase MB isoenzyme was found [80].

Evening primrose oil (EPO): It is the oil obtained from genus *Oenothera* (Onagraceae). It was administered (1.25 g/kg b.w/day p.o.) for two weeks in STZ induced male rats. Reduction of the size of islets of Langerhans, fatty degeneration in the pancreatic acini with dilation, irregularity, increased thickness of blood vessels, and multiple vaculations, partial separation of myelinated nerve fibres with axonal atrophy, endoneural edema, and increased collagen fibres in sciatic nerves of diabetic rats, was found by Omran to be partially recovered by the treatment. Significant decrease in myelin breakdown and improvement in the ultra structural features of axons was aloso found [81].

DIABETIC NEPHROPATHY

Diabetic nephropathy, one of the major complications associated with diabetes involves renal failure, which is characterized by the development of renal hypertrophy, polyuria, hyperfiltration, microalbuminuria, abnormal changes in the renal tissue, reduction in basement membrane thickening and mesangial proliferation formation. If left untreated over a long period of time, it results in uremia, which is fatal. Once nephropathy is established, severe alterations with respect to blood pressure is observed which may lead to cardiovascular disease [4].

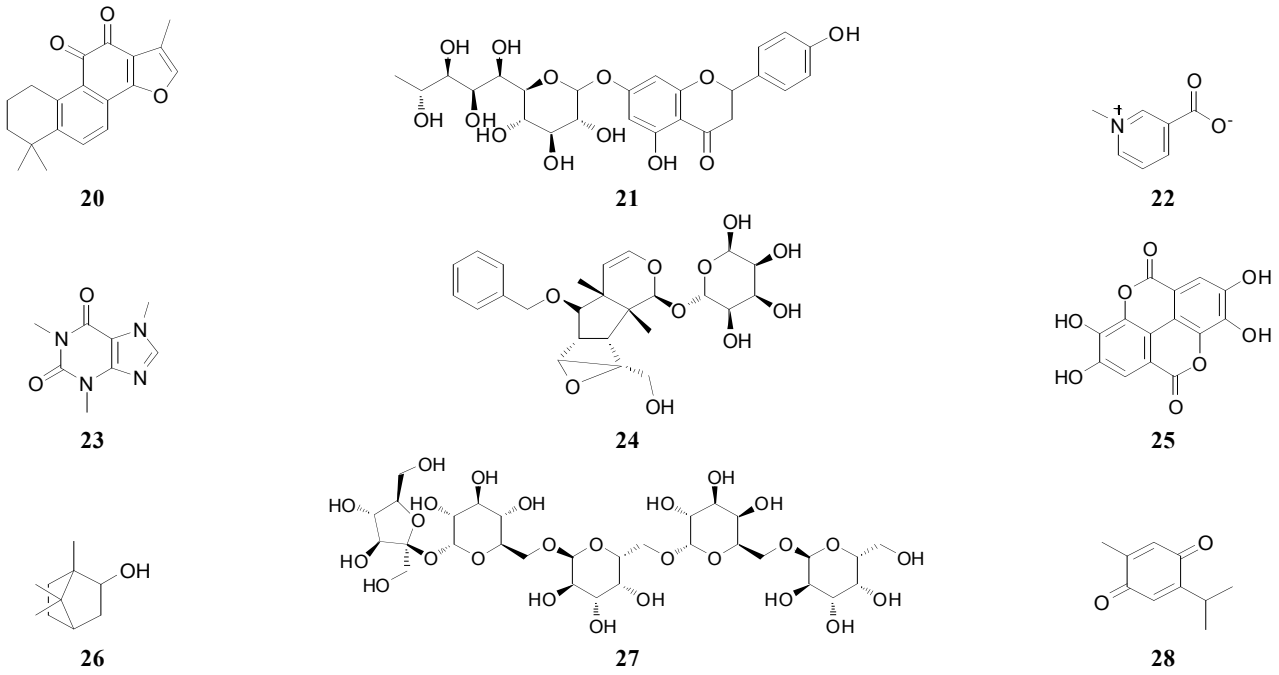

Fig. (3). Structures of phytochemicals (20-28) active against diabetic neuropathy.

Table 3. Plants and their extracts reported to have protective effect in diabetic neuropathy.

Plant Name (Family)	Plant Parts and Extracts	Study Models	Dose, Duration, Route of Administration/ Concentration	Effects	Ref.
Tinospora cordifolia Willd. Miers. (Menispermaceae)	Aqueous stem bark extract	*In vitro* AR assay	IC_{50} value of 103 µg/mL	Inhibition of AR *in vitro* and decrease in the reaction to tail flick, increase in the reaction time	[67]
		STZ induced female wistar albino rats	25, 100, 200 and 400 mg/kg b.w/day p.o. for 15 days		
Cannabis sativa L. (Cannabaceae)	Extract with high cannabidiol (64.5%)	STZ induced male wistar rats	15 or 30 mg/kg b.w/day p.o. for eight days	Relieved mechanical allodynia through increase in the GSH content	[68]
Ginkgo biloba L. (Gingkoaceae)	EGb 761 (Standardised extract of leaves which contains 24% flavone glycosides, 6% terpene lactones)	Spontaneously diabetic BB/OK rats	—	Improved Schwann cells by altering postsynaptic β1-adrenergic receptor-adenylyl cyclase coupling system	[69]
		STZ induced male wistar rats	50 mg/kg b.w/day p.o. for 120 days	Preservation of submucosal and myenteric plexuses of jejunum and ileum by inhibition of AR	[70]
		STZ induced wistar albino rats	25, 50 and 100 mg/kg b.w/day for 14 days	Dose-dependent alleviation in mechanical allodynia, and thermal hyperalgesia	[71]
Phoenix dactylifera L. (Areaceae)	Aqueous fruit extract	STZ induced male wistar rats	4 mL/kg b.w/day p.o. for six weeks	Increase in MNCV of the sciatic nerve, upregulation in the myelinated fibre diameter	[72]
Vitis vinifera L. (Vitaceae)	Proanthocyanidin rich seed extracts	STZ induced male wistar rats	250 mg/kg b.w/day i.g. for 24 weeks	Increase in the MNCV through reduction of MDA and AGEs, improvement in the Schwann cells	[73]
Emblica officinalis L. (Euphorbiaceae)	Aqueous extract	STZ induced male wistar rats	250, 500 and 1000 mg/kg b.w/day p.o. for four weeks	Dose dependent decrease in the tail-flick latency due to reduced TNF-α and TGF-β1 in the sciatic nerve	[74]

(Table 3) contd….

Plant Name (Family)	Plant Parts and Extracts	Study Models	Dose, Duration, Route of Administration/ Concentration	Effects	Ref.
Artemisia dracunculus L. (Asteraceae)	PMI-5011 (standard ethanolic extract)	STZ induced C57BL6/J mice	500 mg/kg b.w/day for seven weeks	Alleviation in MNCV, tactile allodynia through activation of spinal cord 12/15-lipoxygenase	[75]
Hygrophila spinosa T. Anders. (Acanthaceae)	Methanolic extract of aerial parts	Alloxan induced wistar rats of either sex	250, 500 and 750 mg/kg b.w/day for six weeks	Increase in the pain threshold levels through restoration of LPO and antioxidant enzyme levels of sciatic nerve	[76]
Terminalia arjuna Wight & Arn. (Combretaceae)	50% aqueous ethanol extract	STZ induced male wistar albino rats	500 mg/kg b.w/day p.o. for 30 days	Alleviation in impairment of the reflex bradycardia through reduction in inflammatory cytokines	[77]

Pure Compounds

Various purified natural products have been tested in different *in vitro* and *in vivo* models for their potential in treatment of diabetic nephropathy (See Fig. **4**) and are described below.

Andrographolide (**29**) ***and 14-deoxy-11,12-didehydroandrographolide*** (**30**): These compounds belonging to the class of diterpene lactones, isolated from *Andrographis paniculata* Nees. (Acanthaceae) Lee *et al.* investigated its effects on murine renal mesangial cell line (MES)-13, an SV40 transformed murine glomerular mesangial cell line, cultured in high concentration of glucose. Reduction in nephropathic phenotypes, reduction of apoptosis marker caspase-3, fibrosis marker TGF-β1, and Plasminogen activator inhibitor-1 (PAI-1) was found at concentrations of 10 and 1 μM respectively. Regulation of intracellular signaling transduction along with clearance of ROS was suggested to be the mechanism behind the effect [82].

Taurine (**12**): Taurine was evaluated by Huang *et al.* for its inhibition of AGE-induced hypertrophy in renal tubular epithelial cells. It was found that the AGE-induced Raf-1/ERK activation was markedly blocked by taurine (10-1000 μM) through which a significant decrease in cell size, cellular hypertrophy index, and protein levels of RAGE, Cyclin-dependent kinase inhibitor 1B ($p27^{Kip1}$), collagen IV and FN was found suggesting its anti-fibrotic activity [83].

Curcumin (**31**) ***and demethoxycurcumin*** (**32**): These compounds belong to the class of Diarylheptanoids obtained from *Curcuma longa* L. (Zingiberaceae). They were evaluated by Liu *et al.* for their activities on AGEs-induced oxidative stress and apoptosis, associated with the damage to mesangial cells. Significant restoration of AGEs-induced apoptosis to normal levels with IC_{50} values of 3.874×10^{-11} M and 6.085×10^{-11} M respectively, reduction of ROS generation in mesangial cells, elevation in AGEs-decreased SOD activity and decrease in AGEs-increased MDA content in cell culture supernatant was found *in vitro* in rat mesangial cell line HBZY-1 [84].

Rhein (**33**): It is an anthraquinone obtained from *Rheum* species (Polygonaceae). Yu *et al.* investigated the effets of rhein on high glucose and Ang II induced renal proximal tubular epithelial cells obtained from anesthetized SD rats by microdissection. Decrease in cell size, 3H-leucine incorporation and cellular protein content was found with 5, 15, and 30 mg/L concentrations of Rhein after 72 hrs [85].

7-O-galloyl-D-sedoheptulose (**34**): It is a phenolic compound isolated from *Cornus officinalis* Torr. ex. Dur. (Cornaceae). Park *et al.* investigated its effects by administering 20 and 100 mg/kg b.w/day p.o. for six weeks to C57BLKS/J db/db mice. Attenuation of renal oxidative stress through reduction of ROS and lipid peroxidation, increase in the ratio of GSH/GSSG, reduction in renal protein expression of NADPH oxidase 4 (Nox 4) and p22 (phox), pro-apoptotic factors (such as Bax and cytochrome c) and NF-kB targeting pro-inflammatory iNOS and COX-2 was found [86]. The renoprotective effect of the compound was also investigated by Yamabe *et al.* on STZ induced male wistar rats administered with 20 or 100 mg/kg b.w/day p.o. for 20 days. Modulation in the levels of TBARS in serum, and methylglyoxal and glycolaldehyde levels in kidney was found [87].

Caffeic acid (**35**) ***and ellagic acid*** (**25**): These compounds belong to the classes of hydroxycinnamic acid and natural phenol antioxidant respectively, Chao *et al.* assessed the nephropreotective effects of these acids where they were mixed in the diet at 2.5 and 5% concentrations and supplied to male Balb/cA mice for 12 weeks. Dose dependent reduction in plasma blood urea nitrogen (BUN), elevation in creatinine clearance and significant decrease in the levels of plasma glycated hemoglobin (HbA1c), urinary glycated albumin, renal carboxymethyllysine, pentosidine, sorbitol and fructose was found. Renal activity of AR and sorbitol dehydrogenase was diminished and the mRNA expression of renal AR was suppressed. Renal levels of IL-6, IL-1β, TNF-α and MCP-1 was lowered. Dose dependent down-regulation of TNF-α and MCP-1 mRNA expression in kidney was also found [88].

Genistein (**16**): It is an isoflavone, majorly found in *Glycine max* L. (Fabaceae). It was investigated by Palanisamy *et al.* that genistein preserved renal ultrastructural integrity and down regulated BP to normal by restoring ACE, PKC-βII and eNOS in fructose fed hypertensive male wistar rats administered with 1 mg/kg b.w/day of genistein [37].

2-Dodecyl-6-methoxycyclohexa-2,5-dien-1,4-dione (**36**): It is a benzoquinone derivative isolated from the tuberous

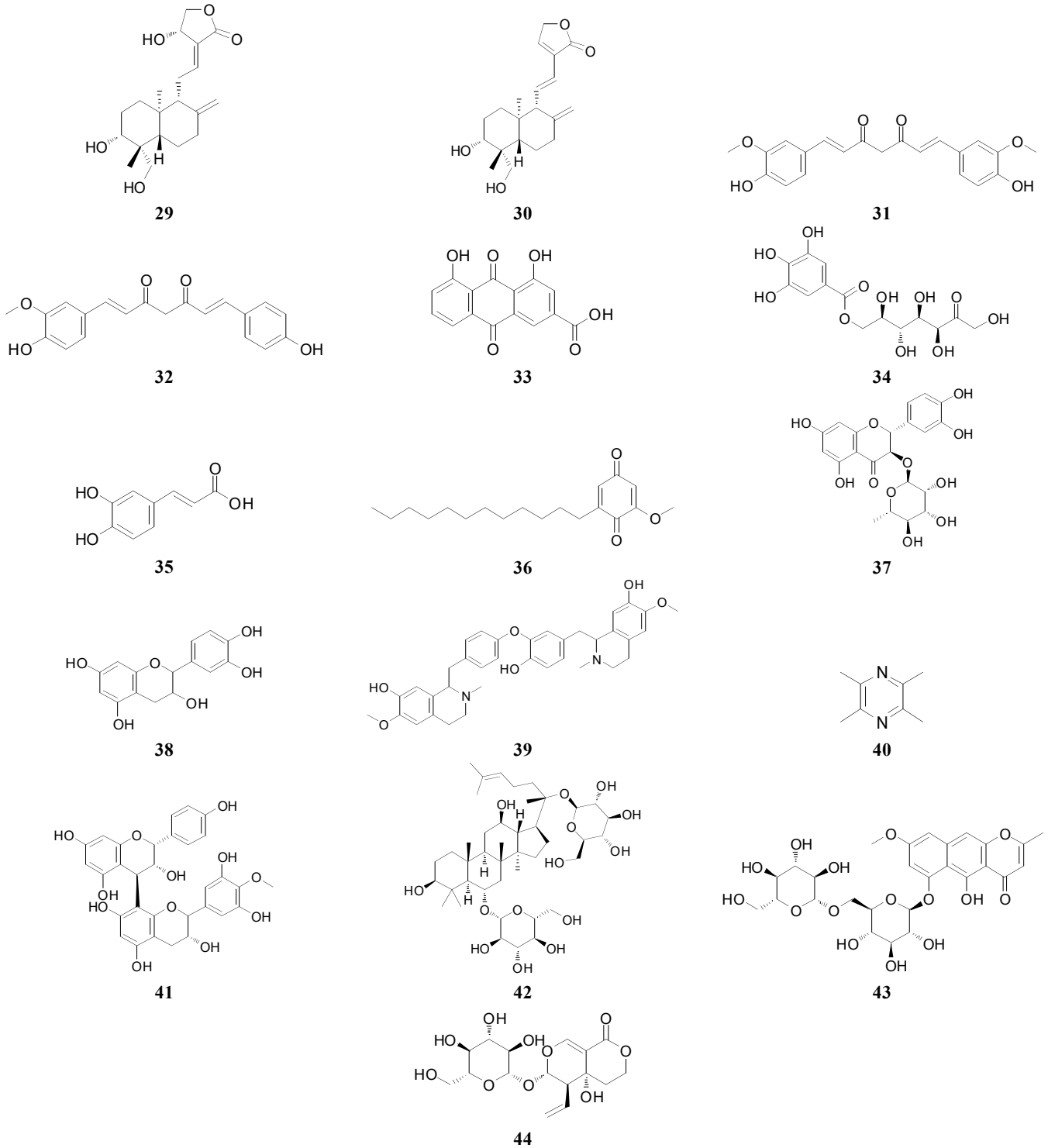

Fig. (4). Structures of phytochemicals (29-44) active against diabetic nephropathy.

roots of *Averrhoa carambola* L. (Oxalidaceae). Zheng *et al.* investigated its effects where the compound was administered to KKAy diabetic mice at doses of 12.5, 25, and 50 mg/kg b.w./day for eight weeks. Decrease in hyperglycemia, renal AGE formation, and the expression of related proteins, such as the AGE receptor, NF-κB, TGF-β1, and N(ε)-(carboxymethyl)lysine, attenuation of glomerular mesangial matrix expansion and upregulation of SOD and GSH peroxidase were found with the treatment [89].

Astilbin (**37**): It is a flavonoid compound, isolated from the rhizomes of *Smilax glabra* Roxb. (Smilacaceae). It was studied by Li *et al. in vitro* and *in vivo* using high glucose stimulated proximal tubule epithelial cell line **(**HK-2) and STZ induced male SD rats. Inhibition of TGF-β1 and CTGF *in vitro* at concentrations from 0.3 to 3 μM, and significant amelioration in renal functions and reduction in kidney index *in vivo* with 2.5 or 5 mg/kg b.w/day i.g of astilbin in a 12 week study was found [90].

(+)-Catechin (**38**): It is one of the major polyphenols of *Camellia sinensis* (L.). Kuntze. (Theaceae). Administration of catechin to STZ induced male SD rats at a concentration of 35 mg/dL/day in drinking water for 12 weeks was found by Chennasamudram *et al.* to lower the levels of ET-1, LPO, concentration of alanine transferase enzyme, and expression of FN and suggested that the co-administration of catechin and enalapril might be useful in reducing albumin excretion as well as improving endothelial function for clinical situations where ACE inhibitors are poorly tolerated [91].

Magnoline (**39**): It is an active constituent isolated from *Magnolia fargesii* Cheng. (Magnoliaceae). It was found to attenuate the levels of P-selectin and TGF-β1 by Zhou *et al.* in STZ induced male SD rats administered with 0.5 and 2 mg/kg b.w/day i.v. for 16 weeks [92].

Icariin (**15**): Qi *et al.* found that the compound reduced elevated MDA and Hydroxyproline levels and upregulated decreased SOD in renal tissues of STZ induced male SD rats at dose of 80 mg/kg b.w/day i.g. for a period of seven weeks [93].

Tetramethylpyrazine (**40**): It is also known as Ligustrazine. It is an alkaloid obtained from genus *Ligusticum* (Apiaceae). Yang *et al.* investigated the nephroprotective effects of tetramethylpyrazine where the compound was administered to STZ induced male SD rats at a dose of 200 mg/kg b.w/day i.g for eight weeks. Decrease in the expression of VEGF was found [94].

Oleanolic acid (**14**): Mapanga *et al.* isolated oleanolic acid from the leaves of *Syzygium cordatum* Hochst. (Myrtaceae), and evaluated its nephroprotective effects in STZ induced male SD rats by administering 60 mg/kg b.w/day p.o. of oleanolic acid for five weeks. Significant increase in Na^+ excretion rates without affecting urine flow, K^+ and Cl^- rates, and increased creatinine clearance with concomitant reduction of plasma creatinine concentration and decreased mean arterial BP was found [95].

Procyanidin B2 (**41**): It is a B type proanthocyanidin majorly found in *Vitis vinifera* L. (Vitaceae). It was investigated by Zhang *et al.* for its nephroprotective effects through proteomic analysis of kidneys of male C57BLKS/J db/db mice treated with 30 mg/kg b.w/day p.o. for 10 weeks. It was found that it down-regulated milk fat globule-Epidermal growth factor 8, along with ERK1/2 and Glycogen synthase kinase-3β signaling pathways [96].

Ginsenoside Rg1 (**42**): It is a steroid glycoside obtained from *Panax quinquefolius* L. (Araliaceae). It was evaluated by Ma *et al.* on STZ induced diabetic nephropathic rats. Reduction in TGF-β1 expression and the levels of serum creatinine, cross reaction protein, TNF-α, ectodermal dysplasia-1 in the renal tissues were found [97].

Extracts

Table **4** summarizes list of plants and their extracts reported to have protective effect in diabetic nephropathy as investigated through various cell culture, *in vitro* and *in vivo* studies.

Miscellaneous

Tangnaikang: The effect of *Tangnaikang* (TNK) on renal interstitial fibrosis was studied by Yang *et al. in vitro* through transdifferentiation of the human renal tubular epithelial cell line HK-2 induced by TGF-β1. Three groups each containing 10 ng/mL of TGF-β1, and 5%, 10% and 20% TNK serum was investigated for cell proliferation, expression of α-SMA, E-cadherin and contents of collagen I, collagen III, and FN. Decrease in the expression of α-SMA, increased expression of E-cadherin and inhibition of cell proliferation and the secretion of collagen I, collagen III and FN was found [129].

Huangkui capsule: It is a TCM preparation containing total flavones of *Abelmoschus manihot* L. (Malvaceae) as major components. It was investigated by Omara *et al.* for its effectiveness in chronic kidney disease. Improvement in immunological reaction, inflammation, renal fibrosis, and renal tubular epithelial injury was found in male SD rats administered with 0.75 g/kg b.w/day p.o. for ten days [130].

Enicostemma littorale and swertiamarin (**44**): In a study conducted by Lee *et al.*, the aqueous extract of *Eincostemma littorale* Blume. (Gentianaceae) and swertiamarin, an iridoid glucoside were administered to STZ induced male SD rats at a dose of 1 g/kg b.w/day and 50 mg/kg b.w/day p.o. respectively for three weeks. Significant decrease in serum urea and creatinine, and improvement in histology of glomerular function was found [131].

Tocotrienol rich fraction (TRF) from palm oil and rice bran oil: Two fractions of the tocotrienol rich extracts, one each from palm oil and rice bran oil were administered to STZ induced male wistar rats at a dose of 200 mg/kg b.w/day p.o. for eight weeks. Zhang *et al.* found an improvement in renal function through reduction of oxidative stress in both the cases with palm oil fraction being more efficient as compared to the fraction of rice bran oil [132].

Croatian propolis: The effect of Row Croatian propolis was studied by Orsolic *et al.* by administering (50 mg/kg b.w/day i.p.) of the water soluble and ethanolic extracts for seven days in alloxan induced Swiss albino mice. Decrease in number of vacuolized cells and degree of vacuolization, improvement in impairment of fatty acid metabolism was found but no alleviation was exhibited in renal histology. Attenuation in diabetic hepatorenal damage through its antioxidative action and detoxification was also found [133].

Schisandrae chinensis, Rhizoma chuanxiong, Cocha ostreae: Zhang *et al.* studied the ethanol extracts of these preparations from TCM by administration to STZ induced male C57BL/6 mice at a dose of 5 g/kg b.w/day p.o for nine weeks. The expressions of FN, α-SMA and PAI-1 were decreased along inhibition of the epithelial to mesenchymal transdifferentiation, endothelial myofibroblast transition and PAI-1 expression [134].

NATURAL PRODUCTS IN CLINICAL STUDIES AGAINST DIABETIC COMPLICATIONS

Apart from the different *in vitro,* cell culture and *in vivo* studies of different natural products on various diabetic complications, one pure phytochemical, 11 plant extracts and 11 herbal formulations have also been investigated in clinical studies for their protective effects on different diabetic complications which are summarized in Table **5**.

Table 4. Plants and their extracts reported to have protective effect in diabetic nephropathy.

Plant Name (Family)	Plant Parts and Extracts	Study Models	Dose, Duration, Route of Administration/ Concentration	Effects	Ref.
Cassia tora L. (Caesalpiniaceae)	Butanol soluble extracts of seeds	SV40 transformed MES-13 cell line	1-100μM	Inhibition of TGF-β1 and FN by suppressing activation of Smad2/3, (ERK)/ (MAPK), Rubrofusarin-6-O-β-*d*-gentiobioside **(43)** was found to be the active component	[98]
Camellia sinensis var. *assamica* (Mast.) Kitamura. (Theaceae)	Aqueous leaf extract	Madin-Darby canine kidney (MDCK) cells	50 μg/L	Increase in viable MDCK cells concentration, decreased MDA and preservation of glomerulus basement membrane was found using MDA and MTT assays	[99]
		Male C57BL/Ks db/db mice	10% extract in diet		
Camellia sinensis (L.) Kuntze. (Theaceae)	Aqueous leaf extract	STZ induced male spontaneously hypertensive rats	13.3 g/L drinking water for 12 weeks	Suppression of 8-hydroxy-2'-deoxyguanosine and nitrotyrosine, NADPH oxidase-dependent superoxide generation, and the expression of renal cortex Nox4	[100]
Piper auritum Kunth. (Piperaceae)	Hexane extract of leaves	1,1-Diphenyl-2-picryl hydrazyl (DPPH) assay	Stepfall in absorbance detection within 5 minutes	Significant reduction in AGEs formation and elevation in renal glucose and TBARS levels in the kidneys of diabetic rats	[101]
		Oxygen Radical Absorbance Capacity	$ORAC_{ROO+}$ value of 48.3 ± 4.28 μmol TE/g DM		
		Trolox Equivalent Antioxidant Capacity	Inhibition of 50.8%		
		STZ induced male diabetic rats	200 and 400 mg/kg b.w/day p.o. for 28 days		
Tripterygium wilfordii Hook. (Celastraceae)	Multi-glycoside rich extract	STZ induced female SD rats	50 mg/kg b.w/day p.o. for eight weeks	Prevention in glomerular lesions due to decrease in urine albumin and amelioration of glomerulosclerosis	[102]
Cinnamomum zeylanicum Blume. (Lauraceae)	Cinnamon oil extracted from inner bark	Alloxan induced wistar albino rats of either sex	5, 10, 20 mg/kg b.w/day i.p. for 14 days	Reduction in the glomerular expansion, eradication of hyaline casts, and decrease in the tubular dilatations	[103]
Azadirachta indica A. Juss. (Meliaceae)	Ethanolic leaf extract	STZ induced male wistar rats	500 mg/kg b.w/day p.o. for 50 days	Absence of nodular glomerulosclerosis and vacuolation of proximal tubule cells in treated rats	[104]
Portulaca oleracea L. (Portulacaceae)	Aqueous extract of aerial parts	C57BL/KsJ-db/db mice	300 mg/kg b.w/day p.o. for ten weeks	Significant reduction in the expressions of TGF-β1, AGEs, and ICAM-1 and suppression of NF-κB p65	[105]
Angelica acutiloba (Siebold & Zucc.) Kitag. (Apiaceae)	Aqueous ethanolic root extract	STZ induced male wistar rats	50, 100, 200 mg/kg b.w/day p.o. for eight weeks	Amelioration of the diabetic-dependent alterations of glomerular mesangial matrix expansion, decreased expression of NF-κB, TGF-β1 and FN	[106]
Allium sativum L. (Amaryllidaceae)	Aqueous garlic bulb extract	STZ induced male albino wistar rats	500 mg/kg b.w/day p.o. for 12 weeks	Significant decrease in the expression of VEGF and ERK-1	[107]
	Aged garlic extract	STZ induced albino wistar rats	500 mg/kg b.w/day p.o. for 12 weeks	Alleviations in the alterations in the serum and urine constituents like creatinine, urea nitrogen and albumin	[108]
Artemisia campestris L. (Asteraceae)	Aqueous extracts of leaves	Alloxan induced male wistar rats	200 mg/kg b.w/day i.p.for three weeks	Reduction in oxidative and nitrosative stress through modulation of MDA, GSH, CAT and SOD	[109]

(Table 4) contd….

Plant Name (Family)	Plant Parts and Extracts	Study Models	Dose, Duration, Route of Administration/ Concentration	Effects	Ref.
Asparagus racemosus Willd. (Liliaceae)	Ethanolic root extract	STZ induced wistar rats of either sex	100 and 250 mg/kg b.w/day p.o. for four weeks	Attenuation in renal hypertrophy, reduction in basement membrane thickening and mesangial proliferation	[110]
Aegle marmelos (L.) Correa. (Rutaceae)	Ethanolic leaf extract	Alloxan induced wistar albino rats of either sex	10-200 mg/kg b.w/day i.p. for 14 days	Decrease in the renal TBARS, glomerular expansion, tubular dilatation and increase in GSH and CAT	[111]
Glycyrrhizha glabra L. (Fabaceae)	Aqueous ethanol extract of roots	STZ induced male wistar rats	1 g/kg b.w/day p.o. for 60 days	Modulation in renal MDA, GSH, SOD, and CAT but no improvement in histopathological alterations	[112]
Ficus exasperata Vahl. (Moraceae)	Aqueous leaf extract	STZ induced wistar rats	100 mg/kg b.w/day p.o. for four weeks	Amelioration in plasma MDA, tissue NO, serum creatinine, kidney hypertrophy, and carotid blood flow	[113]
Vitis vinifera L. (Vitaceae)	Proanthocyanidin rich seed extract	STZ induced male SD rats	500 mg/kg b.w/day p.o. for six weeks	Significant decrease in LPO and augmentation of the activities of antioxidant enzymes like SOD and CAT	[114]
Zingiber officinalis Roscoe. (Zingiberaceae)	Ethanolic extract of rhizome	STZ induced male wistar albino rats	200 mg/kg b.w/day p.o. for 30 days	Increase in the activities of glucose-6-phosphate, succinate and glutamate dehydrogenases	[115]
Hibiscus sabdariffa L. (Malvaceae)	Methanol extracts of dried flowers	STZ induced male SD rats	100 and 200 mg/kg b.w/day p.o. for eight weeks	Alleviation in hydropic change of renal proximal convoluted tubule, increase in CAT, GSH and TBARS	[116]
Panax quinquefolius L. (Araliaceae)	Alcoholic root extract	STZ induced type 1 and 2 diabetic male C57BL/6 mice	200 mg/kg b.w/day p.o. for two to four months	Reduction in the NF-κB p65 levels, and down regulation of extracellular matrix proteins and vasoactive factors	[117]
Gymnema montanum Hook. (Asclepiadaceae)	Ethanolic leaf extract	Alloxan induced male albino wistar rats	200 mg/kg b.w/day i.g. for three weeks	Modulation of lipid peroxidation markers and antioxidant enzymes SOD, CAT, GSH and GST	[118]
Smallanthus sonchifolius (Poeppig and Endlicher). H. Robinson. (Asteraceae)	10% water decoction of leaves	STZ induced male wistar rats	70 mg/kg b.w/day p.o. for four weeks	Attenuation in kidney hypertrophy and basement membrane thickening mediated through TGF-β1/ Smad 2/3 signaling and reduced expression of collagen IV, laminin-1, FN	[119]
Mesona procumbens Hemsl. (Lamiaceae)	Aqueous leaf extract	STZ induced female SD rats	1.5 g/kg b.w/day i.g. for four weeks	Decrease in TSP-1 expressions in the kidney	[120]
Rosa laevigata Michx. (Rosaceae)	Aqueous extracts of fruits	STZ induced male SD rats	5 g/kg b.w/day i.g. for 24 weeks	Decrease in the MDA through inhibition of NF-κB p65 and MCP-1 and increase in the IκB-α protein	[121]
Psidium guajava L. (Myrtaceae)	Aqueous and ethanol extracts of the fruit	STZ induced male Balb/cA mice	1% and 2% of diet for 12 weeks	Decrease in IL -6, TNF-α and IL-1β levels in kidney, along with renal N (ε)-(carboxymethyl)lysine, pentosidine and suppression of renal AR	[122]
	Total triterpenoid extract	STZ induced diabetic rats	60, 120, and 240 mg/kg b.w/day p.o. for six weeks	Decrease in the levels of BUN, creatinine and improvement in the renal structural damage	[123]

(Table 4) contd….

Plant Name (Family)	Plant Parts and Extracts	Study Models	Dose, Duration, Route of Administration/ Concentration	Effects	Ref.
Schisandra chinensis (Turcz.) Baill. (Schisandraceae)	95% ethanolic fruit extract	STZ-induced male C57BL/6 mice	5 g/kg b.w/day p.o. for seven weeks	Decrease in the urine albumin excretion rate (UAER) and urinary albumin to creatinine ratio (UACR) and attenuation of glomerulosclerosis	[124]
Salvia miltiorrhiza Bunge. (Lamiaceae)	Aqueous extract	STZ induced male SD rats	500 mg/kg b.w/day p.o. for eight weeks	Significant reduction in serum and kidney levels of TGF-β1 and the kidney levels of collagen IV	[125]
Carum carvi L. (Apiaceae)	Aqueous extract of the seeds	STZ induced male wistar rats	30 and 60 mg/kg b.w/day p.o. for 60 days	Decreased serum levels of urea, creatinine, total urinary protein due to flavonoids and carvone	[126]
Acacia nilotica L. P.J.H.Hurter & Mabb. (Fabaceae)	Aqueous methanol extract of pods	STZ induced male SD rats	150 and 300 mg/kg b.w/day p.o. for 60 days	Attenuation in infiltration of the lymphocytes in the interstitial spaces, glomerular hypertrophy, basement membrane thickening and tubular necrosis	[127]
Trigonella foenum graecum L. (Fabaceae)	Aqueous seed extract	STZ induced male SD rats	440, 870, and 1740 mg/kg b.w/day i.g. for six weeks	Decrease in kidney/body weight ratio and MDA, increase in 8-hydroxy-2'-deoxyguanosine in urine and renal cortex DNA.	[128]

Table 5. Summary of different formulations, Plant extracts and pure phytochemicals investigated in clinical studies for their effects in diabetic complications.

Formulation/Extracts/Pure Compounds	Study Model and Treatment Period	Effects	Ref.
Meriva (Lecithinized curcumin delivery system)	38 diabetic patients treated with 2 tablets/day [each tablet containing 100 mg curcumin] for a period of four weeks	Protective effect in diabetic retinopathy and microangiopathy through improvements in the retinal flow and retinal oedema (Steigerwalt's scale) and visual acuity (Snellen scale), and significant improvement in the venoarteriolar response	[135]
Qiming granule (Chinese medicine complex prescription consisting of principle components extracted from *Radix Astragali, Radix Puerariae, Radix Rehmanniae* and *Fructus Lycii*	A multi-center, randomized, parallel controlled clinical trial on diabetic patients orally administered with 4.5 g of the capsule, thrice a day for three months	Protective effect in diabetic retinopathy through significant reduction in the retinal arterio-venous circulation time from 7.635 ± 3.149 seconds to 5.165 ± 3.382 seconds and reduction in the arm-to-retinal circulation time from 17.867 ± 3.872 seconds to15.643 ± 4.648 seconds	[136]
Hydrophilic extract of roots of *Salvia miltiorrhiza* Bunge. (Labiatae)	Diabetic patients with Chronic Heart Disease (CHD) treated with 5 g twice a day for 60 days	Reduction in the levels of sVCAM-1 and vWF in serum; and reduction in MDA level at day 30 in the treatment group, increase in the activities of GSH, SOD and Paraoxonase	[137, 138]
Sour tea infusion from *Hibiscus sabdariffa* L. (Malvaceae)	Double-blind randomized controlled trial on 60 diabetic patients treated with two glasses/day for one month	Significant decrease in systolic and diastolic BPs	[139]
	100 mild hypertensive diabetic patients with three glasses/day for four weeks		[140]
Green tea infusion from the leaves of *Camellia sinensis* L. (Theaceae)	100 mild hypertensive diabetic patients treated with three glasses/day for four weeks	Significant decrease in systolic and diastolic BPs	[140]

(Table 5) contd….

Formulation/Extracts/Pure Compounds	Study Model and Treatment Period	Effects	Ref.
Panax quinquefolius L. (Araliaceae)	Randomized, double-blind, parallel design on 64 subjects treated with 3 g/day for 12 weeks as an adjunct	Reduction in Augmentation index and systolic BP by 5.3% and 11.7% respectively	[141]
Raw fruits of *Solanum lycopersicum* L. (Solanaceae)	32 type 2 diabetic patients treated with 200 g/day for eight weeks	Significant decrease in systolic and diastolic BPs and significant increase in apolipoprotein A-1	[142]
Vitis vinifera L. (Vitaceae)	32 type 2 diabetes patients in double-blinded randomized crossover trial treated with 600 mg/day for four weeks	Protective in cardiovascular disease through significant changes in fructosamine (282 ± 40.9 vs. 273 ± 50.2 mmol/L) and CRP (3.2 ± 3.65 vs. 2.0 ± 2.2 mg/L)	[143]
Danzhijiangtang capsule	62 type 2 diabetes mellitus patients identified with subclinical vascular lesions. randomly divided into a control group and treatment group, administered with 15 capsules/day (each capsule contains 1.8 g of the extract) or placebo for 12 weeks	Significant improvement in fasting insulin, insulin resistance index, HbA1c, blood lipids and hemorheology indices and reduction in thrombomodulin, vWF, P-selectin and MCP-1 mRNA levels	[144]
Compound Danshen Dripping Pill (CDDP)	108 patients with type 2 diabetes mellitus randomized into 3 groups and administered orally with aspirin (0.1 g, once daily), vitamin E (0.1 g, twice daily) and CDDP (10 pills, thrice daily) for 18 months	Protective in diabetic cardiovascular disease through decrease in the levels of HbA1c, serum total cholesterol and low density lipoprotein cholesterol (LDL-C) and lesser increment of carotid and femoral arterial intima-media thickness	[145]
Shuxuetong injection	260 type 2 diabetes mellitus patients with lower extremity atherosclerotic obliterans divided randomly into 2 groups and treated for four weeks	Significant increase in the inner diameter and blood flow of all the arteries	[146]
Ligustrazine ***(40)*** and *citicoline* (An intermediate in the biosynthesis of phosphatidyl choline in humans and animals)	Double-centered randomized controlled trial on 300 patients randomly assigned to 3 groups treated with combination (group A), ligustrazine (group B) and citicoline (group C) for four weeks	Symptomatic integral at the end of 3 month follow up in group A was better than in the other two groups with values of 6.39 ± 2.04 vs 8.36 ± 1.17 and 8.05 ± 1.34 respectively	[147]
Seed extract of *Myristica fragrans* Gronov. (Myristicaceae)	Double blind, controlled study on 74 diabetic subjects treated with topical application for four weeks	Protective in diabetic neuropathy through significant reduction in pain scores, sleep and mood scores, burning, pins, needles and tingling scores	[148]
Sativex (*Cannabis* based medicinal extract)	Randomized controlled trial with 38 diabetic neuropathic patients treated sub-lingually through pump action spray for four times a day	Significant improvement in pain scores in both the groups was determined, but no significant mean change between groups	[149]
Naoxintong and mecobalamin	180 patients with diabetic neuropathy classified as five syndrome types treated with Naoxintong (Group A), mecobalamin (Group B), and Naoxintong + mecobalamin (Group C) for four weeks	Reduction of MNCV, prolongation of F-wave latency and skin sympathetic reflex latency along with improvement in nerve electrophysiological index and the diameter of *arteriae tibialis* anterior	[150]
Neuragen PN (FDA registered homeopathic topical oil consisting of *Hypericum perforatum* L., *Aconitum napellus* L., *Lycopodium clavatum* L., Phosphorus, *Rhus toxicodendron* and *Secale cornutum*)	Double blind, randomized, placebo controlled study by taking 60 participants with plantar cutaneous (foot sole) pain	Significant pain reduction within 30 minutes was found without any adverse effects	[151]
Salacia chinensis L. (Celastraceae)	30 diabetic patients with chronic kidney disease treated with 1000 mg dose twice a day	Stabilization of renal function through alleviation of serum creatinine and creatinine clearance. Significant decline in serum homocysteine and IL-6 levels	[152]

(Table 5) contd….

Formulation/Extracts/Pure Compounds	Study Model and Treatment Period	Effects	Ref.
Dioscorea bulbifera L. (Dioscoreaceae)	Single-center open-label randomized study for six months on 137 patients with diabetic nephropathy divided into Group A (n = 46) on fosinopril (5-40 mg/day), Group B (n = 45) on *Dioscorea bulbifera* (500 mg/day) and Group C (n = 46) on placebo	Significant decrease in the systolic and diastolic BPs, LDL, serum TGF-β, IL-6 and CRP	[153]
Leaf extract of *Gingko biloba* L. (Gingloaceae)	Randomized study on 64 diabetic nephropathy patients treated with three tablets/day for eight weeks (Each tablet contains 19.2 mg of flavonol glycoside and 4.8 mg of terpene lactone)	Increase in the brachial arterial endothelium dependent dilating function in the treated group from 4.91 ± 2.31% to 6.78 ± 3.89%, decrease in the level of vWF from 182.05 ± 64.13% to 128.56 ± 48.98%	[154]
Huang Qi elixir	Three groups of diabetic human subjects (n=36) treated with 10 g, 20 g or decoction thrice daily for 12 weeks	Positive effect on Proteinuria	[155]
Shenyan Kangfu tablet (A formulation of Chinese herbal tea)	Double-blind, randomized controlled trial on 80 participants with two groups; SYKFT plus irbesartan and placebo plus irbesartan, treated with two courses of medication each lasting eight weeks	Amelioration in the quantitative 24-hr urinary protein level, UAER and UACR	[156]
Qi supplementing, Yin nourishing, Blood stasis dispersing, Collateral dredging recipe(QYBCR)	Random study on 78 nephropathic patients divided into two groups (one treated with QYBCR and other, Irbesartan)	Decrease in the levels of UAER, Creatinine and BUN from [161.03 ± 20.01 μg/min, 101.11 ± 14.33 μmol/L, 6.54 ± 1.12 mmol/L] to [65.78 ± 9.67 μg/min, 93.20 ± 12.99 μmol/L, 5.69 ± 1.21 mmol/L]	[157]
Bailing capsule	Randomized trial on 60 patients with early diabetic nephropathy for 16 weeks	Decrease in levels of 24h urinary protein, UAER, CRP from 0.87 ± 0.31 g/24h, 81.59 ± 35.69μg/min, 2.55 ± 1.66 mg/L to 0.25 ± 0.29g/24h, 57.32 ± 31.11μg/min, 0.49 ± 0.38 mg/L	[158]

CONCLUSION

In this review, recent discoveries on utilization of natural products for treatment of diabetic complications from 2008–2014 have been discussed with 158 references which include *in vitro,* cell culture, *in vivo* and clinical studies. In total 44 pure phytochemicals, 61 plants and around 20 traditional medicinal formulations have been explored for their potential against diabetic complications. Extracts of three plants namely *Salvia miltiorrhiza*, *Panax quinquefolius*, and *Vitis vinifera* were found to be effective in treating diabetic nephropathy, cardiomyopathy and retinopathy, respectively. EGCG was the only compound reported to be effective in three diabetic complications (retinopathy, cardiomyopathy and neuropathy). Thus it proves the potential of natural products in treatment of diabetic complications. However there is an urgent need to further investigate EGCG for its potential to develop it into clinical drug against diabetic complications. Also there is need for isolation and characterization of the active extracts to identify the bioactive phytochemicals. Such phytochemicals may act as possible leads to develop new drugs that may be used singly or in combination therapy for treating diabetic complications.

Natural products have been widely used for the treatment of diabetes and its complications in folk medicine/traditional system of medicines. However the major hurdle in popularization and commercialization of this class of therapeutics has been often ascribed to geographical and seasonal variations. Another reason for decline in popularizations of natural products has been the scarcity of authoritative clinical data related to the effectiveness in improving diabetic complications. At times the observed clinical activity has also been ascribed to group of phytochemicals displaying synergy. Hence it is important to answer these questions to popularize this therapeutics. Defined clinical studies coupled with state of art analytical experiments for assuring the quality product are the need of the hr. With high public interest in usage of natural product based therapeutics for diabetes and related complications it is important to explore the potential of this therapeutics. Thus the present review highlights the potential of natural products for treatment of diabetic complications and also urges the natural product and analytical chemists to solve the enigma of natural products with the help of modern technology.

ABBREVIATIONS

α-SMA = α-Smooth muscle actin

ACE = Angiotensin converting enzyme

AGEs = Advanced Glycation End products

AR = Aldose reductase

ARPE-19 = Arising retinal pigment epithelial
BP = Blood pressure
BUN = Blood urea nitrogen
CAT = Catalase
COX-2 = Cyclooxygenase-2
CRP = C-reactive protein
EGCG = Epigallocatechin-3-gallate
eNOS = Endothelial nitric oxide synthase
EPO = Evening primrose oil
ERK = Extracellular signal-regulated kinase
FN = Fibronectin
FOXO = Forkhead box O
GSH = Reduced glutathione
GSSG = Oxidized glutathione
GST = Glutathione-S-transferase
HbA1c = Hemoglobin A1c
HK-2 = Proximal tubule epithelial cell line
ICAM = Intercellular adhesion molecule
iNOS = Inducible nitric oxide synthase
JNK = c-Jun-N-terminal kinase
ILs = Interleukins
LADA = Latent Autoimmune Diabetes in Adults
LPO = Lipid peroxide
MAPK = Mitogen activated protein kinase
MDA = Malondialdehyde
MNCV = Motor nerve conducting velocity
NF-kB = Nuclear factor kappa B
Nox-4 = NADPH oxidase 4
SOD = Superoxide dismutase
PAI-1 = Plasminogen activator inhibitor-1
PKC = Protein kinase C
PPAR γ = Peroxisome proliferator activated receptor
RLAR = Rat lens aldose reductase
SD = Sprague-Dawley
SGLT = Sodium-glucose symporters
SGLT1 = Sodium-glucose co-transporter 1
SGLT2 = Sodium-glucose co-transporter 2
STZ = Streptozotocin
TBARS = Thiobarbituri acid reactive substances
TCM = Traditional Chinese Medicine
TGF = Transforming growth factor
TNF = Tumour necrosis factor
TRB = Tribbles homolog
TRF = Tocotrienol rich fraction
TSP = Thrombospondin
TXB_2 = Thromboxane B_2
UACR = Urinary albumin to creatinine ratio
UAER = Urine albumin excretion rate
vCAM = Vascular cell adhesion molecule
VEGF = Vascular Endothelial Growth Factor
VSMC = Vascular smooth muscle cells
vWF = Von Willebrand factor

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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PATIENT'S CONSENT

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