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Hypoglycemic Effect of *Moringa oleifera* Aqueous Extract in Diabetic Animal Studies: A Mechanisms Review

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ABSTRACT
Diabetes is a chronic hyperglycemic condition which the therapy by maintaining blood glucose levels. Herbal plants can be an alternative therapy in reducing blood glucose levels. Indonesia is rich in herbaceous plants, one of which is *Moringa oleifera* Lam. Herbal plant of *Moringa oleifera* Lam. has been ethnopharmacology to reduce blood glucose levels. This review purpose of explaining the existing literature published until June 2020 on the mechanism of aqueous extract of *Moringa oleifera* leaves in hypoglycemic effect and their blood glucose levels in diabetic animal studies. *Moringa oleifera* aqueous extract was statistically significant in reducing blood glucose levels. The hypoglycemic mechanisms of *Moringa oleifera* aqueous extract inhibit the activity of Glucose Transporter Protein (GLUT2 and GLUT4), increases insulin secretion in pancreatic β-cells, and regenerating damaged pancreatic β-cells. This review provides evidence that an aqueous extract of *Moringa oleifera* leaves as a possible mechanism in reducing blood glucose levels in animal studies.

Keywords: *Moringa oleifera, aqueous extract, hypoglycemic, animal studies*

1. INTRODUCTION

Diabetes is a significant health issue that reaches danger signal levels; nearly half a billion people with type 2 diabetes mellitus (T2DM) worldwide. In 2019, it was 463 million people have T2DM, approximately in 2030, it will reach 578 million, and in 2045, it will reach 700 million[1]. T2DM is a chronic hyperglycemic condition. T2DM causes an inherent medical and economic dependence on individuals and society. T2DM patients tend to experience fluctuating hyperglycemia due to factors such as a progressive decrease on the function of islet pancreatic β-cells, impair the mechanism for regulating blood glucose levels, poor adherence to therapy[2]. According to the World Health Organization (WHO), traditional medicine is health practices, approaches, knowledge and belief in the benefits of herbal plants. Besides, the meaning of conventional medicine is an animal and mineral medicine, spiritual healing, exercise and manual technique, applied singly and or in combination to treat, prevent illness, maintaining body health and well-being[3]. In recent years, especially in developing countries, the uses of traditional medicines has increased and had become a significant source of healthcare[4].

Indonesia has many herbal plants that have pharmacological activities to reduce blood glucose levels for companion therapy and alternative therapies for T2DM. *Moringa oleifera* is an endemic plant in tropical Indonesia and is a herbal plant because it has many advantages[5]. *Moringa oleifera* leaves have secondary metabolites such as phenols, flavonoids and tannins[6]. These active compounds can be useful as an antioxidant, preventing hyperglycemia and hyperlipidemia[7]. Different parts of *Moringa oleifera* is high in carotenoids, alkaloids, flavonoids, glycosides, anthocyanin, anthraquinone, saponins, streroids, tannins and terpenoids. These phytochemicals play an essential role in preventing various health problems such as T2DM, cardiovascular disease, and inflammation. The phytochemicals compounds mentioned above also have hypoglycemic properties in different parts of *Moringa oleifera* [8]. *Moringa oleifera* can also improve insulin resistance and increase Total Antioxidant Activity (TAC) [9]. Research on the safety of oral administration of *Moringa oleifera* leaves aqueous extract in mice with doses of 400, 800, 1600, and 2000 mg/kg body weight[10]. Potential toxicology effects found in a single oral dose of 5000 mg/kg of Moringa oleifera aqueous extract and an oral dose of up to 1000 mg/kg Moringa oleifera extract for 14 days in mice [11].

Various parts of the *Moringa oleifera* tree are currently being investigated to study possible useful effects on the treatment of metabolic diseases, particularly in T2DM condition. *Moringa oleifera* has antihyperglycemic activity in animal models [12] and can have an impact on reducing blood glucose levels in mice induced diabetes[13]. The main objective of this scientific article is to review all effects of Moringa oleifera on blood glucose and insulin and to provide preclinical and clinical information regarding the use of *Moringa oleifera* aqueous extract in these aspects. Within this content framework, we have focused on animal studies of

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T2DM and analyzed the potential therapeutic target mechanisms of *Moringa oleifera*.

2. METHODS

2.1. Study Search

We conducted this review based on electronic databases such as PubMed, Cochrane Library, Web of Science. The search terms include diabetes, the aqueous extract of Moringa oleifera, animal models, effect and mechanisms. Database search until June 2020 and no language restrictions. We looked for additional studies that might improve quality from the conference article and reference articles identified for inclusion in the article discussion. After conducting a quality assessment, researchers took data from 6 journals and classify important data in journals using tables.

2.2. Ethics

This study does not use patient-specific data, and ethical approval is not required.

3. RESULTS

Several studies have reported hypoglycemic properties of the aqueous extract of *Moringa oleifera* leaves in animal models. There are six animal studies in this review where there are research subjects: one study used mice animal model, and five studies used rat animal models. From six studies, *Moringa oleifera* aqueous extract caused a statistically significant reduction in blood glucose levels in animal models.

Table 1 Evidence of The Effect of Aqueous Extract of Moringa oleifera Leaves Treatment in Diabetes Animal Models.

Animal Mode	Moringa oleifera Treatment	Result of Moringa oleifera Treatment (Blood Glucose)	Ref
STZ-induced diabetic Wistar rats	Treatment time: 3 weeks MO: 100, 200, and 300 mg/kg MO Diabetic MO: 100, 200, and 300 mg/kg MO Diabetic positive : Glipizide 2.5 mg/kg	MO can significant reduce blood glucose levels in diabetic rats. Reduction after 1, 2, and 3 weeks with 200 mg was 25.9%, 53.5%, and 69.2%, respectively	[14]
Alloxan-induced diabetic Wistar rats	Treatment time: 18 days Untreated Diabetic Control: Untreated Control with MO: 250 mg/kg MO Diabetic MO: 250 mg/kg MO	MO can reduce blood glucose levels in diabetic rats from 400 mg/dL to 200 mg/dL, $p < 0.05$	[13]
STZ-induced diabetic Sprague-Dawley rats	Treatment time: 4 weeks Control: Untreated Control with MO: 200 mg/kg MO Diabetic Control: Untreated Diabetic MO: 200 mg/kg MO	MO can reduce blood glucose levels in diabetic rats, from 266.50 ± 2.17 mg/dL to 148.83 ± 2.44 mg/dL after 200 mg of MO treatment, $p < 0.001$.	[15]
Alloxan-induced diabetic Wistar rats	Treatment time: 18 days Control: Untreated Diabetic Control: Untreated Control with MO: 250 mg/kg MO Diabetic MO: 250 mg/kg MO	MO can reduce blood glucose levels in diabetic rats. Blood glucose levels lowered 3.6-fold, as compared with controls, $p < 0.05$.	[16]
STZ-induced diabetic Wistar rats.High-fat diet-induced diabetes C57BL/6 mice	Treatment time: 3 weeks Control: Untreated Control MO: 100 mg/kg (rats); 200 mg/kg (mice) Diabetic Control: Untreated Diabetic MO: 100 mg/kg (rats); 200 mg/kg (mice) Diabetic positive Control: metformin 42 mg/kg	MO can reduce blood glucose levels, acutely and chronic significant in diabetic rats and mice. In rats, a reduction of 53.2% in fasting glucose after four hour of oral administration of MO, whereas reduction of 41.7% was observed after eight hour, on day 1 and day 2, $p < 0.05$. In mice, a reduction of 34.23% on day 2, and 58.69% on day 3, $p < 0.01$	[17]
Glucose tolerance test. High-fat diet induced diabetes C57BL/6 mice	Treatment time: 14 days MO: 200, 400 or 600 mg/kg body weight, glibenclamide at the dose of 10 mg/kg (positive control) and distilled water at 10 ml/kg (control group)	MO can significant reduce blood glucose levels acutely in diabetic mice. Glibenclamide and Moringa oleifera Lam. leaf extract groups exhibited glycaemia similar to non-diabetic mice compared with diabetic controls ($P < 0.05$).	[18]

MO : Moringa oleifera, STZ: Streptozotocin

Some studies identified the aqueous extract of *Moringa oleifera* have a total of 43 bioactive compounds that are polar and 40 lipophilic bioactive compounds. In general, the aqueous extract of *Moringa oleifera* contains bioactive compounds with polar properties, and that several fatty acids with bioactive compounds that are nonpolar due to their solubility are separate according to the partition coefficient. The previous concept, Chromatography-Mass Spectroscopy (GC-MS) analyze polar and lipophilic metabolites. High-Performance Liquid Chromatography (HPLC) and GC-MS analysis to identify elements contained in the aqueous extract of *Moringa oleifera* which have a bioactive compound or

polar secondary metabolites such as glycosides, phenols, saponins, and tannins and some primary metabolites such as carbohydrates and proteins. Generally, nonpolar bioactive compounds such as carotenoids found in the ethanol extract of *Moringa oleifera*. The carotenoids in the aqueous extract of *Moringa oleifera* are not found[17]. The presence of chlorogenic acid, alkaloid and tannins affect the cardiovascular effects and hypoglycemic activity [19].

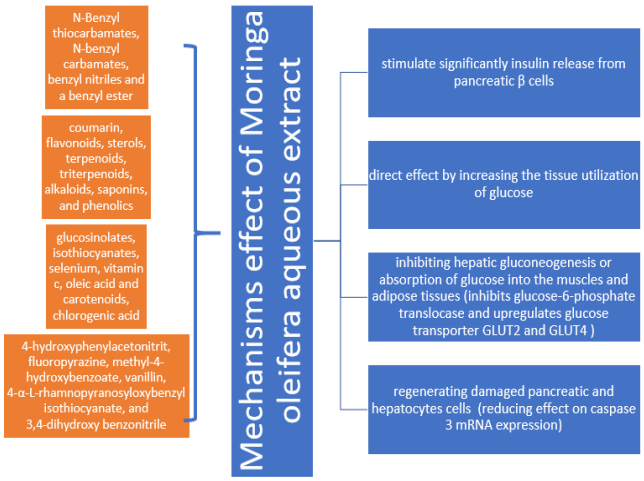

Figure 1 Bioactive Compound and Mechanisms Effect of Aqueous Extract of Moringa oleifera Leaves

Bioactive compound affects the mechanism effect of aqueous extract of *Moringa oleifera* leaves. The extraction methods of *Moringa oleifera* leaves can affect the hypoglycemic mechanisms due to the different composition of the extracts [20]. The bioactive compound can repair the abnormal carbohydrates and lipid metabolisms of T2DM patient relieve metabolic syndrome [21]. The following chart describes the bioactive compound and mechanisms effect.

Table 2 Bioactive Compound and Mechanisms Effect of Aqueous Extract of Moringa oleifera Leaves

Animal Mode	**Active Compound of Moringa oleifera**	**Mechanisms of Effect**	**Ref**
STZ-induced diabetic Wistar rats	N-Benzyl thiocarbamates, N-benzyl carbamates, benzyl nitriles and a benzyl ester	stimulate insulin release significantly from the rats pancreatic beta cells and have cyclooxygenase enzyme and lipid peroxidation inhibitory activities, direct effect by increasing the tissue utilization of glucose, inhibiting hepatic gluconeogenesis or absorption of glucose into the muscles and adipose tissues	[14]
Alloxan-induced diabetic Wistar rats	coumarin, flavonoids, sterols, terpenoids, triterpenoids, alkaloids,	minimizing gluconeogenesis and regenerating damaged hepatocytes and pancreatic cells	[13]
	saponins, and phenolics		
STZ-induced diabetic Sprague-Dawley rats	bioflavonoids	stimulation of glucose uptake, glucose-induced insulin secretion from the existing-cells or stimulate its release from the bound form, thus decreasing serum glucose levels in treated diabetic rats	[15]
Alloxan-induced diabetic Wistar rats	flavonoids, sterols, terpenoids, alkaloids,glucosinolates, isothiocyanates, thiocarbamates and phenolics, selenium, vitamin c, oleic acid and carotenoids, chlorogenic acid	protect and enhance the regeneration and viability of damage β–cells; hepatoprotective effect its reducing effect on caspase 3 mRNA expression, inhibits glucose-6-phosphate translocase in rats' hepatocytes with subsequent decreasing hepatic gluconeogenesis and glycogenolysis	[16]
STZ-induced diabetic Wistar rats.High-fat diet-induced diabetes C57BL/6 mice	phenolics and flavonoids	scavenging effect of free radicals produced by STZ, increasing glucose tolerance, decrease the postprandial glucose level by inhibiting the activity of α-amylase and α-glucosidase, which are essential enzymes in the digestion of the complex carbohydrates into absorbable monosaccharides in the food	[17]
Glucose tolerance test. High-fat diet-induced diabetes C57BL/6 mice	4-hydroxyphenylacetonitrit, fluoropyrazine, methyl-4-hydroxybenzoate, vanillin, 4-α-L-rhamnopyranosyloxybenzyl isothiocyanat	stimulates the Akt pathway in the muscle. The insulin-dependent Akt pathway known to be involved in hepatic glucose and lipid homeostasis, upregulates glucose transporter GLUT4 expression through an Akt-dependent pathway in the muscle, signalling pathways involved in glucose uptake in the muscle, stimulates	[18]

Animal Mode	Active Compound of Moringa oleifera	Mechanisms of Effect	Ref
STZ-induced diabetic Wistar rats	N-Benzyl thiocarbamates, N-benzyl carbamates, benzyl nitriles and a benzyl ester	stimulate insulin release significantly from the rats pancreatic beta cells and have cyclooxygenase enzyme and lipid peroxidation inhibitory activities, direct effect by increasing the tissue utilization of glucose, inhibiting hepatic gluconeogenesis or absorption of glucose into the muscles and adipose tissues	[14]
	e, and 3,4-dihydroxy benzonitrile	PPARα and SREBP-1 in the liver	

STZ: Streptozotocin

4. DISCUSSION

M*oringa* oleifera aqueous lea*ves* extract to improve the elevated mRNA expression of pyruvate carboxylase (PC) in the diabetic rats' livers degrading hepatic gluconeogenesis. Moringa oleifera leaves contain chlorogenic acid, which inhibits glucose-6-phosphate translocase in rats' livers, reducing hepatic gluconeogenesis and glycogenolysis. PC mRNA expression is one of the key enzymes of gluconeogenesis[13]. The phenolic compounds, selenium, vitamin c, oleic acid and carotenoids have mechanisms increases the activities of antioxidant enzymes superoxide dismutase. The catalase hepatoprotective effect of Moringa oleifera extract impacted the effect on caspase three mRNA expression. The gluconeogenesis and glycogenesis suppress and enhance effects in hepatocytes through decreasing and increasing their key enzymes, PC, and GS, mRNA expression[16]. The protective and regenerative impact of Moringa oleifera aqueous leaves extract on the intact functional cells, and cells damage by alloxan. The Moringa oleifera contents flavonoid, terpenoids, quercetin, and kaempferol preserve and increase the regeneration and viability of damage cells and succeeding secretion of insulin by its antioxidant activities, quercetin significantly increased hepatic glucokinase activity, which has an insulin-like effect[13]. The metabolites that prevent glucose-6-phosphate translocase in rats hepatocytes with subsequent decreasing hepatic formation of glucose and breakdown of glycogen[16].

The reactive oxygen species can cause oxidative destructed in cell tissues. The oxidative stress plays an important role in the degenerate vascular complications in T2DM [22]. The therapeutic effects of aqueous extract of *Moringa oleifera* leaves on diabetic rats were histopathology with the cells recovering their standard form almost identical to the control group. However, several of their mitochondria still had indiscernible cristae. In the reviewed literature, no electron microscopic studies observed at the ultrastructure of the pancreas in diabetic rats treated with aqueous extract of *Moringa oleifera* leaves. Such pathological changes attribute to glucotoxicity, which arises from excessive uptake of glucose by islet pancreatic β-cells in T2DM. The excess sugar drives glycation reactions and the mitochondrial electron transport chain, resulting in macromolecules that are damaged by Reactive Oxygen Species (ROS), at levels beyond the antioxidant capacities of the cells. The oxidative stress destruct insulin synthesis and secretion of insulin, initiates a cascade of cellular events that eventually induce pancreatic β-cells cytotoxicity and pancreatic β-cells death [15]. The flavonoid, terpenoids, quercetin, and kaempferol protect and increase the regeneration and viability of destructed pancreatic β-cells[16].

In the kinetic parameter, when observed the maximum velocity (Vmax) is the absorption rate of glucose when there is an aqueous extract of *Moringa oleifera* leaves or when there is no aqueous extract of *Moringa oleifera* leaves. The presence of the aqueous extract of *Moringa oleifera* leaves, Vmax reduces glucose absorption through the intestinal membrane, which indicates that transmembrane glucose transport significantly decreases and vice versa for glucose absorption in skeletal muscle. However, Km remained unchanged in ex vivo experiments with or without *Moringa oleifera* extract. This phenomenon indicates that aqueous extract of *Moringa oleifera* leaves works by bringing about a non-competitive type of inhibition of glucose transport at the level of the small intestine caused by inhibition of Glucose Transporter Protein (GLUT) activity [17].

The vanillin,4-hydroxyphenylacetonitrit, 3,4-dihydroxy benzonitrile, fluoropyrazine, methyl-4-hydroxybenzoate, and 4 α-L-rhamnopyranosyloxy benzyl isothiocyanate encourage the Akt pathway in the muscle. Hepatic glucose and lipid homestasis contain an insulin dependent Akt pathway that can reset GLUT4 expression via a muscle-dependent Akt and signaling pathways, including glucose uptakes in muscles. *Moringa oleifera* increased the muscle GLUT4 protein levels in mice ($P<0,05$), stimulates PPARα and SREBP-1 in the liver[18].

Aqueous extract of *Moringa oleifera* can inhibit glucose absorption through α-amylase inhibition [12]. In vitro, α-amylase and α-glucosidase inhibition test showed that aqueous extract of *Moringa oleifera* leaves had an inhibitory effect that was identical with a reduce IC_{50} value compared to the standard drug acarbose. In vitro studies show that aqueous extract of *Moringa oleifera* leaves can reduce postprandial glucose levels by inhibiting the activity of α-amylase and α-glucosidase, which are essential enzymes indigestion that converts complex carbohydrates in food into monosaccharides that can be absorbed by the intestine[17]. The way to stimulate glucose uptake in peripheral tissue regulation of the expression of enzyme activity that limits the rate of glucose uptake in peripheral tissues involves carbohydrate metabolism, insulin secretion which induces glucose from existing-cells or stimulates its release from the bound form, thereby reducing blood glucose levels in diabetic rats[15].

This review providing explanation on the role of aqueous extract of *Moringa oleifera* leaves in blood glucose control as well as their mechanism of action. In the reviewed studies, an aqueous extract of *Moringa oleifera* leaves used in

the animal (rat/mice) studies were in the dose range of 100-600 mg/Kg body weight. The several studies, metabolites isolate from aqueous extract of *Moringa oleifera* leaves showed hypoglycemic effects. They are suggesting that phytochemicals isolated from that aqueous extract of *Moringa oleifera* leaves can also play a significant role in T2DM. Therefore, further studies could focus on isolating another bioactive compound from *Moringa oleifera* leaves and the hypoglycemic potential of bioactive compounds. The consumption of *Moringa oleifera* leaves showed no adverse effects in the reviewed studies. These studies are limited in numbers and animals model (in vitro and in vivo). Moreover, long-term human studies are needed to study in-depth safety and efficacious doses of *Moringa oleifera* for prescribe to T2DM subjects for managing blood glucose control.

5. CONCLUSION

The studies have shown that aqueous extract of *Moringa oleifera* leaves consumption decreases blood glucose levels. The mechanisms of bioactive compounds from aqueous extract of *Moringa oleifera* leaves is described in these studies for its hypoglycemic effects including inhibition of α-amylase and α-glucosidase activities, increased glucose uptake in the muscle and liver, inhibition of glucose uptake from the intestine, decreased gluconeogenesis in the liver, protect and enhance the regeneration and viability of destructed pancreatic β-cells and increased insulin secretion and sensitivity. This review provides evidence that the aqueous extract of *Moringa oleifera* leaves can control blood glucose levels in T2DM.

AUTHORS' CONTRIBUTIONS

Conceived the ideas, experimental design of the study[1,2]
Performed data collection[1,2,3]
Data analysis and interpretation[1,2,3]
Primary author (wrote most of the paper)[1]

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