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

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.\[7-7\]

DIABETES MELLITUS COMPLICATIONS

The patients with DM are at increased risk of complications such as peripheral vascular disease, retinopathy, nephropathy, neuropathy, coronary heart
Lack of exercise dramatically increases the risk of diabetes mellitus (DM) increases the risk of complications, which include diabetic nephropathy, diabetic retinopathy, and diabetic neuropathy. 

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 [21-26].

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 | Gilbenclamide, Glipizide, Chlorpropamide, Tolbutamide | Hypoglycemia, Weight gain |
| Biguanides         | Increase in insulin sensitivity and reduce hepatic glucose production | a-Glucosidase inhibitors | Thiazolidinediones Activation of peroxisome proliferator-activated receptor gamma and improvement of insulin action |
| Metformin          | Diarrhea, nausea, abdominal pain, Lactic acidosis | Metallic taste, Acarbose, Rosiglitazone | Diarrhea, abdominal cramping, flatulence, Hepatotoxicity |
| DPP-4 inhibitors (Glipitins) | 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\cite{31-33} or for reduction of the side-effects of hypoglycemic drugs,\cite{30-40}

**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,\cite{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.\cite{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.\cite{36-48} Overexpression of catalase in STZ-treated transgenic mice attenuated the onset of diabetic complications, indicating the therapeutic potential of catalase.\cite{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\cite{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.\cite{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.\cite{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.\cite{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.\cite{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.\cite{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.\cite{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.\cite{41-44} however, this finding has been questioned.\cite{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.\cite{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.\cite{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.\cite{48-49} 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.\cite{48-49} 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. 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.

**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. 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.

A possible benefit of vegetables and fruit is from their antioxidant components and thus a contribution to reduction of systemic oxidative stress. 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.

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

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. 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. 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. 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.

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. This oxidative stress usually causes or exacerbates chronic hard curable diseases such as diabetes, hypertension, cardiovascular, cancer, cognitive diseases, and pain or exacerbation of some other diseases like infectious disorders.

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. Other than the plants which were introduced here, a lot of other plants have antioxidant activities.

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. Therefore, they also might be effective on DM.

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Table 2: Anti-diabetic plants

| Extraction solvent | Positive control | Family | Animal model | Solvent | Positive control | Reference |
|-------------------|------------------|--------|--------------|---------|------------------|-----------|
| **Plant species** |                  |        |              |         |                  |           |
| Aegle marmelos, Artocarpus heterophyllus, Vangueria madagascariensis, Azadirachta indica, Eriobotrya japonica, Syzygium 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 sajabalsuk | 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] |
| Cinnamomum cassia | Lauraceae | C57BLKsJ 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 | Myrtaceae | In vitro, a-glucosidase; in vivo, STZ rats (p.o.) | Aqueous | Acarbose (25 mg/kg); guava leaf extract (500 mg/kg) | [72] |
| Eugenia operculata | Myrtaceae | Normal STZ rats (p.o.) | Aqueous | – | [73] |
| Clerodendrum capitatum | Verbenaceae | Normal rats (p.o.) | Aqueous | Glibenclamide (5 mg/kg) | [74] |
| Cornus mas L. | Cornaceae | STZ rats (i.p.) | 70% ethanol | Glibenclamide (150 mg/kg) | [75] |
| Cucurbita pepo | Cucurbitaceae | STZ rats (i.p.) | 70% ethanol | – | [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] |
| Hemsionitis arifolia | Hemisponidaceae | 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)

| Extraction solvent | Positive control | Family | Animal model | Solvent | Positive control | Reference |
|--------------------|------------------|--------|--------------|---------|------------------|-----------|
| **Huntoria umbellata** | Apocynaceae | ALX and high fructose induced hyperglycemic rats (p.o.) | Aqueous | Glibenclamide (1 mg/kg) | [91] |
| **Hypoxis hemerocallidea** | Hypoxidaceae | STZ rats (p.o.) | Water | Chlorpropamide (250 mg/kg p.o.) | [92] |
| **Ichnocarpus frutescens** | 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 stellata** | Nymphaeaceae | ALX rats (p.o.) | Ethanol | Glibenclamide (2 g/kg) | [94] |
| **Indigofera myrsinensis** | 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 rats (p.o.) | Methanol | Tolbutamide (80 mg/kg) | [99] |
| **Leucas cephalotes** | Lamiaceae | ALX rats (IDDM) | Ethanol | Glibenclamide (600 mg/kg), metformin (500 mg/kg) | [100] |
| **Lepidium sativum** | Brassicaceae | ALX rats (NIDDM) | Ethanol | Metformin (500 mg/kg), glibenclamide (600 mg/kg) | [100] |
| **Liriophy spicata** | Liliaceae | STZ mice (p.o.) | Water, crude polysaccharide fraction | Tolbutamide (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 | Short-circuit current technique; in vivo: OGTT in normal rats (p.o.) | Ethanol | 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** | Celaspineaceae | 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** | Fabaceae | ALX mice (p.o.) | Petroleum | Gliburide (10 mg/kg) | [115] |
| **Posidonia oceanica** | Posidoniaceae | ALX rats (p.o.) | Aqueous ethanol | - | [116] |

(Continued)
| Extraction solvent | Positive control | Family | Animal model | Solvent | Positive control | Reference |
|---------------------|------------------|--------|--------------|---------|-----------------|-----------|
| **Plant species**   |                  |        |              |         |                 |           |
| Prunella vulgaris   | Positive control | 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, Paonia 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, Euclae undulate, Elseodendron 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 ascdendens | | Liliaceae | 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) | [127] |
| Siraitia grosvenori |                  | Cucurbitaceae | GK | Aqueous | – | [128] |
| Stachytarpheta angustifolao | | 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] |
| Tecomastans         |                  | Bignonieae | 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 |                | Chrysanthenum | 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] |
| Vernonla anthelminta |                | 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 subfractions | 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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