Antidiabetic Properties of *Moringa oleifera*: A Review

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing my degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material that has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

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Ethics Statement

This study does not involve any kind of animal trial or human trial.

Abstract

Diabetes mellitus is a metabolic disorder that affects people all over the world. Currently, drugs made from herbs are used as medicinal plants which can treat a wide range of illnesses. Besides, plant-derived drugs improve health and increase the body's resistance to disease. Plants such as *Moringa oleifera* may have hypoglycemic and other beneficial properties. The study aims to examine how *M. oleifera* affects plasma glucose levels in both humans and animals. Moreover, the acute antihyperglycemic effects of the extract of *M. oleifera* extract on diabetic animal models appear to be stronger than in humans. Furthermore, evidence for changes in insulin levels as a consequence of *M. oleifera* treatment is unclear in both animal and human trials. Therefore, additional elaborated research is required to determine whether *M. oleifera* affects insulin levels or activity.

Keywords: Diabetes, *M. oleifera*, hypoglycemia, methanol extract, anti-diabetic activity.

Dedication:

I want to dedicate this project to my respectable supervisor Dr. Sharmind Neelotpol, Associate Professor, School of Pharmacy, BRAC University for her continuous and relentless guidance throughout my project. I want to dedicate this project to my family as well for their unwavering support and motivation to fulfill my desired goal.

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List of Acronyms

STZ: Streptozotocin

HDLc: High-Density Lipoprotein cholesterol

LDLc: Low-Density Lipoprotein cholesterol

VLDL: Very Low-Density Lipoprotein

GLUT2: Glucose Transporter 2

GLUT4: Glucose Transporter protein Type-4

Chapter 1

Introduction

Diabetes mellitus (DM) is a condition which has been identified as a common chronic medical condition in many countries (Shaw et al., 2010). There are several risk factors such as insufficient exercise, unbalanced diet, overweight, alcohol drinking, environment issues, and infectious diseases can lead to diabetes in the human body. These poor habits contribute to incorrect protein, carbohydrate, and lipid metabolism, which results in metabolic diseases such hyperlipidemia and hyperglycemia (Abd El Latif et al., 2014). Diabetes is connected with a number of clinical problems including nephropathy, diabetic neuropathy, retinopathy or blindness, and erectile problems (Smolek et al., 2013). Oral hypoglycemic medications and food restriction are the most typical treatments for diabetes in elderly people (Warjeet Singh, 2011). However, hypoglycemic drugs simply regulate blood glucose levels and do not cure the condition. For many decades, sulfonylureas and metformin drugs have been used in the treatment for diabetes. But treatment with these two drugs show side effects such as weight gain, skin rash, bloating and diarrhea. It has been discovered that medicinal plants offer strong anti-diabetic potential with no negative side effects. Besides, the particular cause of diabetes is the disease's progression and expression are significantly influenced by an enhanced oxidative stress, increased lipid peroxidation and impaired antioxidant defense system. (Jaskova et al., 2014) (Yassa & Tohamy, 2014). As a result, much research is being done on traditional medicines with anti-diabetic ability as an alternative to standard diabetes treatment (AL-Malki. A. & EL Rabey. AH., 2015).

Naturally occurring medicinal plants are recognized to offer therapeutic potential to treat a wide range of diseases (Gnanaraj et al., 2017). The horseradish plant, *M. oleifera* is basically native to South Asia, where it grows in the foothills of the Himalayas, although it is commonly cultivated

throughout the tropics (Coppin et al., 2015). *M. oleifera* is called as "Sajna, Sojna, or Khonjhon" in various areas of Bangladesh (Amaglo et al., 2010). *Moringa* is a small to medium-sized evergreen or deciduous tree that can reach a height of 10-12 meters (Patois, 2009). It features a wide, spreading crown that is often umbrella-shaped and the roots are very deep. It contains high levels of nutrients including protein, potassium, calcium, manganese, zinc, iron, phosphorus, various vitamins such as vitamin A, vitamin C, vitamin D and E, and as well as huge amount of antioxidants, including flavonoids, glucosinolates, phenolic acids, isothiocyanate, tannins, alkaloids and saponins (Patil et al., 2022). The Indian people have traditionally utilized the entire Moringa plant staring from the leaves, bark, stem, root, pods, flowers and seed, for medical purposes and also a good source of nutrition (Jaiswal et al., 2009).

M. oleifera is therefore sometimes referred to "tree of life" since it is abundant in nutrients and antioxidants, may be ingested to improve human health. Recent reports (Tuorkey, 2016) provide a thorough description of *M. oleifera's* antidiabetic action with various range of pharmacological benefits. Pharmacological research on *M. oleifera* has revealed that it has other medicinal properties including anti-cancer, hepatoprotective, anti-inflammatory, anti-hypertensive, antimicrobial, wound healing, anti-fungal, anti-ulcerative, and diuretic (Igado & Olopade, 2017). Chemical analysis of *M. oleifera* showed that contains glucosinolates, kaempferol, vanillin, caffeic acid, chlorogenic acid, p-coumaric acid, ferulic acid, quercetin, epicathechin and cinnamic acid. So, may be these chemical constituents add potential medical value to this plant (Omodanisi et al., 2017). It has been established that several medicinal plants have therapeutic properties for treating diabetes mellitus. The therapeutic and dietary benefits of *M. oleifera* are well known and it has also been suggested that it contains potent hypoglycemic properties.

M. oleifera's anti-diabetic activities have been demonstrated in a few earlier studies (Edoga et al., 2013) (Gupta et al., 2012). Due to their high medicinal content, *M. oleifera* leaf extracts in both aqueous and methanolic form have been shown to have anti-hyperglycemic effects on streptozotocin (STZ)-induced rats and diabetic mice (alloxan-induced) (Abd El Latif et al., 2014) (Yassa & Tohamy, 2014) (Wang et al., 2022) (Omodanisi et al., 2017). In this study, a variety of human and animal models of diabetes are reviewed to discuss whether *M. oleifera* would be useful for further research on the possibility of establishing useful drugs based on Moringa for human benefits.

1.1 Aim of the study

The aim of this review study is to investigate the effect of *M. oleifera* on diabetes.

1.2 Objectives of the study

1. To investigate the therapeutic effect of *M. oleifera* on diabetic patient.
2. To evaluate the mechanism of action of *M. oleifera* on diabetes.

Chapter 2

Methodology

The review article is created using a methodical process that includes examining electronic data from reliable sources. The information and data of the research were compiled from the reputed journal articles. To gather the journals connected to this topic, an electronic search has been done. The journals, research, and review papers that were used to compile this article are including, Google Scholar, PubMed, UCLA Library Journal Search, Web of Science and CORE. After searching it was found that, more than 140 articles have been published, of which 110 have been downloaded and are pertinent to the topic. Additionally, the data was extracted from those papers and used them in writing. Each piece of information was thoroughly researched before being written up. To prevent plagiarism and information was paraphrased. Furthermore, this review paper was cited in Mendeley.

Chapter 3

Discussion

3.1 Constituents of *M. oleifera*

M. oleifera include a variety of phytochemical compounds such as phenolic acids, alkaloids, steroids, tannins, glucosinolates, terpenes, flavonoids, polyphenols and saponins (Koukoui et al., 2015). These phytoconstituents provide critical nutrients and essential compounds that benefit in the illness prevention and treatment (Rani et al., 2018). Numerous studies have shown *M. oleifera* to be a healthful, nutritional herb with positive impacts on humans. Evidence from in-vitro and in-vivo studies shows that the bioactive components have promising pharmacological effectiveness. Different components of *M. oleifera* tree are now being studied for their potential benefits in diabetes and other metabolic conditions (Vergara-Jimenez et al., 2017).

Polyphenolic substances contain phenolic acid and flavonoids which are found in *M. oleifera's* dehydrated leaves, flowers, pods, stems, roots and seeds. The most common phytochemical constituents in plants are flavonoids, which are secondary metabolites. In addition to, it boost the human body's nutrition and help to prevent numerous ailments (Bhalla et al., 2021). The leaves of *M. oleifera* contain several flavonoids, however the most abundant flavonoids with high pharmacological activity are quercetin, apigenin, kaempferol, and isorhamnetin (Makita et al., 2016). According to (M. Lin, J. Zhang, and X. Chen, 2018), when *M. oleifera* seeds are colorimetrically analyzed, where amount of flavonoids were found 2.900 mg (Lin et al., 2018). Moreover, flavonoids have been shown to have anticancer and *antioxidant* properties, as well as anti-inflammatory, anti-allergic, anti-microbial, and other benefits. Among all other phenolic substances, Quercetin 3-β-D-glucoside has the highest antioxidant activity (Zhu et al., 2020).

M. oleifera is rich in amino acids, organic acids, different vitamins, protein, and minerals. Various vitamins such as vitamin A, B and C are required for human body because they contain nutritious chemical substances. The concentration of Vitamin A, Vitamin B, and Vitamin C present in the leaf extract of *M. oleifera* is includes, 80 g, 2.4 mg, and 8.8 mg. According to an experimental investigations, beta carotene and vitamin C, and that have significant bioavailability and support a balanced diet, are particularly beneficial. (Khalid Abbas et al., 2018) (Saa et al., 2019).

Glucosinolates, which have bioactive and nutraceutical properties and are the most recognized secondary metabolites in plants (Panda et al., 2013). *M. oleifera* includes two powerful glucosinolates, 4-rhamnopyranosyloxybenzyl glucosinolate and acetyl-4-rhamnopyranosyloxybenzyl glucosinolate isomer III, both of which have substantial anticancer effect (Galuppo et al., 2015). *M. oleifera* also contains glucomoringin which is a rare glucosinolate that carry powerful anti-microbial agent and anti-proliferative activity (Park et al., 2011). Additionally, the transformation of glucosinolates into isothiocyanates with the availability of the myrosinase enzyme, which mainly found in part of plant as well as the human GIT tract. The transformed isothiocyanates are an important component that has antioxidant and anti-inflammatory properties (Doerr et al., 2009) (Tumer et al., 2015).

Figure 1: M. oleifera leaves and flowers (Olson, 2010)

Tannins, which are phenolic, water-soluble compounds, have the ability to extract proteins, alkaloids, and gelatin from the leaves of *M. oleifera*. They range from 13.2 to 20.6 g of tannin/kg in dried leaves, with freeze-dried leaves having a slightly higher amount. Hepatotoxic, anti-cancer, anti-inflammatory and anti-atherosclerotic effects are all attributed to tannins (Adedapo et al., 2015).

The leaves of the *M. oleifera* plant contain saponins, that are organic substances consisting of an aglycone which is derived from isoprenoidal. There were 64 to 81 g/kg dry weight of saponin in the freeze-dried leaves of *M. oleifera.* (Augustin et al., 2011).

Alkaloids are a type of chemical constituents that mostly include basic nitrogen atoms. Several of these compounds have been identified from *M. oleifera* leaves, including N, -l-rhamnopyranosyl vincosamide, 4′-hydroxyphenylethanamide-α-l-rhamnopyranoside and its glucopyranosyl

derivative (Sahakitpichan et al., 2011). The total alkaloids from extracted *M. oleifera* were evaluated for antihypertensive effects (Vergara-Jimenez et al., 2017).

3.2 Potential role of *M. oleifera* in the treatment of diabetes mellitus

Diabetes is a metabolic disorder in which body's ability to manage blood sugar is impaired because the pancreas either cannot generate enough insulin (Gardner & Shoback, 2011). Numerous important physiological systems, including the cardiovascular and nervous systems are damaged by this uncontrolled high blood sugar state (Razaq, R. A. ., Mahdi, J. A. ., & Jawad, R. A., 2020). There are two main types of diabetes such as type 1 and type 2 (Saedi et al., 2016). Insulin production is halted by type 1 diabetes, which is thought to be brought on by an immunological response. Because of improper insulin production, type two diabetes makes it difficult for the body to keep blood sugar levels within normal ranges (Kitabchi et al., 2009). Type 1 diabetes is genetically inherited, but type 2 diabetes is caused by a lifestyle or environmental factors (Rother, 2007). According to the WHO (World Health Organization), the number is constantly rising over time. For example, in 2014, 8.5% of populations aged 18 or older had diabetes, while in 2019, 1.5 million people died directly from diabetes (Atlas, 1955). The alarming fact is that almost 50% of deaths occur before the age of 70 (Bourne et al., 2021).

Over the time, the prevalence of diabetes has increased, especially in low- and middle-income countries, which has adverse effects on human health and economics. Many treatment strategies had been made using medicinal plants to address various illnesses. Medicines derived from plants improve health condition and increase the body's resilience to sickness. Moreover, given the high expense of medications and their negative effects on patients, medicinal plants could be effectively used in the treatment of diabetes in an optimal strategy for better cost-effectiveness. In view of this, the importance of Moringa plant increases due to important findings about its ability to fight

against diabetes. Apart from these, the main problem of diabetes is the degeneration of neurons due to the damage caused by free radicals produced in the diabetic condition (Carris et al., 2019). Several studies have been conducted on the Moringa plant to determine its ability to treat both type I and type II diabetes. The following table (Table 1) summarizes some recent studies on the antidiabetic effects of *M. oleifera* (MO) in the treatment of diabetes in animal models.

Table 1: Antidiabetic effects of M. oleifera (MO) in the treatment of diabetes in animal models

Animal Model	**Part of MO Tree**	**Treatment**	**Results**	**Reference**
Alloxan induced diabetic Wister rats	MO leaf extracts	Treatment time: 21 days Control group: Untreated Moringa leaf extract-treated diabetic group: 150 mg / Kg / day Moringinine-treated diabetic group: 3600 µmole/Kg /day	Significant decrease of HDLc (High-density lipoprotein cholesterol) in diabetic group. Highly significant increase in alanine amino transferase, aspartate amino transferase and Gama glutamyl transferase activities in diabetic rats. In the treatment groups there was a significant decrease in triacylglycerol & LDLc (Low-density lipoprotein cholesterol) and a significant elevation in HDLc	(F. T. Ali et al., 2015)

		Quercetin treated diabetic group: 30 mg/Kg/day	compared to the diabetic control rats.	
Alloxan induced diabetic Albino rats	MO leaves	Treatment time: 18 hours Control group: normal saline (2 ml/kg) Group treated with tolbutamide: 200mg/kg Diabetic MO group: 100, 200 and 300 mg/kg	Normoglycemic rats showed a significant decrease in blood glucose level including 23.14%,27.05%,33.18%,33.29%,2% in the dose of 100 mg/kg, 200 mg/kg, 300 mg/kg, 200 Tolbutamide and 2 (ml/kg) Normal Saline. Alloxan-induced hyperglycemic rats showed significant reduction of glucose at a percentage of 31.22%,40.69%,44.96%,46.75%,2.26% in the dose of 100 mg/kg, 200 mg/kg, 300 mg/kg, 200 Tolbutamide and 2 (ml/kg) Normal Saline.	(Edoga et al., 2013)

STZ Induced Albino rats	MO seed powder	Treatment time: 4 weeks Control group: 0.1 mol/L citrate buffer (pH 4.5) Diabetic MO group: 50, 100 mg/kg	Blood glucose level decreases from 266 mg/dL to 148 mg/dL. Significant decrease in HbA_{1C} (Hemoglobin A1c). Significant reduction in lipid peroxide. Significant increase in antioxidant enzymes.	(AL-Malki. A. & EL Rabey. AH., 2015)
Goto-Kakizaki (GK) diabetic rats and nondiabetic Wistar rats used as controls	MO leaf powder	Treatment time: 120 min Control group: glucose 2 g/kg MO group: glucose 2 g/kg and 200 mg/kg MO	Blood glucose decreased at 20, 30, 45, and 60 min ($p<0.05$) as compared with controls. At 20, 30, 45 and 60 min the blood glucose level decreased from 390 to 320 mg/dL, 410 to 341 mg/dL, 395 to 350 mg/dL and 375 to 335 mg/dL, respectively.	(Ndong et al., 2007)
Alloxan induced diabetic mice	Aqueous leaf extracts	Treatment time: 21 days Control group: Untreated Doses: 100 mg/kg	Alloxan induction increased the level of glucose in mice (321.2 ± 33.93 mg/dL) ($p<0.05$). Doses of MO significantly reduced the hyperglycemia, maintaining total	(Tuorkey, 2016)

		MO aqueous leaf extract	glucose levels at 249.2 ± 11.77 mg/dL ($p<0.05$).	
Alloxan-induced diabetic Sprague-Dawley rats	MO leaf powder	Treatment time: 8 weeks Control group: Saline MO diabetic group: 100 mg/kg, 200 mg/kg, 500 mg/kg	After hyperglycemia induction, the diabetic groups showed glucose values of 300 mg/dL. At the second week, a significant reduction was observed in blood glucose level in diabetic rats from 300 mg/dL to 100 mg/dL.	(Villarruel-López et al., 2018)
Alloxan-induced diabetic mice	MO leaf powder	Treatment time: 1, 3 and 5 h Diabetic positive Control group: Insulin 0.7 IU/kg\ MO diabetic group: 100 mg/kg, 300 mg/kg and 500 mg/kg.	Blood glucose level reduced in diabetic rats at 5h with administration of 300 mg/kg and 500 mg/kg of MO ($p<0.01$). After 1, 3, and 5 hours, the 500 mg/kg dose showed significant decreases of blood glucose level at 34.3%, 60.9%, and 66.4% respectively.	(Paula et al., 2017)
STZ-induced diabetic Wistar rats	MO aqueous leaf extract	Treatment time: 3 weeks Control group: Untreated	Significant reduction in fasting blood glucose of diabetic rats treated with aqueous leaf extract of MO.	(Jaiswal et al., 2009)

		Control MO group: 100 mg/kg, 200 mg/kg, and 300 mg/kg Diabetic MO group: 100 mg/kg, 200 mg/kg, and 300 mg/kg MO Diabetic positive control group: Glipizide 2.5 mg/kg	Reduction after 1, 2, and 3 weeks with 200 mg/kg of MO was 25.9%, 53.5%, and 69.2% respectively. Observation of other improvements include hemoglobin and total protein levels.	
Alloxan-induced diabetic Wistar rats	MO aqueous leaf extract	Treatment time: 18 days Control group: Untreated Diabetic control group: Untreated Control MO group: 250 mg/kg MO Diabetic MO group: 250 mg/kg MO	Blood glucose level reduction occurs from 400 mg/dL to 200 mg/dL in diabetic rats ($p < 0.05$). Significant reduction in triglycerides and malondialdehyde (MDA).	(Abd El Latif et al., 2014)

STZ-induced diabetic Sprague-Dawley rats	MO aqueous leaf extract	Treatment time: 4 weeks Control group: Untreated Control MO group: 200 mg/kg MO Diabetic control group: Untreated Diabetic MO group: 200 mg/kg MO	Reduction in blood glucose level in diabetic rats from 266.50 ± 2.17 mg/dL to 148.83 ± 2.44 mg/dL ($p < 0.001$) after 200 mg of MO treatment administration.	(Yassa & Tohamy, 2014)
Alloxan-induced diabetic Wistar rats	MO methanolic leaf extract	Treatment time: 6 weeks Control group: Untreated Diabetic control group: Untreated Diabetic MO group: 300 or 600 mg/kg Diabetic positive control group:	At 300 mg/kg and 600 mg/kg, the blood sugar was reduced by 76% and 84%. Additionally, 300 or 600 mg/kg of MO methanolic extract improved glucose tolerance by 56% or 57%, respectively ($p < 0.001$). Significant increase of insulin level in the diabetic rats. Serum insulin levels increased 1.3–1.7 times in the rats.	(Olayaki et al., 2015)

		metformin 100 mg/kg		
STZ-induced diabetic Wistar rats	MO methanolic leaf extract	Treatment time: 3 weeks Control group: Untreated Diabetic control group: Untreated Diabetic MO group: 200 mg/kg	Reduction of glucose level in the blood occurs from 229 ± 9.05 mg/dL to 86 ± 4.2 mg/dL in diabetic MO group ($p<0.05$). Normalization of mitochondrial function in liver.	(Alejandra Sánchez-Muñoz et al., 2018)
Alloxan-induced diabetic Wistar rats	MO ethanolic leaf extract	Treatment time: 6 weeks Control group: Untreated Diabetic control group: Untreated Diabetic positive control group: Sitagliptin 50 mg/kg Diabetic MO group: 300 mg/kg MO	Acute but not chronic significant reduction of glucose level in diabetic rats. The co-administration of sitagliptin and MO produced a decrease of 60% (90.00 ± 9.77 mg/dL) in fasting glucose level after 2 weeks compared to day 1 (226.85 ± 21.81 mg/dl) ($p<0.05$). In diabetic rats, insulin level remains unchanged.	(Olurishe et al., 2016)

		Both Sitagliptin and MO group: 50 mg/kg Sitagliptin and 300 mg/kg MO		
STZ-induced diabetic Long Evan rats	MO ethanolic leaf extract	Treatment time: 120 min Diabetic control group: Untreated Diabetic MO group: 250 mg/kg MO Diabetic positive control group: Glibenclamide 0.5 mg/kg	Blood glucose level reduced from 6.5 mmol/L to 5.5 mmol/L in diabetic rats ($p<0.05$).	(Azad et al., 2017)
Alloxan-induced Swiss-Webster mice	MO N-hexane seeds extract	Treatment time: 8 days Control group: Untreated MO group: 40, 60, and 80 mg/kg MO Diabetic MO group: 40 mg/kg,	Significant reduction of blood glucose level observed in both acute (less than 6 hour) and sub-chronic treatment (up to 8 days) in the diabetic mice. For 40 mg/kg, 60 mg/kg and 80 mg/kg diabetic MO group showed better reduction in blood glucose	(Raafat & Hdaib, 2017)

		60 mg/kg and 80 mg/kg Diabetic beta-sitosterol group: 18 mg/kg, 25 mg/kg and 35 mg/kg	level after 6 hours (49.2%, 130 mg/dL), (53.4% ,115 mg/dL), and (60.6%, 100 mg/dL) respectively, than the control group (240 mg/dL). Diabetic beta-sitosterol group (18 mg/kg, 25 mg/kg and 35 mg/kg) have shown a significant blood glucose lowering potential after 6 hours of administration by 64.0%, 66.1% and 69.1% ($p<0.05$). Insulin levels increased when treated with 40 mg/kg MO to 2.7 mg/L, 60 mg/kg to 3 mg/L, and 80 mg/kg to 3.7 mg/L, compared to 1.5 mg/L in the control group ($p<0.05$).	

3.3 Interpretation of information collected from animal studies

Ali et al., (2015) found *M. oleifera* leaf extracts as a potential antidiabetic agent by performing experiment in active phyto-ingredients such as quercetin, chlorogenic acid and moringinine (F. T. Ali et al., 2015). These three active ingredients are belonging to alcoholic extracts of *M. oleifera*. All of the extracts were subjected to testing on rats that had been given alloxan to make them diabetic. Animals receiving alloxan through injection or administration develops an insulin-dependent diabetes called alloxan-induced diabetes (Ighodaro et al., 2017). Furthermore,

determination of antidiabetic activity was followed by experimenting pancreatic histopathology, liver function tests, oxidative stress markers, glucose level, lipid profile and some C-peptide. The research showed that *M. oleifera* leaf extract reduced the effects of alloxan-induced diabetes in wister rats by bringing their high levels of total cholesterol, triacylglycerol, glucose, malondialdehyde, protein content, and C-peptide back to normal. In that case, the extracts quercetin, moringinine and chlorogenic acid all have the greatest potential for antidiabetic action. Quercetin had the highest potential activity in the extract of the three studied components, followed by moringinine and chlorogenic acid (F. Ali et al., 2016). Therefore, these ingredients contribute significantly for the extract's anti-diabetic effect.

According to an investigations performed on albino rats, the result shows that *M. oleifera* leaves has a strong hypoglycemic efficacy with a dose dependent action in normoglycemic and alloxan-induced rats and it is nearly as effective as tolbutamide (Edoga et al., 2013). Tolbutamide is a sulfonylurea oral hypoglycemic medicine that is a first-generation potassium channel blocker. At the very beginning of the study different categories of albino rats (normoglycemia, hyperglycemia and alloxan induced hyperglycemia) were treated with three different doses for example aqueous extracts, tolbutamide and normal saline. Following this, the result explains the aqueous extract reduced blood sugar levels in normoglycemic and hyperglycemic rats in a dose-dependent manner ($P<0.05$). Consequently, within 6 hours of administration the aqueous extract decreases the glucose levels in plasma by 23.14%, 27.05%, and 33.18% in normoglycemic rats, while tolbutamide reduced blood glucose levels by 33.29% ($P<0.05$). Similarly, Aqueous extracts reduction occurs in blood glucose level in the rats with diabetes by 33.29%, 40.69%, and 44.06% within 6 hours of injection, whereas tolbutamide provided a 46.75% reduction. The authors conclude that *M. oleifera* is comparable to the reference medication tolbutamide based on

the findings. So, *M. oleifera's* comparable activity with tolbutamide on both normoglycemic and hyperglycemic rats may indicate similar mechanisms of action (Edoga et al., 2013). It is possible that there's a gap in research concerning the active ingredients of *M. oleifera*. This impact of the *M. oleifera* extract was attributed to its active ingredients, which have not yet been identified or the mode of action of the extract's hypoglycemic effect is not established. For that reason, more research is needed to determine the active principles responsible for the hypoglycemic impact.

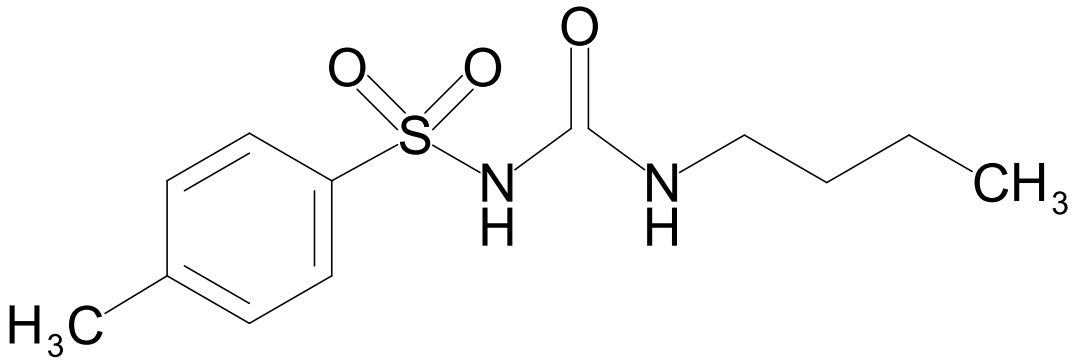

Figure 2: Tolbutamide

Another study examines the effects of *M. oleifera's* antidiabetic properties on immunological tolerance. A dosage of 100 mg/kg *M. oleifera* aqueous extract was delivered orally to diabetic mice that had previously been induced with alloxan. In order to identify insulin resistance, the levels of both glucose and insulin were tested. Serum creatinine and total antioxidant capacity were all measured. Moreover, percentages of CD44, CD69, and IFN-γ were also studied to examine important regulator of immune responses. Insulin resistance in diabetic mice was measured using a homeostasis model and was shown to be 4.5 times higher in control group than in the group receiving moringa therapy, while it was also found to be 1.3 times lower. The level of total antioxidant capacity decreased 1.94 times in diabetic mice and increased 1.67 times in the group that had received treatment for diabetes. Creatinine and blood urea nitrogen levels in diabetic mice

were considerably decreased by treatment with *Moringa oleirefa*, with significant reductions of 1.42 and 1.2 times respectively. In diabetic mice, the relative proportion of CD44 did not change, while the relative percentage of CD69 increased and INF-γ (Interferon-gamma) was reduced 2.4 times in diabetic mice (Tuorkey, 2016). So, based on the results presented above, it is possible to conclude that aqueous extracts of *M. oleifera* may reduce insulin resistance, boost overall antioxidant capacity, and improve cardiovascular health.

AL-Malki. A. & EL Rabey. AH., (2015) discovered that, treatment with low doses of *M. oleifera* in STZ induced diabetes rats exhibited a safe and excellent antidiabetic action due to its abundance of antioxidant substances such as glucomoringin and flavonoids. In practically, it restores the normal glycemic level in diabetic rats and maintains a healthy condition. Moreover, it was investigated if two small doses of Moringa seed powder such as 50 and 100 mg/kg might treat male rats with STZ-induced diabetes. The STZ diabetic rats in the positive control group had considerably higher average serum fasting blood sugar values than normal. However, giving powder from Moringa seeds as various doses to these rats about four weeks and results shows reduced their fasting blood sugar levels significantly. The larger dose of Moringa seeds powder (100 mg/kg) has greater anti-diabetic efficacy than the lower dose. The researchers could not find enough information about low doses of *M. oleifera* in their studies. Nevertheless, it is extremely efficient as an anti-diabetic medication, as well as maintaining serum electrolyte levels, liver enzymes, and lowering glycosylated hemoglobin and interleukin-6 levels in the blood (Kristiansen & Mandrup-Poulsen, 2005). Low doses of moringa, which are currently being studied that may have significant medicinal benefits when used as a dietary supplement for diabetics.

Another study related with STZ induced diabetic rats and normoglycemic Wister rats showed that, ethanolic extracts of *M. oleifera* leaves decrease high amount of blood glucose level in

experimented diabetic rats than normoglycemic rats (Tende et al., 2011). The authors experimented that, *M. oleifera* leaf extracts have been given in dosages of 250 and 500 milligrams to batches of fasting STZ diabetic and healthy rats, respectively. In the meanwhile, the result of hypoglycemia was compared with both STZ diabetic rats and fasted normal rats. Followingly, only in the fasted STZ diabetic rats the ethanolic extracts demonstrate dose-dependent action and significantly reduces the level of plasma glucose. Accordingly, after deliver both doses for a long duration (approximately 1-7 hours), the STZ induced diabetic group's blood glucose levels significantly decreased as compared to the control group. In contrast, there was a moderate decrease in blood glucose level as compared to control group of rats at both 250 and 500 mg high doses (Tende et al., 2011). In order to distinguish between the two doses, higher doses demonstrated more efficacy than lower ones.

A research employing two diabetic male rats including Goto-Kakizaki rats and Wistar rats which had, were given with *M. oleifera* extracts decreased glucose intolerance. Goto-Kakizaki rats experienced a noticeable drop in glucose at 60 and 120 minutes after glucose delivery, but considerable decrease observed in control Wistar rats (Ndong et al., 2007). Other investigations exhibited that male diabetic Wistar rats induced by STZ elevated glucose sensitivity in rats with diabetes and also lowering glycemia at control group rats. Administration of doses whether 50 or 100 mg/kg of seed of *M. oleifera* powder to rats with STZ-induced diabetes, which significantly reduced glycemia but did not return to normal values (Jaiswal et al., 2009). So, it is clear that the glucose reducing capacity of the seed powder is not as effective as that of the leaf extract.

A comparable investigation with Long Evan rats with STZ-induced diabetes found that *M. oleifera* ethanolic leaf extract (90 mg/kg) performed better than glibenclamide which is generally known as a sulfonylurea typically used to treat diabetes mellitus (Azad et al., 2017). Despite the fact that

M. oleifera -treated diabetic animals have no significant changes in the insulin levels. Another investigation employing diabetic Wistar rats and treats with methanolic extract of *M. oleifera* demonstrated a huge decrease in glycemia and also a great rise in the level of insulin in comparison to diabetic animals that weren't treated. Similar results were obtained with diabetic Sprague-Dawley rats when treated with *M. oleifera* and a subsequent paper reported that treatment with glibenclamide replicated similar results (Olayaki et al., 2015).

Alloxan-induced Wistar female rats that had been given 100 mg/kg of *M. oleifera* aqueous leaf extract showed normal lipid metabolism and reduced blood sugar levels after receiving treatment (Abd El Latif et al., 2014). Administration of *M. oleifera* methanolic leaf extract resulted in increased levels of heme oxygenase-1 and glutathione and also decreased reactive oxygen species production and lipoperoxidation on mitochondria of the liver of Wistar rats induced by STZ (Paula et al., 2017).

Olurishe et al., (2016), reported that continuous treatment (almost 6 weeks) of *M. oleifera* ethanolic leaf extract in combination with sitagliptin (an oral antihyperglycemic medication in type two diabetes mellitus) was effective for lowering glycemia in specific alloxan-induced diabetic Wistar rats (Olurishe et al., 2016). While only delivery of *M. oleifera* itself produced a substantial drop fasting plasma sugar on third week of the experiment. However, it was unable to provide a meaningful reduction at other points in the investigation. Additionally, the same article revealed that therapy with *M. oleifera* extract had no noticeable impact on insulin levels and had no effect on the pathologic lesions (tumors that form in the eyes) in the retina caused by hyperglycemia. Since the everlasting effects were only assessed up to 22nd day and was very unclear whether this study's findings would have been comparable to those of who examined glycaemia for up to 42 days. Additionally, after receiving *M. oleifera* treatment, both diabetic rats and mice showed

improved hepatic functioning, a large drop in total cholesterol, triglycerides, LDL, and VLDL, and a considerable rise in HDL. The benefits of leaf extract of aqueous *M. oleifera* were much more potent on diabetic mice than on diabetic rats.

3.4 Mechanism of action of *M. oleifera* on diabetic animal models

The *M. oleifera's* aqueous extract particularly the leaves in animal models have been shown in numerous studies to exhibit hypoglycemic effects. Researchers believe that phytochemicals extracted from *M. oleifera* leaves (aqueous/ethanol extract) can also play an important role in Type 2 diabetes mellitus. According to various investigations, aqueous extract derived from *M. oleifera* contains 43 polar bioactive chemicals and 40 lipophilic bioactive compounds (Khan et al., 2017). In order to regulate the components of the aqueous extract of *M. oleifera* that have a bioactive molecule or polar secondary metabolites such as tannins, phenols, glycosides and saponins and certain primary metabolites including such proteins and carbohydrates, researchers used High Performance Liquid Chromatography (HPLC) and Chromatography-Mass Spectroscopy (GC-MS) analysis (Dzuvor et al., 2022). On the other hand, nonpolar bioactive substances such carotenoids are present in the ethanolic extract of *M. oleifera*. *M. oleifera's* aqueous extract does not contain any carotenoids. The hypoglycemic activity is influenced by the appearance of alkaloids, chlorogenic acid and tannins. The various compositions of the extracts from *M. oleifera* leaves can vary the hypoglycemic processes. The bioactive component can restore type 2 diabetes mellitus patient's defective glucose and lipid metabolisms and also alleviate metabolic syndrome (Jin et al., 2020). The following figure represents the bioactive chemical and its mechanisms of action.

Table 2: Chemical constituents of aqueous extracts of M. oleifera (MO) and their mechanism of action

Animal Model	**Part of MO Constituents**	**Mechanism of Action**	**Reference**
STZ-induced diabetic Wistar rats	N-Benzyl thiocarbamates, N-benzyl carbamates, benzyl nitriles and a benzyl ester	Significantly stimulate the beta cells in the pancreas of rats to produce insulin. Enhance the tissue's utilization of glucose while inhibiting the activity of the cyclooxygenase enzyme and lipid peroxidation. Inhibits the absorption of glucose into the muscles and fat tissues by hepatic gluconeogenesis.	(Jaiswal et al., 2009)
STZ-induced diabetic Sprague-Dawley rats	Bioflavonoids	Stimulates of glucose uptake. Secrete glucose-induced insulin from the existing-cells or stimulate its release from the bound form.	(Yassa & Tohamy, 2014)

Alloxan-induced diabetic Wistar rats	Flavonoids, alkaloids, sterols, terpenoids and triterpenoids.	Reducing gluconeogenesis and repairing damaged pancreas and hepatocyte cells.	(Abd El Latif et al., 2014)
Alloxan-induced diabetic Wistar rats	Flavonoids, alkaloids, sterols, terpenoids, glucosinolates, isothiocyanates, phenolics, vitamin c, oleic acid, and chlorogenic acid.	Protect and improve the ability of damaged β-cells to regenerate and remain viable. Show hepatoprotective effect by reducing effect on caspase 3 mRNA expression. Inhibits hepatic glycogenolysis and gluconeogenesis in rats by blocking the enzyme glucose-6-phosphate translocase.	(Mabrouk Attia Abd Eldaim, 2018)
High-fat diet induced diabetes C57BL/6 mice	4-hydroxyphenylacetonitrit, fluoropyrazine, methyl-4-hydroxybenzoate, vanillin, 4-α-L rhamnopyranosyloxybenzy-l-isothiocyanate	Stimulates the Akt pathway in the muscle. The insulin dependent Akt pathway upregulates glucose transporter GLUT4 expression through an Akt-dependent pathway in the muscle.	(Attakpa et al., 2017)
STZ-induced	Phenolics and flavonoids	Shows scavenging effect of free radicals produced by STZ.	(Khan et al., 2017)

diabetic Wistar rats		Inhibits the activity of α-amylase and α-glucosidase and increases glucose tolerance and lowers postprandial glucose levels.	

The enhanced mRNA expression of pyruvate carboxylase (PC) which inhibits hepatic gluconeogenesis in diabetic rats can be improved by using an aqueous leaf extract from *M. oleifera*. Chlorogenic acid, which is present in the leaves of the Moringa plant has the ability to inhibit glucose-6-phosphate translocase in the liver or rats. The inhibition mechanism decreases hepatic gluconeogenesis and glycogenolysis. A crucial enzyme present in gluconeogenesis is PC mRNA expression (Mabrouk Attia Abd Eldaim, 2018). *M. oleifera* aqueous leaf extract has a protecting and regenerative effect on healthy functional cells and cells damaged by alloxan. According to its antioxidant activities, *M. oleifera* contains flavonoid, terpenoids, quercetin, and kaempferol, which preserve and increase the regeneration and viability of damaged cells and subsequent insulin secretion. Quercetin is also significantly increased hepatic glucokinase activity which has an improved insulin effect (Abd El Latif et al., 2014). The compounds that inhibit the rat hepatocyte's ability to translocate glucose-6-phosphate result in a reduction in the production of glucose and the breakdown of glycogen in the liver. In type 2 diabetes, the islet pancreatic β-cells absorb an abnormally large amount of glucose (Prentki & Nolan, 2006). As a result, the presence of excess sugar stimulates glycation reactions and the mitochondrial electron transport chain. Consequently, reactive oxygen species (ROS) may damage macromolecules to a greater extent than the cell's antioxidant capability. The destruction of insulin synthesis and secretion caused by oxidative stress initiates a series of cellular events that finally

cause pancreatic β- cell cytotoxicity and death. Flavonoids, terpenoids, quercetin, and kaempferol protect and has the ability of injured pancreatic β-cells to regenerate and function more effectively (Mabrouk Attia Abd Eldaim, 2018). Another mechanism suggests that while inhibiting glucose transporter protein (GLUT) function, *M. oleifera* leaf extracts causes a uncompetitive inhibition of glucose uptake at the small intestine level (Khan et al., 2017).

M. oleifera aqueous extract can reduce glucose absorption by inhibiting α-amylase (Azad et al., 2017). When compared to the standard drug acarbose, in vitro α-amylase and α-glucosidase inhibition studies demonstrated low IC_{50} value with an antagonistic effect in aqueous extract of leaves. In vitro experiments with a leaf extract of *M. oleifera* revealed that it reduced glucose levels after having meal by decreasing the activities of α-amylase. The α-amylase and α-glucosidase are two vital indigestion-causing enzymes that break down complex carbohydrates in food into monosaccharides that mainly absorbed by the intestine (Khan et al., 2017). The process of stimulating glucose uptake in peripheral tissue involves carbohydrate metabolism, insulin production which initiates glucose from pre-existing cells and encourages its release from the bound form and ultimately reduce glucose levels in blood of diabetic rats. This process also regulates the expression of enzyme activity that controls the rate of glucose absorption in peripheral tissues (Yassa & Tohamy, 2014). Therefore, the hypoglycemic mechanisms of *M. oleifera* aqueous extract boost insulin production in pancreatic beta-cells, limit the activity of glucose transporter protein (typically GLUT2 and GLUT4), and regenerate injured beta-cells. Hence, based on the data presented, an aqueous extract of *M. oleifera* leaves is a potential method of lowering blood glucose levels in animal studies.

3.5 Interpretation of data collected from clinical studies

Despite the numerous in vitro and animal research demonstrating *M. oleifera's* antihyperglycemic benefits, a few human clinical trials or studies have been carried out. According to Kumari, (2019), a study conducted that the efficacy of *M. oleifera* leaves powder with another herbal powders called Azadirachta indica seed extract in non-insulin-dependent diabetics patients leads to average change in overall plasma glucose levels, postprandial blood glucose levels, and total plasma lipid levels (Kumari, 2019). In the clinical investigation, people of different ages were divided into three groups. The result from clinical trial suggests that, a considerable drop in fasting blood glucose, a significant reduction in postprandial hyperglycemia in both groups (a group of treated people with *M. oleifera* leaves powder (8gm) and another group of people treated with Azadirachta indica seeds powder (6gm)), and no change occurs in the control group. According to the research, among the two herbs used *M. oleifera* leaves powder was found more effective than Azadirachta indica seeds powder.

According to another study done on postmenopausal women without diabetes, taking 7 g of *M. oleifera* leaf powder orally daily for three months dramatically decreased fasting blood glucose levels and raised hemoglobin levels. Furthermore, they have experienced reduced antioxidant markers in their blood and also huge reduction occurs in malondialdehyde. The authors of this article made no reference to any adverse or secondary consequences following *M. oleifera* administration. Although the authors did not state whether the background diet was controlled or monitored. As a result, it is not exactly clear whether food related or environmental issues influenced the outcomes (Kushwaha et al., 2014). Another study on male and female healthy individuals who were given progressively lower doses (1 g, 2 g, and 4 g) of the leaves of Moringa powder every two weeks. It was discovered no huge drop of glucose however a major increase in

insulin levels observed on the participants. The greatest increase on insulin observed while individuals were given 4 g of *M. oleifera* leaf powder. Furthermore, neither any changes in blood urea nitrogen, creatinine, alanine aminotransferase, nor aspartate aminotransferase were seen after *M. oleifera* intake. The investigators did not specify whether the baseline diet was regulated or monitored, so it was unclear whether the insulin changes were caused by an external factor (Anthanont et al., 2016). In a different study, healthy individuals received 500 mg of aqueous leaf extract from *M. oleifera* orally. At 30, 60, 90, and 120 minutes later, there were no noticeable changes in plasma glucose. However, there were immediate changes in other areas, with reports of a significant drop in malondialdehyde levels and an elevation in antioxidant markers. Prior to ingesting *M. oleifera*, participants were instructed to fast for at least eight hours. They were also instructed to keep up their usual routines for eating, exercising, and living throughout the duration of the study (Ngamukote et al., 2016). In the article, the background diet was not stated to be controlled or under observation by the authors. The results of a recent study on healthy volunteers and type 2 Diabetes patients from a in refugee camps revealed a significant decrease in glycemia and α-amylase activity following *M. oleifera* consumption. Glycemia was measured postprandial at 30, 60, 90, 120, 150, and 180 minutes after participants received a 20 g of *M. oleifera* leaf powder with the regular meal (Leone et al., 2018). Healthy patients showed no significant variations in glycaemia, however diabetics showed significant decreases in glycaemia 90, 120, and 150 minutes after receiving *M. oleifera* therapy. For the participated individuals, the authors developed a customized meal consisting of 160 g of camel stew and 80 g of rice. As a result, the diet was strictly regulated and same for every participant. The levels of insulin or hemoglobin A1c (HbA1c) were not mentioned. The following table (Table 2) summarizes the antidiabetic effects of *M. oleifera* (MO) in human studies.

Table 3: Antidiabetic effects of M. oleifera (MO) in human studies

Type of the Study	**Part of MO Tree**	**Treatment**	**Results**	**Reference**
Healthy individuals	MO leaf powder	There were ten healthy participants between the ages of 24-34. The individuals were administered oral doses of MO at increasing dosages of 0, 1, 2, and 4 g after every two weeks. Plasma glucose and insulin levels were measured at baseline as well as 0.5, 1, 1.5, 2, 4 and 6 hours after each MO dose delivery.	At 0, 1, 2, and 4 g doses of MO showed increased level of insulin 2.3 ± 0.9 μU/ml, 2.7 ± 1.0 μU/ml, 3.3 ± 1.4 μU/ml, and 4.1 ± 1.7 μU/ml, respectively. No significant differences in plasma glucose level were observed (for 0, 1, 2, and 4 g doses of MO, recorded glucose level were 77 ± 6 mg/dl, 78 ± 5 mg/dl, 79 ± 6 mg/dl, and 79 ± 5 mg/dl).	(Anthanont et al., 2016)
Healthy individuals	MO aqueous leaf extract	Ten individuals were involved. During initial visit, 500 mg were given followed by	There were minor changes observed in the blood glucose level. During initial visit glucose level was 75.5±2.1 mg/dL.	(Ngamukote et al., 2016)

		another 500 mg two weeks later.	After two doses of MO glucose level were found 71.5±2.3 mg/dL.	
Postmenopausal females	MO leaf powder	The study included thirty females aged 45 to 60 years old. For three months 7 g of MO was given daily.	Fasting blood glucose levels decreased from a baseline of 125.6 ±9.15 mg/dL to 106.7±7.23 mg/dL.	(Kushwaha et al., 2014)
Healthy individuals and type-2 diabetes patients	MO leaf powder	Ten healthy and seventeen type-2 diabetes patients were participated. Participants received a single dosage of 20g MO.	Blood glucose levels in diabetic individuals who received the 20g MO dosage from the beginning of the meal were consistently lower than those in the group who had the control meal. Average glucose level of control meal was 296 ± 17 mg/dL and MO administrated group was 268 ± 18 mg/dL.	(Leone et al., 2018)

			Glycemia is significantly reduced up to 150 minutes after MO consumption.	
Type-2 diabetes patient	MO leaf powder capsules	Sixteen participants (9 females and 7 males) were involved. For one month, 4 g MO was administered before breakfast and dinner.	Result showed there were no noticeable changes in plasma glucose level and insulin level.	(Taweerut chana et al., 2017)
Type-2 diabetes patient	MO leaves powder with *Azadirachta indica* seed powder	Fifty-five participants (36 men and 19 women) in the age group of 30-60 ages. 8 gm MO powder and 6 gm *Azadirachta indica* seed powder for 40 days.	Significant reduction in fasting blood glucose and the post prandial blood glucose levels. Significant reduction in the mean blood lipid levels. Did not show any significant effect on the HDL cholesterol levels.	(Kumari, 2019)

The technique used in the preparation of moringa was a few of the main distinctions between tests on humans and those on animals. The vast majority of human research used powdered leaves of moringa which were given to patients. Most frequently, rats were given extracts of either aqueous or ethanol-based moringa in the majority of animal trials. It would be interesting to explore whether the animal test results can be more precisely replicated in humans with aqueous or ethanol-based moringa extracts. Extraction of water or ethanol solution may be able to draw out more of *M. oleifera* therapeutic properties by increasing bioavailability and enhancing absorption. In future investigations, standardizing moringa administration would make it easier to compare results. It seems that the new extraction pattern of *M. oleifera* will help in getting the desired results. So, in the future the upcoming studies might emerged some updated methods of applying moringa to humans and that can be prioritized in every aspect.

Overall, the majority of controlled trial publications highlighted some of *M. oleifera's* beneficial effects. Regrettably, there were major limitations due to the small sample numbers, brief trial durations, and inability to address problems including diet management, disease duration, and the presence of co-morbidities. Therefore, further research is required to properly understand the consequences in type 2 diabetic patients.

Chapter 4

Conclusion

The tree *M. oleifera* has been suggested and investigated as a potential anti-diabetic agent. In this review, findings of *M. oleifera* may play potential role in diabetes with a focus on changing glycemia and insulin included for both human and animal in vivo studies. In addition, with that, mechanism of action of *M. oleifera* in antidiabetic is reviewed.

Treatment with *M. oleifera* results in significant alterations in blood sugar levels. This study evaluates all recent animal studies that explains reduction in glycemia or glucose tolerance test. Whatever the component of the tree or extract type (it can be aqueous, ethanolic, powder and methanolic) utilized, most animal models with hyperglycemia exhibited a remarkable reduction in glycaemia in mice treated with *M. oleifera*. There is strong evidence that *M. oleifera* extract has immediate antihyperglycemic benefits in diabetic animal models, but further long-term investigations are required. This is vital because future treatment therapies must consider for the chronic character of diabetes mellitus and metabolic syndrome. The wide range in the reported parameters is a key limitation of the research considered in this review. In particular, the results on the efficacy of *M. oleifera* therapy in animal models of diabetes are constrained by the lack of other supportive tests of glycolysis for example glycosylated hemoglobin. As a result, future study should investigate at not just the hypoglycemic effects of *M. oleifera*, but also other factors connected to glucose function.

In contrast to animal studies, a review of results from human studies found two types of results, some showing glucose reduction and some failing to show reduction. These findings are difficult to compare because each study used a different methodology and a wide range of dosages. Similar

to healthy human individuals, various animal investigations found no significant decrease in glycaemia with *M. oleifera* usage in nondiabetics indicating that regulation of glucose may be more successful in diseased state. The phytochemicals in *M. oleifera* which have acute or long-term effects on glycaemia must be identified with more careful separation and characterization. A potential limitation in human investigations particularly long-term trials, may be connected to the flavor of *M. oleifera*, as this tree has been shown to have low taste acceptance in meals. Additionally, only a small number of studies employed seeds or fruits and the majority used *M. oleifera* leaves. Thus, further comparative studies between different plant segments are recommended to identify the most effective branches.

There is less convincing evidence for changes in insulin levels based on *M. oleifera* interventions than for antihyperglycemic benefits. Although some research on rats and mice indicated a significant increase in insulin levels but do not able to show same result on other studies. Similar results were observed in human investigations. Therefore, more study is required to determine whether *M. oleifera* affects insulin activity or levels. This is significant in identifying the type of diabetes mellitus.

4.1 Limitation of the study

There are a few drawbacks with the current review that should be addressed. Primarily, some important information published in other languages were missed because most of the studies are written in the English language. Due to the fact that, journals which published in peer-reviewed works were considered. Secondly, the publications included in this study had been using a variety of methods to prepare and give *M. oleifera* to individuals. It is possible that several elements of the plant may be handled differently by individuals due to differences in these mechanisms. It is also possible that these various ratios of *M. oleifera's* constituents had varying impacts on blood

sugar levels. Furthermore, there is a lack of information in the studies regarding whether or how long the effects of *M. oleifera* last. As, the vast amount of article could not evaluate the longer effects of *M. oleifera*, so the effects on blood glucose will disappear with time. As a result, the unknown long-term negative consequences will outweigh the beneficial outcomes discovered with the plant. Furthermore, despite the fact that Moringa has been studied for a while, there are not many well organized and carefully monitored human trials that examine how it affects blood sugar levels. It was also challenging to properly compare and contrast these studies because the different animal trials included in this research used different techniques for inducing diabetes, extracting constituents of *M. oleifera*, treating the animals for different lengths of time, and using different types of animals.

4.2 Future research plan

Future human study should concentrate on several forms of Moringa administration, including as aqueous extract, ethanol extract and other extracts to establish the most effectivity on human blood glucose levels. The study would require to look at what dose and duration of Moringa therapy is most beneficial for decreasing sugar levels in blood. Future studies might also compare *M. oleifera*'s glucose-lowering benefits with currently used diabetes medications like metformin or sulfonylureas. Lastly, even though Moringa has been experimented for quite some time now, there are still not many well established and properly monitored human trials that shows how *M. oleifera* affects the blood glucose level. Therefore, more extensive and detailed human trials must be conducted to check the beneficial effects of *M. oleifera*.

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