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Asian Pacific Journal of Tropical Biomedicine

journal homepage: www.elsevier.com/locate/apjtb

Review article http://dx.doi.org/10.1016/j.apjtb.2016.08.006

A review on promising phytochemical, nutritional and glycemic control studies on *Moringa oleifera* Lam. in tropical and sub-tropical regions

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ARTICLE INFO

Article history:
Received 22 Feb 2016
Received in revised form 22 Mar, 2nd revised form 10 May 2016
Accepted 15 Jun 2016
Available online 26 Aug 2016

Keywords:
Antihyperglycemic
Aqueous
Ethanol
Moringa oleifera
Antidiabetic

ABSTRACT

Plants have provided sources to find novel compounds. These plants are being used as therapeutic purposes since the birth of mankind. The traditional healers normally utilize medicinal plants as crude drugs while scientists using the folk claim as guides to explore medicinal plants. *Moringa oleifera* is a famous edible plant having therapeutic and nutritive values. The present study was designed to cumulate the research data regarding to what extent, phytochemical, nutritional and glycemic control studies has been explored using its different extracts. The articles indicated that the powder, aqueous, methanol and ethanol extracts of *Moringa oleifera* (leaves, pods, seeds, stem and root bark) have significant therapeutic herbal potential to treat diabetes mellitus. Collectively, the mechanism behind is intestinal glucose inhibition, insulin release as well as decrease in insulin resistance probably regeneration of β-cells of pancreas, increase in glutathione and reduction in malondialdehyde. Conclusively, this article give descriptive information about antidiabetic effect, claimed marker compounds and proposed antihyperglycemic mechanism of a single plant. It can be suggested a potential herbal source to treat diabetes mellitus as being widely accepted by major population as nutrition and therapeutic agent.

1. Introduction

1.1. Diabetes mellitus – a syndrome

Diabetes mellitus is a heterogeneous assembly of syndromes, with persistent high blood glucose level due to disturbance in various metabolic processes like glycolysis, Krebs cycle, gluconeogenesis, hexose monophosphates hunt pathway, glycogenesis and glycogenolysis, cholesterol synthesis, synthesis and release of insulin [1]. According to World Health Organization, it is a chronic metabolic disorder characterized by common features of chronic hyperglycemia [2]. The chronic hyperglycemia is linked with long-term damage of organs, particularly the eyes, kidneys, nerves, heart, and blood vessels [3].

1.2. Drug discovery

The natural sources (plants, animals and microorganisms) provide a big source for deriving active compounds. Predominantly, the plant kingdom offers a variety of species act as remedies for several diseases in many parts of the world [4,5]. As stated by Newman and Cragg [6] that natural product and their structures played a highly significant role in drug discovery and development process. These are secondary metabolites like alkaloids, terpenoids and phenolic compounds, synthesized by plants as defense against herbivores and pathogens.

1.3. Moringa oleifera Lam. (M. oleifera) tree

M. oleifera Lam. (*Moringa pterygosperma* Gaertn), belongs to Moringaceae family of perennial angiosperm plants, having twelve more species [7] and is a single genus family of shrubs (Figure 1) [8,9].

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Foundation Project: Supported by Ministry of Education, Malaysia (Grant No. 203/PFARMASI/6711451) and Faculty Development Scholarship provided by University of Sargodha, Sargodha, Punjab, Pakistan.
Peer review under responsibility of Hainan Medical University. The journal implements double-blind peer review practiced by specially invited international editorial board members.

Figure 1. *M. oleifera* tree located in Universiti Sains Malaysia, Pulau Pinang, Malaysia.

1.3.1. Local names of M. oleifera

The local names [10–12] includes: Punjabi (Sohanjna), Sanskrit (Shigru), Hindi (Soanjna), Bengali (Sajna), Tamil (Murungai), English (Drum stick tree, Horseradish tree), kelor tree [13], Nile valley-'Shagara al Rauwaq' [14].

1.3.2. Botanical description of M. oleifera

The taxonomic description includes: kingdom: Plantae, subkingdom: Tracheobionta, superdivision: Spermatophyta, division: Magnoliphyta, class: Magnoliopsida, subclass: Dilleniidae, order: Brassicales, family: Moringaceae, genus: *Moringa* and species: *oleifera* [15–17].

All *Moringa* species are native to Asia, from where they have been introduced into other warm countries, such as Malaysia and other tropical countries. The tree can tolerate temperatures from 19 to 28 °C [18] and has height from 5 to 10 m and can be cultured throughout the plains [19]. It tolerates a wide range of rainfall annually from 250 mm to over 3 000 mm [20]. It has nutritive and pharmacological potentials like antimicrobial, anticancer, antihyperlipidemic, antidiabetic, antiulcer, analgesic, antifertility, anticonvulsant, hepatoprotective [21] and just about all parts (leaves, roots, barks, flowers, pods and seeds) of *M. oleifera* have been tested for the treatment of diabetes [22]. Having extensive nutritive and therapeutic potential, there was no study regarding cumulative and expanded data about antidiabetic potential of this plant. Therefore, in this study the effort was made to highlight the antidiabetic importance of *M. oleifera* (Figure 2).

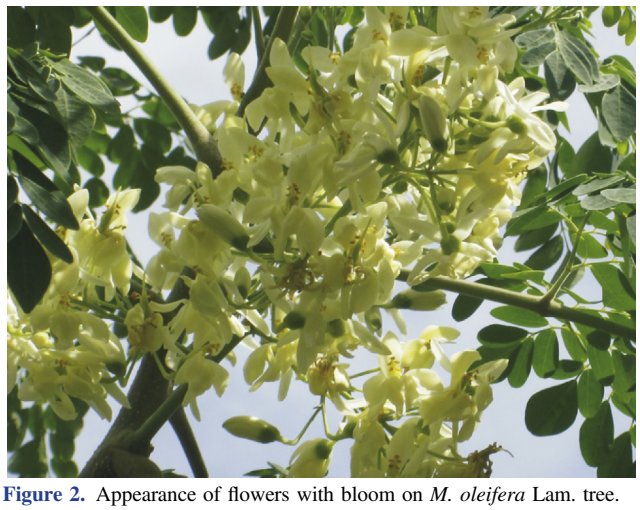

Figure 2. Appearance of flowers with bloom on *M. oleifera* Lam. tree.

2. Screening of aqueous leaves extract of *M. oleifera*

2.1. Streptozotocin (STZ), alloxan-induced, Goto-Kakizaki (GK) and insulin resistant (IR)-rat models

Many diabetic patients rely on herbal medicines for the management of their ailment particularly in underdeveloped subcontinent like Asia [5]. It is estimated that about 80% of the population in African and Asian countries depend on conventional medicine for pathology [23] and major population have an ease access to take such medication as well as locally well accepted [24]. The *M. oleifera* being potential therapeutic agents for diabetes had been used in Wistar and GK rats-model for type 2 diabetes. Major polyphenols were determined by high performance liquid chromatography, among them includes: quercetin glucosides, rutin, kaempferol glycosides, chlorogenic acids. The leaves significantly decreased the fasting blood glucose (FBG) and improved glucose tolerance with 200 mg/kg body weight dose at 20, 30, 45 and 60 min for GK rats and at 10, 30 and 45 min for Wistar rats, might be due to the presence of quercetin-3-glucoside [25]. The blood glucose tolerance efficiency in normal and mildly diabetic mice was 25.99%, 31.25%, 43.19% and 45.17%, 53.31%, 59.16% treated with 100, 200 and 300 mg/100 g body weight, respectively [26].

In another study of 21-days, in normal and mild STZ induced diabetic rats, a maximum fall observed was 31.1% and 32.8%, respectively on the 200 mg/kg dose, while in severely diabetics, fasting blood and postprandial glucose were reduced to 69.2% and 51.2%, respectively [27]. The extract was evaluated in IR and type 1 diabetic rat models. In which, IR was induced by high fructose diet and type 1 diabetes was induced by intraperitoneal injection of STZ. The results showed increased glucose intolerance in both IR and STZ diabetic rats, severity being more in IR rats. Administration of extract with 200 mg/kg dose for 60 days restored all the alterations near to normal [28].

M. oleifera extracts (stem bark, leaves and root bark) were mainly consumed as supplement as well as medicine to measure blood glucose in hyperglycemic rats in this study. The result declared decrease in body weight and 15 mg/dL reduction in blood glucose in the group treated with *M. oleifera* stem bark. The report also indicated the presence of phytochemicals such as alkaloids, flavonoids, glycosides, tannins and steroids, responsible for its hypoglycemic effects [29].

In this study, the hypoglycemic and antihyperglycemic effect was compared with that of glibenclamide and blood glucose concentration was reduced from (339.00 ± 35.12) to (129.20 ± 21.31) mg/dL at 200 mg/kg dose [30] at the second hour in fasted normal and alloxan induced diabetic rabbits. The maximum percentage reduction was seen with 200 mg/kg dose when compared to control [31]. Moreover, in another exploration, tolbutamide (200 mg/kg body weight) was used as positive control drug and the blood glucose was determined by 0-toluidine spectrophotometric method at 0, 1, 3 and 6 h after the administration of extract. The maximum reduction ($P < 0.05$) in blood sugar levels of normal and alloxan induced diabetic rats was found to be 33.18% and 44.96% respectively at administration of 300 mg/kg dose [32].

The aqueous extract also normalized the elevated serum levels of glucose, triglycerides, cholesterol, malondialdehyde, and mRNA expression of the gluconeogenic enzyme pyruvate carboxylase in hepatic tissues of alloxan-induced diabetic rats. In addition, it restored the normal histological structure of the liver

and pancreas [33]. Equally, a 30-days study presented a significant decline from (460.10 ± 22.20) and (468.20 ± 16.46) mg/dL to (124.80 ± 2.48) and (118.00 ± 1.00) mg/dL at the doses of 200 and 400 mg/kg respectively in blood glucose level at day 7, 14, 21 and promotes insulin level through regeneration of β-cells [34].

Multiple dose treatment (250, 500, 1000 mg/kg once a day for 56 days) with aqueous extract also reduced FBG ($P < 0.05$), dose dependant reduction in food intake and body weight as well as total cholesterol and triglycerides as compared to normal control in normal Wistar rats [35].

2.2. Comparative study

Comparative study of mistletoe and *M. oleifera* showed that after one week of treatment, the glucose and insulin level became close to normal value. There was also an average increase in body weight observed for both plants in the third week and sixth week. Pancreatic malondialdehyde levels in *Moringa* and mistletoe treated groups were significantly less while superoxide dismutase and glutathione concentrations increased [36]. In an added study, *M. oleifera* was compared with *Bridelia ferruginea* leaves in alloxan diabetic rats. The blood glucose and liver enzymes measurement were done by glucometer and spectrophotometric methods. The highly significant reduction ($P < 0.05$) was found in blood glucose and alanine aminotransferase levels in diabetic rats treated with aqueous extract of 200, 400 and 800 mg/kg bid for one week [37].

From two groups (15 rats in each), five animals from each group were weighed and sacrificed. In hyperglycemia, the remaining 10 animals, was induced through intraperitoneal injection of alloxan. After one week, the animals were treated with 0.5 mL of 30% aqueous extracts of *M. oleifera* leaf and *Myristica fragrans* seed, respectively for another week. The results indicated significant hypoglycemic effect, increase in body weight and glutathione and reduction in malondialdehyde concentration in treated rats. There was also inhibition of superoxide dismutase activity [38].

3. Evaluation of ethanol and methanol extracts

3.1. Ethanol extract

The 70% ethanol extract of *M. oleifera* leaves was given to normal and STZ induced diabetic Wistar rats. The two different doses were administered intraperitoneally against insulin as positive standard and negative control rats. It was concluded that the said extract possessed dose dependent antihyperglycemic activity in STZ induced diabetic Wistar rats only and maximum reduction was found (74.0 ± 6.6) mg/dL at 7-h at 500 mg/kg body weight dose [39]. Alike, the 80% ethanol extract of *M. oleifera* and *Vernonia amygdalina* plants (500 mg/kg dose) were studied separately and also given as combined treatment in normal and diabetic rats. After 28-days treatment, the animals were euthanized and blood was collected by cardiac puncture for experimental procedures. There was a significant reduction (below 100 mg/dL) in FBG, aspartate aminotransferase and alanine aminotransferase levels, while increase in total protein was observed in all treated groups [40]. In a different study, the vacuum dried 95% ethanol extracts of *M. oleifera* lowered blood glucose level close to normal level giving once, twice or thrice daily [41]. The reduction in insulin, liver glycogen, protein, superoxide dismutase and total antioxidant capacity levels observed in the STZ-induced control diabetic rats, were reversed by treatment with 1 g/kg body weight per day intraperitoneally and 15 g/kg body weight per day (16% in diet) for 45 days *M. oleifera* and also caused a reduction in blood glucose level in normal rats [42].

Insulin resistance plays a central role in the pathogenesis of type 2 diabetes mellitus, increase the risk of development and progression of diabetic complications. The 70% ethanol extract of *M. oleifera* leaves (500 and 250 mg/kg body weight for two weeks) and metformine (320 mg/kg) have been shown to lower insulin resistance and FBG significantly at day 7 and 14 in high-fat diet and STZ induced diabetic rats [43]. Alcoholic extract of *M. oleifera* leaf, moringinine, quercetin and chlorogenic acid were tested in diabetic rats. The results indicated normalized elevated serum glucose, triacylglycerol, total cholesterol, protein carbonyl content, malondialdehyde, total antioxidant capacity and C-peptide after 21 day therapy at 150 mg/kg dose. Moreover, it restored the normal histological structure of the pancreas in diabetic rats. The effects observed due to the presence of quercetin, chlorogenic acid and moringinine in the extract [44]. Recently, it is reported that 95% ethanol extract of *M. oleifera* leaves have significant acute antidiabetic effect at dose 1 g and 0.5 g/kg body weight orally after 7 h in diabetic rats while 14-day treatment indicated reduction in cholesterol, triglyceride and body weight along with antihyperglycemic effect [45]. The 20%, 40% and 80% ethanol extracts also claimed its potential in alloxan induced diabetic mice [46].

3.2. Methanol extract

The oral administration of methanol extracts of *M. oleifera* 300 or 600 mg/kg for six weeks significantly ($P < 0.001$) reduced lipid-profile and enhanced serum level of high-density lipoprotein by 2.4–3.2-fold (Figure 3). Glycogen synthase activities and glycogen contents were higher and enhanced glucose uptake and glycogen synthesis through stimulation of insulin release was noted [47]. Osteoporosis may be the result of diabetes mellitus. In a different study, *M. oleifera* was investigated using its different methanol extracts (leaf, fruit and flower) each with 200 mg/kg dose on bone health markers in diabetic osteoporosis rats. The treatment resulted in reduction in glucose levels and so for increase in ostoblastic marker alanine aminotransferase. Among all the three parts of *M. oleifera* exposed, it was fruit which exhibited the maximum amelioration [48].

Figure 3. *M. oleifera* leaves.

4. Antidiabetic study on diabetic patients

The tablet (98.34% dehydrated *M. oleifera* leafy powder) formulation was used to study the antihyperglycemic activity in 100 type 2 diabetic patients (40–58 years) visiting at private clinic. There was 28.57% reduction in post-prandial blood glucose as compared to initial value after 90-days of supplementation, two tablets once a day while glycosylated hemoglobin was reduced to 7.4% [49]. Likewise, it was found that *M. oleifera* leaf powder supplement significantly lowered serum glucose in type 2 diabetes mellitus obese patients. The supplement was prepared by adding 5% of salt, 7% of red chili powder and 7% of coriander powder to the dried powder and slightly fried in open pan without any oil to increase acceptance. The powder was supplied to all subjects in 50 g pouches and was advised to use this powder with their food regularly for 40 days [50].

In randomized control design study, 18–55 years old individuals with low density lipoprotein (LDL) greater than 100 mg/dL were given *M. oleifera* leaves as commercial 350 mg capsule (2 capsules *tid* for 30 days). A significant reduction of 13.76 mg/dL LDL concentration verses control was observed and prevents the rise in serum glucose 2 h after 75 g oral glucose [51].

The effect of *M. oleifera* and *Solanum nigrum* was checked in 20 diabetics and 10 healthy individuals [(35–60) years]. The glucose concentration, glycosylated hemoglobin, total cholesterol, triglyceride and low density lipoprotein-cholesterol was reduced to 22.18, 20.48, 12.45, 39.49 and 17.66% from its initial value, while high density lipoprotein-cholesterol was increased to 18.99%. The tannins, phenols, alkaloids, flavonoids and carotenoids were supposed to be responsible for hypoglycemic effects [52].

5. *M. oleifera* pods

The methanol extracts of *M. oleifera* pods were investigated in diabetic rats to determine changes in biochemical parameters in the serum and pancreatic tissue (Figure 4). Two phytoconstituents, namely quercetin and kaempferol, were also isolated from the extract. A significant reduction (33.34%) in serum glucose, increases in serum insulin and protein levels were observed when diabetic rats were treated with 50 mg/kg body weight in diet for four weeks. Furthermore, enhanced antioxidant effect also observed in pancreatic tissue and degenerative changes in the β-cells [53].

Figure 4. *M. oleifera* pods.

6. *M. oleifera* seeds

The *Moringa* seed powder was used in diet (100 mg/kg body weight for four weeks) in STZ induced diabetes male rats. The diabetic rats ameliorated the levels of all these parameters (lipid profile, FBG, glycosylate hemoglobin) approaching the negative control values and restored the normal histology of both kidney and pancreas [54]. In one more study, the hypoglycemic effect of *M. oleifera* seed oil (petroleum ether and dichloromethane) extracts was carried out in normal rats. The three different doses of both extracts were tested along with standard (500 μg/kg body weight) in dimethyl sulphoxide. The petroleum ether extract showed maximum reduction (14.10%) in blood glucose level at 2.0 mL/kg dose while dichloromethane 15.22%. Additionally, acute toxicity results indicated no sign of toxicity at higher dose up to 5 mL/kg body weight [55]. Correspondingly, mild and severe diabetic rats were administered aqueous extract of *M. oleifera* seeds with 400 mg/kg body weight orally as well as intraperitoneally for two weeks. The study indicated a significant decrease in the blood glucose level in acute and after 14-days chronic study of both oral and intraperitoneal treatment in mild and severe diabetic rats [56].

7. *In-vitro* study

7.1. Study on intestinal α-glucosidase enzymes

The α-glucosidase enzymes are located at the intestinal brush border of the intestine [57,58] which is responsible for the digestion of carbohydrates and absorption of glucose in the digestive tract. The management of diabetes can be achieved by reducing post-prandial hyperglycemia by delaying the activities of α-amylase and α-glucosidase, respectively [59,60]. The α-glucosidase, pancreatic α-amylase inhibitory activity, *in vitro* bile acid binding capacity, inhibition of cholesterol micellization, pancreatic lipase, and cholesterol esterase activity were determined by *M. oleifera* leaf extract. The extract inhibited α-glucosidase activity and somewhat pancreatic α-amylase and cholesterol esterase activity [61]. Among the ethanol extracts of leaves, roots, flowers, stem and seed, only leaves and seeds produced significant α-amylase and glucosidase inhibitory activity [62].

7.2. Study on pancreatic β-cells

Pulverized *M. oleifera* leaves were extracted with dichloromethane, acetone, ethyl acetate and water and tested in clonal pancreatic β-cells. Insulin concentration was measured by radioimmunoassay and lactate dehydrogenase release by non-radioactive assay kit (Promega, UK). Amongst, the aqueous extract produced the best insulinotropic effect, with a maximum stimulation of 347% ($P < 0.001$) of basal rate while dichloromethane and acetone extracts produced stimulatory effects

130% of basal rate at 100 μg/mL [63]. In a further article, morphometric measurements of β-cells of pancreas (modified Gomori's stain) and collagen fibers (Mallory's trichrome stain) were determined. The plant treatment significantly reduced glucose from 380% to 145%, glutathione from 22% to 73% and malondialdehyde from 385% to 186% as compared to control. Morphometric analysis indicated significant increased in the area from 60% to 91% and decreased collagen fibers from 199% to 120% compared to control values [30].

8. Chemical and phytochemical screening

8.1. Chemical screening

The fresh *M. oleifera* leaves contained less nutrients as compared to dried ones, as the dried leaves enclosed 17 times Ca of the milk, ten times vitamin A of the carrots, 15 times K of the bananas and 25 times the iron of spinach, 27.2% (protein) or 0.58–0.73 g protein/g, 5.9% moisture, 17.1% fat, 38.6% carbohydrates, essential amino acids and carotenoids [64–67]. The secondary metabolites were also observed, appeared to be involved in plant defense mechanisms and the trypsin inhibitor against serine proteinases [68–70].

8.2. Phytochemical screening

Flavonoids and phenolic acids are collectively referred as phenolic compounds. They are classified into several subgroups including: flavone, flavanone, flavonol, isoflavonoid, anthocyanidin, and chalcones [71].

The high performance liquid chromatography analysis also indicated the presence of phenolic acids (Gallic, ellagic, chlorogenic and ferulic acid) and flavonoids: kaempferol, quercetin, isoquercetin, astragalin and rutin [72–76]. Quercetin and kaempferol, in their as 3-O-glycoside forms were the predominant flavonols in *M. oleifera* leaves. The leaves as well enclosed niazirin, niazirinin, 4-[(4′-O-acetyl-Lrhamnosyloxy) benzyl] isothiocyanate, niaziminin A and B, quercetin-3-O-(6″-malonyl-glucoside), kaempferol-3-O-glucoside and kaempferol-3-O-(6″-malonyl-glucoside), 3-caffeoylquinic and 5-caffeoylquinic acid [77,78]. It was also reported that the leaves had enough amount of carotenoids, epicatechin and o-coumaric acid [79].

9. Conclusion

It is concluded from the article that the powder, aqueous, ethanol and methanol extracts of *M. oleifera* (leaves, seeds, pods, root and stem bark) provides good glycemic control in diabetic animal and human models. Preliminary findings indicated the presence of quercetin glucoside, querecetin and kaemferol. Cumulatively, the mechanism behind is intestinal glucose inhibition, insulin release as well decreasing insulin resistance probably regeneration of β-cells of pancreas, increase in glutathione and reduction in malondialdehyde. Therefore, it can be a potential source to treat diabetes and widely accepted by major population as nutrition and therapeutic agent.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

The present study was supported by Ministry of Education, Malaysia (Grant No. 203/PFARMASI/6711451) and Faculty Development Scholarship provided by University of Sargodha, Sargodha, Punjab, Pakistan.

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