REVIEW ARTICLE

Antioxidant plants and diabetes mellitus

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The incidence of diabetes mellitus (DM) is increasing rapidly and it is expected to increase by 2030. Other than currently available therapeutic options, there are a lot of herbal medicines, which have been recommended for its treatment. Herbal medicines have long been used for the treatment of DM because of the advantage usually having no or less side-effects. Most of these plants have antioxidant activities and hence, prevent or treat hard curable diseases, other than having the property of combating the toxicity of toxic or other drugs. In this review other than presenting new findings of DM, the plants, which are used and have been evaluated scientifically for the treatment of DM are introduced.

Key words: Diabetes mellitus, herbal drugs, diabetic nephropathy

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INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic disorders in which the blood sugar is higher than normal level either because the production of insulin is not enough (type 1 DM) or the cells do not properly respond to the insulin (type 2 DM).[1]

According to a report from World Health Organization, about 220 million people have type 2 DM. Its incidence is increasing rapidly, and it is expected to increase to more than 365 million by 2030.[2] DM occurs throughout the world. However, it is more common in the more developed countries. It is noteworthy that the highest increase in prevalence is expected to occur in Africa and Asia.[3] The increase in incidence in developing countries follows the trend of urbanization and lifestyle changes, perhaps most importantly a "Western-style" diets.[3]

Other than currently available therapeutic options, there are a lot of herbal medicines, which have been recommended for the treatment of DM,[4,5] hyperlipidemia[4-7] and other cardiovascular risk factors.[4-9]

Herbal medicines have long been used for the treatment of DM. This is because such herbal plants have hypoglycemic properties and other beneficial effects. Herbal medicines have the advantage of usually having no or less side-effects.[10,11] Most of these plant have antioxidant activities[12,13] and hence, prevent or treat hard curable diseases, other than having the property of combating the toxicity of toxic[14,15] or other drugs.[16-19] In this review other than presenting new findings of DM the plants which are used for the treatment of DM are introduced.

DIFFERENT FORMS OF DIABETES MELLITUS

There are several types of DM, three main types of them are type 1, type 2 and gestational diabetes. Type 1 diabetes mellitus "juvenile diabetes or insulin-dependent diabetes mellitus" results from the pancreas failure to produce insulin, and requires the patients to use insulin. Type 2 DM "adult-onset diabetes or noninsulin-dependent diabetes mellitus results from insulin resistance, a condition in which cells cannot use insulin properly. Gestational diabetes occurs when pregnant women develop a high blood glucose level without a previous diagnosis of diabetes. This kind of diabetes may precede the development of type 2 DM. Other forms of DM include steroid diabetes induced by high doses of glucocorticoids, congenital diabetes, which is due to genetic defects of insulin secretion, cystic fibrosis-related diabetes, and several forms of monogenic diabetes.[1-7]

DIABETES MELLITUS COMPLICATIONS

The patients with DM are at increased risk of complications such as peripheral vascular disease, retinopathy, nephropathy, neuropathy, coronary heart

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disease. The exact causes of type 2 diabetes are still need to be clear.[1-7] DM increases the risk of complications, which may develop after 10-20 years, however, may be the first symptom in patients who have not diagnosed before that time. The major long-term complications are related to damage to blood vessels. DM approximately doubles the risk of cardiovascular diseases. The main "macro-vascular" diseases are peripheral vascular disease, angina, myocardial infarction and stroke.[1-7,20]

Diabetes mellitus damages the capillaries causing micro-angiopathy. Diabetic retinopathy, which affects blood vessel in the eye retina, causes visual symptoms including reduced vision and blindness.[21-23] Diabetic nephropathy usually leads to changes in the kidney tissue, loss of progressively larger amounts of protein in the urine and chronic kidney disease.[21-24]

Diabetic neuropathy commonly causes tingling, numbness and pain in the feet. It also increases the risk of skin damage due to altered sensation. Vascular complications in the legs contribute to the risk of diabetes-related foot problems such as diabetic foot ulcers that might be difficult to treat and occasionally require amputation.[5,21-24]

Compared to the subjects without diabetes, those with the disease have about 1.5-fold greater rate of deficit in cognitive function, and herbal medicines with hypoglycemic activities have been shown to counteract this complication.[21-26]

DIABETES MELLITUS PATHOGENESIS

The cause of diabetes depends on the type of DM. Type 1 is, at least in part, inherited. It may also be triggered by certain toxins or infections. In patients susceptibility to some of these triggers a genetic element has been traced to particular HLA genotypes. However, even in patients genetically susceptible, type 1 DM usually requires an environmental trigger. In contrast to type 1 DM in which its onset is unrelated to lifestyle, type 2 DM is primarily due to lifestyle factors other than genetics. The most important lifestyle factors, which are known to be involved in the development of type 2 DM include: Urbanization, poor diet, lack of physical activity, stress, and obesity or body mass index of >30.[1-4]

Dietary factors also seem to have influence on development of type 2 DM. Consumption of drinks sweetened in excess increases the risk of type 2 DM. Trans fatty acids and saturated fats also increase the risk. In contrast monounsaturated and polyunsaturated fat decrease the risk.[1,5,27,28] Lack of exercise dramatically increases the risk of cases.[1,5,27,28]

DIABETES MELLITUS MANAGEMENT

There is no known cure for DM except in very specific situations. Management of DM concentrates mostly on keeping blood sugar to normal levels as possible, which is usually accomplished with exercise, diet, and use of appropriate medications.[1,5,27,28]

The complications of diabetes are less common and less severe in patients who have well-managed blood sugar levels. Therefore, patient participation is vital. The goal of treatment is keeping an HbA1C level of 6.5%, however, it should not be less than that.[1,5,27-29] Attention should also be paid to other factors which may accelerate the deleterious effects of diabetes, including elevated cholesterol level, obesity, high blood pressure, smoking, and lack of regular exercise.[27-29]

Several lines of medications are used in the treatment of MD [Table 1]. The current used therapies for type-2 DM include sulfonylureas, biguanides, inhibitors of a-glucosidase, thiazolidinediones, and inhibitors of dipeptidyl peptidase-4. Metformin is generally used as first line treatment for type 2 DM, as it has shown to decrease mortality rate.[30] When blood sugar is very high and insulin is used in type 2 diabetes, usually a long-acting drug is added initially, while continuing oral medications Type 1 DM is typically treated with synthetic insulin and usually a combination of regular and NPH insulin.[30]

Table 1: Oral anti-diabetic drugs currently available for the treatment of diabetes mellitus

Drug group	Mechanism	Example	Side effects
Sulfonylureas/insulinotropics	Inhibiting of KATP channels and increase in insulin release	Glibenclamide, Glipizide, Chlorpropamide, Tolbutamide	Hypoglycemia, Weight gain
Biguanides	Increase in insulin sensitivity and reduce hepatic glucose production	a-Glucosidase inhibitors Inhibition of carbohydrate digestion and absorption	Thiazolidinediones Activation of peroxisome proliferator-activated receptor gamma and improvement of insulin action
Metformin	Diarrhea, nausea, abdominal pain, Lactic acidosis	Metallic taste Acarbose Rosiglitazone	Ddiarrhea, abdominal cramping, flatulence Hepatoxicity
DPP-4 inhibitors (Gliptins)	Inhibition of DPP-4 and reduction of glucagon and blood glucose	Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin	Nasopharyngitis, Headache, Nausea, Hypersensitivity, Skin reaction

The available synthetic drugs for the treatment of DM mostly are expensive and produce serious side effects [Table 1]. Hence, safer and more effective anti-diabetic drugs are urgently needed. Nowadays medicinal plants with antioxidant activity have been on the focus of the researchers for their hypoglycemic activities[31] or for reduction of the side-effects of hypoglycemic drugs.[31-33]

ANTIOXIDANT AND OTHER THERAPIES

As the pathogenesis of DM involves oxidative stress, antioxidant therapies should have a potential value in its treatment. Many trials in animal models of diabetes and diabetic patients have attempted to determine the role of antioxidant therapy on prevention or treatment of diabetes complications.[32-34]

Furthermore, significant increase in endogenous prooxidant activity and decrease in antioxidants has been shown to contribute to the oxidative stress in diabetes. A marked decrease in glutathione peroxidase (GSHPx) and superoxide dismutase (SOD) activities have been reported in diabetic animals.[30-34] Treatment with probucol, which has antioxidant activity resulted in a significant improvement in myocardial activities of catalase, SOD and GSHPx (antioxidant enzymes) providing evidence that diabetic cardiomyopathy was associated with an antioxidant deficit.[30-35] Overexpression of catalase in STZ-treated transgenic mice attenuated the onset of diabetic complications, indicating the therapeutic potential of catalase.[32-36]

Several pharmacologic agents effective in reducing diabetic mortalities have been shown to have antioxidant activities. For example, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, angiotensin-converting enzyme (ACE) inhibitors or statins have beneficial effects on diabetic patients[30-37] that may involve antioxidant effects. Interestingly, ACE inhibitors, which act partially to prevent the prooxidant effects of angiotensin II, were shown to prevent the onset of type 2 diabetes.[32-38] Vitamin E supplementation has been associated with a significant decline in protein oxidation, lipid peroxidation and enhancement in the antioxidant defense system. Vitamin E may promote beneficial effects on diabetic complications through the attenuation of oxidative stress.[35-39]

Peroxynitrite and other reactive species can also induce oxidative DNA damage. Inhibitors of specific components of ROS-sensitive signaling cascades such as CGP53353 and ruboxistaurin, which are specific inhibitors of protein kinase C, are able to attenuate hyperglycemia-induced vascular cell adhesion molecule-1 expression and nuclear factor-kappa-B activation in human aortic endothelial cells.[30-40]

Coenzyme Q10, a lipid-soluble antioxidant, has been shown to scavenge superoxide and improve endothelial function in diabetes. Caffeic acid phenethyl ester (CAPE), a flavonoid-like compound, has an ameliorating effect on oxidative stress in cardiac tissue via its antioxidant property, indicating that CAPE should be considered for preventing oxidative stress in the diabetic heart.[36-41]

Medicinal plants with antioxidant activities have also been shown to be protective in diabetic rats by scavenging oxygen free radicals and decreasing the expressions of intercellular cell adhesion molecule-1 protein.[35-42]

CLINICAL PERSPECTIVES OF ANTIOXIDANT THERAPY

Despite several experimental studies suggesting beneficial effects antioxidants in reduction of diabetes complications, results from clinical trials on beneficial effects of traditional antioxidants such as Vitamin E or C have been disappointing.[40-43] A meta-analysis of clinical trials, studying Vitamin E therapy suggests that the use of high-dose Vitamin E (greater than 400 IU/day) may actually increase mortality ;[41-44] however, this finding has been questioned.[42-45] Zinc and melatonin in combination with a regularly used metformin have been shown to significantly reduce fasting glucose and glycated hemoglobin levels in patients with type 2 diabetes.[43-46] However, not all studies supported this notion. Several studies indicated no improvement in the glucose metabolism in either type 1 or type 2 diabetic patients after zinc treatment.[44-47]

These contradictory results may have emerged from a variety of factors, such as patient diversity and zinc speciation.

Although initial studies have suggested that antioxidant supplementation might promote health, however, large clinical trials declared no benefit and even suggested that excess supplementation with certain antioxidants might be harmful.[40-48] From the literature review it might be concluded that supplementation with single antioxidant may not be beneficial, but the diets high in antioxidants (fruits and vegetables) are nearly always useful. The possible explanation is that, in fruits and vegetables there are mixture of antioxidants and it is well recognized that they work as a continuous chain, while supplementation is usually given using one or two substances. Therefore, the antioxidant chain is not completely available.[40-48] In this situation, after scavenging free radicals, if an antioxidant is not restored by the following suitable antioxidant

in the chain, it begins to be a pro-oxidant. Hence, the final effect of such supplementations would be no effect or damaging.[40-49] Therefore, in antioxidant therapy complimentary antioxidants cannot always substitute the fruits and vegetables high in antioxidants. However, consumption of vegetable and fruits as well as medicinal plants with high antioxidant content is recommended.[40-50]

MEDICINAL PLANTS WITH ANTI-DIABETIC ACTIVITIES

The results of the studies suggest a trend towards the benefit of consuming vegetables and fruits consumption in DM.[48-51] Several studies examining dietary patterns and incidence of type 2 diabetes have also shown that vegetables and fruits are important components of the dietary patterns associated with a decreased risk of type 2 diabetes.[48-52]

A possible benefit of vegetables and fruit is from their antioxidant components and thus a contribution to reduction of systemic oxidative stress.[50-53] Vegetables and fruits have been shown to contain high concentrations of antioxidants, which might reduce the risk of diabetes especially type 2 DM. Vegetables and fruits are also good sources of α linolenic acid, an omega 3 polyunsaturated fatty acid.[49-54]

Medicinal plants also have played an important role in the management of DM, worldwide [Table 2]. Medicinal plants have a long history in the treatment of diseases. In traditional medicine, about 800 plants are used for the treatment of DM.[50-55]

With rapid advancement of technologies and the increase in research on anti-diabetic plants, many new herbs and their active principles have been discovered which may lead us to develop novel anti-diabetic agents to supplement the current chemotherapies. Jung *et al*. (2006) reviewed the hypoglycemic effects of several plants with anti-diabetic properties, as well as the plants by-products discovered during 2001-2005 having anti-diabetic actions.[55-57] In this paper, the newly identified anti-diabetic plants (2005-2013) are summarized in Table 2, in which the reliable hypoglycemic plants are included. Although in many cases these agents have the same mechanism as synthetic agents act, however, some of them may act with a different way. These probable mechanisms should be evaluated when searching new agents and their mechanisms of actions.

DISCUSSION AND CONCLUSION

Medicinal plants have a long history in the treatment of diseases including DM.[50-55] The beneficial effects of medicinal plants in DM have been confirmed in several studies.

In this paper, the newly identified anti-diabetic plants (2005-2013) were summarized in Table 2. Although in many cases the mechanism actions of these agents were presented and it was shown that they may have the same mechanism as synthetic agents act, however, the exact mechanism action of these drugs are poorly established. Hence, more works are needed to realize the exact mechanisms of these plants.

A possible mechanism and benefit of medicinal plants is from their antioxidant activities. Most of medicinal plants with anti-diabetic property possess antioxidant activity.[50-53] In this regards, it has been confirmed that vegetables and fruits, in comparison to synthetic antioxidants, are more effective and are able to decrease the risk of DM.[48-52]

It has been shown that under stressful conditions free radicals are over-produced, inducing oxidative stress. Oxidative stress occurs when there is an imbalance between free radical formation and antioxidant defense capacity.[139-143] This oxidative stress usually causes or exacerbates chronic hard curable diseases such as diabetes,[144-148] hypertension,[149,150] cardiovascular[151-153] cancer,[154-156] cognitive diseases,[157-160] and pain[161-165] or exacerbation of some other diseases like infectious disorders.[166-172]

Although, in some cases, synthetic antioxidants have also been effective in reduction of DM, however, in contrast to natural antioxidants, synthetic antioxidants usually produce side effects such as toxicity. Hence, preparation of natural products with antioxidant activities with property to prevent and treat free radical-associated diseases is essential.[172-174] Other than the plants which were introduced here, a lot of other plants have antioxidant activities.[175-181]

These plants have drawn much attraction because they have protective or curative properties against most of hard curable diseases such as cognitive deficit, memory impairment, cancer, and cardiovascular diseases which have been attributed to their antioxidant activities.[182-190] Therefore, they also might be effective on DM.

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Table 2: Anti-diabetic plants

Plant species	Family	Animal model	Solvent	Positive control	Reference
Aegle marmelos, *Artocarpus heterophyllus*, *Vangueria madagascariensis*, *Azadirachta indica*, *Eriobotrya japonica*, *Syzigium cumini*	Poaceae, Rutaceae, Moraceae, Rubiaceae, Meliaceae, Rosaceae	*In vitro*: a-amylase inhibition	Water	Glibenclamide (5 mg/kg)	[58]
African black tea, *Camellia sinensis*	Theaceae	Male KK-AY/TaJcl mice (p.o.)	Hot water	–	[59]
Amaranthus spinosus	Amaranthaceae	STZ rats (p.o.)	Methanol	Glibenclamide (5 mg/kg)	[60]
Angelica hirsutiflora	Umbelliferae	High-fat diet-induced diabetic mice (p.o.)	Methanol	Glibenclamide (10 mg/kg bw)	[61]
Annona squamosal	Annonaceae	STZ rats (p.o.)	Water	Insulin (6 unit kg^{-1})	[62]
Artemisia princeps, Pampanini sajabalssuk	Asteraceae	C57BL/KsJ-db/db mice (p.o.)	Ethanol	Rosiglitazone (0.005/100 g diet)	[63]
Begonia malabarica	Begoniaceae	STZ rats (p.o.)	Methanol	Glibenclamide (5 mg/kg)	[64]
Butea monosperma	Papilionaceae	ALX rats (p.o.)	Water and methanol extracts	Glibenclamide (0.4 mg/kg)	[65]
Caralluma sinaica	Asclepiadaceae	STZ rabbits (p.o.)	Aqueous	Glibenclamide (5 mg/kg bw)	[66]
Caralluma sinaica	Asclepiadaceae	STZ rabbits (p.o.)	Ethanol	Glibenclamide (5 mg/kg)	[67]
Cecropia pachystachya	Cecropiaceae	ALX rats (p.o.)	Methanol extract	Metformin (120 mg/kg), glibenclamide (3 mg/kg)	[68]
Cecropia pachystachya	Cecropiaceae	ALX rats (p.o.)	Methanol	Metformin (120 mg/kg), glibenclamide (3 mg/kg)	[68]
Cichorium intybus	Compositae	STZ rats (p.o.)	80% ethanol	Metformin (500 mg/kg)	[69]
Cinnamomi cassia	Lauraceae	C57BIKsj db/db mice (p.o.)	Water extract containing 5% cinnamonaldehyde	–	[70]
Cinnamomum parthenoxylon	Lauraceae	STZ rats (p.o.)	Polyphenolic oligomer-rich	Glymepiride (5 mg/kg bw)	[71]
Cleistocalyx operculatus *Eugenia operculata*	Myrtaceae	*In vitro*, a-glucosidase; *in vivo*, STZ rats (p.o.)	Aqueous	Acarbose (25 mgkg); guava leaf extract (500 mg/kg)	[72]
Clerodendrum capitatum	Verbenaceae	Normal rats (p.o.)	Aqueous	–	[73]
Cornus mas L.	Cornaceae	STZ rats (i.p.)	70% ethanol	Glibenclamide (5 mg/kg)	[74]
Cucurbita pepo	Cucurbitaceae	STZ rats (i.p)	70% ethanol	Glybenclamide (150 mg/kg)	[75]
Cymbopogon citratus	Graminaceae	Normal Wistar rats (p.o.)	Aqueous	–	[76]
Cyperus rotundus	Cyperaceae	ALX rats (p.o.)	70% ethanol	Metformin (450 mg/kg)	[77]
Diospyros peregrine	Ebenaceae	STZ rats (p.o.)	Methanol	Glibenclamide (1 mg/kg bw)	[78]
Dryopteris fragrans	Aspidiaceae	STZ rats (p.o.)	Aqueous	–	[79]
Eriobotrya Japonica	Rosaceae	ALX rats (p.o.)	70% ethanol extract	Phenformin (100 mg/kg)	[80]
Eugenia jambolana	Myrtaceae	ALX rabbit (p.o.)	Water; ethanol	Tolbutamide (250 mg/kg, bw)	[81]
Garuga pinnata	Burseraceae	STZ rats (p.o.)	Water	Glibenclamide (0.25 mg/kg)	[82]
Genista tenera	Fabaceae	STZ rats (p.o.)	n-butanol	Glibenclamide (0.5 mg/kg bw)	[83]
Heinsia crinata	Rubiaceae	ALX rats (p.o.)	Ethanol	Glibenclamide (10 mg/kg)	[84]
Helichrysum graveolens	Asteraceae	STZ rats (p.o.)	Aqueous, ethanol	Tolbutamide (100 mg/kg)	[85]
Helichrysum plicatum	Asteraceae	STZ rats (p.o.)	Aqueous, ethanol	Tolbutamide (100 mg/kg)	[86]
Helicteres isora	Sterculiaceae	STZ rat (p.o.)	Water	Tolbutamide (250 mg/kg)	[87]
Heliotropium zeylanicum	Boraginaceae	STZ rats (p.o.)	Methanol; chloroform	Tolbutamide (10 mg/kg)	[88]
Hemionitis arifolia	Hemionitidaceae	ALX rats (p.o.)	Ethanol extract, subsequently ethyl acetate fraction	Insulin (5 IU/kg, i.p.)	[89]
Hibiscus rosasinensis	Malvaceae	ALX rats (p.o.)	Ethanol	Glibenclamide (10 mg/kg)	[90]

(Continued)

Table 2: (Continued)

Plant species	Family	Animal model	Solvent	Positive control	Reference
Hunteria umbellata	Apocynaceae	ALX and high fructose induced hyperglycemic rats (p.o.)	Aqueous	Glibencalmide (1 mg/kg)	[91]
Hypoxis hemerocallidea	Hypoxidaceae	STZ rats (p.o.)	Water	Chlorpropamide (250 mg/kg p.o.)	[92]
Ichnocarpus frutescence	Apocynaceae	Normal rats, glucose-fed rats, STZ rats (p.o.)	Methanol and n-hexane extracts	Glibenclamide (0.6 mg/kg)	[93]
Indian water lily, *Nymphaea stellate*	Nymphaeaceae	ALX rats (p.o.)	Ethanol	Glibenclamide (2 g/kg)	[94]
Indigofera mysorensis	Fabaceae	C57BL/KsJ-db/db mice (p.o.)	Ethanol	Rosiglitazone (0.005/ 100 g diet)	[95]
Juglans regia	Juglandaceae	ALX rats (i.p.)	Ethanol	Glibenclamide (0.6 mg/kg)	[96]
Juniperus chinensis	Cupressaceae	ALX rats (p.o.)	Aqueous and ethanol	Glibenclamide (0.2 mg/kg)	[97]
Kalanchoe crenata	Crassulaceae	High calories sucrose diet (p.o.)	Hydroalcohol	Glibenclamide (10 mg/kg)	[98]
Laportea ovalifolia (Scham and Thonn)	Urticaceae	ALX rat (p.o.)	Methanol methylene chloride (1:1)	Tolbutamide (80 mg/kg)	[99]
Leucas cephalotes	Lamiaceae	ALX rats (IDDM) STZ rats (NIDDM) (p.o.)	Ethanol	Glibenclamide (600 mg/kg), metformin (500 mg/kg)	[100]
Leucas cephalotes	Lamiaceae	ALX rats (IDDM), STZ rats (NIDDM) (p.o.)	Ethanol	Metformin (500 mg/kg), glibenclamide (600 mg/kg)	[100]
Liriope spicata	Liliaceae	STZ mice (p.o.)	Water, crude polysaccharide fraction	Rosiglitazone (2 mg/kg)	[101]
Matricaria chamomilla	Asteraceae	STZ rats (p.o.)	Ethanol	Glibenclamide (5 mg/kg)	[102]
Mucuna pruriens	Fabaceae	STZ rats (p.o.)	Water	Tolbutamide (250 mg/kg)	[103]
Murraya koenigii, *Mentha piperitae*, *Ocimum sanctum*, *Aegle marmelos*	Rutaceae, Lamiaceae, Lamiaceae, Rutaceae	STZ rats (p.o.)	Ethanol extract	–	[104]
Musanga cecropioides	Urticaceae	ALX rats (p.o.)	Aqueous, ethanol	Metformin (20 mg/kg)	[105]
Nigella sativa	Ranunculaceae	*In vitro*: Short-circuit current technique; *In vivo*: OGTT in normal rats (p.o.)	Aqueous	Metformin (300 mg/kg)	[106]
Nymphaea stellata	Ethanol extract	ALX rats (p.o.)	Ethanol	Metformin (11.3 mg/kg)	[107]
Olea europaea	Oleaceae	STZ rats (p.o.)	Ethanol	Glibenclamide (0.6 mg/kg)	[108]
Orthosiphon stamineus	Lamiaceae	STZ rats (p.o.)	Water	Glibenclamide (0.5 mg/kg)	[109]
Parinari excels	Chrysobalanaceae	ALX rats (p.o.)	Water	Glibenclamide (200 mg/kg)	[110]
Parkia biglobosa	Mimosaceae	ALX rats (p.o.)	Ethanol	Glibenclamide (0.01 mg/150 g bw)	[111]
Parkinsonia aculeata	Cesalpineaceae	ALX rats (p.o.)	Aqueous extract	Insulin NPH (3 U rat^{-1}, s.c.)	[112]
Phyllanthus amarus	Euphorbiaceae	Normal swiss mice (p.o.)	Aqueous	–	[113]
Plantago ovata	Plantaginaceae	STZ rats (p.o.)	Aqueous	–	[114]
Pongamia pinnata	Fabacae	ALX mice (p.o.)	Petroleum	Gglyburide (10 mg/kg)	[115]
Posidonia oceanica	Posidoniaceae	ALX rats (p.o.)	Aqueous ethanol	–	[116]

(Continued)

Table 2: (Continued)

Plant species	Family	Animal model	Solvent	Positive control	Reference
Prunella vulgaris	Lamiaceae	STZ rats (p.o.)	Hydroalcohol	Glibenclamide (5 mg/kg)	[117]
Psidium guajava	Myrtaceae	STZ rats (p.o.)	Aqueous ethanol	–	[118]
Pterocarpus marsupium	Leguminosae	ALX rats (p.o.)	Butanol subfraction of alcohol	Phenformin (300 mg/kg)	[119]
Rhus chirindensis	Anacardiaceae	STZ rats (p.o.)	Aqueous	Chlorpropamide (250 mg/kg)	[120]
Rhus verniciflua, *Agrimonia pilosa*, *Sophora japonica*, *Paeonia suffruticosa*	Anacardiaceae, Rosaceae, Fabaceae, Paeoniaceae	STZ rats (p.o.)	80% ethanol	Green tea extract (10 mg/kg)	[121]
Rosa damascena	Rosaceae	*In vitro*, a-glucosidase; *in vivo*, STZ rats (p.o.)	Methanol	Acarbose (50 mg/kg)	[122]
Salvia officinalis	Lamiaceae	Diabetes	70% ethanol	Glibenclamide (5 mg/kg)	[123]
Schkuhria pinnata, *Euclea undulate*, *Elaeodendron transvaalense*	Asteraceae Ebenaceae Celastraceae	*In vitro* assays: aglucosidase and amylase inhibition in C2C12 myocytes, 3T3-L1 preadipocytes and Chang liver cells	Acetone/ethanol	Insulin (1 mm)	[124]
Sclerocarya birrea	Anacardiaceae	STZ rats (p.o.)	Methylene chloride/ methanol	Metformin (500 mg/kg)	[125]
Shweta musali (in India), Sutaid musk (in Pakistan), *Asparagus adscendens*	Liliacea	*In vitro* clonal pancreatic beta cell line, BRIN-BD11; 3T3-L1 adipocytes	Water	–	[126]
Siberian ginseng, *Acanthopanax senticosus*	Araliaceae	Ob/ob mice (p.o.)	50% ethanol	Metformin (300 mg/kg) 108	[127]
Siraitia grosvenori	Cucurbitaceae	GK	Aqueous	–	[128]
Stachytarpheta angustifoloa	Verbanaceae	ALX rats (p.o.)	Aqueous	Metformin (500 mg/kg), chlorpropamide (250 mg/kg), glibenclamide (1 mg/kg)	[129]
Syzygium cumini	Myrtaceae	*In vitro*, a-glucosidase; *in vivo*, GK rats (p.o.)	Acetone	Acarbose (*in vitro*); N/A (*in vivo*)	[130]
Tecoma stans	Bignoniaceae	*In vitro*, a-glucosidase inhibition *In vivo*, STZ rats (p.o.)	Aqueous	Acarbose (50 mg/kg), tolbutamide (60 mg/kg)	[131]
Terminalia superba, *Canarium schweinfurthii*	Combretaceae; Burseraceae	STZ rats (p.o.)	Methanol/methylene chloride (1:1) extract	Insulin (3 IU)	[132]
Tithonia diversifolia	Chrysanthemum	KK-Ag-mice (p.o.)	80% ethanol	Insulin	[133]
Tragia cannabina	Euphorbiaceae	STZ rats (p.o.)	Ethanol	Glibenclamide (0.5 mg/kg)	[134]
Trema micrantha	Ulmaceae	ALX rats (v.o.)	Ethanol	Glibenclamide (200 mg/kg)	[135]
Tridax procumbens	Asteraceae	ALX rats (p.o.)	50% methanol extract	Glibenclamide (10 mg/kg)	[136]
Vernonia anthelmintica	Asteraceae	STZ rats (p.o.)	Ethanol extract followed by fractionation with silica gel chromatography	Glibenclamide (20 mg/kg)	[137]
Vitex megapotamica	Verbenaceae	ALX rats (p.o.)	Ethanol, hexane, ethyl acetate, butanol, dichloromethane, methanol sub-fractions	Insulin (0.3 IU); tolbutamide (100 mg/kg)	[138]

GK = Goto-Kakizaki; STZ = Streptozotocin; ALX = Alloxan; IDDM = Insulin-dependent diabetes mellitus; NIDDM = Noninsulin dependent diabetes mellitus; OGTT = Oral glucose tolerance test; N/A = Not available

AUTHOR'S CONTRIBUTIONS

HN, HSh, MRK contributed in the design of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. AB, MRK contributed in the design of the work, Editing the final version, approval of the final version of the manuscript, and agreed for all aspects of the work. All authors wrote the manuscript equally.

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