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Review Article

Therapeutic potentials and pharmacological properties of Moringa oleifera Lam in the treatment of diabetes mellitus and related complications

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Abstract

Diabetes mellitus (DM) is a major health problem not only in urban areas, but also in rural areas. DM is a metabolic disorder resulting from abnormal insulin secretion. This leads to chronic hyperglycemia with disturbances of carbohydrate metabolism. Hyperglycemic-induced oxidative stress has been shown to be actively involved in the onset and progression of diabetes. Plants have played a vital role in improving the quality of life and maintaining human health.

It also serves as important components for medicines, beverages and seasonings. Many plants contain flavonoids, glycosides, alkaloids, terpenoids, and carotenoids with anti-diabetic and antioxidant properties. Moringa oleifera (MO) is one of such plants which have been used for centuries as a folk remedy for the treatment and management of various diseases including diabetes. This review is aimed at providing an overview of the potentials of MO in the treatment and management of diabetes and its possible applications in the treatment of other diseases.

Keywords: *Moringa oleifera, Diabetes mellitus, Hyperglycemia, Oxidative stress.*

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INTRODUCTION

Despite the presence of many methods, approaches and medicines, the management of type 2 diabetes mellitus remains unsatisfactory [1]. The increasing prevalence of diabetes in both developed and developing countries have challenged scientists to the discovery of various therapeutic agents that can be used to ensure efficient treatment and management of diabetes [2]. Also, with the increasing incidence of diabetes mellitus (DM) in rural population of Africa, many drugs have been formulated for the management of this chronic hyperglycemic disorder. However, there are limitations in the use of anti-hyperglycemic medications resulting from the side effects, high cost, limited action and secondary failure rates. There is a clear need for the development of indigenous, inexpensive herbal sources for diabetic treatment [3]. There is presently no cure for diabetes and the drugs available for the treatment and management of this disease are still unable to impair insulin deficiency. Less privileged diabetic patients are unable to purchase expensive drugs to manage this conditions or maintain their life style [4].

For several years, plants have been known to improve the quality of life and maintain human

health. In addition, the components of plants have been used as seasonings, beverages, cosmetics, dyes, fertilizers and water purification. Interestingly, many indigenous plants containing flavonoids, glycosides, alkaloids, terpenoids, and carotenoids have been shown to contain both anti-diabetic and antioxidant properties. Moreover, *Moringa oleifera* (MO) has been found to be effective in ayurveda medicine; as a potent therapeutic agent with little or no adverse effect [5]. This review is aimed at providing an overview in the therapeutic potential and pharmacological properties of MO in the treatment and management of diabetes mellitus and other ailments.

The use of medicinal plants could be an alternative means of improving health care globally [6]. Medicinal plants are locally available, easily accessible and obtainable regardless of social status [7]. Concurrently, phytochemicals offer notable prospect for the exploration of new varieties of therapeutics. As a result, efforts are being geared globally towards the exploitation of medicinal plants containing phytochemicals to manage diabetes and associated complications [3].

DM remains a major global public health problem. It is a metabolic syndrome of multiple aetiologies characterized by chronic hyperglycemia resulting from defects in insulin, insulin actions or both. Hyperglycemia in DM has been associated with increased formation of reactive oxygen species (ROS) and inflammatory mediators. Consequently, if this metabolic syndrome is left untreated, it can lead to severe complications. Globally, increase in weight, obesity and sedentary lifestyle is gradually becoming prevalent resulting to diabetes. This may be due to a change of diet and lifestyle. Diabetes is projected to become the seventh leading cause of death worldwide by the year 2030 and total death from diabetes is estimated to rise by more than 50 % in the next 10 years [8, 9]. Many drugs have been designed for the treatment and management of this disease. However, there are limitations in the use of anti-hyperglycemic medications due to the side effects, high cost, limited actions and secondary failure rates [10]. There is increasing prevalence of diabetes in both developed and developing countries which have challenged scientists to further conduct research in sourcing for potent and affordable therapeutic agents from natural sources in the treatment and management of diabetes [6].

There are various evidences which indicate an increase in the generation of ROS and systemic markers of inflammation in both types of diabetes [11]. Increase in inflammatory cytokines such as IL-6, IL-18, IL-1 and TNF-α have been observed in the blood of patients with diabetes [12,13]. Chronic hyperglycemia and increased oxidative stress (disruption in the balance between the production of reactive molecules and antioxidant defenses) are the major factors in the development of secondary diabetic complications such as nephrotoxicity and hepatic injury [14-16].

Possible risk factors of diabetes

Oxidative stress, genetic factor, life style and environment are possible risk factors of diabetes. Diets have a significant role to play in the growth and development of the body [17]. Oxygen free radicals and other ROS are constantly produced in the human body. ROS are reactive species with partially reduced metabolites of oxygen. These metabolites initiate damaging effects to biomolecules which eventually lead to a change in the structure and function of these biomolecules. Studies have shown that type 2 diabetes is associated with increased oxidative damage to all biomolecules in the body [18]. Usually, the ROS are detoxified by antioxidant defense systems, although sometimes it reaches a point when there is an excess production of these ROS or inadequate antioxidant defense, which leads to oxidative damage. Increased oxidative stress is observed in diabetic patients as a result of free radical production [19]. Oxidative damage due to free radicals is associated with vascular disease in people with types 1 and 2 diabetes mellitus [20]. These factors have been implicated in the causative of several diseases in humans, such as diabetes, cancer, liver cirrhosis, atherosclerosis, neurodegenerative and cardiovascular diseases [18,20]. Individuals with type 1 diabetic parents have higher risk of inheriting diabetic genes. This can also be activated by other environmental factors and life style. In addition, physical inactivity is a risk factor of cardiovascular diseases, hypertension and dyslipidemia [18].

DIABETES AND MORINGA OLEIFERA

MO plant has been used in folklore medicine for the treatment of diabetes and other diseases [5]. Many indigenous plants such as *Vernonia amygdalina* (VA) [21], *Garcinia kola* [22], contain alkaloid, flavonoids, terpenoids, glycosides and carotenoids which have all been shown to contain anti-diabetic activities [23]. Ayurvedic medicine uses natural plants to promote self-healing, attain good health and longevity. Researchers have indicated that *Moringa oleifera* can offer the nutrients and therapeutic

ingredients to prevent, mitigate or treat many diseases or conditions [24]. This plant has been reported to possess antidiabetic, antioxidant and other medicinal properties which may be helpful in managing diabetes and its associated complications, and could possibly act as an effective remedy for the management of diabetes especially in low-income African communities [25-27].

MO is known in English by the names miracle tree, horseradish, drumstick, benzolive tree and named in respective native languages in other regions where it is grown. In Hindu, it is called Saijan, in Yoruba Ewe ile, in Filipino Mulanggay, in Hausa Zogale and in Igbo Odudu oyingbo [28, 29]. MO belongs to the family of *Moringaceae*, which is widely distributed in the tropics and sub-tropics of Asia and Africa [30]. The *oleifera* species has been in existence as far back as early 2000 BC, and is one of the world's most useful plants because of its medicinal properties [31]. MO has its origin in Agra and Oudh, in the northwest region of India, south of the Himalayan Mountains [32]. There are twelve (12) other known species: *stenopetala* which is a staple food of the indigenes of Ethiopia, *pygmaea*, *peregrina* (Forssk.), *rivae, arborea, borziana, ruspoliana, longituba, concanensis, drouhardii*, *hilde- brandtii,* and *ovalifolia.* *Moringa oleifera* shown in Figure 1 is the most researched among them [33-36].

Uses of *Moringa oleifera*

MO called miracle tree because every part of this plant is useful, has high nutritive value, and possesses numerous medicinal properties that can be used in treating or managing various diseases. *MO* is a plant which can be eaten as a vegetable and used as beverages. A wide variety of nutritional and medicinal potentials have been attributed to its roots, bark, leaves, flowers, fruits, and seeds [31,37].

Various parts of MO such as the leaves (Figure 2), roots, seeds (Figure 3&4), bark, fruit, flowers and immature pods act as cardiac and circulatory stimulants, possess antitumor, antiulcer, antipyretic, antiepileptic activities [38]. In addition, MO has been used for the treatment and management of different ailments in traditional medicine because of the antihypertensive, antioxidant, antimicrobial, antibacterial, antispasmodic, antifungal, anti-inflammatory, anti-tuberculosis, analgesic, anti-diabetic, diuretic, cholesterol lowering, and hepatoprotective properties [31]. MO shows hypolipidaemic, antiatherosclerotic and immune boosting effects [39-41].

MO has been used for centuries as a folk remedy for stomach complaints, catarrh, cancer, gastric ulcers, skin diseases, lowering blood sugar, increasing bone density, nervous conditions, diabetes, fatigue, increase lactation, hay fever, impotence, oedema, cramps, hemorrhoids, headaches, sore gums; liver, gall, digestive, respiratory and immune system, as a blood cleanser, blood builder and wound healing [42,43]. The leaves of MO are anthelmintic aphrodisiac (increases sexual desire), cures hallucinations, dry tumors, hiccough and asthma [44]. MO is also used as stimulants, expectorant, and antilithic. Furthermore, it also provides a local solution to malnutrition [32]. MO is well known traditionally for the treatment of diabetes mellitus, hepatotoxicity, rheumatism, venomous bites and also for cardiac stimulation [27,45,46].

Moringa oleifera is used in alley cropping (biomass production), biogas (from leaves), domestic cleaning agent (crushed leaves), animal forage (leaves and treated seed-cake), blue dye (wood), pulp (wood), fertilizer (seed-cake), green manure (from leaves), gum (from tree trunks), medicine (all plant parts), honey- and sugar cane juice-clarifier (powdered seeds), honey (flower nectar), foliar nutrient (juice expressed from the leaves),

Figure 1: *Moringa oleifera* growing plant

Figure 2: *Moringa oleifera* fresh leaf

ornamental plantings, bio pesticide (soil incorporation of leaves to prevent seedling damping off), tannin for tanning hides (bark and gum), water purification (seeds) [29]. The oil extracted from MO seed known as Ben oil, is a sweet non-sticking and non-drying oil that resists rancidity [41].

People in many developing countries, especially in Africa have been using *Moringa oleifera* to treat and manage the symptoms of diabetes for years. The International Diabetic Federation (IDF), in a report stated that over 246 million people worldwide were suffering from the disease and the prevalence is expected to rise to 380 million by the year 2026 [6]. It is interesting to note that this plant can also grow in any type of soil and can be grown in the garden space at home. MO grows best in sandy or loamy soil with a slightly acidic pH and has a height ranging from 5 to 12 m with a straight trunk 10 - 30 cm thick [47].

Constituents of *Moringa oleifera*

The leaves of MO contain phytochemicals such as niazirin and niazirinin [44]. In addition, MO contains high level of vitamins A, B and C minerals (especially iron) amino acids (leucine, glutamic, valine, aspartic, alanine and so on), fatty acid, carotenoids (carotene, lutein xanthin, flavonoids, polyphenols (tannins), high in protein and antioxidants [31].

MO contains glucosinolates and flavonoids, anthocyanins, proanthocyanidin and cinnamates [33]. The leaves contain 4-(α-L-rhamnopyranosyloxy) - benzylglucosinolate and three monoacetyl isomers of glucosinolate. Quantitative analysis carried out on the leaves revealed the presence of phenolic compounds quercetin 3-(6''-malonyl-glucoside) structure in Figure 5, quercetin-3-O-glucoside, and reduced concentration of kaempferol-3-O-glucoside (astragalin) with structure presented in Figure 6 and kaempferol-3-O-(6''-malonyl-glucoside), flavonoids and trace amount of alkaloid, 3-caffeoylquinic and 5-caffeoylquinic acid [30,44]. Also, ethanolic and freeze dried leaves extract of MO has been reported to contain quercetin and kaempferol [48].

Phytochemicals in *Moringa oleifera*

Phytochemical studies on MO showed high polyphenols (kaempferol glycosides, rutin, quercetin glucosides, and chlorogenic acids) [49]. Some flavonol glycosides and benzoic acid 4-O-beta-glucoside, benzoic acid 4-O-alpha-rhamnosyl-(1→2)-beta-glucoside and benzaldehyde 4-O-beta-glucoside have been isolated and characterized from methanolic extract of MO leaves [50]. Water soluble polysaccharides such as d-galactose, 6-O-Me-D-galactose, D-galacturonic acid, l-arabinose, and l-rhamnose in a molar ratio of 1:1:1:1 were isolated from an aqueous extract of pods from *Moringa oleifera* [51]. Also, the seed of MO is reported to contain various sterols, tocopherols and fatty acids from n-hexane extract [37].

Figure 3: *Moringa oleifera* seeds with husk

Figure 4: *Moringa oleifera* seeds without husk

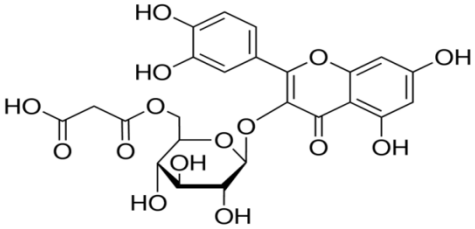

Figure 5: Quercetin 3-(6''-malonyl-glucoside),

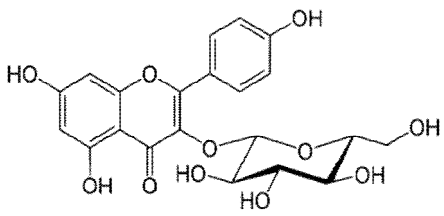

Figure 6: Kaempferol-3-O-glucoside

Therapeutic potentials of *Moringa oleifera*

Currently available therapies for diabetes include insulin and various oral anti-diabetic agents such as sulfonylureas, biguanides, thiazolidine diones and glinides. Many of these drugs have some serious adverse effects. Therefore, there is a need to consider possible and safe hypoglycemic agents such as MO in the treatment and management of diabetes mellitus. A major mechanism in forestalling damage by oxidative stress is the balance of ROS and antioxidants, thus requiring the utilisation of dietary supplementation of antioxidant-rich plants such as MO which could be a promising approach in the treatment of diabetes [24]. Its beneficial effects in various pathological conditions through its anti-oxidative and anti-inflammatory properties have been researched on, hence the need to explore its potentials in diabetic conditions [24]. MO extract is reported to cause a reduction in the serum level of glucose and glycosylated protein in diabetic conditions while showing observable improvements in impaired glucose metabolism [31].

Anti-diabetic activity of *Moringa oleifera*

Several medicinal plants have been evaluated for their potential as beneficial agents in the treatment and management of diabetes. MO is also an important member of such plants. The leaves of MO was reported to significantly decrease blood glucose concentration in Wistar rats and Goto-Kakizaki (GK) rats, model type 2 diabetes [49]. Other studies also indicated MO's potency to effectively lower blood sugar levels [52,53,54]. The reduction in glucose concentration can be rationalized by the presence of potent polyphenols such as quercetin-3- glycoside, rutin and kaempferol glycosides in MO.

Studies undertaken in India to ascertain the hypoglycemic and anti-hyperglycemic outcome of *MO* aqueous extract in normal (normoglycemic) and alloxan-induced diabetic rabbits respectively indicated that the aqueous extract of the leaves demonstrated hypoglycemic and anti-hyperglycemic activities [53]. Jaiswal et al. [55] examined the effect of the aqueous leaf extracts on glucose level, hemoglobin, total protein, urine sugar, urine protein and body weight of rats using three (3) different doses 100, 200 and 300 mg/kg. The results reveal that aqueous extract of MO leaf has significant hypoglycemic and anti-diabetic potential [55].

Clinical studies were carried out to investigate the hypoglycemic effect of the seeds of *Moringa oleifera* (*MO*) and *Azadirachta indica* (AI) seeds in 55 type 2 diabetic subjects (36 men and 19 women in the age group of 30-60 years). Results revealed that there was a significant reduction in the mean blood lipid levels. Among MO and AI seeds carefully chosen, MO seed powder was found to be more effective followed by *Azadirachta indica* seeds powder [56].

Studies on MO and other plants, investigated the hepato-protective properties using combined extracts of MO and VA in streptozotocin (STZ)-induced diabetic using Wistar strain rats. It was observed that single and combined extracts of MO and VA have hepatoprotective effects and may be safer in preventing diabetes-induced damage to the liver [21]. Another study by Iwara *et al* [57] indicated that MO leaf extract combined with VA on STZ-induced diabetic rats was effective in reducing kidney damage. The result suggests a synergistic effect of the plants in the amelioration of nephrotoxicity associated with diabetes mellitus. Under this premise, one cannot conclude which particular plant extract has the potent active compound to treat and manage diabetes, therefore further and detailed studies are suggested [57].

Investigations were carried out on the effects of MO on glucose tolerance in Wistar rats and Goto-Kakizaki (GK) rats induced with diabetes with the knowledge that the major polyphenols in *MO* powder are quercetin glucosides, rutin, kaempferol, glycosides and chlorogenic acids [49]. The study indicated that MO has an ameliorating effect for glucose intolerance, and the effect might be mediated by quercetin-3-glucoside and fiber contents in MO leaf powder [49].

Studies carried out on MO view it as a very promising medicinal plant that can be used in the management and treatment of diabetes with minimal side effects. MO has also been shown to possess glucose lowering effect in STZ- induced diabetic rats by possibly stimulating the β-cells of the islets of Langerhans or due to its insulin-like activity [58].

Anti-lipidaemic activity of *Moringa oleifera*

MO leaves contain bioactive phytoconstituent, (beta-sitosterol) with cholesterol lowering effect. This compound is capable of reducing cholesterol level from the serum of high fat diet fed rats [38]. Mehta et al. [59] reported that the fruits of MO were reported to possess

hypolipidaemic effect. They were found to lower the serum cholesterol, phospholipid, triglyceride, VLDL, LDL, cholesterol to phospholipid ratio and atherogenic index in hypercholesterolaemic rabbits, but were found to increase the HDL ratio (HDL/ HDL-total cholesterol) when compared with the control groups [59].

Anti-inflammatory activity of *Moringa oleifera*

The ethanolic extract of MO seeds was evaluated by Mahajan et al. [60] for its anti-inflammatory activity against immune-mediated inflammatory responses in toluene diisocyanate (TDI) as antigen-induced asthma in Wistar rats. Similarly, another research was conducted in 2009 where anti-inflammatory activity of MO seeds (butanolic extract) against ovalbumin-induced airway and inflammation in guinea pigs were evaluated [61]. Another study evaluated the antinociceptive and anti- inflammatory effects of the aqueous extract of the *Moringa oleifera* leaves, using the writhing, hot-plate and formalin tests as the antinociceptive assays, and carrageenan-induced paw oedema test as the anti-inflammatory assay. The extract (10, 30 and 100 mg/kg) exhibited significant ($P < 0.05$) antinociceptive activity, which occurred in a dose-dependent manner in all tests used [61]. The extract also exhibited significant ($P < 0.05$) anti-inflammatory activity in a dose dependent manner. From the study, MO leaves were shown to possess anti-nociceptive and anti-inflammatory activities which confirmed its traditional usage in the treatment of ailments, related to pain and inflammation [62].

Antimicrobial activity of *Moringa oleifera*

Antimicrobial activity of ethanolic extract of MO flowers, leaves and seeds was investigated. The study was carried out by Renita et al. [63] using micro-organisms; *Escherichia coli, Salmonella typhi A Klebsiella pneumoniae*, *Candida albicans. Enterobacter spp*, *Pseudomonas aeroginosa*, *Proteus mirabilis* and *Staphylo-coccus aureus.* The treatment with the leaves led to a significant reduction in the growth of these organisms. MO has the potency to combat microorganisms. The steam distillate was tested on fungal and bacterial by Kekuda et al. [64]. It was observed that the growth of fungi was inhibited by a decrease in colony diameter in plates poisoned with distillate compared to the control plates. Results from the study indicated more inhibition of *E. coli* compared to *S. aureus, K. pneumoniae, P. aeruginosa and B. subtilis* [64].

Antioxidant activity of *Moringa oleifera*

Antioxidants are chemicals derived from plants, vitamins and other nutrients which protect the cells of the body system from damage caused by free radicals; thus acting as free radical scavengers. Antioxidants are important in diabetes, they inhibit the oxidation of other molecules at low levels [65]. Reports on the antioxidant and free radical scavenging properties of methanol, ethanol and aqueous extracts of the dried leaves of MO have shown that the leaf extracts have free radical scavenging properties. Experimental study showed that methanol (80 %) and ethanol (70 %) were found as best solvents for the extraction of antioxidant compounds from MO leaves [66]. Also, protective effects of MO extract using 1,1-diphenyl-2-picrylhydrazyl radicals (DPPH) and Trolox had IC (50) of 78.15+/-0.92 and 2.14+/-0.12microg/ml respectively [39] has been reported.

Anticancer activity of *Moringa oleifera*

MO has been documented to contain anticancer properties. The extracts were tested using brine shrimp lethality assay and haemolysis assay to demonstrate the anticancer activity [67]. Cytotoxic effects were studied on human multiple myeloma cell lines using extracts of MO leaves and results showed the least viability at the highest dose [68].

Hepato-protective activity of *Moringa oleifera*

Hepato-protective action of MO against acetaminophen-induced liver injury in Sprague-Dawley rats have been reported using silymarin as a standard drug. The activity was a significant reduction of the level of alkaline phosphatase (ALP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in groups pretreated with MO extract compared to those treated with acetaminophen alone. The level of glutathione (GSH) was found to be restored in MO treated animals compared to the groups treated with acetaminophen alone [69].

Hepato-protective effect of MO seed extract was evaluated on liver fibrosis, which was induced orally by administering 20 % carbon tetrachloride (CCL_4) and *Moringa oleifera* seed extract (1g/kg/day) simultaneously. Liver fibrosis is the excessive accumulation of extracellular matrix proteins including collagen that occurs in most types of chronic liver diseases [70]. The CCL_4-induced elevation of serum aminotransferase activities and globulin level was reduced as a

result of the administration of MO seed extract. Treatment with MO also results in the reduction of the elevations of myeloperoxidase activity and hepatic hydroxyproline content [71].

PREVENTION OF DIABETES

Obesity is a serious chronic disease that may lead to type 2 diabetes and insulin resistance [71]. As a preventive measure against diabetes, engaging in regular exercise (aerobics, walking and jogging) will help maintain a normal growth and development, improve tissue sensitivity to insulin and keep the body physically fit. Eating healthy meals, fruits and fresh vegetables (including MO) will provide the needed nutrients for long-term weight maintenance. Physical activity also improves insulin sensitivity, glycemic control, and reduce selected risk factors for cardiovascular diseases (CVD) [17].

As a result of the numerous health benefits of this miracle plant, more studies to investigate its potential to treat and manage diabetes using an animal model in a more extensive study could potentially revolutionize natural products in the treatment and management of diabetes.

CONCLUSION

Diabetes mellitus is becoming a leading cause of death globally in both rural and urban areas. MO has been used in traditional medicine to treat diabetes and various diseases. Its pharmacological properties have drawn the interest of researchers to this plant. It can be used as an anti-diabetic, cholesterol lowering, anti-inflammatory, analgesic, hepatoprotective, anti-oxidant, anticancer, antiviral and wound healing agent. MO has shown beneficial effects in various pathological conditions in experimental animal models by acting as an anti-oxidative and anti-inflammatory agent through different mechanisms. The flowers, leaves, bark, and seeds of this plant are shown to possess active compounds that can help combat the issue of malnutrition, and to prevent and treat many disease conditions and promote good health. In view of the evidences of the potential effects of MO as revealed in previous studies, there is still the need for further studies to be done on the standardization of the extracts, and isolation of various active compounds present in the plant and their possible mode of action. Hence, more clinical trials should be carried out. Consequently, this will lead to its acceptance as a good therapy in the treatment and management of diabetes, thus potentially revolutionizing natural products in the treatment and management of diabetes.

DECLARATIONS

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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