

Review

Traditional medicinal plants used for the treatment of diabetes in the Sudan: A review

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The prevalence of metabolic disorders such as diabetes among population is of increasing concern worldwide. Sudan is a developing country, where several areas frequently depend on folk medicine. Several herbal preparations have been used in folklore practice in Sudan for the management of diabetes with claims asserting their hypoglycemic effect. Basic research relating to these plants are reviewed in this paper with the intention to highlight their therapeutic potential for the treatment of diabetes and promote their regular use in Sudan. Ethnobotanical information was obtained by an assessment of the available literature in electronic data bases with publications describing the medicinal plants used for the treatment of diabetes. In this review paper, different parts of 38 plant species, are described that are used in the Sudanese traditional medicine and belong to 35 genera and 23 families. Thirty three plants have been documented in scientific literature to possess *in vivo* antidiabetic activity and only one was ineffective in lowering blood glucose level, namely *Striga hermonthica*. Many of the plants in the study review have been studied in *in vitro* models (such as α -amylase or α -glucosidase inhibition) in an effort to explain some of their biomedical interaction. The role of isolated bioactive compounds like trigonelline and 3, 5-dicaffeoylquinic acid in diabetes management is also evaluated in the present review. Ten plants original from Sudan have been already used in clinical trials for the treatment of type 2 diabetes. This review provides useful information on the characterization of such herbal medicines that are utilized in the Sudanese traditional medicine for the control of metabolic syndromes such as diabetes.

Key words: Diabetes, Sudan, ethnopharmacology, pharmacology, toxicology.

INTRODUCTION

Diabetes is a metabolic disorder characterized by chronic hyperglycemia which results from insulin deficient secretion or impaired cellular action of the hormone.

Insufficient insulin secretion caused by immune destruction of pancreatic β -cells are vital for insulin secretion and consequent development of insulin-

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dependent diabetes (Type 1). In case of abnormal insulin cellular action, type-2 diabetes is developed due to a gradual development of insulin resistance and pancreatic β -cell dysfunction. Symptoms are worsen due to obesity and lack of physical activity by the sedentary lifestyle (Gutch et al., 2014).

Diabetes prevalence is on the rise worldwide as a result of accumulating risk factors well pronounced in economically growing nations. An estimated 69% rise is observed for the prevalence of the disease in adults in developing countries versus 20% for adults in developed countries (Shaw et al., 2010). The prevalence rate of diabetes in Sudan ranks the disease high among others that are of raising great concern for the community and for the medical service (Ahmad et al., 2008).

The total population in Sudan is about 34 million, with 70% of it in the Northern parts. Prevalence of type 1 diabetes is estimated at 0.1% among school-age children 7 to 14 years old while type 2 diabetes is estimated at 10.4% among adult population (over 25 year of age) in Northern Sudan (Elamin et al., 1989; Motala et al., 2003).

A complex mechanism involving enzymes and other factors influences the action of insulin in the management of hyperglycemia. Mainstream drugs that are used to control diabetes fall into three main categories. The first category of drugs aims to enhance endogenous insulin availability and includes agents that act on the sulfonyl urea receptors in the pancreas to promote insulin secretion and others that have an impact on the small intestinal mucosal epithelium.

Medicines categorized as group two are directed to potentiate the response to insulin, among them being thiazoline. This group of drugs seems to act as initiator of peroxisomal receptors responsible for regulation of metabolism of carbohydrates, lipids and proteins. The drugs categorized as group three are represented by α -glucosidase inhibitors and are targeted at reducing the metabolism of complex sugars (Sheehan, 2003; Thompson and Davis, 2017).

Current glycemic medications burden patients due to variable contraindications and interactions with other drugs as well as limited efficacy, limited tolerability and significant side effects arising from their complex mechanisms of action (Moller, 2001; Rotenstein et al., 2012). Existing pharmacotherapy is still far from achieving optimal blood sugar control in such patients, as an effect of a dysfunction in insulin secretion, action, or both (Gupta et al., 2016).

A number of reviews from different countries have highlighted the significance of medicinal plants application for the control of diabetes (Ezuruike and Prieto, 2014). Despite the wide-spread traditional use of these plants for diabetes management in Sudan, scientific support for the safe and effective use of such plants does not exist. The aim of the present work was to collect data relevant to the traditional control of diabetes with plants wellknown for their medicinal effects in Sudan.

Traditional medicinal plants for the control of diabetes

Data about the use of plants in folklore medicine for the control of diabetes relates either with previously conducted ethnobotanical studies or published papers demonstrating the antidiabetic impact of certain plants in Sudan. The experimental evidence of the antidiabetic activity is highlighted in this review, along with biochemical analysis (where available). Considering comprehensiveness and increasing interest in antioxidant activity in relation to antidiabetic effect of plants, the antioxidant activity of these plants are also reviewed (Ezuruike and Prieto, 2014). A literature search of electronic databases on these plants was carried out and for each of the identified plants, synonyms (for plants which were not identified with their accepted names in the original publication), family name, local name, and plant part used are compiled in Table 1. Available pharmacological evidence of these plants for their therapeutic use is also summarized, and most toxicological relevant studies are presented in Table 2.

Experimental evidence concerning medicinal plants and their phytoconstituents that are used in management of diabetes

Acacia nilotica

A dose of 400 mg/kg body weight (b.w) of an aqueous methanol extract of *A. nilotica* pods significantly reduced the levels of blood glucose, the plasma total cholesterol (TC), total triglyceride (TTG), low-density lipids (LDL), the activity of serum glutamate oxaloacetate (GOT) and pyruvate transaminase (GPT) after one month of treatment in diabetic rabbits compared to the untreated diabetic ones. Furthermore, the same dose also significantly increased the plasma high density lipids (HDL) levels of the treated rabbits but not significant effect on creatinine clearance was observed (Ahmad et al., 2008). Hot water extract of *A. nilotica* pods decreased significantly the plasma glucose level of alloxan-induced Albino mice after 1 to 2 h of administration (Abd el-aziz et al., 2013). A similar observation was obtained in Wistar albino rats treated with 400 to 800 mg/kg of aqueous extract of *A. nilotica* pods and 800 mg/kg of ethyl-acetate and *n*-butanol fractionated from aqueous extract after 12 to 18 h of administration (Auwal et al., 2013). Moreover, Tanko et al. (2013) demonstrated that ethyl acetate fraction obtained from the methanolic extract of *A. nilotica* leaves had a remarkable hypoglycemic effect in alloxan-induced diabetic rats after treatment with 50 and 100 mg/kg for 7 to 12 days. Modified lignin extracted from the hardwood of *A. nilotica* exhibited increased glucose binding efficiency as demonstrated by the decreased glucose diffusion and enhanced α -amylase inhibition in

Table 1. Plants used in Sudanese traditional medicine for treatment of diabetes.

S/N	Plant species	Family	Local name	Part used	References
1	<i>Acacia nilotica</i> (L.) Willd. ex Delile	Fabacea	Garad	Pod, bark	(Gaber et al. (2013)
2	<i>Acacia senegal</i> (L.) Willd.	Fabaceae	Hashab	Fruit	(Hilmi et al. (2014)
3	<i>Aloe sinkatana</i> Reynolds	Xanthorrhoeaceae (Aloaceae)	Sabar	Leaf	Gaber et al. (2013)
4	<i>Allium cepa</i> L.	Amaryllidaceae	Basal	Bulb	TajEldin et al. (2009)
5	<i>Allium sativum</i>	Amaryllidaceae	Toom	Bulb	Ebrahim et al. (2012)
6	<i>Ambrosia maritima</i> L.	Asteraceae	Damesisa	Leaf	Yagi et al. (2013)
7	<i>Ammi visnaga</i> (L.) Lam.	Apiaceae	Bizrat al khalla	Fruit	Hilmi et al. (2014)
8	<i>Balanites aegyptiaca</i> (L.) Del.	Zygophyllaceae	Laloub	Fruit	Gaber et al. (2013)
9	<i>Bauhinia rufescens</i> Lam.	Fabaceae	Kulkul	Leaf	El-Ghazali et al. (1997)
10	<i>Capparis decidua</i> (Forssk.) Edgew.	Capparaceae	Tundub	Stem	Zia-Ul-Haq et al. (2011)
11	<i>Catunaregam nilotica</i> (Stapf) Tirven (Syn. <i>Randia nilotica</i> Stapf)	Rubiaceae	Kir Kir	Fruit	Alamin et al. (2015)
12	<i>Cicer arietinum</i> L.	Fabaceae	Kabkabe	Seed	Mustafa et al. (2013)
13	<i>Cinnamomum verum</i> J. Presl (Syn. <i>Cinnamomum zeylanicum</i> Blume)	Lauraceae	Gerfa	Stem bark	Mustafa et al. (2010)
14	<i>Citrullus colocynthis</i> (L.) Schrad.	Cucurbitaceae	Hundal	Seed	El-Ghazali et al. (1997)
15	<i>Cyperus rotundus</i> L.	Cyperaceae	Sieda	Rhizome	El-Ghazali et al. (1997)
16	<i>Eucalyptus globulus</i> Labill.	Myrtaceae	El kafour	Leaf	Houacine et al. (2012)
17	<i>Faidherbia albida</i> (Delile) A. Chev. (Syn. <i>Acacia albida</i> Delile)	Fabaceae	Haraz	Root bark	Gaber et al. (2013)
18	<i>Foeniculum vulgare</i> Mill.	Apiaceae	Shamar	Fruit	Anitha et al. (2014)
19	<i>Geigeria alata</i> (Hochst. & Steud. ex DC.) Oliv. & Hiern	Asteraceae	Al Gadad	Root	Hafizur et al. (2012)
20	<i>Guiera senegalensis</i> J.F.Gmel.	Combretaceae	Ghubeish	Leaf	Gaber et al. (2013)
21	<i>Hyphaene thebaica</i> (L.) Mart.	Arecaceae	Nabag	Epicarp	Gaber et al. (2013)
22	<i>Khaya senegalensis</i> (Desr.) A. Juss.	Meliaceae	Mahogany	Stem bark	El-Ghazali et al. (1997)
23	<i>Kigelia africana</i> (Lam.) Benth (Syn. <i>Kigelia pinnata</i> (Jacq.) DC.)	Bignoniaceae	Um Shutour	Fruit	Priya et al. (2014)
24	<i>Lupinus termis</i> Forssk. <i>Mitragyna inermis</i> (Willd.) Kuntze (Syn. <i>Mitragyna africana</i> (Willd.) Korth., nom. illeg.)	Papilionaceae	Turmus	Fruit	Gaber et al. (2013)
25		Rubiaceae	Um Gatto	Fruit	Alamin et al. (2015)
26	<i>Momordica balsamina</i> L.	Cucurbitaceae	Abu el Efain	Leaf & seed	Houacine et al. (2012)
27	<i>Nauclea latifolia</i> Smith	Rubiaceae	Karmadoda	Leaf	Alamin et al. (2015)
28	<i>Nigella sativa</i> L.	Ranunculaceae	Al Haba Alsoda	Seed	Hilmi et al. (2014)
29	<i>Rhynchosia minima</i> (L.) DC.	Fabaceae	Irg el Dam	Root	EL-Kamali and EL-amir (2010)
30	<i>Salvia officinalis</i> L.	Lamiaceae	Maaramya	Leaf	Houacine et al. (2012)
31	<i>Sclerocarya birrea</i> (A. Rich.) Hochst	Anacardiaceae	Hommaid	Stem bark	Mariod et al. (2012)
32	<i>Senna obtusifolia</i> (L.) H.S. Irwin & Barneby (Syn. <i>Cassia tora</i> L.)	Caesalpiniaceae	Kawal	Fermented leaf	EL-Kamali and EL-amir (2010)
33	<i>Sesamum indicum</i> L.	Pedaliaceae	Simsim	Seed	Hilmi et al. (2014)
34	<i>Striga hermonthica</i> (Delile) Benth.	Orobanchaceae	Al-buda	Whole plant	Alamin et al. (2015)
35	<i>Tinospora bakis</i> (A.Rich.) Miers	Menispermaceae	Irg El Haggar	Seed	Alamin et al. (2015)
36	<i>Trigonella foenum-graecum</i> L.	Fabaceae	Hilba	Seed	Gaber et al. (2013)
37	<i>Vangueria madagascariensis</i> J.F. Gmel.	Rubiaceae	Soum Eyown	Root	Musa et al. (2011)
38	<i>Zygophyllum coccineum</i> L.	Zygophyllaceae	Tartir	Whole plant	Gaber et al. (2013)

Table 2. Toxicological studies on plants used in Sudanese traditional medicine for treatment of diabetes.

Plant	Interaction/toxicity studies	References
<i>Acacia nilotica</i>	Co-incubation of 0.01% of the extract in Caco-2 cell monolayers decreased the integrity of the monolayer and the secretory transport of CsA indicating possible inhibition of P-gp	Deferme et al. (2003)
<i>Acacia senegal</i>	Toxicity studies of the ethanol extracts of the stem bark revealed that they exhibited no significant toxicity against <i>Artemia salina</i> .	Okoro et al. (2012)
<i>Allium sativum</i>	Components of aged garlic extract did not produce significant inhibition of Cytochrome P450 enzymes <i>in vitro</i> and in humans	Markowitz et al. (2003) and Greenblatt et al. (2006)
<i>Ambrosia maritima</i>	A single dose of 2000 mg/kg Body weight of the methanolic extract of <i>A. maritima</i> was fatal to rats, but a daily dose of 500 and 250 mg/kg b.w was not fatal.	Afaf et al. (2007)
<i>Ammi visnaga</i>	Acute toxicity (LD ₅₀) of intraperitoneal administration of aqueous extract of <i>A. visnaga</i> fruit in rats was 3.6 g/kg	Jouad et al. (2002)
<i>Bauhinia rufescens</i>	In the brine shrimp lethality assay, ethyl acetate and methanol extracts of the leaves of the plant were found toxic to the <i>Artemia salina</i> with IC ₅₀ values of 0.059 mg/mL and 0.389 mg/mL. While, both the petroleum ether and ethyl acetate extracts of the stem bark were not toxic to the larva.	Muhammad and Sira (2013)
<i>Capparis decidua</i>	Petroleum ether, chloroform, ethyl acetate and butanol extracts were not toxic against brine shrimps and vero cell lines.	Abdallahman et al. (2016)
<i>Catunaregam nilotica</i>	Aqueous extract of fruits was safe up to a dose of 2000 mg/kg body weight.	Alamin et al. (2015)
<i>Citrullus colocynthis</i>	A single daily dose of alcoholic extract of <i>C. colocynthis</i> (50, 100, 200, 400 g/kg) can have toxic effects on liver cells which may induce hepatocyte necrosis and liver fibrosis	Dehghani and Shahin (2006)
<i>Cyperus rotundus</i>	Ethanol extract of rhizomes was safe up to the dose 2000 mg/kg to Wistar rats	Jebasingh et al. (2012)
<i>Eucalyptus globulus</i>	Ethanol leaf extract have shown moderate brine shrimp lethality with LC ₅₀ value of 55.95 µg/mL.	Houacine et al. (2012)
<i>Faidherbia albida</i>	Ethanol stem bark extract of <i>F. albida</i> is relatively safe when used sub-acute in rats.	Oluwakanyinsola et al. (2010)
<i>Guiera senegalensis</i>	Ethanol leaf extract have shown moderate brine shrimp lethality with LC ₅₀ value of 26.94 µg/mL	Houacine et al. (2012)
<i>Kigelia africana</i>	Fruits of the plant given to the experimental rats at doses 100, 200 and 400 mg/kg/day orally were toxic but not fatal.	Adam et al. (2013)
<i>Lupinus termis</i>	Lupins contain certain secondary compounds including toxic alkaloids, such as lupinine	Rahma and Narasinga (1984)
<i>Mitragyna inermis</i>	Alkaloid rich extract derived from <i>M. inermis</i> induced a strong inhibition of protein synthesis in mammalian cells but did not exhibit mutagenic or genotoxic activity	Traore et al. (2000)
<i>Momordica balsamina</i>	<i>In vitro</i> toxicity results raise concern for chronic use	van de Venter et al. (2008)
<i>Nauclea latifolia</i>	An alkaloid rich extract derived from <i>N. latifolia</i> could interact <i>in vitro</i> with DNA of bacteria and mammalian cells, leading to G2-M cell cycle arrest and heritable DNA-damage, as well as inducing <i>in vivo</i> single-strand breaks in liver, kidney and blood cells	Traore et al. (2000)
<i>Rhynchosia minima</i>	The plant is reported as toxic to fish. The seeds are bitter and poisonous and seed extract shows specific agglutinating action on human RBC	Mali and Mahale (2008)

Table 2. Cont'd.

<i>Salvia officinalis</i>	Ethanol leaf extract have shown moderate brine shrimp lethality with LC ₅₀ value of 37.21 µg/mL	Houacine et al. (2012)
<i>Sclerocarya birrea</i>	Stem-bark aqueous and methanolic extracts are relatively safe but <i>in vitro</i> toxicity test has raised concerns over chronic use of <i>S. birrea</i> extracts	Ojewol (2003)
<i>Senna obtusifolia</i>	The leaves can cause marked toxic effects on rats, and the processing of the leaves by fermentation to produce kawal did not alter the toxic activity of the ingredients in the leaves	Yagi et al. (1998)
<i>Sesamum indicum</i>	Sesame oil or its lignans, due specifically to their methylenedioxyphenyl group, could interact with the P450 isozymes and affect the drug metabolisms or dispositions in human	Gokbulut (2010)
<i>Striga hermonthica</i>	Aqueous extract of whole plant was safe up to a dose of 2000 mg/kg body weight	Alamin et al. (2015)
<i>Tinospora bakis</i>	Aqueous extract of seeds was safe up to a dose of 2000 mg/kg body weight.	Alamin et al. (2015)
<i>Trigonella foenum-graecum</i>	Short-term (90 days) and long term (24 week) feeding of fenugreek seeds to rats at levels equivalent to 2 and 4 times the therapeutic dose recommended for humans (25 g/day) produced no toxic effects.	Udayasekhara et al. (1996) and Sharma et al. (1996)

comparison to the controls (Barapatre et al., 2015).

Acacia senegal

Administration of 200 and 400 mg/kg b.w of ethyl acetate extract from the stem bark of *A. senegal* significantly lowered the levels of blood glucose, serum TC, serum TTG, serum LDL, serum urea and creatinine, and increased the serum HDL level in alloxan-induced diabetic albino rats on day 16 after the administration (Batra et al., 2013). Treatment of CCl₄-induced acute hepatotoxicity in albino Wistar rats with 400 and 800 mg/kg/day of the hydroalcoholic (70% ethanol) extract of *A. senegal* pods, orally for 7 days, significantly reduced the liver damage and the symptoms of liver injury by restoration of architecture of liver as indicated by lower levels of serum bilirubin and prevention of hepatic damage (Pal et al., 2014). The components extracted by ethanol from the leaves of *A. Senegal* decreased the activity of sucrose enzyme and appeared to support the control of carbohydrate hydrolysis, and consequently reduces the rise of postprandial blood glucose in diabetics (Abdelhady and Youns, 2014).

Aloe sinkatana

The effects of aqueous extracts of *A. sinkatana* leaves on blood glucose and lipid profile in type 2 diabetic patients

was evaluated by Gaber et al. (2013). The volunteers of the experimental group received the aqueous extract (500 g/l) at a dose of 5 mL/day. A significant reduction in levels of fasting blood sugar, TTG, TC and LDL and a significant increase in HDL levels was observed.

Allium cepa

A detailed review on the positive antidiabetic activity effect of *A. cepa* in different animal models, and its antioxidant activity as well as clinical studies on diabetic patients was presented by Akash et al. (2014).

Allium sativum

Administration of aqueous extract of *A. sativum* to induced diabetic rats reduced the blood glucose level, total serum lipids and cholesterol (Thomson et al., 2007; Ozougwu and Eyo, 2010; Badole et al., 2013; Thomson et al., 2016).

Ambrosia maritima

Administration of water, 50% ethanolic, ether or petroleum ether extracts of *A. maritima* whole plant to albino rats significantly reduced blood glucose after 1.5 and 2 h, however without significant changes in insulin

levels (Ammar et al., 1993). Alloxan-induced diabetic albino rats treated orally with 28.5 mg/kg b.w. of aqueous extract of *A. maritima* aerial parts twice/day showed significant improvement in most of biochemical parameters (levels of fasting blood glucose, serum insulin, total proteins, albumin, globulin, HDL, aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, creatinine, uric acid, serum TC, TTG and LDL) (Helal et al., 2014).

Ammi visnaga

Aqueous extract of *A. visnaga* at the dose of 20 mg/kg b.w. significantly reduced blood glucose in induced-streptozotocin diabetic rats after repeated oral administration for nine days (Jouad et al., 2002).

Balanites aegyptiaca

The addition of 10 % whole or extracted pulp of *B. aegyptiaca* fruits instead of starch in the basal diet of alloxan-induced albino rats, for 20 days, caused a significant decrease in serum glucose level and inhibited the activities of serum GOT and GPT (El-Saadany et al., 1986). Aqueous extract of mesocarps of the fruits exhibited a prominent antidiabetic activity when offered orally in streptozotocin-induced diabetic mice (Kamel et al., 1991). Administration of fruits aqueous extract (1.5 g/kg b.w. daily for 45 days) in streptozotocin-induced Wistar albino diabetic rats significantly reduced the mean plasma glucose and malondialdehyde levels, and significantly increased the mean plasma insulin, liver-pyruvate kinase, and total antioxidant capacity levels. An obvious increase in the weight of the pancreas and the size of the islets of Langerhans, and improvement in the histoarchitecture were also evident in the treated groups compared to untreated ones (Khalil et al., 2016). The antidiabetic activities of different fruit extracts and fractions of *B. aegyptiaca* were tested in cultured C2C12 skeletal muscle cells and 3T3-L1 adipocytes. An 18 h treatment with 200 µg/mL of the sugars fraction, dichloromethane (E) and ethyl acetate (F) successive extracts increased basal glucose uptake in muscle cells. Only E and F extracts accelerated the triglyceride accumulation in pre-adipocytes undergoing differentiation (Motaal et al., 2012). Dichloromethane and ethyl acetate extracts of the fruit were standardized by high-performance liquid chromatography to contain 0.031 and 0.239% of rutin, and 0.007 and 0.004% of isorhamnetin, respectively (Abdel Motaal et al., 2012). Trigonelline (3-carboxy-1-methyl pyridinium) was identified in the fruits (8 and 13 mg in the peel and pulp respectively) in addition to the flavonoids quercetin, isorhamnetin flavonol and epicatechin (Farag et al., 2015). Saponins, 26-O-beta-D-glucopyranosyl-(25R)-furost-5-ene-3 beta, 22, 26-triol 3-O-[alpha-L-rhamnopyranosyl-(1-2)]-[beta-D-xylopyranosyl-

(1--3)]-[alpha-L-rhamnopyranosyl-(1--4)]-beta-D-glucopyranoside and its 22-methyl ether, 26-O-beta-D-glucopyranosyl-(25R)-furost-5-ene-3 beta,22,26-triol 3-O-(2,4-di-O-alpha-L-rhamnopyranosyl)-beta-D-glucopyranoside and its methyl ether were also isolated and identified. It was revealed that the individual saponins did not show antidiabetic activity, while their combination resulted in significant activity.

Bauhinia rufescens

The oral administration of 200, 300, and 400 mg/kg b.w. methanol extract from the leaves of *B. rufescens* (once a day, for four weeks) significantly lowered the blood glucose levels in alloxan-induced diabetic rats in a dose dependent manner (Aguh et al., 2013).

Catunaregam nilotica

Acute and chronic treatment of streptozotocin-induced diabetes rats with aqueous extracts of *C. nilotica* (Syn. *Randia nilotica*) fruit at 400 mg/kg significantly lowered blood glucose, serum lipid and creatinine levels, and brought back the activity of AST enzyme to normal level. Histopathological studies showed that the aqueous extracts of the plant reinforced the protection of liver (Alamin et al., 2015). Methanolic extracts of leaves, bark and seedcake of *C. nilotica* possess good antioxidant activity and high phenolic content (Mariod et al., 2012).

Capparis decidua

Fruits of *C. decidua* decreased the lipid peroxidation and altered free radical scavenging enzymes such as superoxide dismutase and catalase in erythrocytes, liver, kidney and heart in alloxan induced diabetic rats (Agarwal and Chavan, 1988; Yadav et al., 1997). Moreover, the fruit extract showed satisfactory inhibitory effect on α -amylase and α -glucosidase enzymes, followed by flowers and leaves extracts (Zia-Ul-Haq et al., 2011).

Cicer arietinum

Administration of petroleum ether extract (400 mg/kg) of the seed to alloxan-induced diabetic mice reduced significantly the serum glucose level in both acute and subacute studies (Yadav et al., 2009). The seed showed significant diphenylpicrylhydrazyl (DPPH), nitric oxide and hydrogen peroxide activity (Vadnere et al., 2013).

Cinnamomum verum

Administration of 200 mg/kg b.w. of cinnamon aqueous extract to alloxan-induced diabetic rats lowered

significantly the levels of fasting blood glucose, TC, HDL, LDL and TG (El-Desoky et al., 2012). Moreover, administration of bark aqueous extract of cinnamon containing 45 and 75% gallic acid equivalents of polyphenol to streptozotocin-induced diabetic rats at 200 mg per kg b.w. for 30 days displayed hypoglycemic and hypolipidemic effects (IM et al., 2014). The bark is rich in volatile oil and polyphenols including rutin, catechin, quercetin, kaempferol and isorhamnetin have been isolated (Yang et al., 2012).

Citrullus colocynthis

Administration of roots aqueous extract (2000 mg/kg) to alloxan-induced diabetic rats showed hypoglycemic effect and improved serum levels of urea and lipid (Agarwal et al., 2012). Moreover, hydroethanol extract (300 mg/kg bw) of the seed reduced significantly the blood glucose level in alloxan-induced diabetic rats (Oryan et al., 2014). Petroleum ether extract (300 and 500 mg/kg bw) of fruit pulp showed significant hypoglycemic effect in streptozotocin-induced diabetes albino rats (Jayaraman et al., 2009).

Cyperus rotundus

The ethanolic extract of *C. rotundus* rhizomes at dose of 250 and 500 mg/kg b.w, for 3 weeks, revealed significant antidiabetic activity and resulted in improvement of body weight and reduction in the levels of biochemical parameters such as GPT, GOT, TC and TTG in streptozotocin-induced diabetic mice (Singh et al., 2015).

Eucalyptus globulus

Administration of leaf aqueous extract of *E. globulus* at a dose of 150 mg/kg b. w decreased the blood glucose and lipid levels in alloxan induced diabetic rats (Patra et al., 2009). Aqueous ethanolic leaf extract at a dose of 400 mg/kg b.w reduced also the blood glucose level in glucose loaded rats (Houacine et al., 2012). Incorporation of *E. globulus* leaf in diet (20 g/kg) and drinking water (2.5 g/L) had hypoglycemic effect and reduced oxidative stress in streptozotocin-induced diabetic rats (Nakhaee et al., 2009).

Faidherbia albida

The administration of an aqueous extract from the stem bark of *F. albida* at dose 125 to 500 mg/kg b.w to alloxan-induced diabetic rats decreased significantly the fasting blood glucose level in a dose dependent manner and ameliorated the serum markers of the liver, feed and fluid

intake, body weight and packed cell volume (Umar et al., 2014).

Geigeria alata

Diabetic rats orally treated with 250 mg/kg of *G. alata* root aqueous methanolic extract for 2 h (acute) appeared to have significantly lower blood glucose levels after 120 min. Constant treatment for 14 days of diabetic rats with 250 mg/kg of *G. alata* extract resulted in a significant decrease in blood glucose level (7.34 ± 0.33 mmol/l) closer to that of nondiabetic rats. At the same time, it significantly decreased serum TTG levels, increased serum insulin levels, improved β -cell function, and the antioxidant status. *G. alata* also showed strong antioxidant and α -glucosidase inhibitory activities in *in vitro* assays (Hafizur et al., 2012).

Guiera senegalensis

A dose-dependent significant reduction in blood glucose levels which was more remarkable at the dose of 400 mg/kg was observed after the application of *G. senegalensis* leaves ethanolic extract (Houacine et al., 2012).

Hyphaene thebaica

Oral administration of aqueous extract of *H. thebaica* mesocarp experimentally caused a significant decrease in blood glucose level in Wistar albino rats, at 12 to 18 h post administration (Auwal et al., 2012). Aqueous extract improved glucose and insulin tolerance, and significantly lowered blood glycosylated hemoglobin levels. Chrysoeriol and 7-O- β -D-galactopyranosyl(1 \rightarrow 2)- α -L-arabinofuranoside, which were isolated in the aqueous extract reduced significantly AST and ALT levels of liver and improved the kidney function (Salib et al., 2013).

Khaya senegalensis

The antidiabetic activity of *K. senegalensis* butanol fraction of the root ethanolic extract in type 2 diabetes model of rats was examined by Ibrahim and Islam (2014). The orally administered extract, at 300 mg/kg b.w, significantly reduced blood glucose level, improved oral glucose tolerance ability and β -cell function (HOMA- β), decreased insulin resistance (HOMA-IR), stimulated hepatic glycogen synthesis, ameliorated serum lipids alterations and prevented hepatic and renal damages compared to untreated diabetic rats. Additionally, the fraction tended to improve weight gain, decrease feed and fluid intake, stimulate insulin secretion and lower

serum fructosamine concentrations. Polyphenolic compounds such as catechin, rutin and procyanidins with significant antioxidant activities were also identified in different parts of the plant (Atawodi et al., 2009).

Kigelia africana

In streptozotocin-induced diabetic rats, daily administration of the defatted methanolic extract of *K. africana* flower at the doses of 250 and 500 mg/kg b.w for 21 days reduced significantly the blood glucose and the TC and TTG levels as well (Kumar et al., 2012). Similarly, methanolic extract from the leaves was found to significantly decrease ($P < 0.01$) serum glucose level in alloxan-induced diabetic rats after the 21 days of oral treatment (Priya et al., 2014). The ethanolic extract, together with compounds catalpol, specioside and minecoside (10 μ M) isolated from the *n*-butanol fraction exhibited significant stimulation of GLUT4 translocation to cell surface from intracellular compartments (Khan et al., 2012). Acetone, ethanol, chloroform, and water extracts of the leaves caused a significant α -amylase inhibitory effect (Dhriti et al., 2014). The root, stem bark, fruit and leaves were found to possess antioxidant activity (Atolani et al., 2011; Sikder et al., 2011; Agyare et al., 2013; Akanni et al., 2014).

Lupinus termis

A dose (75 mg/100 g b.w) of aqueous suspension from *L. albus* orally administered daily to alloxan-diabetic rats restore the changes in the levels of glucose, urea, creatinine and bilirubin and the enzymic activities of AST, ALT and lactate dehydrogenase (LDH) to their normal levels after 4 weeks of treatment (Mansour et al., 2002). In contrast, Sewani-Rusike et al. (2015) reported that the use of *L. albus* may not be effective in treating hyperglycaemia in type 1 diabetes but effective for treating diabetes induced dyslipidemia. They found that *L. albus* demonstrated significant hypoglycaemic effects in normal rats but not in diabetic rats after acute and long term treatment. Normal treated rats showed higher insulin levels compared to normal controls but insulin remained very low in diabetic rats. However, *L. albus* was effective in reducing atherogenic lipid levels.

Mitragyna inremis

Oral administration of aqueous extracts from *M. inremis* fruits at the level of 400 mg/kg to streptozotocin-induced diabetic rats, for 14 days, resulted in a significant antihyperglycemic effect and have the capacity to correct the metabolic disturbances associated with diabetes. Histopathological studies showed that the aqueous

extracts of the plant reinforced the protection of liver (Alamin et al., 2015).

Momordica balsamina

Aqueous extract of *M. balsamina* seeds at the level of 500 mg/kg b.w dose caused a significant increase in the blood glucose levels of streptozotocin-induced diabetic rats. Furthermore, after three weeks of treatment of the diabetic animals with the aqueous extract (500 mg/kg b.w) blood sugar level was significantly higher compared to untreated diabetic rats; at the same time, lipid profile and body weight were improved (Bhardwaj et al., 2010). Moreover, aqueous and organic extracts of *M. balsamina* was screened against chang liver, C2C12 muscle and 3T3-L1 adipose cells using a glucose utilization assay. Results showed that *M. balsamina* extracts were active in myocytes and stimulated glucose utilisation in hepatocytes (van de Venter et al., 2008).

Nauclea latifolia

Aqueous leaves extracts of *N. latifolia* at the level of 200 mg/kg b.w significantly lowered glucose levels of the alloxan-induced diabetic rats within 4 h (Gidado et al., 2005). Moreover, the aqueous and ethanolic extracts significantly lowered the fasting blood glucose levels of the streptozotocin-diabetic Wistar rats in a dose-dependent manner after 1-6 h of administration (Gidado et al., 2008). The same results were observed when ethanolic extracts (100, 200 and 400mg/kg b.w) of the leaves were provided orally for 45 days to streptozotocin-induced diabetic rats (Abubakar et al., 2009). Significant reduction was found in the fasting blood glucose, lipid profile (TG and LDL) levels in diabetic rats administered 150 and 300 mg/kg b. w. of *n*-hexane and methanolic leaves fractions of *N. latifolia* (Effiong et al., 2014). Treatment of Swiss albino mice with 200 mg/kg b.w of ethanolic extract of leaves, twice a day for 21 days, decreased significantly blood glucose in diabetic animals and caused significant decrease ($p < 0.05$) in TC, LDL level and ALT and AST activities (Sylvester and Dan, 2015).

Nigella sativa

Several studies demonstrated the hypoglycemic effect of *N. sativa* seed (Benhaddou-Andaloussi et al., 2011; Sathivelu et al., 2013; Ikram and Hussain, 2014; El Rabey et al., 2017). The seed was shown to ameliorate biochemical and histopathological changes caused by diabetes, decrease oxidative stress, elevate level of insulin, reduce resistance of insulin and hepatic gluconeogenesis, enhance renewal of β -cells of islets of

Langerhans and create direct insulin-like effects at the cellular and molecular levels in various organs. Seed volatile oil and thymoquinone were found to possess the highest antidiabetic activity (Bamosa, 2015).

Salvia officinalis

The hypoglycemic effect of the aqueous ethanolic extract of *S. officinalis* leaves at the dose of 200 to 400 mg/kg is revealed as a dose-dependent significant reduction of blood glucose levels (Houacine et al., 2012).

Sclerocarya birrea

Following acute treatment, relatively moderate to high doses of *S. birrea* stem-bark aqueous extract (25 to 800 mg/kg b.w) induced a dose-dependent, significant reduction in the blood glucose concentrations of fasted streptozotocin-treated diabetic rats (Ojewole, 2003). Results from male Wistar rats subjected to oral load of glucose (4g/kg) after receiving a dose of 35 mg/kg of aqueous extracts of fresh leaves and barks of *S. birrea* showed that the extracts caused significant antihyperglycemic effects after 2 and 4 h (François et al., 2014). Aqueous and methanolic extracts of the stem bark inhibited the activities of α -amylase and α -glucosidase in a concentration dependent manner. Both extracts possess antioxidant activity, with the methanolic extracts displaying the strongest free radical scavenging capacity. Extracts also significantly increased glucose uptake in C2C12 myotubes, 3T3-L1 adipocytes and HepG2 hepatocarcinoma cells. However, insulin secretion from RIN-m5F cells was not affected (Mousinho et al., 2013). Crude *S. birrea* stem bark methanolic and acetone extracts inhibited human urinary α -amylase more potently than acarbose. Crude hexane extract displayed a strong inhibition of α -glucosidase and weak inhibition of α -amylase. Furthermore, the hexane extract significantly suppressed the rise in postprandial glucose level after oral administration of sucrose but failed to induce similar effects after oral administration of starch and glucose in both normal and diabetic rats (Mogale et al., 2011).

Sesamum indicum

Treatment of streptozotocin-induced diabetic rats with 500 mg/kg b.w ethanolic extract of *S. indicum* seeds for 8 weeks increased significantly the blood glucose and glycosylated hemoglobin levels but decreased significantly the serum insulin and hemoglobin levels. The liver glycogen level was significantly decreased in diabetic rats closer to normal revealing its potential effect to control hyperglycemia (Bhuvanewari and

Krishnakumari, 2012). Alloxan-induced diabetic rats provided with 10% and 20% seeds either raw or roasted as supplemented diet had significantly ($p < 0.05$) lower levels of blood glucose, lipids and some serum enzymes (Akanya et al., 2015). Takeuchi et al. (2001) found that hot-water extract from defatted sesame seed and its methanolic fraction had a reductive effect on the plasma glucose concentration of KK-Ay mice, and this effect is suggested to have been caused by the delayed glucose absorption. Amutha and Godavari (2016) demonstrated that *S. indicum* can be used to reduce the postprandial hyperglycemia by inhibiting carbohydrates metabolizing enzymes α -amylase and α -glucosidase, and also to combat the free radicals due to its antioxidant activity. It has been reported that sesame seeds can improve oxidative status due to the activities of their contents including sesamin, sesamol, sesamol, and sesame (Wichitsranoi et al., 2011).

Striga hermonthica

Daily oral administration of *S. hermonthica* whole plant aqueous extract (400 mg/kg b.w) to streptozotocin-induced diabetic rats for 14 days appeared to increase the blood glucose level, and did not improve the levels of TC, LDL, HDL, urea and blood urea nitrogen indicating that it has no antihyperglycemic effect (Alamin et al., 2015). Kiendrebeogo et al. (2005) found that the aqueous extract of *S. hermonthica* whole plant possessed antioxidant activity and they suggested that the isolated luteolin could be responsible for this activity.

Tinospora bakis

Acute and chronic treatment of streptozotocin-induced diabetes rats with aqueous extracts of *T. bakis* seeds at 400 mg/kg significantly lowered blood glucose levels, and had the capacity to correct the metabolic disturbances associated with diabetes. Histopathological studies showed that the aqueous extracts of the plant reinforced the healing of liver (Alamin et al., 2015).

Trigonella foenum-graecum

Animal's standard diet supplemented with seeds of *T. foenum-graecum* (5%) for 30 days to alloxan induced diabetic rats significantly decreased the levels of glucose, TG, TC and LDL-CH and increased the level of HDL-CH. Also it reduced the oxidative stress by improving the superoxide dismutase, catalase and glutathione peroxidase activities both in serum and in pancreas homogenate (Beji et al. 2016). Administration of *T. foenum-graecum* seeds (2.5 and 5 g) for 4 weeks to Tunisian type 2 diabetic patients, improved blood glucose

level in dose-dependent and the dose of 5 g reduced significantly TC and TG levels and serum α -amylase activity (Khlifi et al., 2016).

Zygodium coccineum

A dose of 1.5 mL of aqueous suspension of *Z. coccineum* herb/100 g b. w (equivalent to 75 mg/100 g b.w), orally administered daily to alloxan-diabetic rats for 4 weeks, restored significantly ($P < 0.05$) the changes at the levels of glucose, urea, creatinine and bilirubin and the activities of AST, ALT, LDH and alkaline phosphatase enzymes in plasma, liver and testes (Mansour et al., 2002). Moreover, 1.5 mL of water soluble extract/kg b.w of the herb, administered orally to alloxan-induced diabetic rats daily for 4 weeks, significantly decreased the blood glucose level and the activity of cytochrome P450, NADPH-cytochrome C reductase, aryl hydrocarbon (benzo(a)pyrene) hydroxylase (AHH), N-nitrosodimethylamine N-demethylase I (NDMA-dI), NADPH-cytochrome C reductase, and detoxified by glutathione S-transferase (GST) and glutathione (GSH) enzymes in the liver of diabetic rats (Sheweita et al., 2002). The leaves were found to possess antioxidant activity (El-Shora et al., 2016). Various compounds from the leaves of *Z. coccineum* were identified by gas chromatography–mass spectrometry (GC/MS) like 1-nonadecene, 9-octadecenoic acid, 2-methyl propanoic acid, β -sitosteol, tricosane and tetracosane, Stigmast-5-en-3-ol, docosene, 1-eicosanol, hexacosane, heptacosane, nonacosane, 6-Ethyl-5-hydroxy-2,3,7-trimethoxynaphthoquinone and pentacosane (El-Shora et al., 2016).

DISCUSSION

Sudan is a developing country that frequently depends on folk medicine in all areas of the country. Several herbal preparations have been used in folklore practice for the management of diabetes with claims asserting their hypoglycemic effect. In this paper, an effort was made to refer to the different parts of 38 plant species that are used in the Sudanese traditional medicine (Table 1). Interestingly, some of these plants have already been reported in previous studies originated from other countries like Algeria (Houacine et al., 2012), Iran (Mikaili et al., 2013), Egypt (Helal et al., 2014), India (Singh et al., 2015), Nigeria (Auwal et al., 2012) and Saudi Arabia (Bamosa, 2010). The reviewed plants have been evaluated, in *in vivo* experiments with diabetic animals that were induced either by alloxan or streptozotocin (Fröde and Medeiros, 2008) in addition to genetically mutated *in vivo* models such as KK-Ay mice. Ten of the characterized plants (*Acacia nilotica*, *Catunaregam nilotica*, *Cicer arietinum*, *Cinnamomum verum*, *Geigeria*

alata, *Guiera senegalensis*, *Khaya senegalensis*, *Mitragyna inremis*, *Momordica balsamina* and *Tinospora bakis*) tested effective in animal models for their antidiabetic potential from samples collected from Sudan.

In vitro pharmacological evidence

From the 38 plants reviewed in this paper, only four of them were not tested for hypoglycaemic activity, either *in vivo* or *in vitro*. Only one from the 34 plant species was ineffective in lowering blood glucose level, namely *Striga hermonthica* (Alamin et al., 2015), suggesting lack of antidiabetic effect. Ezurike and Prieto (2014) reported that the absence of an *in vivo* antihyperglycemic effect of some plants would not be a reason to stop their use as antidiabetics, since they may be used in multicomponent preparations because of their benefits in co-morbid conditions or possibly be the foundation for comprehensive control of the disease and consequent complications. In fact, components aqueously extracted from *S. hermonthica* whole plant reduced the TG level, improved several liver parameters (reduced ALT activity) and possessed high antioxidant activity (Alamin et al., 2015; Kiendrebeogo et al., 2005). Many of the plants described in the present review have been studied in *in vitro* models that could possibly explain some of their mechanisms of action. Information on the mechanism of action would be an important element in implementing a therapeutic plan for diabetes, considering the likely benefit of the synergy of medicinal plants (Ezurike and Prieto, 2014). Four plants (*Acacia nilotica*, *Capparis decidua*, *Geigeria alata* and *Sclerocarya birrea*) have inhibitory effects against either α -amylase or α -glucosidase enzymes; Seven plants (*Ambrosia maritima*, *Balanites aegyptiaca*, *Geigeria alata*, *Hyphaene thebaica*, *Khaya senegalensis*, *Sclerocarya birrea* and *Sesamum indicum*) induce secretion of insulin from β -cells of the pancreas; five plants (*Balanites aegyptiaca*, *Cinnamomum verum*, *Kigelia africana*, *Momordica balsamina* and *Trigonella foenum-graecum*) enhance glucose absorption in muscles or liver or increase GLUT4 gene expression leading to enhanced glucose absorption by muscle and fat tissue and one plant decrease the activity of sucrose enzyme and offer a support to control carbohydrate hydrolysis in diabetic disease.

Bioactive compounds

A number of active compounds have been identified from the plants in this review paper but their role in diabetes management was not proved for most of them. However, trigonelline (3-carboxy-1-methyl pyridinium) was identified in *Balanites aegyptiaca* fruits (8 and 13 mg in the peel and pulp respectively) by Farag et al. (2015). Its discovery provides novel insight into the balanite fruits

antidiabetic properties as the compound is known for a pronounced hypoglycemic effect (Frag et al., 2015). More recently, 3, 5-dicaffeoylquinic acid was found to be the dominant acylquinic acid in *Geigeria alata* roots (25.96±2.08 mg/g dry weight) and ameliorated significantly ($P < 0.05$) the blood glucose and liver biochemical parameters in streptozotocin-induced (40 mg/kg, i.p.) diabetic normotensive Wistar rats and spontaneously hypertensive rats (Simeonova et al., 2016).

Clinical studies

Clinical evaluation, involving human subjects, of biologically active plants is necessary towards the progress of incorporation of medicinal plant products in the health service system (Ezuruike and Prieto, 2014). In this review, 10 plants sourced from Sudan were subjected to clinical trials in Type 2 diabetic patients and results showed that the order of effectiveness of the aqueous extracts of the studied plants to lower fasting blood sugar level was *Lupinus albus* > *Balanites aegyptiaca* > *Allium Sativum* > *Allium cepa* > *Guiera senegalensis* > *Aloe sinkatana* > *Hyphaene thebaica* > *Trigonella foenum-graecum* (Gaber et al., 2013). Capsules containing *Nigella sativa* seeds were administered orally to human volunteers, in Saudi Arabia, in a dose of 1, 2 and 3 g/day for three months. The dose of 2 g/day caused significant reduction in fasting blood glucose levels, while β -cell function was increased after 12 weeks of treatment (Bamosa, 2010).

Toxicological evidence

Assessment of the safety and toxicity profile of herbal medicine is essential to ensure its therapeutic potential. A summary of the studies that describe the toxicological effects of medicinal plants is presented in Table 2. It has been noted that the majority of the investigations corresponded mainly to the determination of acute toxicity and safe dose and included very limited information concerning toxicological and herb–drug interactions. However, some of the plants listed in Table 2, like *Allium cepa*, *A. sativum*, *Cinnamomum verum* and *Trigonella foenum-graecum* are actually consumed frequently in Sudan and other countries, and are usually perceived as safe. However, Zaid et al. (2010) reported that garlic and onion bulbs share many similar active compounds (for example, allyl propyl and diallyl sulfide) and decrease blood glucose levels also by normalizing liver hexokinase and glucose-6-phosphatase activities and increase insulin secretion from the pancreas but excessive consumption of these two bulbous plants might lead to harmful effects. *T. foenum-graecum* and *C. verum* exhibited cytotoxic effects at concentrations higher than 500 μ g/mL (Kadan et al., 2013). Moreover, consumers

are usually aware of possible health hazards occurring after consumption of certain plants and the necessity of their proper process to remove toxicants before utilization. For example, the toxic lupinine found in Lupins (*Lupinus termis*) is removed through debittering process, including soaking in water and daily replacement of water until bitterness disappears before the seeds could be safely consumed. Although, people in Sudan and other African countries consume kawal (fermented fresh leaves of *Senna obtusifolia*), studies have shown that fermentation has not altered the toxic activity of the ingredients in the leaves (Yagi et al., 1998). Thus, toxicological evaluation of medicinal plants is equally significant as their evaluation for efficacy and there is an urgent need for a vibrant pharmacovigilance system to ensure their use in therapeutic management (Shaw et al., 2012).

Conclusion

The quest for control of diabetes has led to an increasing research at different fronts, among which is medicinal plants. Given the observation of an increasing use of medicinal plants for diabetes in Sudan, this necessitates validation of efficacy and safety. *In vitro* experiments are carried out to ascertain the mechanism of action of medicinal plants. The hypoglycemic effect of certain plants arises as a side effect of their *in vivo* toxicity (Marles and Farnsworth, 1995). However, a risk may be posed by the fact that such hypoglycemic effect is probably partially exhibited via an unfavourable physical mechanism overriding a physiological one. As for the validation of experiments, ethical considerations concerning animal use are increased (Festing and Wilkinson, 2007), and therefore the use of non-animal models should be seriously considered. A number of standardization measures, such as reference pharmacopoeial monographs, are necessary to assert the medicinal value of these herbal medicines as reliable and therapeutically effective. Case studies involving standardized medicinal plant products should be carried out in order to validate the usefulness of plant preparations in diabetes management, which will give support to the pre-clinical results.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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