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Moringa Oleifera Leaf Extract as an Antioxidant on Malondialdehyde (MDA) and Glutathione Peroxidase (GSH-Px) Levels in Rats with Hyperglycemia: A Systematic Literature Review

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ABSTRACT

Hyperglycaemia is a clinical indicator of Diabetes Mellitus (DM), chronic hyperglycemia in diabetes is associated with damage to organ systems, such as kidney damage, eyes, nerves, and blood vessels, and even death through oxidative stress processes, resulting in an imbalance between antioxidants and free radicals. One of the plants that contain antioxidants is Moringa Oleifera (MO), MO has been utilized as a food source material. This plant has low toxicity, natural antioxidants, and important bioactive phytochemicals and is an excellent source of alternative natural therapies to synthetic drugs. Exogenous antioxidants in Moringa leaves may have potential as free radical scavengers. Studies published between 2017 and 2023 were systematically reviewed through identification in Research Gate, Science Direct, PubMed, and Google Scholar databases. Studies that met the inclusion criteria were included for review. The results of the literature review of the articles carried out can be concluded that the administration of moringa leaf extract is able to reduce blood sugar levels, reduce MDA levels and increase antioxidants in the body, such as Superoxide Dismutase (SOD), Catalase (CAT) and Glutathione Peroxidase (GSH-Px).

Keywords: *Hyperglycaemia, Diabetes, Leaf Extract Moringa Oleifera, Oxidative Stress, Antioxidant*

INTRODUCTION

Diabetes Mellitus (DM), is a global health threat, where the prevalence of DM patients has increased from year to year. In 2021 there were 537 million (10.5%) people with DM, this number is predicted to increase to 643 million in 2030. Southeast Asia has the third highest number of people with DM after the Middle East and North America. **(1)** Indonesia is the fifth largest country with DM after China, India, Pakistan, and the United States. According to Basic Health Research Data (Riskesdas) in 2018, the prevalence of DM in Indonesia increased from 2013 to 2018 by 0.5%, based on gender, women have a higher percentage than men. **(2)**

Hyperglycaemia can lead to organ and tissue damage through oxidative stress. **(3,4)** Oxidative stress is a condition caused by an imbalance between oxidants and antioxidants in biological systems, where oxidants are higher than antioxidants. **(5,6)** resulting in the formation of excessive Reactive Oxygen Species (ROS) or when antioxidant defense mechanisms are weakened. The body's natural antioxidant defense system is defeated when ROS production is excessive. **(7)** Increased ROS can cause damage to Deoxyribo Nucleic Acid (DNA), proteins, and lipids. **(8,9)**

An increase in the amount of ROS occurs because lipid peroxidases can attack highly

saturated fatty acids in the cell membrane. Lipid peroxidation caused by oxidative stress will initiate cell death and cell enzyme activity. [10] Antioxidants originating from within the body are not able to neutralize free radicals, so antioxidants are needed from outside the body (exogenous antioxidants), antioxidants based on their sources are classified into endogenous and exogenous antioxidants. Endogenous antioxidants function in the body's defense system, especially against the activity of ROS compounds that can cause oxidative stress and prevent the formation of new radicals. These antioxidants consist of SOD, CAT, and GSH-Px. [11,12] Antioxidant compounds are substances needed to neutralize and prevent damage caused by free radicals (ROS). One source of exogenous antioxidants can be obtained from MO, also known as the miracle tree. [13]

Indonesia itself does not know much about the benefits of this plant. usually, it is only used for food mixture or animal feed, and there are also those who use it to bathe corpses or sheds. [14] his plant contains 46 types of antioxidants and more than 90 nutrients, besides containing 36 anti-inflammatory compounds. [15] So, this plant is medically popular because it has shown great health benefits. [16]

METHODS

The systematic literature review was proposed in the Universitas Andalas. The search was undertaken start from August to September 2023. The methods and reporting were developed and conducted using systematic methodology and consistent with Preferred Reporting Items For Systematic Review And Meta-Analyses (PRISMA) report guidelines. Based on this search, 435 articles were obtained. After reading and tracing the contents of the article through the abstract and its contents adjusted to the author's objectives, only 10 articles were found that were suitable.

Source Of literature

Systematic Literature Review (SLR), using secondary data obtained from database articles namely Google Scholar, PubMed, Elsevier, and Science Direct which can be downloaded for free, with a span of 6 years published in 2017. Based on the literature review, research results were selected that showed several research variables related to Moringa leaf extract as an antioxidant against oxidative stress marker conditions.

Search Terms

Search terms are applied using various boolean operators using keywords “Hyperglycemia” OR “Diabetes”, “Leaf extract moringa oleifera”, “Anti-Oxidant”, and “Oxidative Stress”.

Inclusion and Exclusion Criteria

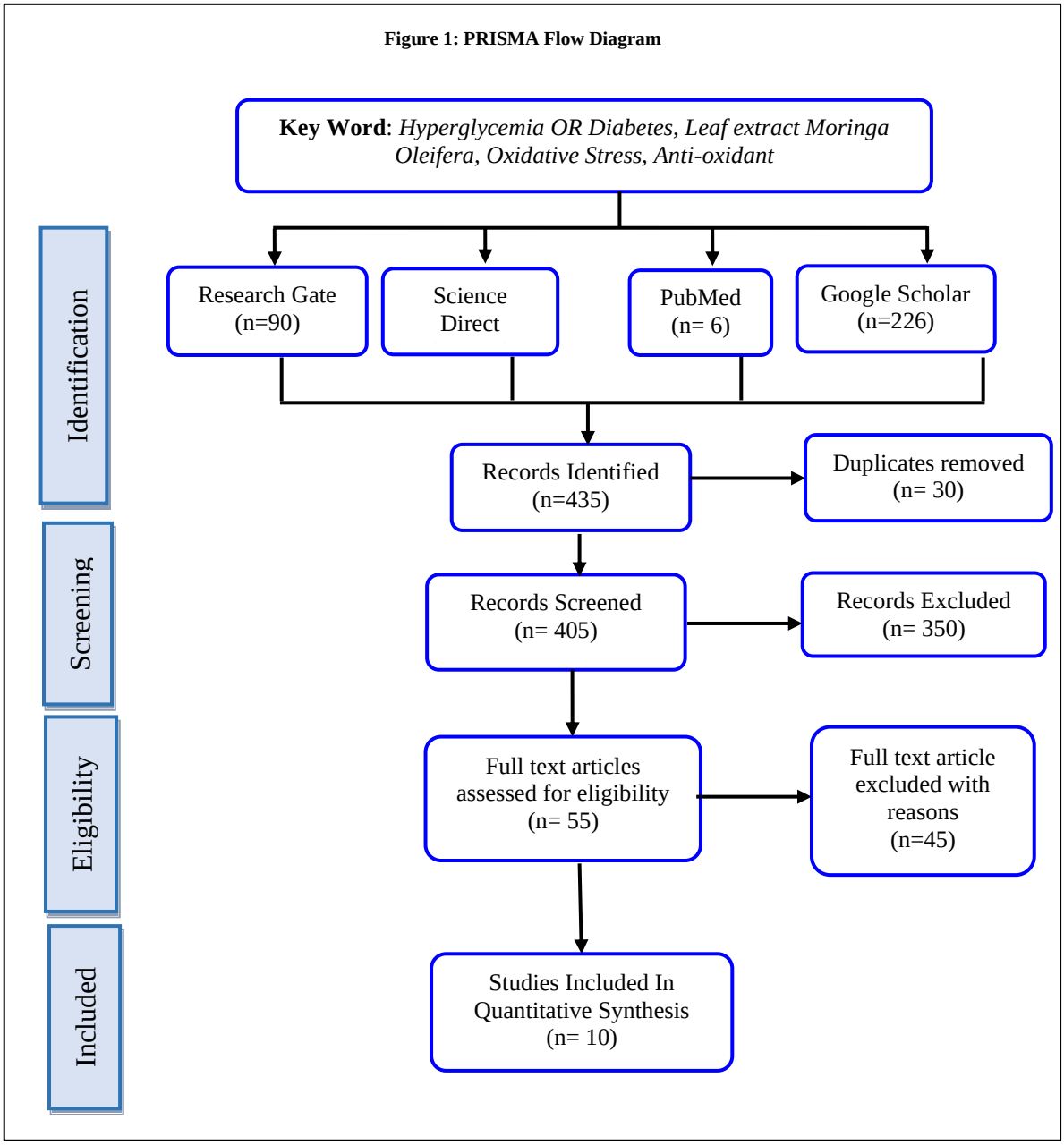
This study used inclusion and exclusion criteria using appropriate journal articles from national and international journals. Study eligibility the set of criteria can be seen in Table 1

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Studies published from 2017-2023 Studies discuss Moringa leaf extract, Antioxidants, oxidative stress, and Hyperglycaemia or diabetes Experimental studies Using animal experiments Text can be accessed in full	Studies published before 2017 Text not accessible

STUDY SELECTION AND DATA EXTRACTION

Figure 1: PRISMA Flow Diagram



RESULT

Data extraction was performed after reviewing the quality of the studies in six well-regarded publications. Data was extracted by evaluating the title, author name, year, place of study, intervention, and outcome of the study. Table 1 shows the results of data extraction. After screening and selection through articles based on inclusion criteria, With the exception and eligibility of articles determined by the authors based on the PRISMA Guidelines format, there are 10 articles in this review. Studies were conducted in various countries, including Egypt, South Africa, Mexico, Indonesia, India, Libya, Nepal, Thailand, and Nigeria with publications from 2017 to 2023.

The results of Eldanim research, et al. (2017) showed that Wistar rats induced with alloxan at a dose of 150 mg / kgBB and then given MO water extract at a dose of 250 mg / kgBB for 2.5 weeks, were able to reduce blood sugar levels, reduce MDA concentration in liver tissue and increase GSH-Px concentration in liver tissue. In a study conducted by Omodanisi, et al., (2017), showed that Wistar rats induced by

Streptozotocin (STZ) at a dose of 50 mg/kgBB, after being given MO leaf ethanol extract for 6 weeks increased endogenous antioxidants, such as CAT, SOD, and GSH-Px and were able to reduce the level of lipid peroxidation (MDA). Meanwhile, the results of research conducted by Badriyah, et al (2023), showed that albino Swiss rats with male sex induced by alloxan at a dose of 200 mg / kgBB, after being given moringa leaf extract at a dose of 50 mg / kgBB for 90 days increased GSH-PX levels and catalase activity and decreased oxidative stress biomarkers Malondialdehyde (MDA), nitric oxide (NO), and protein carbonyl (PC)).

Tabel 2 Summary Of Included Studies

No	Tittle	Source/ years	Study Setting	Model Experiment, Effective Dose and Intervention	Outcomes
1.	An aqueous extract from moringa oleifera leaves ameliorates hepatotoxicity in alloxan- induced diabetic rats [17]	Eldanim, et al (2017)	Egypt	Diabetes induced by alloxan150 mg/kg BB using wistar rats were given moringa oleifera leaf water extract at a dose of 250 mg/kgBB for 2.5 weeks.	Moringa leaf aqueous extract reduced hyperglycaemia in alloxan-induced diabetic rats, reduced liver tissue MDA concentration, increased liver tissue GSH-Px concentration
2.	Assesment of the anti-hyperglycaemic, anti-inflammatory and antioxidant activities of the methanol extract of moringa Oleifera in diabetes- incluced nephrotoxic male wistar rats [18]	Omodanisi, et al (2017)	Afrika Selatan	STZ-induced diabetes at a dose of 55 mg/kgBB. In Wistar rats treated with Moringa Oleifera leaf methanol extract at a dose of 250 mg/kgBB for 6 weeks.	Increases Antioxidants such as CAT, SOD, GSH-Px and reduces the level of lipid peroxidation (MDA).
3.	Streptozotocin-Induced Adaptive Modification of Mitochondrial Supercomplexes in Liver of Wistar Rats and the Protective Effect of *Moringa oleifera* Lam [19]	Sanchez-Munoz, et al (2018)	Meksiko	STZ-induced diabetes in wistar rats treated with moringa oleifera methanol extract at a dose of 200 mg/kgBB for 3 weeks	Increased antioxidant molecules, such as CAT, GST, and GSH-Px and decreased levels of lipid oxidation (MDA) in the brain.
4.	Antioxidant Activity of Moringa Leaves (Moringa oleifera) in Induced Diabetic Rats Alloxan [20]	Yudi Priyanto, et al (2023)	Indonesia	Alloxan-induced diabetes in Wistar rats with Moringa leaf extract doses of 200 mg/kgBB, 400 mg/kgBB and 600 mg for 21 days.	Moringa leaf extract can help reduce MDA levels and increase SOD levels.
5.	Protective role of *Moringa oleifera* leaf extract on cardiac antioxidant status and lipid peroxidation in streptozotocin induced diabetic rats [21]	B. Y. Aju, et al (2019)	India	Streptozotocin-induced diabetes in rats with a dose of moringa oleifera methanol extract 300mg/kgBB for 60 days.	Lower blood glucose and increase antioxidant enzyme activities (SOD, CAT, GSG-Px) in diabetic rat heart.
6.	Evaluation of Antidiabetic Effect of Combined Leaf and Seed Extracts of *Moringa oleifera* (*Moringaceae*) on Alloxan-Induced Diabetes in Mice: A Biochemical and Histological Study [22]	Badriyah Aljazzaf, et al (2023)	Libya	Diabetes induced by alloxan with a single dose of 200 mg/kgBB in adult male swiss albino rats with a dose of moringa oleifera methanol extract 500mg/kgBB for 90 days	GSH-PX levels and catalase activity were increased and oxidative stress biomarkers MDA, nitric oxide (NO), and protein carbonyl (PC) were decreased).
7.	Efficacy of moringa oleifera aqueous leaf extracts on hyperglycemia in streptozotocin-induced diabetic wistar rats [23]	Rakhi das, et al (2022)	Nepal	Streptozotocin-induced diabetes in wistar rats with a dose of moringa methanol extract 200mg/kgBB for 6 weeks	The group given moringa leaf extract had lower pancreatic MDA levels and increased pancreatic GSH-Px levels compared to the control group.
8.	Moringa oleifera leaf extract ameliorates early stages of diabetic nephropathy in streptozotocin-induced diabetic rat [24]	Ruttiya Thongrung, et al (2023)	Thailand	Diabetes induced with streptozotocin 50 mg/kgBB in male Sprague-dawley rats with doses of moringa oleifera water extract 200 mg/kgBB and 300mg/kgBB for 8 weeks	Reduced MDA levels in serum, and increased SOD and catalase activity
9.	Ethanolic extreact of moringa Oleifera leaves shows anti-hyperglycemi potencies on experimental wistar rats: a focus on optimization of biomarkers of type 2 diabetes [25]	Nuria Oganezi, et al (2023)	Nigeria	Diabetes induced with streptozotocin 120 mg/kgBB in rats with doses of moringa oleifera ethanol extract 250 mg/kgBB, 500 m/kgBB, 750 mg/kgBB, 1000 mg/kgBB and 1250 mg/kgBB for 30 days.	Increase in SOD concentration after administration of the extract at larger doses, increase in GSH-Px showed better with increasing doses. MDA levels were reduced in rats given the extract at larger doses

10.	Moringa Oleifera Leaves queous extract ameliorates Hepatotoxicity in alloxan-induced Diabetic Rats [26]	Mabrouk Attia Abd Eldaim, et al (2017)	Egypt	Diabetes induced with Alloxan 150 mg/kgBB in albino rats with a dose of Moringa leaf aqueous extract 250 mg/kgBB for 18 days	Significantly increased GSH-Px concentration, maintained SOD and Catalase and significantly decreased MDA concentration.

DISCUSSION

This study presents a systematic review of Moringa Oleifera Leaf Extract as an Antioxidant on Malondialdehyde and Glutathione Peroxidase Levels in Rats with Hyperglycaemia The results show that experimental models in rat animals induced by alloxan and STZ cause hyperglycaemia conditions, alloxan and STZ are common and most widely used diabetogenic, for reasons of affordability and availability. **(27)** Hyperglycaemia contributes to oxidative stress conditions due to excess products of ROS. Oxidative stress occurs through the activity of several pathways, such as increased protein kinase C activity, production of AGEs, polyol pathway, and hexosamine pathway. **(28)**

ROS production induced by hyperglycemia and oxidative stress correlates with the pathogenesis and development of metabolic diseases. To counteract the harmful effects of ROS, endogenous antioxidants or exogenous antioxidants are required to neutralise them and maintain homeostasis. **(29)** ROS plays a role both physiologically and pathologically. At moderate concentrations, ROS is involved in physiological functions such as regulating intracellular signal transduction and redox reactions. However, excess ROS production (pathologically) can result in damage to DNA, proteins, and lipids. **(30)** The primary reactive oxygen species (ROS) consist of the superoxide anion (O2 ·−), hydroxyl radical (OH·), peroxyl radical (ROO·), and alkoxyl radical (RO·) to prevent damage from ROS, a balance between pro-oxidants and antioxidants must be maintained.

Increased free radicals will lead to lipid peroxidation, DNA and protein oxidation. Continuous lipid oxidation reactions by ROS or free radicals will produce peroxyl radicals (ROO·), this condition causes an increase in oxidative stress markers, such as MDA and carbonyl compounds, but conversely endogenous antioxidant levels such as glutathione and SOD decrease because they are used to counteract free radicals. **(32,33)**

Free radicals are an integral part of life and metabolism, in order to survive the attack of radicals, a defense system called antioxidants is needed. Antioxidants are compounds that can delay, slow down, and prevent lipid oxidation. Antioxidants are divided into two types, namely endogenous antioxidants (enzymatic) and exogenous antioxidants (non-enzymatic), The enzymatic antioxidants consist of SOD, CAT, GSH-Px, and Glutathione Reductase (GR). Meanwhile, non-enzymatic antioxidants can be obtained from outside the body, including Vitamin C, Vitamin E, Polyphenols, Carotene, Coenzyme Q10, and others. **(30)**

According to Mthiyane (2022), revealed that one of the plants that showed significant beneficial effects on human health, is Moringa Oleifera (MO). Leaf extracts from MO showed effects capable of strengthening intracellular antioxidant defences and lowering lipid peroxidation products and reducing proinflammatory markers. **(34)** The antioxidant activity of MO leaves is influenced by the age of the leaves and the extraction solvent used. Ethanol solvent was most efficient for the production of extracts with high flavonoid content, while methanol solvent was used to obtain extracts rich in polyphenols. Among these solvents, ethanol showed higher antioxidant activity than water extract. Thus, the water extract showed the lowest antioxidant activity and phytochemical content. **(35)** The pharmacological activity of MO is one of them as an antioxidant, the antioxidants contained in MO leaf extract include compounds of flavonoids, polyphenols tannins, terpenoids, alkaloids,

phenolics, saponins, and (Vitamins A, C, and E). **(36)**

As for the role of each antioxidant, Vitamin E (tocopherol) is a fat-soluble vitamin, that works on cell membranes and lipoproteins so as to prevent lipid peroxidation, the working principle of antioxidants is able to provide hydrogen ions so that free radicals become stable. The main function of antioxidant vitamin E is to prevent lipid peroxide. Vitamin E can end the chain process of free radicals inhibit the production of new free radicals and limit damage to the cell membrane area. The clinical function of vitamin E antioxidants in food as antioxidants in preventing the peroxidation process of Polyunsaturated Fatty Acids (FUFAs).

The antioxidant properties of flavonoids can act as prooxidants under certain circumstances. It depends on the structural characteristics of flavonoids and their ability to interact with and penetrate the lipid bilayers of cells. Flavonoids can directly capture ROS, inhibit enzymes that play a role in generating superoxide anions, and prevent the peroxidation process by reducing alkoxyl and peroxyl radicals, so flavonoids act as radical-scavenging antioxidants. **(37)**

Polyphenols or phenolics act as antioxidants by chelating metal ions so as to reduce the capacity of metals to produce free radicals, polyphenols are said to be antioxidants if they fulfil two conditions, namely if they are present in low concentrations relative to the substrate to be oxidised, polyphenols will inhibit, prevent, reduce auto-oxidation or oxidation mediated by free radicals and the resulting form of free radicals after scavenging must be stable to interfere with the oxidation chain reaction, Phenolics inhibit fat prooxidants by rapidly donating hydrogen atoms to the peroxyl chain (ROO·) resulting in the formation of alkyl hydroperoxides (ROOH). **(37)**

Vitamin C as a strong water-soluble antioxidant has the ability to donate hydrogen atoms and form relatively stable ascorbyl free radicals, as an antioxidant vitamin C is able to work well inside or outside the cell and can neutralise free radicals and prevent damage due to free radicals, Vitamin C is an effective scavenger against ROS and nitrogen oxides, such as superoxide radical ions, H_2O_2, hydroxyl radicals and singlet oxygen. **(30)**

The potential of vitamin A (Retinol) as an antioxidant prevents oxidation or rancidity of fats. **(38)** Vitamin A is able to suppress the effect of linoleic acid on the oxidation process so that it can interact with radicals and prevent lipid peroxidation in cells. **(39)**

Saponins may affect H_2O_2 induced ROS formation in hepatocytes. Nuclear factor-erythroid-2 related factor 2 (Nrf2), NRF2 is a potential regulator of cell resistance to oxidants, and it exhibits many cell protective effects against various toxicities and chronic diseases associated with oxidative stress. **(40)** When cells are exposed to oxidative stress, Glutamate Cysteine ligase (GCL) is rapidly activated by NRF2, contributing to NRF2-mediated cell protection following oxidative stress**.** **(41)** Saponins activate and increase the expression of these antioxidant enzymes, thereby reducing oxidative stress in cells which is a transcription factor that can increase the transcription of various antioxidants and detoxification enzymes.

Enzymatic endogenous antioxidants or antioxidant enzymes produced by the human body as an antidote to free radicals, namely SOD, CAT dan GSH-Px. Enzymatic antioxidants are also called secondary antioxidants, which capture free radicals and stop the formation of free radicals. (42) SOD is a metalloenzyme that catalyzed the reduction reaction of superoxide anion radical (O_2·) into hydrogen peroxide (H_2O_2) and O_2. Catalase is an enzyme that catalyzes the reduction reaction of hydrogen peroxide (H_2O_2) compounds to O_2 and H_2O. While GSH-Px catalyses the reduction reaction of H_2O_2 into organic hydroperoxide compounds. **(43)**

Based on this literature review, the general use of MO leaf extracts in the range of more than 200 mg/KgBB from a duration of

administration of more than two weeks, so it is necessary to develop future research on MO as a functional food in the management of diabetes.

CONCLUSION

MO is a plant that contains antioxidants. The antioxidants it contains include flavonoids and their derivatives, Polyphenol, Terpenoid, Alkaloid, Saponin, vitamin C, vitamin E, Vitamin A. so they can repel free radicals, this can be judged from markers of oxidative stress, where leaf extract moringa oleifera was given in hyperglycemic experimental animals for several weeks can reduce blood sugar, malondialdehyde levels and increase endogenous antioxidants in the body, such as Superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px).

Declaration by Authors

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