European Journal of Medicinal Plants

Volume 35, Issue 6, Page 21-31, 2024; Article no.EJMP.118778
ISSN: 2231-0894, NLM ID: 101583475

Anti-Hyperglycemic Effects of *Moringa oleifera*: A Comprehensive Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: https://doi.org/10.9734/ejmp/2024/v35i61205

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/118778

Systematic Review Article

Received: 22/04/2024
Accepted: 24/06/2024
Published: 17/08/2024

ABSTRACT

In recent years, the price of westernized medication for the treatment of diabetes in developing countries has increased, which has led to an increase in the search for indigenous medicinal plants that have the potential to be utilized for the treatment and management of diabetes. Previous studies have demonstrated that *Moringa oleifera* Lam., belonging to the Moringaceae family, possesses promising anti-diabetes potency. These properties include its ability to reduce hyperglycemia, the regeneration of β-cells, and a rise in blood insulin levels. On the other hand, there is a striking lack of evidence concerning its anthological discoveries. In the course of this review, we attempted to compile and analyze research that investigated the efficacy of MO in the

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Cite as: *Dwomoh, Joshua, Samuel A. Ofori, Martin L. Aggrey, Dennis Kwabena Frimpong, Peter Atakora, and Enoch Owusu Yeboah. 2024. "Anti-Hyperglycemic Effects of Moringa Oleifera: A Comprehensive Review". European Journal of Medicinal Plants 35 (6):21-31. https://doi.org/10.9734/ejmp/2024/v35i61205.*

treatment of diabetes. A thorough literature search was conducted using the terms "Diabetes," "Diabetes Mellitus," and "MO Lam" in conjunction with the Boolean operator "AND." The search was conducted on various scientific electronic libraries and databases, including Google Scholar, Research Gate, Elsevier, Science Direct, Springer, PubMed, and WHO, among others. The inclusion criteria required that the research be conducted on the effectiveness of MO in treating diabetes, and the abstracts had to be written in English at the very least. Mo extract was found to increase insulin sensitivity, glucose tolerance, and restore insulin levels, in addition to lowering lipid abnormalities and promoting weight normalization, according to an analysis of the data that was extracted. Additionally, it has been demonstrated to defend against oxidative stress, which demonstrates its effectiveness in treating the oxidative stress that is associated with diabetes. Furthermore, the intake of MO extract promoted the regeneration of the pancreatic tissues. There are a variety of phytochemical components found in MO, which have been associated to the plant's ability to inhibit the development of diabetes. The qualities of the plant have the potential to impact metabolic parameters that are linked to diabetes mellitus, hence preventing the development of complications such as neuropathy, retinopathy, nephropathy, and cardiovascular disorders. In the future, research should be conducted with the purpose of determining the optimal dosage of MO that is capable of exerting hypoglycemic effects.

Keywords: Moringa oleifera (MO); diabetes; hyperglycemia; insulin; islet cells; insulin resistance.

1. INTRODUCTION

Diabetes mellitus, a chronic metabolic disorder characterized by elevated blood glucose levels, continues to pose a significant global health burden. Approximately 463 million adults were living with diabetes in 2023, and this number is projected to rise to 700 million by 2045 [1,2]. This poses a public health threat to the global populace. This suggests that a greater percentage of the global populace will be at risk of complications associated with diabetes, such as neuropathy, retinopathy, nephropathy, and cardiovascular disorders [3]. Therefore, maintenance of blood glucose is essential for survival. A condition in which the body's mechanism fails to maintain optimal blood glucose levels as a fallout of impaired insulin production [4]. The global prevalence of diabetes mellitus (DM) has garnered significant attention in low and middle-income nations due to its increasing incidence [5]. Over the years, the scientific community has provided various treatment and management plans ranging from nutrition, lifestyle modification, and insulin therapy for diabetes management, yet we have not reached a point of satiation [5]. In recent years, there has been growing interest in exploring natural remedies for the management of diabetes, with an emphasis on plant-based interventions [6,7,8,9].

Moringa oleifera (MO), commonly known as the drumstick tree, is a fast-growing deciduous tree native to the Indian subcontinent but is now widely cultivated in tropical and subtropical regions globally [10]. People have been using MO for a long time in traditional medicine because it has many different health benefits. It contains various bioactive compounds like vitamins, minerals, polyphenols, flavonoids, alkaloids, and glucosinolates, which are known to be good for health [11].

The high cost of orthodox prognosis and treatment for diabetes has left the destitute population in the developing countries to depend on traditional medicinal plants for the treatment of a diverse range of diseases, including diabetes. MO has long been used as an unconventional medicine with potential diabetes therapeutics with fewer side effects, and relatively low costs [12]. Several studies have investigated the potential anti-hyperglycemic effects of MO in preclinical and clinical settings. The plant extract or its bioactive components have demonstrated promising outcomes in reducing blood glucose levels, improving insulin sensitivity, and mitigating diabetes-related complications [13]. The promising anti-diabetic efficacy of MO has been attributed to its diverse phytochemical constituents [11]. However, it is necessary to carefully examine the existing research to understand the full potential of MO regarding it anti-hyperglycemic effects as well as therapeutic potential and elucidate the underlying mechanisms.

1.1 Biotechnical Description of *Moringa oleifera* (MO)

Moringa is the generic name for a group of medicinal plants that are significant in both ethnobotanical and pharmacological contexts.

Since the beginning of time, it has been utilized in many traditional medical practices to treat a variety of ailments. There are 13 different species in the moringa family: *Moringa oleifera, Moringa stenopetala, Moringa hildebrandtii, Moringa arborea, Moringa borziana, Moringa drouhardii, Moringa longituba, Moringa ovalifolia, Moringa peregrina, Moringa pygmaea, Moringa rivae, Moringa ruspoliana, Moringa stenopetalosa*, all of which have been found widespread [14]. They further indicated that the optimum temperature for growing is between 18 and 28 ◦C, and it grows in any soil type, waterlogged and with heavy clay (pH between 4.5 and 8), at an altitude of up to 2000 m. MO plant possesses culinary properties, as all of its parts such as leaves, roots, fruits, flowers, and nutritious pods are consumable. Consequently, this plant has gained significant popularity and is extensively utilized in numerous places worldwide [15].

It has been given the names "nature's gift" and "wonder tree" as a result of the extensive research that has been done on its potential and properties [16]. MO is the most well-known species of moringa due to the abundance of nutrients it contains and the myriad of positive effects it has on health. This is mostly attributable to the Ayurvedic tradition that it is associated with [17]. According to a botanical description of the MO plant, the tree can typically grow to a height of 10-15 meters, with an approximate diameter of 45 centimeters and an abnormal-looking bole that is forked from the roots. In addition, the tree has been known to produce fruit that has a high oil content. The bark of the trees has a smooth, even texture and a good hue. The shading is subdued, and the color is a light yellow. The crown is frequently characterized as having the shape of an umbrella, with an opening that is stretched out, and branches and shoots that are short and bristly. The softwood has leaves that can reach a maximum length of 90 centimeters and is arranged in alternate and opposing pinnae in inverse sets beginning 5 centimeters above the stalk [15]. In addition to this, the MO flower exudes an enticing smell and possesses five asymmetrical petals that are somewhat longer than the sepals [18].

1.2 Phytochemical Constituents of MO

MO plant has been found to contain a distinct phytochemicals that are responsible for the plant's various pharmacological effects. The phytochemicals found in MO are tocopherols (α, γ, δ), carotenoids, flavonoids, phenolic acid, folate, and polyunsaturated fatty acids [19] Bhattacharya et al. [20] have also reported on the presence of these phytocheimicals; n-hexadecanoic acid, tetradecanoic acid, cis-vaccenic acid, octadecanoic acid, palmitoyl chloride, beta-l-rhamnofuranoside, 5-O-acetyl-thio-octyl, gamma-sitosterol, and pregna-7-diene-3-ol-20-one in MO using gas chromatography and mass spectrometry [20]. A study conducted by Bennett et al. in 2003 indicated that E-lutein is the predominant carotenoid present in the leaves of MO. The radicle of the plant contains 4-(α-l-rhamnopyranosyloxy)-benzylglucosinolate and benzylglucosinolate. Bennett et al. have additionally demonstrated the presence of Beta-sitosterone, vanillin, 4-hydroxymellein, β-sitosterol. Mohanty et al. [10] have documented the presence of alkaloids (moringine and moringinine), 4-hydroxymellein, octacosanoic acid, and β-sitosterol in the stem of MO. The plant's blooms include phytochemicals such as sucrose, amino acids, alkaloids, and flavonoids, including rhamnetin, isoquercitrin, and kaempferitrin [15,19,20].

2. METHODOLOGY

2.1 Literature Search

A systematic search was conducted in electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar, to identify relevant studies. The following search terms and combinations were used: "*Moringa oleifera*," "diabetes," "anti-hyperglycemic effects," and "mechanisms." Only articles published in English from 2010 to 2023 were included. Additionally, the reference lists of identified articles were manually screened to ensure the inclusion of all relevant studies.

2.2 Study Selection

Two independent reviewers screened the titles and abstracts of the retrieved articles to assess their eligibility based on predefined inclusion and exclusion criteria. Full-text articles of potentially eligible studies were obtained and further evaluated for final inclusion. Any discrepancies or disagreements between the two reviewers was resolved through consensus with a third reviewer. A total of 80 articles were initially assessed base on titles and abstracts for eligibility on predefined inclusion and exclusion criteria. Full-text articles of 16

potentially eligible studies were obtained and further evaluated for final inclusion. The flowchart of the study selection process is presented in Fig. 1, illustrating the number of articles screened, excluded, and included at each stage.

2.3 Data Extraction

A standardized data extraction form was developed to capture relevant information from the included studies. The following data was extracted: study characteristics (author, year, study design), model (animal or human), intervention details (*Moringa oleifera*) extract or bioactive components used, dosage, duration), outcome measures (changes in blood glucose levels, insulin sensitivity, diabetes-related complications), and reported mechanisms of action.

2.4 Quality Assessment

The quality and risk of bias of the included studies were assessed using appropriate tools. For randomized controlled trials (RCTs), the Cochrane Risk of Bias tool was employed, while the Newcastle-Ottawa Scale was used for non-randomized studies. The quality assessment considered factors such as study design, sample size, randomization, blinding, allocation concealment, follow-up, and reporting of results. The quality assessment aided in the interpretation and synthesis of the findings and highlighted the strength of the evidence.

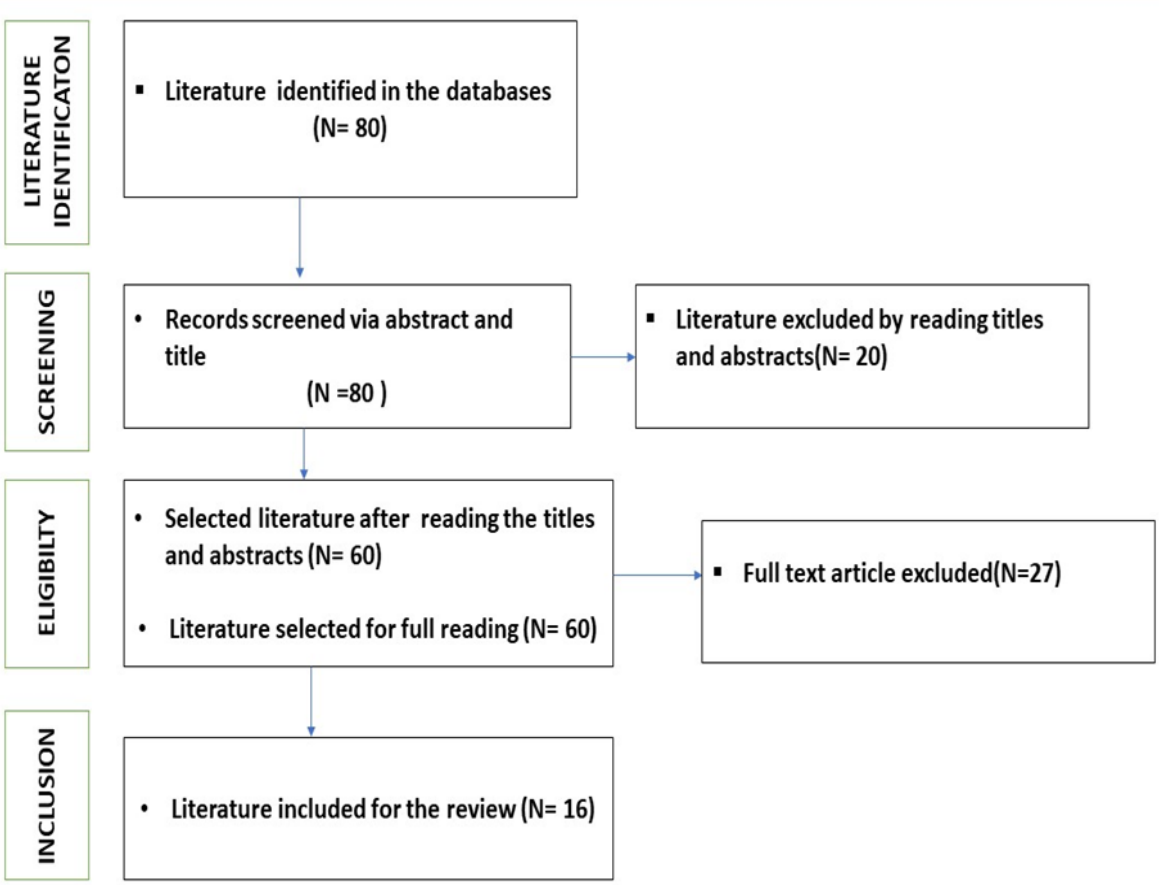

Fig. 1. Prisma Flow Chart statement summarizing the number of records excluded at each stage of the literature review process

Source: Survey data , 2024

3. RESULTS

Table 1. Effects of MO extract administration on diabetes parameters in animal studies

Reference	Dosage	Duration	Key findings
[21]	The study administered a dose of 100 mg/kg of Moringa extract orally to the diabetic treated mice.	21 days	Moringa extract (MO) to diabetic mice improved their insulin resistance, increased their antioxidant defenses, and improved kidney function. Specifically: • Insulin resistance decreased • Antioxidant capacity increased • Kidney function improved (creatinine and BUN levels decreased) • T-cell activation decreased (CD69 levels decreased) • Pro-inflammatory cytokine INF-γ levels decreased in diabetic mice, but increased in mice treated with MO
[12]	200 mg/kg	8 weeks	The study found that administering Moringa leaf decoction to diabetic rats led to increased expression of pancreatic regeneration markers, reduced fasting blood glucose levels, and improved tissue health in the pancreas, liver, and kidneys. The decoction also showed antioxidant effects, reducing oxidative stress. The study suggests that Moringa leaf decoction may have curative and protective effects against type 1 diabetes in rats, possibly through its antioxidant action and promotion of pancreatic regeneration.
[22]	100, 200 and 300 mg/kg of the aqueous extract	NL	It was reported that the aqueous extract of Moringa leaves reduced blood sugar levels in both normal and diabetic rats in a dose-dependent manner. The extract's hypoglycemic activity was comparable to the standard drug tolbutamide. The study confirms the traditional use of Moringa in managing diabetes and suggests that it has potential as a natural treatment for the condition.
[23]	The study used a dosage of 8 grams per day of MO leaf capsules. Participants received either 8 capsules (4 grams) of MO	4 Weeks	MO leaf capsules did not show a significant effect on glycemic control (measured by fasting plasma glucose and HbA1C levels) in therapy-naïve type 2 diabetes patients. There was a tendency of blood pressure reduction (5 mmHg decrease in

Reference	Dosage	Duration	Key findings
	leaf capsule or matched placebo before breakfast and dinner.		systolic blood pressure) in the MO leaf group compared to baseline, although this difference was not statistically significant. The study highlighted the need for further investigation regarding the potential blood pressure-lowering effects of MO leaf in type 2 diabetes patients.
[24]	250 mg/kg and 500 mg/kg of ethanolic leaf extract of MO	NL	The ethanolic leaf extract of MO significantly lowered fasting blood glucose levels in diabetic rats compared to the control group. There was a significant increase in serum insulin levels in the control group compared to the groups treated with the MO extract and metformin. The MO extract, at both doses tested (250 mg/kg and 500 mg/kg), as well as metformin, significantly improved insulin resistance (HOMA-IR) in diabetic rats. The study suggests that the ethanolic leaf extract of MO may have potential benefits in improving insulin resistance and glycemic control in diabetes
[25]	100, 200, 400 and 800 of mg/day/kg of *MO* powder		MO powder administered at a dose of 800 mg/day/kg BW reduced trophoblast cell apoptosis. The treatment group showed a significant difference in the mean number of trophoblast cells undergoing apoptosis compared to the control group. Hyperglycemia conditions in pregnant rats with diabetes mellitus can lead to trophoblast cell damage. The study suggests that MO powder may be effective in preventing trophoblast cell damage in preeclamptic pregnant rats with diabetes
[26]	200 mg/kg body weight of aqueous extract of *MO.*	60 days	The study found that the aqueous extract of Moringa leaves had significant antihyperglycemic effects in both insulin-resistant and diabetic rats. The extract improved insulin sensitivity, glucose tolerance, and restored insulin levels, while also reducing lipid abnormalities and promoting weight normalization. The study suggests that the extract has potential as a therapeutic agent for managing insulin resistance and diabetes-related complications, and may offer benefits for individuals with these conditions.

Reference	Dosage	Duration	Key findings
[27]	Low dose of 150, and high dose of 300 mg/kg of MOMtE	21 days	Methanol extract of *Moringa oleifera* pods (MOMtE) showed significant antidiabetic activity in diabetic rats, reducing serum glucose and nitric oxide levels, and increasing insulin and protein levels. The extract also increased antioxidant levels in pancreatic tissue, protected against oxidative stress, and reversed degenerative changes in pancreatic beta cells. The active constituent's quercetin and kaempferol were identified, and the study suggests that *Moringa oleifera* pods have potential as effective antidiabetic and antioxidant agents.
[28]	200 mg/kg of the lyophilized powder of MO	21days	Diabetic rats had increased oxidative stress, inflammation, and kidney damage, as well as diabetic complications such as high blood sugar and kidney dysfunction. However, treatment with low doses of Moringa seed powder (50 and 100 mg/kg body weight) improved these parameters, restoring them to near-normal levels. The treatment also reversed kidney and pancreas tissue damage, suggesting that Moringa seed powder may have antidiabetic and nephroprotective effects in diabetic rats.

4. DISCUSSION

A study conducted by Aja et al. (2015) examined the effectiveness of orally administering ethanolic extract of MO in treating diabetes, utilizing the glucometer method. The study's findings demonstrated a significant reduction in blood glucose levels in the experimental models that were treated with ethanol extract of MO. This reduction was observed in dose dependent manner. Additionally, the extract resulted in a significant increase in the body weight of the rats induced with alloxan [29]. This implies that MO has the ability to counteract the reduction in body weight commonly observed in individuals with diabetes as a result of a reduced appetite. The study concluded that the presence of phytochemicals such as flavonoids, terpenoids, glycosides and alkaloids as bioactive compounds may have caused the extract to elicit the observed anti-diabetic effect by causing an increase in insulin output or by inhibiting intestinal absorption of glucose or to the facilitation of metabolites in insulin dependent processes. Similarly, diabetic induce mice were orally administered 100 mg/kg of Moringa extract for two weeks. The results showed enhanced insulin sensitivity, increased total antioxidant capacity (TAC), and improved immunological tolerance. The study revealed a significant increase in glucose levels, by 1.7 times, in diabetic mice treated with Moringa compared to the control group [21]. However, as a result of the administration of Moringa, the glucose level exhibited a reduction of 1.28-fold in comparison to the diabetic group [21]. These findings indicate that moringa has the potential to effectively decrease hyperglycemia by regulating glucose levels within the normal range.

In a study conducted by Elendu et al. [30], reported on the ameliorative effect of aqueous leaf extract of MO on diabetes induced appetite. This study revealed that MO promote testicular health through its anti-diabetic potential [30]. It was discovered that administering MO leaf decoction to rats with streptozotocin-induced diabetes mellitus for a period of eight weeks resulted in a significant decrease in blood sugar levels compared to the diabetic group [12]. Additionally, the study provided evidence supporting the effectiveness of MO extract in treating diabetes by enhancing insulin production and release. The aqueous extract of MO leaves had significant hypoglycemic and antioxidant properties, highlighting its crucial therapeutic significance. The hypoglycemic activity of MO is attributed to its capacity to reduce blood sugar levels by interacting with anti-insulin antibodies and stimulating the release of insulin from the beta-cells of the pancreas. The groups treated with MO, both before and after the onset of diabetes, showed an increase in the relative expression of PDX-1, Ngn3, VEGF, IGF, and GLUT-2 mRNA. This suggests that MO has both preventive and therapeutic effects on pancreatic beta-cells. One way the MO extract works is by interacting with certain substances in the body that block the effects of insulin, a hormone that helps regulate blood sugar. By doing this, the extract helps the body release more insulin from the pancreas, which helps to lower blood sugar levels. The study also showed that the MO extract has benefits for the cells in the pancreas that produce insulin. These cells showed increased activity when treated with the extract, suggesting that it can help to protect and improve their function. This is important because these cells are important for producing insulin and controlling blood sugar levels. In addition to its effects on blood sugar, the MO extract also has antioxidant properties which help in reduction of damage caused by harmful substances in the body and is especially important in diabetes where there is often increased oxidative stress.

A study by Edoga and others examine the impact of MO on albino rats with hyperglycemia. Findings from the study demonstrated that the aqueous extract of MO leaves exhibits a substantial, dosage-dependent hypoglycemia impact in alloxan-induced diabetic rats, comparable in efficacy to the standard medication [22]. Additionally, this feature reinforces its application in the traditional treatment of diabetes. The extract had hypoglycemic effects in alloxanized rats, suggesting its potential for exerting extra pancreatic actions. The study established that the hypoglycemic effects associated with MO extract is a result of its bioactive active ingredients. However, the specific constituents responsible for this effect and the mechanism by which the extract works are yet unknown. According to a study by Chinedu et al. (2014) which investigated the impact of the ethanolic leaf extract of MO on insulin resistance in streptozotocin induced diabetic rats [30]. The extract significantly lowered the fasting blood glucose, a significant increase in serum insulin level was observed. The effects of the extract were comparable to the standard drug metformin used in the study. Similarly, aqueous extract of MO leaves on body weight, plasma glucose,

insulin, lipid profile, and oral glucose tolerance test in insulin resistant and diabetic rat models [26]. Administration of MO extract to the diabetic induced rats restored all alteration to normal or near normal. The study unequivocally demonstrates that the aqueous extract of MO leaf exhibits strong antihyperglycemic properties in rat models with both Insulin resistance and Insulin deficiency. The increase in plasma insulin levels in the diabetic rats induced by streptozotocin was attributed to the bioactive compounds present in the plant extract such as flavonoids which has been studied to regenerate damaged β-cells in the alloxan induced diabetic rats, in accordance to this a recent study on anemia using MO also attributed increase in blood parameters by similar bioactive compounds [31]. These compounds either stimulated the secretion of insulin, protected the intact functional of β -cells from further damage, or facilitated the regeneration of the β-cells that were destroyed by streptozotocin. This is likely due to the presence of quiescent cells in the pancreas that possess the ability to regenerate [32,33].

Furthermore**,** MO has been shown to induce a significant reduction in serum glucose and nitric oxide, with a resultant increase in serum insulin levels, additionally the extract increased antioxidant activity in pancreatic tissues, with a concomitant decrease in levels of athiobarbituric acid-reactive substances [27]. Histological examination of the pancreas from the diabetic rats showed degenerative changes in β-cells; this observation was significantly restored the histoarchitectural damage to the islet cells following the administration 150, 300 mg／kg for MO 21 days.

5. FUTURE PERSPECTIVE

Further investigation is required to determine, isolate, and chemically analyze the bioactive chemicals that are responsible for the antihyperglycemic effects, regeneration of the β-cells, and increase in blood insulin levels observed in previous experimental trials.

6. CONCLUSION

MO has shown effectiveness in reducing high blood sugar levels, promoting the regrowth of β-cells, and increasing insulin levels in animal models. The plant's characteristics can modify metabolic parameters linked to diabetes mellitus, hence preventing the occurrence of neuropathy, retinopathy, nephropathy, and cardiovascular disorders complications. MO exhibits potential as a viable substitute therapy for diabetes. Nevertheless, forthcoming investigations should focus on determining the optimal dosage of MO to get the most favorable therapeutic outcome in human subjects.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declares that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
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