Review Article

Antioxidant plants and diabetes mellitus

Hamid Nasri, Hedayatollah Shirzad[1], Azar Baradaran[2], Mahmoud Rafieian-kopaei[1]
Departments of Nephrology and [2]Pathology, Isfahan University of Medical Sciences, Isfahan, [1]Medical Plants Research Center, Shahrekord University of Medical Sciences, Sharekord, Iran

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

How to cite this article: Nasri H, Shirzad H, Baradaran A, Rafieian-kopaei M. Antioxidant plants and diabetes mellitus. J Res Med Sci 2015; 20:491-502.

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

Address for correspondence: Prof. Mahmoud Rafieian-kopaei, Medical Plants Research Center, Shahrekord University of Medical Sciences, Sharhekord, Iran. E-mail: rafieian@yahoo.com
Received: 07-06-2014; **Revised:** 28-01-2015; **Accepted:** 14-04-2015

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.

ACKNOWLEDGMENT

Thanks to Research Deputy of Shahrekord University of Medical Sciences for support. There is no grant for this work.

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.

REFERENCES

1. Shoback D, Gardner DG, editor. Greenspan's Basic & Clinical Endocrinology. 9th ed. Ch. 17. New York: McGraw-Hill Medical; 2011.
2. Nasri H. On the occasion of the world diabetes day 2013; diabetes education and prevention; a nephrology point of view. J Renal Inj Prev 2013;2:31-2.
3. Shahbazian H. World diabetes day; 2013. J Renal Inj Prev 2013;2:123-4.
4. Nasri H, Rafieian-Kopaei M. Herbal medicine and diabetic kidney disease. J Nephropharmacol 2013;2:1-2.
5. Tavafi M. Diabetic nephropathy and antioxidants. J Nephropathol 2013;2:20-7.
6. Nasri H, Sahinfard N, Rafieian M, Rafieian S, Shirzad M, Rafieian-kopaei M. Effects of *Allium sativum* on liver enzymes and atherosclerotic risk factors. J HerbMed Pharmacol 2013;2: 23-8.
7. Tamadon MR, Baradaran A, Rafieian-Kopaei M. Antioxidant and kidney protection; differential impacts of single and whole natural antioxidants. J Renal Inj Prev 2014;3:41-2.
8. Tolouian R, T Hernandez G. Prediction of diabetic nephropathy: The need for a sweet biomarker. J Nephropathol 2013;2:4-5.
9. Nasri H, Yazdani M. The relationship between serum LDL-cholesterol, HDL-cholesterol and systolic blood pressure in patients with type 2 diabetes. Kardiol Pol 2006;64:1364-8.
10. Nasri H, Shirzad H. Toxicity and safety of medicinal plants. J HerbMed Plarmacol 2013;2:21-2.
11. Mogharabi M, Abdollahi M, Faramarzi MA. Safety concerns to application of graphene compounds in pharmacy and medicine. Daru 2014;22:23.
12. Rafieian-Kopaei M, Baradaran A, Rafieian M. Plants antioxidants: From laboratory to clinic. J Nephropathol 2013;2:152-3.
13. Mardani S, Nasri H, Hajian S, Ahmadi A, Kazemi R, Rafieian-Kopaei M. Impact of Momordica charantia extract on kidney function and structure in mice. J Nephropathol 2014;3: 35-40.
14. Nasri H. Impact of diabetes mellitus on parathyroid hormone in hemodialysis patients. J Parathyr Dis 2013;1:9-11.
15. Rahimi Z, Mansouri Zaveleh O, Rahimi Z, Abbasi A. AT2R-1332 G: A polymorphism and diabetic nephropathy in type 2 diabetes mellitus patients. J Renal Inj Prev 2013;2:97-101.
16. Ardalan MR, Rafieian-Kopaei M. Is the safety of herbal medicines for kidneys under question? J Nephropharmacol 2013;2:11-2.
17. Roshan B, Stanton RC. A story of microalbuminuria and diabetic nephropathy. J Nephropathol 2013;2:234-40.
18. Kafeshani M. Ginger, micro-inflammation and kidney disease. J Renal Endocrinol 2015;1:e04.
19. Nasri H, Behradmanesh S, Ahmadi A, Rafieian-Kopaei M. Impact of oral Vitamin D (cholecalciferol) replacement therapy on blood pressure in type 2 diabetes patients; a randomized, double-blind, placebo controlled clinical trial. J Nephropathol 2014;3:29-33.
20. Asadi-Samani M, Bahmani M, Rafieian-Kopaei M. The chemical composition, botanical characteristic and biological activities of Borago officinalis: a review. Asian Pac J Trop Med 2014;7(Suppl 1):22-28.
21. Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, Lafont S, Bergeonneau C, Kassaï B, *et al*. Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: Meta-analysis of randomised controlled trials. BMJ 2011;343:d4169.
22. Rafieian-Kopaei M, Nasri H. Vitamin D therapy in diabetic kidney disease. J Nephropharmacol 2014;3:3-4.
23. Bahmani M, Zargaran A, Rafieian-Kopaei M, Saki M. Ethnobotanical study of medicinal plants used in the management of diabetes mellitus in the Urmia, Northwest Iran. Asian Pac J Trop Med 2014;7(Suppl 1):348-354.
24. Rouhi H, Ganji F. Effects of N-acetyl cysteine on serum lipoprotein (a) and proteinuria in type 2 diabetic patients. J Nephropathol 2013;2:61-6.
25. Rafieian-Kopaei M, Behradmanesh S, Kheiri S, Nasri H. Association of serum uric acid with level of blood pressure in type 2 diabetic patients. Iran J Kidney Dis 2014;8:152-4.
26. Ardalan MR, Sanadgol H, Nasri H, Baradaran A, Tamadon MR, Rafieian-Kopaei R. Impact of Vitamin D on the immune system in kidney disease. J Parathyr Dis 2013;1:17-20.
27. Ajabshir S, Asif A, Nayer A. The effects of Vitamin D on the renin-angiotensin system. J Nephropathol 2014;3:41-3.
28. Nasri H. Correlation of serum magnesium with serum levels of 25-hydroxyvitamin D in hemodialysis patients. J Parathyr Dis 2014;2:11-3.
29. Nasri H, Behradmanesh S, Ahmadi A, Baradaran A, Nasri P, Rafieian-Kopaei M. Association of serum lipids with level of blood pressure in type 2 diabetic patients. J Renal Inj Prev 2014;3:43-6.
30. Nasri H, Rafieian-Kopaei M. Metformin improves diabetic kidney disease. J Nephropharmacol 2012;1:1-2.
31. Ayodhya S, Kusum S, Saxena A. Hypoglycaemic activity of different extracts of various herbal plants. Int J Res Ayurveda Pharm 2010;1:212.
32. Abdollahi M, Farshchi A, Nikfar S, Seyedifar M. Effect of chromium on glucose and lipid profiles in patients with type 2 diabetes; a meta-analysis review of randomized trials. J Pharm Pharm Sci 2013;16:99-114.
33. Rafieian-Kopaei M, Nasri H. Ginger and diabetic nephropathy. J Renal Inj Prev 2013;2:9-10.
34. Nasri H, Rafieian-Kopaei M. Tubular kidney protection by antioxidants. Iran J Public Health 2013;42:1194-6.
35. Ardalan MR, Sanadgol H, Nasri H, Baradaran A, Tamadon MR, Rafieian-Kopaei R. Vitamin D therapy in diabetic kidney disease; current knowledge on a public health problem. J Parathyr Dis 2014;2:15-7.
36. Turdi S, Li Q, Lopez FL, Ren J. Catalase alleviates cardiomyocyte dysfunction in diabetes: Role of Akt, Forkhead transcriptional factor and silent information regulator 2. Life Sci 2007;81:895-905.
37. Rafieian-Kopaie M. Metformin and renal injury protection. J Renal Inj Prev 2013;2:91-2.
38. Eurich DT, Majumdar SR, Tsuyuki RT, Johnson JA. Reduced mortality associated with the use of ACE inhibitors in patients with type 2 diabetes. Diabetes Care 2004;27:1330-4.
39. Rafieian-Kopaei M, Baradaran A. Combination of metformin with other antioxidants may increase its renoprotective efficacy. J Renal Inj Prev 2013;2:35-6.
40. Rahimi Z. ACE insertion/deletion (I/D) polymorphism and diabetic nephropathy. J Nephropathol 2012;1:143-51.
41. Tavafi M. Complexity of diabetic nephropathy pathogenesis and design of investigations. J Renal Inj Prev 2013;2:59-62.
42. Ghamarian A, Abdollahi M, Su X, Amiri A, Ahadi A, Nowrouzi A. Effect of chicory seed extract on glucose tolerance test (GTT)

and metabolic profile in early and late stage diabetic rats. Daru 2012;20:56.
43. Song Y, Cook NR, Albert CM, Van Denburgh M, Manson JE. Effects of Vitamins C and E and beta-carotene on the risk of type 2 diabetes in women at high risk of cardiovascular disease: A randomized controlled trial. Am J Clin Nutr 2009;90:429-37.
44. Miller ER 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: High-dosage Vitamin E supplementation may increase all-cause mortality. Ann Intern Med 2005;142:37-46.
45. Greenland S. Weaknesses of Bayesian model averaging for meta-analysis in the study of Vitamin E and mortality. Clin Trials 2009;6:42-6.
46. Fikree M, Hanafi B, Hussain ZA, Masuadi EM. Glycemic control of type 2 diabetes mellitus. Bahrain Med Bull 2006;28:1-6.
47. Chausmer AB. Zinc, insulin and diabetes. J Am Coll Nutr 1998;17:109-15.
48. Rafieian-Kopaei M, Baradaran A, Rafieian M. Oxidative stress and the paradoxical effects of antioxidants. J Res Med Sci 2013;18:629.
49. Hajivandi A, Amiri M. World kidney day 2014: Kidney disease and elderly. J Parathyr Dis 2014;2:3-4.
50. Rafieian-Kopaei M, Baradaran A. Teucrium polium and kidney. J Renal Inj Prev 2013;2:3-4.
51. Tamadon MR, Ardalan MR, Nasri H. World kidney day 2013; acute renal injury; a global health warning. J Parathyr Dis 2013;1:27-8.
52. Rafieian-Kopaie M, Nasri H. Silymarin and diabetic nephropathy. J Renal Inj Prev 2012;1:3-5.
53. Hulbert AJ, Turner N, Storlien LH, Else PL. Dietary fats and membrane function: Implications for metabolism and disease. Biol Rev Camb Philos Soc 2005;80:155-69.
54. Nasri H, Behradmanesh S, Maghsoudi AR, Ahmadi A, Nasri P, Rafieian-Kopaei M. Efficacy of supplementary Vitamin D on improvement of glycemic parameters in patients with type 2 diabetes mellitus; a randomized double blind clinical trial. J Renal Inj Prev 2014;3:31-4.
55. Hung HY, Qian K, Morris-Natschke SL, Hsu CS, Lee KH. Recent discovery of plant-derived anti-diabetic natural products. Nat Prod Rep 2012;29:580-606.
56. Asgari A. Herbal medicines and kidney; friends or foes? J Nephropharmacol 2014;3:5-6.
57. Kotowaroo MI, Mahomoodally MF, Gurib-Fakim A, Subratty AH. Screening of traditional antidiabetic medicinal plants of Mauritius for possible alpha-amylase inhibitory effects *in vitro*. Phytother Res 2006;20:228-31.
58. Shoji Y, Nakashima H. Glucose-lowering effect of powder formulation of African black tea extract in KK-A(y)/TaJcl diabetic mouse. Arch Pharm Res 2006;29:786-94.
59. Sangameswaran B, Jayakar B. Anti-diabetic, anti-hyperlipidemic and spermatogenic effects of *Amaranthus spinosus* Linn. on streptozotocin-induced diabetic rats. J Nat Med 2008;62:79-82.
60. Leu YL, Chen YW, Yang CY, Huang CF, Lin GH, Tsai KS, *et al.* Extract isolated from *Angelica hirsutiflora* with insulin secretagogue activity. J Ethnopharmacol 2009;123:208-12.
61. Ajikumaran Nair S, Shylesh BS, Gopakumar B, Subramoniam A. Anti-diabetes and hypoglycaemic properties of *Hemionitis arifolia* (Burm.) Moore in rats. J Ethnopharmacol 2006;106:192-7.
62. Jung UJ, Baek NI, Chung HG, Bang MH, Yoo JS, Jeong TS, *et al.* The anti-diabetic effects of ethanol extract from two variants of *Artemisia princeps* Pampanini in C57BL/KsJ-db/db mice. Food Chem Toxicol 2007;45:2022-9.
63. Pandikumar P, Babu NP, Ignacimuthu S. Hypoglycemic and antihyperglycemic effect of *Begonia malabarica* Lam. in normal and streptozotocin induced diabetic rats. J Ethnopharmacol 2009;124:111-5.
64. Somani R, Kasture S, Singhai AK. Antidiabetic potential of *Butea monosperma* in rats. Fitoterapia 2006;77:86-90.
65. Krisanapun C, Peungvicha P, Temsiririrkkul R, Wongkrajang Y. Aqueous extract of *Abutilon indicum* Sweet inhibits glucose absorption and stimulates insulin secretion in rodents. Nutr Res 2009;29:579-87.
66. Habibuddin M, Daghriri HA, Humaira T, Al Qahtani MS, Hefzi AA. Antidiabetic effect of alcoholic extract of *Caralluma sinaica* L. on streptozotocin-induced diabetic rabbits. J Ethnopharmacol 2008;117:215-20.
67. Aragão DM, Guarize L, Lanini J, da Costa JC, Garcia RM, Scio E. Hypoglycemic effects of *Cecropia pachystachya* in normal and alloxan-induced diabetic rats. J Ethnopharmacol 2010;128: 629-33.
68. Dimo T, Rakotonirina SV, Tan PV, Azay J, Dongo E, Kamtchouing P, *et al.* Effect of *Sclerocarya birrea* (Anacardiaceae) stem bark methylene chloride/methanol extract on streptozotocin-diabetic rats. J Ethnopharmacol 2007;110:434-8.
69. Kim SH, Hyun SH, Choung SY. Anti-diabetic effect of cinnamon extract on blood glucose in db/db mice. J Ethnopharmacol 2006;104:119-23.
70. Park SH, Ko SK, Choi JG, Chung SH. *Salicornia* herbacea prevents high fat diet-induced hyperglycemia and hyperlipidemia in ICR mice. Arch Pharm Res 2006;29:256-64.
71. Mai TT, Chuyen NV. Anti-hyperglycemic activity of an aqueous extract from flower buds of *Cleistocalyx operculatus* (Roxb.) Merr and Perry. Biosci Biotechnol Biochem 2007;71:69-76.
72. Adeneye AA, Adeleke TI, Adeneye AK. Hypoglycemic and hypolipidemic effects of the aqueous fresh leaves extract of *Clerodendrum capitatum* in Wistar rats. J Ethnopharmacol 2008;116:7-10.
73. Shamsi F, Asgari S, Rafieian R, Kazemi S. Effects of *Cornus mas* L. on blood glucose, insulin and histopathology of pancreas in alloxan-induced diabetic rats. J Isfahan Med Sch 2011;29: 927-37.
74. Kazemi S, Asgari S, Moshtaghian SJ, Rafieian-Kopaei M, Mahzooni P. Preventive effect of Pumpkin (*Cucurbita pepo* L.) on diabetic index and histopathology of pancreas in Alloxan-induced diabetes in rats. J Isfahan Med Sch 2011;28:872-81.
75. Adeneye AA, Agbaje EO. Hypoglycemic and hypolipidemic effects of fresh leaf aqueous extract of *Cymbopogon citratus* Stapf. in rats. J Ethnopharmacol 2007;112:440-4.
76. Raut NA, Gaikwad NJ. Antidiabetic activity of hydro-ethanolic extract of *Cyperus rotundus* in alloxan induced diabetes in rats. Fitoterapia 2006;77:585-8.
77. Dewanjee S, Das AK, Sahu R, Gangopadhyay M. Antidiabetic activity of *Diospyros* peregrina fruit: Effect on hyperglycemia, hyperlipidemia and augmented oxidative stress in experimental type 2 diabetes. Food Chem Toxicol 2009;47:2679-85.
78. Khookhor O, Bolin Q, Oshida Y, Sato Y. Effect of Mongolian plants on *in vivo* insulin action in diabetic rats. Diabetes Res Clin Pract 2007;75:135-40.
79. Li WL, Wu JL, Ren BR, Chen J, Lu CG. Pharmacological studies on anti-hyperglycemic effect of folium eriobotryae. Am J Chin Med 2007;35:705-11.
80. Sharma SB, Nasir A, Prabhu KM, Murthy PS. Antihyperglycemic effect of the fruit-pulp of Eugenia jambolana in experimental diabetes mellitus. J Ethnopharmacol 2006;104:367-73.
81. Shirwaikar A, Rajendran K, Barik R. Effect of aqueous bark extract of *Garuga pinnata* Roxb. in streptozotocin-nicotinamide induced type-II diabetes mellitus. J Ethnopharmacol 2006;107:285-90.
82. Rauter AP, Martins A, Lopes R, Ferreira J, Serralheiro LM, Araújo ME, *et al*. Bioactivity studies and chemical profile of the antidiabetic plant *Genista tenera*. J Ethnopharmacol 2009; 122:384-93.

83. Okokon JE, Umoh EE, Etim EI, Jackson CL. Antiplasmodial and antidiabetic activities of ethanolic leaf extract of *Heinsia crinata*. J Med Food 2009;12:131-6.
84. Aslan M, Orhan DD, Orhan N, Sezik E, Yeşilada E. A study of antidiabetic and antioxidant effects of *Helichrysum graveolens* capitulums in streptozotocin-induced diabetic rats. J Med Food 2007;10:396-400.
85. Aslan M, Deliorman Orhan D, Orhan N, Sezik E, Yesilada E. *In vivo* antidiabetic and antioxidant potential of *Helichrysum plicatum* ssp. plicatum capitulums in streptozotocin-induced-diabetic rats. J Ethnopharmacol 2007;109:54-9.
86. Kumar G, Banu GS, Murugesan AG, Pandian MR. Hypoglycaemic effect of *Helicteres isora* bark extract in rats. J Ethnopharmacol 2006;107:304-7.
87. Murugesh K, Yeligar V, Dash DK, Sengupta P, Maiti BC, Maity TK. Antidiabetic, antioxidant and antihyperlipidemic status of *Heliotropium zeylanicum* extract on streptozotocin-induced diabetes in rats. Biol Pharm Bull 2006;29:2202-5.
88. Kamtchouing P, Kahpui SM, Dzeufiet PD, Tédong L, Asongalem EA, Dimo T. Anti-diabetic activity of methanol/methylene chloride stem bark extracts of *Terminalia superba* and *Canarium schweinfurthii* on streptozotocin-induced diabetic rats. J Ethnopharmacol 2006;104:306-9.
89. Venkatesh S, Thilagavathi J, Shyam Sundar D. Anti-diabetic activity of flowers of *Hibiscus rosasinensis*. Fitoterapia 2008;79:79-81.
90. Adeneye AA, Adeyemi OO. Further evaluation of antihyperglycaemic activity of *Hunteria umbellata* (K. Schum) Hallier f. seed extract in experimental diabetes. J Ethnopharmacol 2009;126:238-43.
91. Ojewole JA. Antinociceptive, anti-inflammatory and antidiabetic properties of *Hypoxis hemerocallidea* Fisch. & C.A. Mey. (Hypoxidaceae) corm ['African Potato'] aqueous extract in mice and rats. J Ethnopharmacol 2006;103:126-34.
92. Subash-Babu P, Ignacimuthu S, Agastian P. Insulin secretagogue effect of Ichnocarpus frutescence leaf extract in experimental diabetes: A dose-dependent study. Chem Biol Interact 2008;172: 159-71.
93. Rajagopal K, Sasikala K. Antihyperglycaemic and antihyperlipidaemic effects of *Nymphaea stellata* in alloxan-induced diabetic rats. Singapore Med J 2008;49:137-41.
94. Chakrabarti R, Damarla RK, Mullangi R, Sharma VM, Vikramadithyan RK, Rajagopalan R. Insulin sensitizing property of *Indigofera mysorensis* extract. J Ethnopharmacol 2006; 105:102-6.
95. Asgary S, Parkhideh S, Solhpour A, Madani H, Mahzouni P, Rahimi P. Effect of ethanolic extract of *Juglans regia* L. on blood sugar in diabetes-induced rats. J Med Food 2008;11:533-8.
96. Ju JB, Kim JS, Choi CW, Lee HK, Oh TK, Kim SC. Comparison between ethanolic and aqueous extracts from Chinese juniper berries for hypoglycaemic and hypolipidemic effects in alloxan-induced diabetic rats. J Ethnopharmacol 2008;115:110-5.
97. Kamgang R, Mboumi RY, Fondjo AF, Tagne MA, N'dillé GP, Yonkeu JN. Antihyperglycaemic potential of the water-ethanol extract of *Kalanchoe crenata* (Crassulaceae). J Nat Med 2008;62:34-40.
98. Momo CE, Oben JE, Tazoo D, Dongo E. Antidiabetic and hypolipidaemic effects of a methanol/methylene-chloride extract of *Laportea ovalifolia* (Urticaceae), measured in rats with alloxan-induced diabetes. Ann Trop Med Parasitol 2006;100:69-74.
99. Bavarva JH, Narasimhacharya AV. Leucas cephalotes regulates carbohydrate and lipid metabolism and improves antioxidant status in IDDM and NIDDM rats. J Ethnopharmacol 2010;127: 98-102.
100. Chen X, Bai X, Liu Y, Tian L, Zhou J, Zhou Q, *et al.* Anti-diabetic effects of water extract and crude polysaccharides from tuberous root of *Liriope spicata* var. prolifera in mice. J Ethnopharmacol 2009;122:205-9.
101. Cemek M, Kaga S, Simsek N, Büyükokuroglu ME, Konuk M. Antihyperglycemic and antioxidative potential of *Matricaria chamomilla* L. in streptozotocin-induced diabetic rats. J Nat Med 2008;62:284-93.
102. Bhaskar A, Vidhya VG, Ramya M. Hypoglycemic effect of *Mucuna pruriens* seed extract on normal and streptozotocin-diabetic rats. Fitoterapia 2008;79:539-43.
103. Narendhirakannan RT, Subramanian S, Kandaswamy M. Biochemical evaluation of antidiabetogenic properties of some commonly used Indian plants on streptozotocin-induced diabetes in experimental rats. Clin Exp Pharmacol Physiol 2006;33:1150-7.
104. Adeneye AA, Ajagbonna OP, Ayodele OW. Hypoglycemic and antidiabetic activities on the stem bark aqueous and ethanol extracts of *Musanga cecropioides* in normal and alloxan-induced diabetic rats. Fitoterapia 2007;78:502-5.
105. Meddah B, Ducroc R, El Abbes Faouzi M, Eto B, Mahraoui L, Benhaddou-Andaloussi A, *et al.* Nigella sativa inhibits intestinal glucose absorption and improves glucose tolerance in rats. J Ethnopharmacol 2009;121:419-24.
106. Dhanabal SP, Raja MK, Ramanathan M, Suresh B. Hypoglycemic activity of *Nymphaea stellata* leaves ethanolic extract in alloxan induced diabetic rats. Fitoterapia 2007;78:288-91.
107. Eidi A, Eidi M, Darzi R. Antidiabetic effect of *Olea europaea* L. in normal and diabetic rats. Phytother Res 2009;23:347-50.
108. Sriplang K, Adisakwattana S, Rungsipipat A, Yibchok-Anun S. Effects of *Orthosiphon stamineus* aqueous extract on plasma glucose concentration and lipid profile in normal and streptozotocin-induced diabetic rats. J Ethnopharmacol 2007;109:510-4.
109. Ndiaye M, Diatta W, Sy AN, Dièye AM, Faye B, Bassène E. Antidiabetic properties of aqueous barks extract of *Parinari excelsa* in alloxan-induced diabetic rats. Fitoterapia 2008;79:267-70.
110. Odetola AA, Akinloye O, Egunjobi C, Adekunle WA, Ayoola AO. Possible antidiabetic and antihyperlipidaemic effect of fermented *Parkia biglobosa* (JACQ) extract in alloxan-induced diabetic rats. Clin Exp Pharmacol Physiol 2006;33:808-12.
111. Oliveira HC, dos Santos MP, Grigulo R, Lima LL, Martins DT, Lima JC, *et al.* Antidiabetic activity of *Vatairea macrocarpa* extract in rats. J Ethnopharmacol 2008;115:515-9.
112. Adeneye AA, Amole OO, Adeneye AK. Hypoglycemic and hypocholesterolemic activities of the aqueous leaf and seed extract of *Phyllanthus* amarus in mice. Fitoterapia 2006;77:511-4.
113. Hannan JM, Ali L, Khaleque J, Akhter M, Flatt PR, Abdel-Wahab YH. Aqueous extracts of husks of *Plantago ovata* reduce hyperglycaemia in type 1 and type 2 diabetes by inhibition of intestinal glucose absorption. Br J Nutr 2006;96:131-7.
114. Badole SL, Bodhankar SL. Investigation of antihyperglycaemic activity of aqueous and petroleum ether extract of stem bark of *Pongamia pinnata* on serum glucose level in diabetic mice. J Ethnopharmacol 2009;123:115-20.
115. Gokce G, Haznedaroglu MZ. Evaluation of antidiabetic, antioxidant and vasoprotective effects of *Posidonia oceanica* extract. J Ethnopharmacol 2008;115:122-30.
116. Zheng J, He J, Ji B, Li Y, Zhang X. Antihyperglycemic activity of Prunella vulgaris L. in streptozotocin-induced diabetic mice. Asia Pac J Clin Nutr 2007;16 Suppl 1:427-31.
117. Shen SC, Cheng FC, Wu NJ. Effect of guava (*Psidium guajava* Linn.) leaf soluble solids on glucose metabolism in type 2 diabetic rats. Phytother Res 2008;22:1458-64.
118. Dhanabal SP, Kokate CK, Ramanathan M, Kumar EP, Suresh B. Hypoglycaemic activity of *Pterocarpus marsupium* Roxb. Phytother Res 2006;20:4-8.

119. Ojewole JA. Analgesic, anti-inflammatory and hypoglycaemic effects of Rhus chirindensis (Baker F.) [*Anacardiaceae*] stem-bark aqueous extract in mice and rats. J Ethnopharmacol 2007;113: 338-45.
120. Gholamhoseinian A, Fallah H, Sharifi far F. Inhibitory effect of methanol extract of *Rosa damascena* Mill. flowers on alpha-glucosidase activity and postprandial hyperglycemia in normal and diabetic rats. Phytomedicine 2009;16:935-41.
121. Lima CF, Azevedo MF, Araujo R, Fernandes-Ferreira M, Pereira-Wilson C. Metformin-like effect of *Salvia officinalis* (common sage): Is it useful in diabetes prevention? Br J Nutr 2006;96:326-33.
122. Deutschländer MS, van de Venter M, Roux S, Louw J, Lall N. Hypoglycaemic activity of four plant extracts traditionally used in South Africa for diabetes. J Ethnopharmacol 2009;124:619-24.
123. Behradmanesh S, Derees F, Rafieian-kopaei M. Effect of Salvia officinalis on diabetic patients. J Ren Inj Prev 2013; 2(2):51-54. DOI: 10.12861/jrip.2013.18.
124. Dimo T, Rakotonirina SV, Tan PV, Azay J, Dongo E, Kamtchouing P, *et al.* Effect of *Sclerocarya birrea* (*Anacardiaceae*) stem bark methylene chloride/methanol extract on streptozotocin-diabetic rats. J Ethnopharmacol 2007;110:434-8.
125. Mathews JN, Flatt PR, Abdel-Wahab YH. Asparagus adscendens (*Shweta musali*) stimulates insulin secretion, insulin action and inhibits starch digestion. Br J Nutr 2006;95:576-81.
126. Park SH, Lee SG, Kang SK, Chung SH. Acanthopanax senticosus reverses fatty liver disease and hyperglycemia in ob/ob mice. Arch Pharm Res 2006;29:768-76.
127. Suzuki YA, Tomoda M, Murata Y, Inui H, Sugiura M, Nakano Y. Antidiabetic effect of long-term supplementation with *Siraitia grosvenori* on the spontaneously diabetic Goto-Kakizaki rat. Br J Nutr 2007;97:770-5.
128. Isah AB, Ibrahim YK, Abdulrahman EM, Ibrahim MA. The hypoglycaemic activity of the aqueous extract of *Stachytarpheta* angustifolia (Verbanaceae) in normoglycaemic and alloxan-induced diabetic rats. Pak J Biol Sci 2007;10:137-41.
129. Shinde J, Taldone T, Barletta M, Kunaparaju N, Hu B, Kumar S, *et al.* Alpha-glucosidase inhibitory activity of *Syzygium cumini* (Linn.) Skeels seed kernel *in vitro* and in Goto-Kakizaki (GK) rats. Carbohydr Res 2008;343:1278-81.
130. Aguilar-Santamaría L, Ramírez G, Nicasio P, Alegría-Reyes C, Herrera-Arellano A. Antidiabetic activities of *Tecoma stans* (L.) Juss. ex Kunth. J Ethnopharmacol 2009;124:284-8.
131. Kamtchouing P, Kahpui SM, Dzeufiet PD, Tédong L, Asongalem EA, Dimo T. Anti-diabetic activity of methanol/methylene chloride stem bark extracts of *Terminalia superba* and *Canarium schweinfurthii* on streptozotocin-induced diabetic rats. J Ethnopharmacol 2006;104:306-9.
132. Miura T, Furuta K, Yasuda A, Iwamoto N, Kato M, Ishihara E, *et al.* Antidiabetic effect of nitobegiku in KK-Ay diabetic mice. Am J Chin Med 2002;30:81-6.
133. Sivajothi V, Dey A, Jayakar B, Rajkapoor B. Antihyperglycemic property of *Tragia cannabina* in streptozotocin-induced diabetic rats. J Med Food 2007;10:361-5.
134. Schoenfelder T, Cirimbelli TM, Citadini-Zanette V. Acute effect of *Trema micrantha* (Ulmaceae) on serum glucose levels in normal and diabetic rats. J Ethnopharmacol 2006;107:456-9.
135. Pareek H, Sharma S, Khajja BS, Jain K, Jain GC. Evaluation of hypoglycemic and anti-hyperglycemic potential of *Tridax procumbens* (Linn.). BMC Complement Altern Med 2009;9:48.
136. Fatima SS, Rajasekhar MD, Kumar KV, Kumar MT, Babu KR, Rao CA. Antidiabetic and antihyperlipidemic activity of ethyl acetate: Isopropanol (1:1) fraction of *Vernonia anthelmintica* seeds in streptozotocin induced diabetic rats. Food Chem Toxicol 2010;48:495-501.
137. Zanatta L, de Sousa E, Cazarolli LH, Junior AC, Pizzolatti MG, Szpoganicz B, *et al.* Effect of crude extract and fractions from *Vitex megapotamica* leaves on hyperglycemia in alloxan-diabetic rats. J Ethnopharmacol 2007;109:151-5.
138. Amiri M, Motamedi P, Vakili L, Dehghani N, Kiani F, Taheri Z, *et al.* Beyond the liver protective efficacy of silymarin; bright renoprotective effect on diabetic kidney disease. J Nephropharmacol 2014;3:25-6.
139. Wiernsperger N. Metformin as a cellular protector; a synoptic view of modern evidences. J Nephropharmacol 2015;4:31-36.
140. Nasri H, Rafieian-Kopaei M. Medicinal plants and antioxidants: Why they are not always beneficial? Iran J Public Health 2014;43:255-7.
141. Hajian S, Rafieian-Kopaei M, Nasri H. Renoprotective effects of antioxidants against cisplatin nephrotoxicity. J Nephropharmacol 2014;3:39-42.
142. Madihi Y, Merrikhi A, Baradaran A, Rafieian-Kopaei M, Shahinfard N, Ansari R, *et al*. Impact of sumac on postprandial high-fat oxidative stress. Pak J Med Sci 2013;29:340-5.
143. Beladi-Mousavi SS, Bashardoust B, Nasri H, Ahmadi A, Tolou-Ghamari Z, Hajian S, *et al*. The theme of the world diabetes day 2014; healthy living and diabetes; a nephrology view point. J Nephropharmacol 2014;3:43-5.
144. Karimi A, Majlesi M, Rafieian-Kopaei M. Herbal versus synthetic drugs; beliefs and facts. J Nephropharmacol 2015;4:27-30.
145. Rafieian-Kopaei M, Nasri H. The ameliorative effect of *Zingiber officinale* in diabetic nephropathy. Iran Red Crescent Med J 2014;16:e11324.
146. Nazar CM. Mechanism of hypertension in diabetic nephropathy. J Nephropharmacol 2014;3:49-55.
147. Asgary S, Sahebkar A, Afshani MR, Keshvari M, Haghjooyjavanmard S, Rafieian-Kopaei M. Clinical evaluation of blood pressure lowering, endothelial function improving, hypolipidemic and anti-inflammatory effects of pomegranate juice in hypertensive subjects. Phytother Res 2014;28:193-9.
148. Baradaran A, Nasri H, Rafieian-Kopaei M. Oxidative stress and hypertension: Possibility of hypertension therapy with antioxidants. J Res Med Sci 2014;19:358-67.
149. Nasri H. The awareness of chronic kidney disease and aging; the focus of world kidney day in 2014. J Nephropharmacol 2014;3:1-2.
150. Tavafi M. Suggestions for attenuation of renal ischemia reperfusion injury based on mechanisms involved in epithelial cells damages. J Nephropharmacol 2015;4:1-3.
151. Madihi Y, Merrikhi A, Baradaran A, Ghobadi S, Shahinfard N, Ansari R, *et al*. Bioactive components and the effect of hydroalcoholic extract of *Vaccinium myrtillus* on postprandial atherosclerosis risk factors in rabbits. Pak J Med Sci 2013;29 1 Suppl:384-9.
152. Setorki M, Rafieian-Kopaei M, Merikhi A, Heidarian E, Shahinfard N, Ansari R, *et al*. Suppressive impact of anethum graveolens consumption on biochemical risk factors of atherosclerosis in hypercholesterolemic rabbits. Int J Prev Med 2013;4:889-95.
153. Shirzad H, Shahrani M, Rafieian-Kopaei M. Comparison of morphine and tramadol effects on phagocytic activity of mice peritoneal phagocytes *in vivo*. Int Immunopharmacol 2009;9: 968-70.
154. Shirzad H, Taji F, Rafieian-Kopaei M. Correlation between antioxidant activity of garlic extracts and WEHI-164 fibrosarcoma tumor growth in BALB/c mice. J Med Food 2011;14:969-74.
155. Shirzad H, Kiani M, Shirzad M. Impacts of tomato extract on the mice fibrosarcoma cells. J HerbMed Pharmacol 2013;2:13-6.
156. Baradaran A, Rabiei Z, Rafieian M, Shirzad H. A review study on medicinal plants affecting amnesia through cholinergic system. J HerbMed Pharmacol 2012;1:3-9.
157. Rabiei Z, Hojjati M, Rafieian-Kopaei M, Alibabaei Z. Effect of *Cyperus rotundus* tubers ethanolic extract on learning and memory in animal model of Alzheimer. Biomed Aging Pathol 2013;3:185-91.

158. Rafieian-Kopaei M, Shahinfard N, Rouhi-Boroujeni H, Gharipour M, Darvishzadeh-Boroujeni P. Effects of Ferulago angulata extract on serum lipids and lipid peroxidation. Evidence-Based Complementary and Alternative Medicine; 2014 (2014), Article ID 680856, 4 pages http://dx.doi.org/10.1155/2014/680856.
159. Rabiei Z, Rafieian-Kopaei M, Mokhtari S, Alibabaei Z, Shahrani M. The effect of pretreatment with different doses of *Lavandula officinalis* ethanolic extract on memory, learning and nociception. Biomed Aging Pathol 2014;4:71-6.
160. Bahmani M, Rafieian M, Baradaran A, Rafieian S, Rafieian-Kopaei M. Nephrotoxicity and hepatotoxicity evaluation of *Crocus sativus* stigmas in neonates of nursing mice. J Nephropathol 2014;3:81-5.
161. Delfan B, Bahmani M, Rafieian-Kopaei M, Delfan M, Saki K. A review study on ethnobotanical study of medicinal plants used in relief of toothache in Lorestan Province, Iran. Asian Pac J Trop Dis 2014;4 Suppl 2:879-84.
162. Saki K, Bahmani M, Rafieian-Kopaei M, Hassanzadazar H, Dehghan K, Bahmani F, *et al*. The most common native medicinal plants used for psychiatric and neurological disorders in Urmia city, northwest of Iran. Asian Pac J Trop Dis 2014;4 Suppl 2:895-901.
163. Chandra A, Biersmith M, Tolouian R. Obesity and kidney protection. J Nephropathol 2014;3:91-7.
164. Nasri H, Rafieian-Kopaei M. Oxidative stress and aging prevention. Int J Prev Med 2013;4:1101-2.
165. Bagheri N, Rahimian GH, Salimzadeh L, Azadegan F, Rafieian-Kopaei M, Taghikhani A, *et al*. Association of the virulence factors of *Helicobacter pylori* and gastric mucosal interleukin-17/23 mRNA expression in dyspeptic patients. EXCLI J 2013;12:5-14.
166. Tamadon MR, Zahmatkesh M, Beladi Mousavi SS. Administration of antioxidants in chronic kidney disease. J Nephropharmacol 2015;4:9-11.
167. Bagheri N, Taghikhani A, Rahimian G, Salimzadeh L, Azadegan Dehkordi F, Zandi F, *et al.* Association between virulence factors of *Helicobacter pylori* and gastric mucosal interleukin-18 mRNA expression in dyspeptic patients. Microb Pathog 2013;65:7-13.
168. Tavakoli M. Kidney protective effects of melatonin. J Nephropharmacol 2014;3:7-8.
169. Amirmohammadi M, Khajoenia S, Bahmani M, Rafieian-Kopaei M, Eftekhari Z, Qorbani M. *In vivo* evaluation of antiparasitic effects of *Artemisia abrotanum* and *Salvia officinalis* extracts on Syphacia obvelata, Aspiculoris tetrapetra and *Hymenolepis nana* parasites. Asian Pac J Trop Dis 2014;4 Suppl 1:S250-4.
170. Motamedi P, Dehghani N, Kiani F, Taheri Z, Torkamaneh S, Nasri H. New concepts in diabetic kidney disease. J Nephropharmacol 2015;4:47-8.
171. Rahimian G, Sanei MH, Shirzad H, Azadegan-Dehkordi F, Taghikhani A, Salimzadeh L, *et al.* Virulence factors of *Helicobacter pylori* vacA increase markedly gastric mucosal TGF-ß1 mRNA expression in gastritis patients. Microb Pathog 2014;67-68:1-7.
172. Baradaran A, Nasri H, Nematbakhsh M, Rafieian-Kopaei M. Antioxidant activity and preventive effect of aqueous leaf extract of *Aloe vera* on gentamicin-induced nephrotoxicity in male Wistar rats. Clin Ter 2014;165:7-11.
173. Rafieian-Kopaei M, Motamedi P, Vakili L, Dehghani N, Kiani F, Taheri Z, *et al*. Green tea and type 2 diabetes mellitus. J Nephropharmacol 2014;3:21-3.
174. Nasri H. Consequences of hypomagnesemia in type 2 diabetes mellitus patients. J Renal Inj Prev 2014;3:99-100.
175. Rafieian-Kopaei M, Nasri H. Re: Erythropoietin ameliorates oxidative stress and tissue injury following renal ischemia/reperfusion in rat kidney and lung. Med Princ Pract 2014;23:95.
176. Baradaran A, Nasri H, Rafieian-Kopaei M. Comment on: Anti-oxidative stress activity of *Stachys lavandulifolia* aqueous extract in humans. Cell J 2013;15:272-3.
177. Baradaran A, Madihi Y, Merrikhi A, Rafieian-Kopaei M, Nematbakhsh M, Asgari A, *et al*. Nephrotoxicity of hydroalcoholic extract of *Teucrium polium* in Wistar rats. Pak J Med Sci 2013;29 1 Suppl:329-33.
178. Amini FG, Rafieian-Kopaei M, Nematbakhsh M, Baradaran A, Nasri H. Ameliorative effects of metformin on renal histologic and biochemical alterations of gentamicin-induced renal toxicity in Wistar rats. J Res Med Sci 2012;17:621-5.
179. Ghaderian SB, Beladi-Mousavi SS. The role of diabetes mellitus and hypertension in chronic kidney disease. J Renal Inj Prev 2014;3:109-10.
180. Taheri Z, Ghafari M, Hajivandi A, Amiri M. Vitamin D deficiency in children and adolescents; an international challenge. J Parathyr Dis 2014;2:27-31.
181. Bahmani M, Zargaran A, Rafieian-Kopaei M. Identification of medicinal plants of Urmia for treatment of gastrointestinal disorders. Rev Bras Farmacognosia 2014;24:468-80.
182. Taghikhani A, Afrough H, Ansari-Samani R, Shahinfard N, Rafieian-Kopaei M. Assessing the toxic effects of hydroalcoholic extract of *Stachys lavandulifolia* Vahl on rat's liver. Bratisl Lek Listy 2014;115:121-4.
183. Heidarian E, Rafieian-Kopaei M. Protective effect of artichoke (*Cynara scolymus*) leaf extract against lead toxicity in rat. Pharm Biol 2013;51:1104-9.
184. Rafieian-Kopaei M, Hosseini M, Shirzad H. Comment on: Effect of pomegranate flower extract oncis platin-induced nephrotoxicity in rats. J Nephropathol 2014;3:121-3.
185. Beladi-Mousavi SS, Bashardoust B, Nasri H, Ahmadi A, Hajian S, Torkamaneh S. Association of serum magnesium with Vitamin D level in normal and renal disease patients. J Parathyr Dis 2014;2:45-6.
186. Asadi SY, Parsaei P, Karimi M, Ezzati S, Zamiri A, Mohammadizadeh F, *et al.* Effect of green tea (*Camellia sinensis*) extract on healing process of surgical wounds in rat. Int J Surg 2013;11:332-7.
187. Rahimi Z. Parathyroid hormone, glucose metabolism and diabetes mellitus. J Parathyr Dis 2014;2:55-6.
188. Gohari AR, Saeidnia S. The role of herbal medicines in treatment of urinary tract diseases. J Nephropharmacol 2014;3:13-4.
189. Nazar CM. Diabetic nephropathy; principles of diagnosis and treatment of diabetic kidney disease. J Nephropharmacol 2014;3:15-20.
190. Rafieian-Kopaei M, Baradaran A. On the occasion of world diabetes day 2105; act today to change tomorrow. J Renal Endocrinol 2015;1:e02.

Source of Support: Nil, **Conflicts of Interest:** None declared.