The Impact of *Moringa oleifera* and *Azadirachta indica* (neem) Leaves Ethanolic Extract on Streptozotocin Induced Diabetes Rats

Sahar A. Abdel-Aziz[1]*, and Azza M. Baghdadi[2]

[1]Department of Nutrition and Food Sciences, Food Industries and Nutrition Institute, National Research Centre, Cairo, Egypt.

[2]Department of Food and Nutrition, Faculty of Human Sciences and Design, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia

Abstract

Diabetes mellitus (DM), especially Type 2, is a worldwide health issue marked by elevated insulin and blood glucose levels. The study aims to explore the impact of Moringa oleifera (MLE) and/or Neem leaves (NLE) ethanolic extract on streptozotocin (STZ) induced diabetes rats. Fifty-Six adult male albino rats were utilized in the study. The rats were split into seven groups as follow: group (1) served as normal, non-diabetic control (ND), while groups two to seven were induced into a diabetic state by intraperitoneal (ip) injection of STZ (40 mg/kg BW). Group two was diabetic rats with no treatment as positive control (D); group three and four received oral MLE at concentrations 250 and 500 mg/Kg, respectively. Groups five and six were given oral NLE at concentrations 250 and 500 mg/Kg, respectively. Finally, group seven comprised diabetic rats administered with a combination of MLE and NLE at concentration 250 mg/kg from each extract. After four experimental weeks, body weight, feed consumed were recorded, fasting serum insulin, glucose, lipid profile and endogenous antioxidant markers were determined. Results showed remarkable ($P \leq 0.05$) reduction in Feed Efficiency ratio (FER) and percentage of body weight gain (BWG %) in group D rats in comparison to ND rats. Additionally, findings revealed that diabetic rats in group (D) exhibited a considerable ($P<0.05$) reduction in serum insulin, endogenous antioxidants markers and HDL, while showed notable ($P<0.05$) increment in serum glucose, malondialdehyde and lipid profile parameters except HDL contrasted with ND rats. Oral administration of MLE, NLE and their combination led to remarkable ($P<0.05$) enhancement on all mentioned parameters. Furthermore, oral administration of MLE and NLE attenuated and ameliorated the histopathological adverse alteration that markedly detected in liver and pancreas tissues in D rats compared to ND rats. Conclusion: The moringa and Neem leaves ethanolic extract exhibited a hypoglycemic effect in STZ-induced diabetic rats.

Keywords: *Moringa oleifera* - *Azadirachta indica* – Diabetes – Hypoglycemic activity.-

INTRODUCTION

The DM is one of the most prevalent noncommunicable diseases all over the world. The International Diabetes Federation (IDF), prophesied that the DM incidence will rise to 629 million by 2045 among age adults (20-79 y), with increase 48% compared to 425 million in 2017. **(IDF, 2023)**. The World Health Organization (WHO) has stated that DM was the seventh of the tenth top causes of death in 2021 (**WHO, 2024**). The DM was more prevalent in low- and middle-income communities, such as African countries (**IDF, 2019**). The WHO defines DM status as having two consecutive instances of fasting plasma glucose levels greater than higher than 126 mg/dl (**American Diabetes Association, 2021**).

According to a study, medicinal herbs are crucial for managing diabetes **(Frimpong *et al*., 2024)**. These medicinal plants' phytochemical components, which function as anti-hyperglycemic agents and include flavonoids, glycosides, and carotenoids, make them beneficial in the treatment of diabetes **(Govindappa, 2015)**. According to available research, the phytochemical components in medicinal plants may have anti-diabetic properties because they stimulate glycogenesis, reduce glucose absorption, and activate β cells, which release insulin to help patients use glucose **(Shewasinad *et al*., 2018)**. Moreover, these components of phytochemistry can help repair damaged β cells **(Kifle *et al*., 2020)**.

Moringa oleifera L. is a member of the *Moringaeceae* family **(Pareek *et al*., 2023)**. It is referred to as the "miracle tree" because of the great nutritional value of its leaves, which can be used as a supply of vitamins, minerals, proteins, and calories. Researches have shown that compared to fresh leaves, dried M. oleifera leaves have higher levels of calories, carbs, protein, dietary fiber, some of vitamin B complex, Minerals (Ca, P, K, Mg, and Fe) **(Amin *et al*., 2024)**. Because Moringa leaves contain bioactive components including phenolic acid and flavonoids, they have a diversity of pharmacological features, such as antibacterial, antioxidant, antifungal, inflammation reducing, diabetic- and cancer-fighting benefits **(Mwamatope *et al*., 2020** and **Abidin *et al*., 2021)**.

The well-known plant neem (*Azadirachta indica*) is a member of the *Meliaceae* family **(Latif *et al*., 2020)**. Because of its anti-inflammatory, immune-stimulating, and anti-ulcer qualities, this huge evergreen tree with fragrant foliage and tasty fruits has been utilized widely for a variety of purposes **(Kaur *et al*., 2020 and Ibrahim *et al*., 2022)**. Additionally, every part of neem tree possesses a wide range of antioxidants, antifungal, antibacterial, and antiviral properties **(Islas *et al*., 2020)**. Neem medicines have been shown to have antidiabetic properties in the past **(Mohammed *et al*.,**

2023 and **Abduallah *et al*., 2023**). By a number of methods, the usage of these plants and phytoconstituents may enhance insulin secretion, postpone the onset of diabetic complications, and control metabolic abnormalities **(Umar *et al*., 2024)**. Therefore, this research evaluated the impact of Moringa, Neem leaves ethanolic extract and their mixing on STZ-induced diabetic rats.

MATERIALS AND METHODS

Material:

Plants:

Moringa oleifera and *Azadirachta indica* (Neem) leaves were procured from Abazeer Trading Establishment (Souk Al Mussadia No. 3), Jeddah, Saudi Arabia.

Chemicals and Kits:

Streptozotocin (STZ) was provided by Sigma-Aldrich Chemical Co., Missouri, USA. Pharmacy Solutions Industry Ltd., Jeddah provided the glucose solution (5%). Rat Insulin enzyme-linked immunosorbent assay kits (ELISA) and Glucose oxidase Kit from ALPCO Diagnostics. The measurement of lipid parameters, Total cholesterol (TC), Triglycerides (TGs), and High-density lipoprotein cholesterol (HDL) were made using enzymatic colorimetric kits that procured from Human Gesellschaft for Biochemical in Germany. The reagents and chemicals consumed in this study were all of excellent analytical quality.

Animals

Fifty-Six male adult albino rats (200–250 g) were procured from animal facility of King Fahd Center for Medical Research, Jeddah, Saudi Arabia. Throughout the study, animal were houses in standard plastic cages environmentally maintained at 24°C ± 2°C in temperature, and clamminess (50% ± 5%), having a daily rhythm of 12 hours of light and 12 hours of darkness for at least one week to adapt. The Unit of Biomedical Ethics, Research Ethics Committee at Faculty of Medicine, KAU, Saudi Arabia, approved the protocol ethically (ethical approval number: Reference No: 103-34)

METHODS:

Preparation of Moringa and Neem:

After 500 grams of fresh Moringa and Neem leaves were cleaned well, dried on air, then macerated in 500 milliliters of ethanol/water (80:20 v/v), the leaves on ethanol were left at room temperature for 48 hours. The filtrates were insert on a water bath to concentrate at 36°C after being evaporated in a rotary evaporator. For every extract, a paste with a green tint was obtained. Before

being employed, the derived Moringa leaves extract (MLE) and Neem leaves extract (NLE) were preserved in storage at < 4°C **(Efiong *et al*., 2013)**.

Induction of DM state:

The development of DM was brought on by a sole ip injection of recently prepared STZ (75 mg STZ / 10 ml citrate buffer) at a dosage of 40 mg/kg rat body weight, which was covered with light-sensitive aluminum foil. The citrate buffer was made by mixing 0.59 g of sodium citrate with 20 milliliters of distilled water, then adjusted pH to 4.5 **(Al-Hariri, 2012)**. Following ip injection, to avoid hypoglycemia shock-related death, a 5% glucose was given to the rats to consume overnight. Seventy-two hours later, diabetes was identified when blood glucose reading exceeded 200 mg/dl, diabetes was established, and the non-diabetic rats were eliminated from the study. Blood were withdrawl from the orbital plexus vein of each STZ treated rat, and the value of blood glucose was detected to affirm incidence of diabetic state **(Somani and Singha, 2008)**.

Experimental protocol:

Male Wister albino rats (n = 56), eight weeks old and weighing 200–250 g, were utilized in this animal model. Throughout the four weeks of the study period, all rats were fed nutritionally balanced standard diet in accordance with **Reeves *et al*., (1993)** and were given unlimited access to water.

At the end of acclimation week, rat split into seven groups, as follow:

(1) ND: Normal non-diabetic rats (n=8), as negative control received a sole i.p. injection of 0.2 ml (0.05 M citrate buffer pH 4.5).

The remaining 48 Wistar rats were treated with STZ to induce DM state as mentioned above, then divided equally into groups as follow:

(2) D: Untreated diabetic rats as positive control.

(3) **D-MLE250:** Rats with diabetes given MLE (250 mg/kg/d).

(4) **D-MLE500**: Rats with diabetes given MLE (500 mg/kg/day).

(5) **D-NLE250:** Rats with diabetes given NLE (250 mg/kg/day).

(6) **D-NLE500**: Rats with diabetes given NLE (500 mg/kg/day).

(7) **D-Comb-500**: Rats with diabetes given both MLE and ALE (250 mg/kg/day) from each extract.

Biological evaluation:

Feed consumed (FC) was noted for each group every other day during the experimental weeks, and each group's rats had twice-weekly weight checks. At the conclusion of the experimentation, the percentage of body weight gain (BWG%) was computed using the following equation:

$$\textbf{BWG \%} = \frac{\text{Final b.wt} - \text{Initial b.wt}}{\text{Initial b.wt}} \text{ X } 100$$

In addition to, calculation of feed efficiency ratio (FER) parameter based on **(Chapman *et al.*1959)**, utilizing the subsequent formula:

FER = (BWG (g)/ FC (g)) x 100.

Collection of blood and separation of serum:

The rats were starved overnight before scarification at the conclusion of the 4-week study period. Each rat's retro-orbital plexus was used to obtain blood samples using a heparinized capillary tube while it was sedated with diethyl ether. The serum was detached by centrifugation at 3000 rpm and kept at -80° C until subsequent biochemical analyses. Animals were slaughtered as soon as blood was drawn, and each animal's liver and pancreas were removed before being maintained for histological examinations in 10% formalin.

Biochemical analysis:

The diabetic state markers:

Fasting serum glucose by enzymatic kits according to **Asatoor and King, (1954).**, Insulin by ELISA technique (**Clark and Hales, 1994**).

Lipid profile parameters:

The TC, TGs, and HDL were assessed by colorimetric enzymatic kits as per the instructions of **Allian *et al.* (1974), Fossati and Prenape (1982) and Albers *et al.* (1983**). Low-density lipoprotein cholesterol (LDL) and very low-density lipoprotein cholesterol (VLDL) were computed based on the formula of **Fruchart, (1982)** as follows:

LDL = TC - (HDL + VLDL)

VLDL = TGs / 5.

Antioxidant indices:

The serum Superoxide dismutase (SOD), and Catalase (CAT) activities, in addition to reduced glutathione (GSH) were assessed based on **Spitz and Oberley (1989), Aebi, (1984)** and **Beutler *et al.*, (1963)**, respectively. Moreover, malondialdehyde (MDA) was evaluated in accordance with **Draper and Hadley (1990),** as lipid peroxidation`s primary byproduct.

Histopathological examination:

Specimens of pancreas and liver were laid in 10% neutrally buffered formalin. Following trimming, the preserved tissues were dehydrated using increasing concentrations of isopropyl alcohol, treated with xylene for cleaning, and

washed with cold saline solution. The tissues impregnated with wax of identical grade were encased in paraffin blocks, which were then thinned out to 3-5µ by a rotary microtome. The sections were positioned on glass slides and placed in a tissue floatation bath at 40 ℃. After melting the portions in an incubator set at 60℃ for five minutes, which were permitted to be cold before being microscopically inspected and treated with hematoxylin and eosin staining in accordance with **Pashapoor *et al*., (2020)**.

Statistical analysis:

All statistical analyses were conducting using SPSS for Windows, version 20.0 (SPSS Inc., Chicago, IL, USA). The data was shown as the mean ±Standard deviation (SD). The Analysis of Variance (ANOVA) was utilized to identify the significances among the various groups **(Armitage and Berry, 1987)**. For every comparison, $p \leq 0.05$ was set as the threshold for statistical significance.

RESULTS AND DISCUSSION

Table (1) displays the amount of FC, FER and BWG% of diabetic rats administered with MLE and/or NLE. The FC was increased in the diabetic (D) group contrasted to normal ND group by 45.23%. Giving diabetic rats oral administration of MLE and NLE in concentration of 250 or 500 mg/ kg body weight, as well mixture of both, resulted in reduced FC contrasted to the diabetic untreated (D) group. The FER in D rats decreased by 50% contrasted to ND rats with a considerable difference ($P \leq 0.05$). Rats in groups D-MLE and D-NLE at both concentrations, and D-Comb rats showed considerable ($P \leq 0.05$) increases in FER contrasted to D rats. In terms of BWG%, the D rats showed a notable decrease of 58.23% compared to ND rats. These observations aligned with studies by **Negm (2020)** and **de Castro Neto et al. (2021)** who found a notable inverse relationship between BWG and FC in STZ treated rats. **Kota *et al*. (2012)** attributed these observed changes to the rise in the neuropeptides Y mRNA that resulted from the increment in dietary intake of diabetic rats; as a result, weight gain was decreased in those rats even though their feed consumption is increased. Moreover, **Perry and colleagues (2016)** revealed that the decreased of BWG in DM patients may have resulted from an increase in muscle atrophy and tissue protein loss. It is important to acknowledge that DM is a wasting disease with a variety of subsequences resulting from the disease. The weight reduction that observed in diabetic rats could perhaps be attributed to the production of free radicals. (**Adedapo et al., 2020**).

The groups receiving MLE and/or NLE showed notable ($p<0.05$) increases in FER compared to D group, while group D-MLE-500 and D-NLE-500 along

with Comb group exhibited FER values comparable to those of the normal ND rats. Although all treated groups showed improvement in BWG% with considerable differences ($p<0.05$) contrasted to the D rats, there were no distinctions among the treated groups themselves (Table 1). Moringa and Neem leaves are abundant in natural antioxidants and are traditionally utilized in medicine for managing and treating various diseases, particularly DM (**Vongsak et al., 2013, de Castro Neto et al., 2021**). The positive effect in body weight of groups treated with MLE are aligned with **Villarruel-Lopez *et al*., (2018), and Aljazzaf *et al*., (2023)** who revealed that MLE at concentrations 100, 250, 300, 500 mg/kg experienced increases in BWG in comparison to the diabetic rats. The ability of *M. oleifera* to suppress angiogenesis in adipose tissue and reduce preadipocyte development could explain some of the observed impacts **(Negm, 2023)**. These studies suggest that the observed weight gain in D-MLE250 or 500 groups might be attributed to the existence of phyto-chemicals, including necessary amino acids and fat soluble vitamins. In addition to, antioxidant components like phenols, coumarins and tannins are known to support growth (**Adedapo et al., 2020)**.

The NLE positive effects on body weight was consistent with that of **de Castro Neto *et al*., (2021)**, who discovered that certain components of NLE may have imitated or replicated the impacts of growth factor, resulting in a rise in weight gain in D-NLE250 or 500 when compared to ND group. While, **Isdadiyanto et al. (2021)** found that NLE on concentration 57, 100, 125 mg/200 g BW didn`t influence on FC or BWG in Wistar rats given high-fat diet. Neem leaves has capability to restore the injured pancreatic tissue, also play a role in this outcome **(Negm, 2023a)**.

Data in **Table (2)** displayed that there were no considerable differences in liver and Pancreas indexes (LI) (RI) in D rats contrasted with the ND rats and also between all treated groups contrasted to the D rats. These findings were agreed with **Zafar and Nagvi** (2010) who found slight non-significant increase on liver weight and unaffected pancreatic weight in STZ-induced diabetic adult albino rats after 12 weeks period. **Aldahmash et al. (2016)** Revealed no changes in liver weight and index in STZ treated Swiss albino mice. On the contrary, **Al-Malki and El Rabey (2015)** study found notable elevation on Li and PI value in STZ treated rats, when Moringa powder at concentration 50 or 100 mg/kg were given to diabetic rats, the LI and PI dropped and eventually approached normal.

Table (1). Impact of Moringa and Neem leaves ethanolic extract (MLE) (NLE) and their combination (Comb) on feed consumed (FC), feed efficiency ratio (FER) and body weight gain percentage (BWG%) in diabetic rats

Experimental groups	FC (g/d)	FER	BWG%
ND	20.43	0.122 ± 0.034 [a]	85.54±5.34 [a]
D	29.67	0.061 ± 0.003 [c]	35.73±2.67[c]
D-MLE250	23.11	0.078 ± 0.009[b]	63.43±4.87[b]
D-MLE500	22.65	0.095± 0.001[a]	60.22±4.66[b]
D-NLE250	25.89	0.074± 0.002[b]	64.34±5.76[b]
D-MLE500	23.77	0.089± 0.004[a]	62.23±4.87[b]
D-Comb-500	21.98	0.093± 0.003[a]	61.22±4.76[b]

Data are expressed as means ± SD, with 8 rats for group.
Means not sharing a common superscript letter are dramatically differ at $P \leq 0.05$.
Superscripts that are alike or partially alike indicate nonsignificant differences.

Table (2). Impact of Moringa and Neem leaves ethanolic extract (MLE) (NLE) and their combination (Comb) on liver and pancreas indexes (LI) (PI) in diabetic rats

Experimental groups	LI (g/100g BW)	PI (g/100g BW)
ND	2.86± 0.65[a]	0.27± 0.08[a]
D	3.45± 0.72[a]	0.30± 0.02[a]
D-MLE250	3.21 ± 0.67[a]	0.33± 0.03[a]
D-MLE500	3.76± 0.28[a]	0.27± 0.05[a]
D-NLE250	3.37 ± 0.52[a]	0.31 ± 0.02[a]
D-MLE500	3.54± 0.63[a]	0.34± 0.01[a]
D-Comb-500	3.73± 0.67[a]	0.32± 0.03[a]

Data are expressed as means ± SD, with 8 rats for group.
Means not sharing a common superscript letter are dramatically differ at $P \leq 0.05$.
Superscripts that are alike or partially alike indicate nonsignificant differences

Table (3) demonstrated the impact of MLE and/or NLE on the values of serum insulin and glucose in male rats with STZ-induced diabetes. One of the most frequently used diabetogenic drugs in animal studies is STZ (**Ghasemi and Jeddi, 2023**). The ways in which STZ triggers diabetes involve causing the death of pancreatic beta-cells through apoptosis and necrosis and inhibiting insulin excretion **(Ghasemi and Jeddi, 2023)**. An established method for inducing diabetic state in rat models involving giving STZ via injection at doses 35-100 mg/kg **(Gupta *et al.*, 2017)**. Our findings showed notable elevation on serum glucose and considerable reduction at ($p \leq 0.05$) on insulin value in the D group when contrasted to the ND group. These findings align with former research, confirming that utilizing STZ in Wistar rats is a well-established model for inducing diabetic state **(Negm, 2020)**. Diabetes syndromes are defined by elevated blood sugar, changed fat and carbohydrate levels, and a higher chance of developing complications from the disease **(American Diabetes Association, 2021)**.

Table (3). Impact of Moringa and Neem leaves ethanolic extract (MLE) (NLE) and their combination (Comb) on fasting serum glucose (FSG) and serum insulin levels of diabetic rats.

Experimental Groups	FSG (mg\dl)	Insulin (mg\ml)
ND	70.94±6.11d	3.22± 0.36a
D	450.06±40.36a	0.73± 0.02c
D-MLE250	129.76±8.24cd	2.35± 0.24a
D-MLE500	79.13±6.53d	2.89± 0.26a
D-NLE250	185.38±14.42bc	1.88±0.17ab
D-NLE500	88.76±9.36d	2.48±0.23a
D-Comb-500	73.82±6.82d	3.05±0.29a

Data are expressed as means ± SD, with 8 rats for group.
Means not sharing a common superscript letter are dramatically differ at $P \leq 0.05$.
Superscripts that are alike or partially alike indicate nonsignificant differences

Treating diabetic rats with MLE and/or NLE considerably alleviated the glucose increment on serum in proportion to dose when contrasted to D rats. Although all groups given MLE and/or NLE showed remarkable refinement in serum insulin and glucose values compared to the D rats, but Combined group exhibited the best improvement in diabetic markers similar to normal ND rats.

These conclusions were harmonized with **Mohamed *et al*., (2019)**, who reported that moringa leaves aqueous extract (300 mg/kg BW) can reversed insulin resistance, while **Adawiyah *et al*., (2024)** found that moringa extract at concentration 800 mg/kg BW showed more pronounced hypoglycemic effect. There are various possible explanations for MLE hypoglycemic action. By boosting the activity of glucose transporters, such as GLUT4 **(Mohamed *et al*., 2019)**, it may improve peripheral glucose absorption, raise insulin secretion, and improve pancreatic β-cell task **(Anthanont *et al*., 2016)**. The moringa leaves antioxidant qualities are shown to disrupt insulin signaling pathways **(Mthiyane *et al*., 2022)**. This comprehensive strategy for controlling glucose affirms the persistence of moringa usage in the handling of diabetes and its aftereffects. The suppression of insulin release from the pancreatic islet of Langerhans β cells, inhibition of glucose uptake from the gastrointestinal tract (as observed in α-glucosidase or pancreatic amylase enzyme inhibitors), and inhibition of gluconeogenesis and glycogenolysis were the methods used to achieve hypoglycemic activity **(Bouyahya *et al*., 2024)**.

On the other hand, our findings exhibited that NLE has comparable impact in reducing blood glucose levels, which align with former studies conclusion, **Jani and Goswami (2017), and Yarmohammadi et al., (2021**) discovered the hypoglycemic capability of NLE in alloxan treated rats. Also study of **Ezeigwe and Francis (2020)** demonstrated the same impact of NLE but in STZ-induced diabetic rats. According to former reports, neem is excellent in preventing and postponing the onset of diabetes and is also very effective at maintaining blood glucose levels (**Yarmohammadi et al., 2021**). The NLE antidiabetic qualities might be associated with its capacity to encourage the pancreas to produce enough insulin, which would help the cells use glucose in a peripheral manner. Another possibility is that the extract could help the cells regenerate so they can resume their normal functions (**Jelodar *et al*., 2005)**. Moreover, **Pingali *et al*., (2020)** revealed that neem extract lowers insulin resistance and boosts peripheral glucose consumption. One explanation could be because adrenaline inhibits glucose metabolism, leading to a greater use of peripheral glucose.

Impact of MLE and/or NLE on lipid profile indices (TC, TGs, HDL -C, LDL -C and VLDL -C) in diabetic rats were shown in **Table (4)**. The findings detected that group D rats had a considerable ($P \leq 0.05$) increment in all lipid profile indices except HDL-C showed notable decrement by 35.8% when contrasted with group ND rats. This could be due to fat breakdown process in adipocytes, leading to hyperlipidemia **(Liu *et al*., 2019)**. These results proportionate with **Kianbakht and Dabaghian (2013), Negm, (2020)** and **Youssef et al., (2024)**, who conducted a link between diabetic complications and fat metabolism impairment, as the raised blood TGs and TC levels in STZ-diabetes rats. However, in normal conditions, insulin triggers the enzyme

lipoprotein lipase that breaks down TGs. The loss of beta cells in rats given STZ resulted in lower plasma insulin levels, leading to the development of hyperlipidemia and hypercholesterolemia, which disrupting metabolic processes **(Pratiwi *et al*., 2021**). Furthermore, the higher quantities of lipids may be the consequence of free fatty acid inflow stimulating the formation of TGs in liver **(Ugbaja, 2016).**

Current study findings illustrated that given MLE and/or NLE in both concentrations and in mixture considerably ($p \leq 0.05$) improved dyslipidemia that caused by STZ injection when compared to group D rats. These observations were aligned with **Metwally *et al*., (2017) and El-Shehawi et al. (2021**), who found that MLE administration to obese male or female albino rats can notably improving visceral fat mass, obesity and dyslipidemia. **El-Gindy *et al*., (2017)** found that supplementing rabbits exposed to moderate heat stress with MLE notably increased HDL-C levels. The drooping in TC, TGs, and LDL-C with simultaneous increasing in HDL-C levels, suggests that moringa leaves possess worthy hypolipidemic property by regulating lipid elimination mechanisms in the body **(Negm, 2019)**. The existence of flavonoids and saponins in moringa resulted in the enhancement of HDL-C and lessening of LDL and VLDL in rats had hypercholesterolemia **(Negm *et al*., 2020)**.

On the other hand, observed hypolipidemic property that shown in administered groups with NLE were aligns with **Shradha and Sisodia (2010), Ezeigwe *et al*., (2020) and Umar *et al*., (2024)**, who detected a considerable rise in HDL-C and substantial decreases in TC, TGs, and LDL in diabetic rats administered with NLE. In a research conducted by **Abdel Moaty and colleagues (2022)**, it was noted that the ability of NLE to reduce blood cholesterol levels might have the potential to prevent the progression of atherosclerosis. The lipid-lowering effect of Neem leaves could be clarified by a recent study that explain the chemical composition of NLE, which includes components like quercetin, myricetin and kaempferol, wholly or partly responsible for its hypolipidemic property (**Vidhya Rekha *et al*. 2022)**. Moreover, the existence of Nimbidin in Neem is known to notably reduce serum cholesterol levels, aiding in the prevention of blood clot formation.

Impact of MLE and/or NLE on enzymatic and non-enzymatic antioxidant markers and lipid peroxidation in rats with diabetes were shown in **Table (5)**.

The findings indicated that antioxidant enzymes CAT and SOD along with non-enzymatic GSH were considerably ($p \leq 0.05$) declined, while the main product of lipid peroxidation MDA was notably ($p \leq 0.05$) heightened in D rats contrasted to ND rats. Many studies have highlighted the involvement of oxidative stress in the advancement of diabetic state, which perform a substantial role in the disease incidence, including impairment of insulin function and increasing the rate of complications **(Asmat *et al*., 2016)**.

Hyperglycemia and lipid peroxidation are strongly correlated. Individuals with high blood glucose are unable to secrete insulin due to dysfunctional beta-cells in the pancreas, while in diabetic animal tissue, there is a shift towards utilizing fatty acids and acetyl CoA **(Udofia *et al*., 2024)**.

Table (4). Impact of Moringa and Neem leaves ethanolic extract (MLE) (NLE) and their combinations (Comb) on lipid profile indices of diabetic rats

Experimental groups	TC (mg\dl)	TGs (mg\dl)	HDL -C (mg\dl)	LDL -C (mg\dl)	VLDL -C (mg\dl)
ND	144.65±8.62^{b}	95.63±7.96^{c}	46.60±4.48^{a}	78.84±6.33^{c}	19.12±1.82^{c}
D	171. 64±9.42^{a}	155.54±13.34^{a}	29. 90±1.96^{c}	110.46±9.30^{a}	31.10±2.99^{a}
D-MLE250	146.94±10.67^{b}	105.84±9.98^{c}	41.38±3.82^{a}	84.56±7.22^{c}	21.00±1.69^{c}
D-MLE500	148.22±8.74^{b}	99.82±7.26^{c}	47.74±4.20^{a}	80.66±7.36^{c}	19.80±1.83^{c}
D-NLE250	150.15±12.34^{b}	125.29±11.19^{b}	32.62±2.97^{b}	92.53±8.26^{b}	25.00±2.37^{b}
D-NLE500	151.94±11.24^{b}	103.69±9.42^{c}	46.51±3.88^{a}	84.63±6.53^{c}	20.60±1.77^{c}
D-Comb-500	145.63±8.93^{b}	97.76±9.10^{c}	46.30±4.11^{a}	79.93±5.39^{c}	19.40±1.80^{c}

Data are expressed as means ± SD, with 8 rats for group.
Means not sharing a common superscript letter are dramatically differ at $P \leq 0.05$.
Superscripts that are alike or partially alike indicate nonsignificant differences
TC: total cholesterol, **TGs**: Triglycerides, **LDL-C**: low density lipoprotein cholesterol, **HDL-C:** high density lipoprotein cholesterol, **VLDL-C**: very low density lipoprotein cholesterol.

Acting as an antioxidant enzyme, SOD is one of the key enzymes responsible for instantly eliminating of reactive oxygen species (ROS), that may abundantly arise within onset of diabetes. By scavenging O_2 from H_2O_2, this essential defense enzyme decreases the adverse effects of ROS damage through secondary reactions **(Dachana *et al*., 2010)**.
Previous research has demonstrated the capability of antioxidants in the handling of both types of diabetes, indicating that oxidative stress is particularly concerning in metabolic disorders including diabetes **(Ceriello *et al*., 2016)**. **Udofia *et al*., (2024)** stated that the decreased levels of SOD in rats with diabetes were due to deactivation brought on by ROS produced by STZ.

Glutathione use in diabetes may result in glutathione depletion **(Deka *et al*., 2021)**. Conversely, this study demonstrated that the groups given MLE and/or NLE and their combinations at the tested concentrations appreciably ($P<0.05$) raised the antioxidants enzymes (CAT, SOD) and non-enzymatic GSH, while considerably reduced MDA contrasted to group D. The findings clearly imply that MLE and NLE can potentially lowering lipid peroxidation and improve the endogenous antioxidant system. It has been previously documented that all types of moringa leaf extracts have the ability to neutralize peroxyl and superoxyl radicals (**Anzano et al., 2021**). Former study indicated that moringa-containing products can protect liver tissue from damage and reduce lipid peroxidation **(Verma *et al*., 2009)**. Furthermore, non-enzymatic glycosylation and oxidation are the mechanisms by which SOD prevents diabetes mellitus. The abundant presence of vitamin C in MLE may have contributed to the animal's level of the measure **(Eid *et al*., 2025)**.

The findings of our study about NLE effect on antioxidant status is aligns with **Hossain *et al*. (2023)** and **Andersa et al. (2024)**, who reported the NLE antioxidant capability in alloxan treated mice, which is regarded as a rich natural antioxidants source (flavonoids, phenols and tannins) that gives it an ability to scavenge free radicals. Our findings of NLE effect on lipid peroxidation process are aligns with **Ezeigwe *et al*., (2020), Mohammed *et al*., (2023) and Umar *et al*., (2024)**, who found that given aqueous NLE to STZ-diabetic rats led to dramatically reduction their MDA in STZ treated rats.

Table (5). Impact of Moringa and Neem leaves ethanolic extract (NLE) (NLE) and their combinations (Comb) on antioxidants status of diabetic rats

Groups	MDA ng/mL	SOD U/Ml	CAT Pg/mL	GSH µmol/mL
ND	111.83±1.52f	0.77±0.007a	19.17±0.37a	71.50±0.44a
D	355.98±1.72a	0.54±0.005e	7.60±0.21e	52.58±0.68e
D-MLE250	341.81±1.48b	0.57±0.004d	8.16±0.27e	56.87±0.50d
D-MLE500	324.41±1.60c	0.60±0.006d	13.75±0.29c	59.21±0.31d
D-NLE250	340.04±1.48b	0.58±0.005d	10.96±0.46d	58.13±0.48d
D-NLE500	302.19±1.74d	0.64±0.003c	14.64±0.35c	63.24±0.55c
D-Comb-500	287.34±1.71e	0.68±0.005b	16.65±0.34b	67.51±0.70b

Data are expressed as means ± SD, with 8 rats for group. Means not sharing a common superscript letter are dramatically differ at $P \leq 0.05$. Superscripts that are alike or partially alike indicate nonsignificant differences. MDA: malondialdehyde, SOD: Superoxide dismutase, CAT: catalase, GSH: reduced glutathione..

.

Histopathological Examination

Liver :

Under a microscope, the livers of the D and ND groups displayed different histological structures, including the normal hepatic lobule and portal vein **(Fig. 1, ND)**, hyperplasia of the bile duct's epithelial lining and fibrosis of its wall **(Fig. 1, D-A)**, congestion of the central vein and hepatic sinusoids **(Fig. 1, D-B)**, and Kupffer cell activation and hepatocytes apoptosis **(Fig. 1, D-C)**. The central vein and hepatic sinusoids of the diabetic rat were enlarged in the liver tissues after it was fed 250 mg/kg/d of Moringa extract orally **(Fig. 2, D-MLE250)**. The diabetic rat was given 500 mg/kg/d of MLE orally, and the liver tissues of the rat appeared to have a normal histological structure **(Fig. 2, D-MLE500)**. Conversely, the liver tissues of the rats with diabetes given 250 mg/kg/d of NLE orally demonstrated activation of Kupfer cells **(Fig. 2, D-NLE250-A)** and mild congestion of hepatic sinusoids with hepatocyte binucleation **(Fig. 2, D-NLE250-B)**. The rats in the oral Neem extract group (500 mg/kg/d) showed normal histological structure **(Fig. 2, D-NLE500)**. Conversely, liver sections from diabetic rats given oral doses of both neem and moringa extracts did exhibit normal histological structure **(Fig. 2, D-Comb)**.

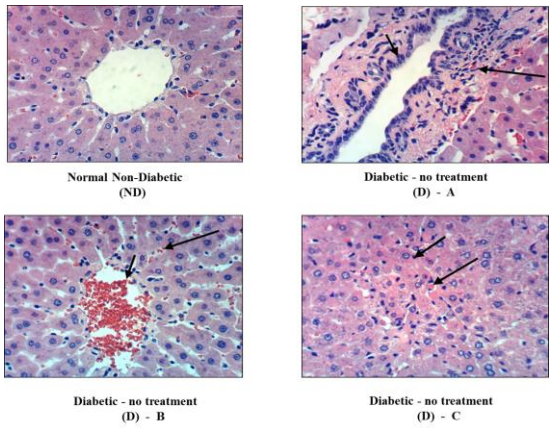

Fig (1) Photomicrographs of Liver tissue. (ND) non-diabetic rat liver shows normal structure of hepatic lobule, (D- A) diabetic untreated rats shows hyperplasia of epithelial lining bile duct and fibrosis of its wall, (D-B) shows hepatic sinusoids and congestion of central vein. (D – C) same group shows kupffer cells activation and hepatocytes apoptosis (H and E, X400).

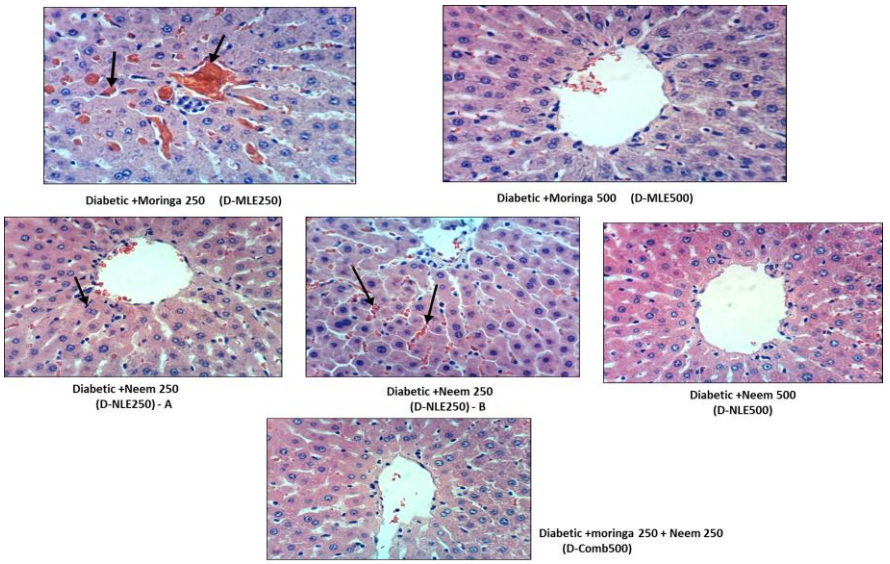

Fig (2): Photomicrographs of Liver tissue. (D-MLE250) diabetic rats given moringa extract 250 mg shows congestion of central vein and hepatic sinusoids. (D-MLE500) diabetic rats given moringa 500 mg shows no histological changes. (D-NLE250)-A, diabetic rats given neem extract 250 mg shows Kupffer cells activation, (D-NLE250)-B shows slight congestion of hepatic sinusoids (black arrow). While (D-NLE500) diabetic rats given neem 500 mg shows no histological alteration. (D-Comb) diabetic rat given both moringa and neem 250 mg for each, shows normal structure of hepatic lobule. (H and E- X400).

The histopathogical findings of liver tissue supported the resulted biochemical indices values, which showing recovery of liver tissue structure. Our results were harmonious with **Adedapo and colleagues (2020)** who detected the same deteriorations in Wistar rat liver`s tissue resulted from STZ dose, and the mild improvement resulted from given 100 mg/kg lyophilized moringa leaf aqueous extract for 14 days. Same results were detected in Wistar rats fed high fat diet and moringa leaf powder at 2 and 4%, which showed remarkable reduction of macro- and microvesicular fat and in liver vessel congestion (**Asgari-Kafrani et al., 2020**). On the other hand, **Seriana et al. (2021)** stated that NLE on concentrations 100, 200, and 300 mg/kg BW for 48 days showed no abnormal changes in male rat liver organ tissue.

Pancreas:

Normal control rats' pancreatic islet cells displayed no histopathological alterations in their histological appearance **(Fig. 3, ND)**. Microscopic analysis of the pancreatic portions from the rats with diabetes and no treatment (D)

group showed vacuolation of the epithelium lining the pancreatic acini **(Fig. 3, D-A)** as well as showed necrosis and vacuolation of the islets of Langerhans cells **(Fig. 3, D-B)**. The activity of STZ in β-cells, which is associated with distinct changes in blood insulin and glucose concentrations, could potentially account for the current findings and cause pancreatic damage **(Koksal, 2015)**. Nonetheless, pancreatic sections of diabetic rats administered 250 mg/kg/d of Moringa extract exhibited mild vacuolation of sporadic islets of Langerhans cells **(Fig. 4, D-MLE250)**. Examined sections of diabetic rats administered 500 mg/kg/d oral Moringa extract did not exhibit any histological alterations **(Fig. 4, D-MLE500)**. Conversely, pancreatic islet tissues from rats with diabetes that given orally 250 mg/kg/d of neem extract displayed a small amount of vacuolation in sporadic islets of Langerhans cells **(Fig. 4, D-NLE250)**. Examined sections of diabetic rats administered 500 mg/kg/d oral Neem extract did not exhibit any histological alterations **(Fig. 4, D-NLE500)**. After given orally 500 mg/kg/d of MLE and NLE mixture to diabetic rats, no histological alterations were observed in the pancreatic sections studied **(Fig. 4, D-Comb)**. Histologically, The MLE and NLE on concentration 500 mg/kg/d alone or in combination for 4 weeks can effectively protect pancreatic cell integrity. Our observations were in line with **Al-Malki and El Rabey's (2015)** and **Helmy et al. (2017)**, who stated that moringa seed powder (50 or 100 mg/kg) and moringa leaf powder (200 or 400 mg/kg/d) can returned the pancreatic histology to normal structure. Moreover, was in line with **Mc Calla et al. (2016)** who found that 0.8% of NLE shows the potential to regenerate beta cell.

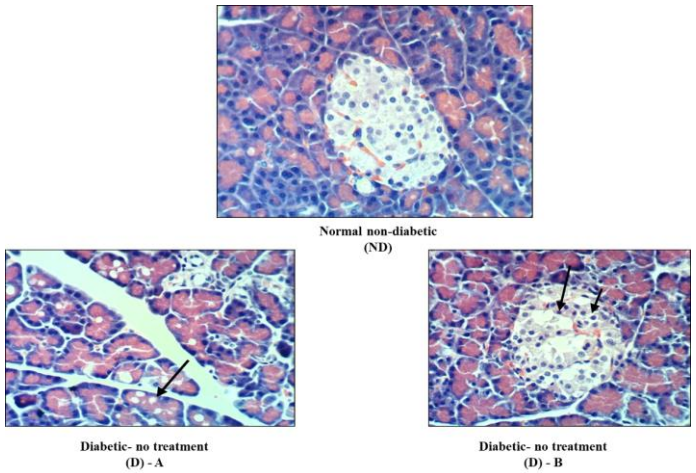

Fig (3). Photomicrographs of Pancreas tissue. (ND) normal rats show normal histological structure. (D)- A diabetic untreated rats show vacuolation of epithelial lining pancreatic acini, and (D)-B shows vacuolation and necrosis of cells of islets of Langerhans.

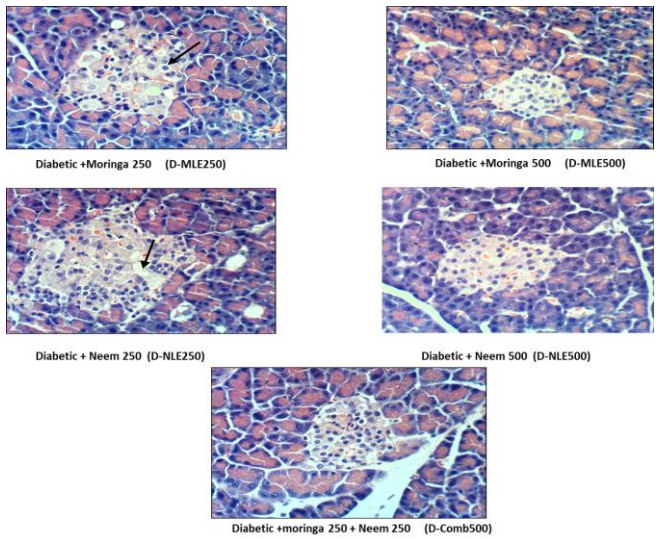

Fig (4). Photomicrographs of Pancreatic tissue (D-MLE250) diabetic rats given Moringa extract 250 mg shows slight vacuolation of sporadic cells of islets of Langerhans. (D-MLE500) rats given Moringa 500 mg shows no histological changes. (D-NLE250) diabetic rats given Neem extract 250 mg shows slight vacuolation of sporadic cells of islets of Langerhans., (D-NLE500) diabetic rats given Neem 500 mg shows no histological alteration. (D-Comb) diabetic rat Given both Moringa and Neem 250 mg for each, shows normal structure of tissue architecture. (H and E- X400).

Conclusion:

Treated STZ-induced diabetic rats with varying concentration of Moringa and Neem leaf extract demonstrated a safe and excellent antidiabetic activity. The combined Moringa/Neem leaves extract at concentration 500 mg/kg was much more effectively than if each extract administered alone at the same concentration. This combination nearly restoring the diabetic rats to their normal state on biochemical and tissue structure levels. Moringa and Neem leaf are recognized as wealthy sources of phytoconstituents that are necessary for nutrition, with the potential to create nutraceuticals and functional foods. This work is one of few studies that applied a mixture of Moringa and Neem leaves extract. Our results point to a possible avenue for advancing the development of a potent antidiabetic remedy derived from *M. oleifera* and *Azadirachta indica* leaves for the treatment and handling of diabetes, although additional clinical studies are required.

REFERENCES

Abduallah, A. M., Ahmed, A. E., Bajaber, M. A. and Alalwiat, A. A. (2023). Evaluation of the antidiabetic effects of methanolic extracts of Neem (*Azadirachta indica*) seeds on the Streptozotocin-induced wistar rats. *Pak. Vet. J.*, *43*(4).

Abidin, Z.; Huang, H.-T.; Liao, Z.-H.; Chen, B.-Y.; Wu, Y.-S.; Lin, Y.-J. and Nan, F.-H. (2021). *Moringa oleifera* leaves' extract enhances nonspecific immune responses, resistance against Vibrio alginolyticus, and growth in whiteleg shrimp (*Penaeus vannamei*). *Animals* , *12*, 42.

Adawiyah, R., Setyawati, T. and Badaruddin, R. (2024). Hypoglychemic activity of Moringa oleifera extract in streptozotocin-induced diabetic rats. *Acta Biochimica Indonesiana*, *7*(1), 130-130.

Adedapo, A.A., Ogunmiluyi, I.O., Falayi, O.O., Ogunpolu, B.S., Oyagbemi, A.A., Orishadipe, A., et al. (2020) The lyophilized aqueous leaf extract of *Moringa oleifera* blunts streptozocin-induced diabetes in rats through upregulation of GLUT 4 signaling pathway and anti-oxidant effect. *Scientific African* 10: e00619.

Abdel Moaty, A.A., El-Kholie, E.A., and Adarous, R.A. (2022). The anti-diabetic effect of Neem leaves (*Azadirachta indica*) in alloxan diabetic rats. *J. Home Econ*. 32(2):19- 31.

Aebi, H. (1984). Catalase in vitro. *Methods Enzymol*., 105:121–126.

Albers, N.; Benderson, V and Warnick, G. (1983). Enzymatic determination of high density lipoprotein cholesterol, Selected Methods, *Clin. Chem*. 10:91-99.

Aldahmash, B.A., El-Nagar, D.M., and Ibrahim, K.E. (2016) Attenuation of hepatotoxicity and oxidative stress in diabetes STZ-induced type 1 by biotin in Swiss albino mice. *Saudi J. Biol. Sci*. 23(2): 311-317.

Aljazzaf, B., Regeai, S., Elghmasi, S., Alghazir, N., Balgasim, A., Ismail, I.M.H., et al. (2023) 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. *Oxid. Med. Cell. Longev*., 2023(1): 9136217.

Al-Hariri, MT. (2012). Comparison the rate of diabetes mellitus induction using streptozotocin dissolved in different solvents in male rats. *J Comp Clin Path Res*.1:96–9.

Allain, CC.; Poon, LS.; Chan, CS.; Richmond, W and Fu, PC. (1974). Enzymatic determination of total serum cholesterol. *Clin. Chem*. 20: 470-475.

Al-Malki, A. L. and El Rabey, H. A. (2015). The antidiabetic effect of low doses of Moringa oleifera Lam. seeds on streptozotocin induced diabetes and diabetic nephropathy in male rats. *BioMed research international*. (1), 381040.

Ameh, S.S. and Alafi, O.F, (2018). Effect of Ethanol Extract of Moringa Oleifera Leaves in Protecting Anaemia Induced in Rats by Aluminium Chloride. IOSR J Biotechnol Biochem, 4(6): 34-52.

American Diabetes Association (ADA) (2021) Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes—2021. *Diabetes Care*, *44*, S15–S33.

Amin, M. F., Ariwibowo, T., Putri, S. A. and Kurnia, D. (2024). *Moringa oleifera*: a review of the pharmacology, chemical constituents, and application for dental health. *Pharmaceuticals*, *17*(1), 142.

Andersa, K.N., Tamiru, M., Teka, T.A., Ali, I.M., Chane, K.T., Regasa, T.K., and Ahmed, E.H. (2024) Proximate composition, some phytochemical constituents, potential uses, and safety of neem leaf flour: A review. *Food Science and Nutrition* https://doi.org/10.1002/fsn3.4336

Anthanont, P., Lumlerdkij, N, Akarasereenont, P. and Vannasaeng, S., Sriwijitkamol, A. (2016). *Moringa oleifera* leaf increases insulin secretion after single dose administration: A preliminary study in healthy subjects. *J. Med. Assoc. Thai*. 99:308-313.

Anzano, A., Ammar, M., Papaianni, M., Grauso, L., Sabbah, M., Capparelli, R. and Lanzotti, V. (2021) *Moringa oleifera* Lam.: A phytochemical and pharmacological overview. *Horticulturae*, 7(10): 409.

Armitage, G. and Berry, W. (1987). Statistical methods 7th Ed. Ames., Iowa State University. Press.39-63.

Asatoor, A.M. and King, E.J. (1954). Simplified calorimetric blood sugar method . Biochem.J.56:XIIV.

Asgari-Kafrani, A., Fazilati, M., and Nazem, H. (2020) Hepatoprotective and antioxidant activity of aerial parts of *Moringa oleifera* in prevention of

non-alcoholic fatty liver disease in wistar rats. South Afric. J. Botany, 129:82–90.

Asmat, U., Abad, K. and Ismail, K. (2016). Diabetes mellitus and oxidative stress—A concise review. *Saudi Pharm. J*., 24(5):547–553.

Beutler, E., Duron, O and Kelly, B.M. (1963). Improved method for the determination of blood glutathione. *J. Lab. Clin. Med*., 61:882–8.

Bouyahya, A., Balahbib, A., Khalid, A., Makeen, **H.A., Alhazmi, H.A., Albratty, M., et al. (2024)** Clinical applications and mechanism insights of natural flavonoids against type 2 diabetes mellitus. Heliyon 10(9): e29718.

Ceriello, A., Testa, R. and Genovese, S. (2016). Clinical implications of oxidative stress and potential role of natural antioxidants in diabetic vascular complications. *Nutr. Metabolism Cardiovasc. Dis*., 26(4):285–292.

Champman, D.; Castilla, R. and Compel, J. (1959). Evaluation of protein in foods. I-A: method for determination of protein efficiency ratio, Can. J. Biochem Physiol., 37: 679 – 686.

Clark ,P.M.S. and Hale,s C.N. (1994). How to measure plasma insulin, Diabet. Metab. Rev., 10: 79-90.

Dachana, K. B., Rajiv, J., Indrani, D. and Prakash, J. (2010). Effect of dried moringa (*Moringa oleifera* lam) leaves on rheological, microstructural, nutritional, textural and organoleptic characteristics of cookies. *J. Food Quality*, 33(5), 660-677.

de Castro Neto, AC, Magalhaes, FO., Ferreira, ICR., Silva, GDO., Vendramini NE, Silva MVO, Leão AV, da Silva JSC, et al. (2021). Feed Consumption and Weight Gain in Diabetic and Non-Diabetic Rats Treated With Azadirachta Indica (Neem) and Plathymenia Reticulata. *J Endocr Soc*. 3;5(Suppl 1):A46–7.

Deka, B., Barge, S.R., Bharadwaj, S., Kashyap, B., Manna, P., Borah, J.C., Talukdar, N.C. (2021). Beneficial effect of the methanolic leaf extract of Allium hookeri on stimulating glutathione biosynthesis and preventing impaired glucose metabolism in type 2 diabetes. *Arch. Biochem. Biophys*. 708:108961.

Neto, A.C.C., Magalhaes, F.O., Ferreira, I.C.R., Silva, G.O., Vendramini, N.E., Silva, M.V.O. et al. (2021) Feed Consumption and Weight Gain in Diabetic and Non-Diabetic Rats Treated With Azadirachta Indica (Neem) and Plathymenia Reticulata. *J. Endocr. Soc.* 5(Suppl 1): A46-A47.

Draper, H. and Hadley, M. (1990). Malondialdehyde determination as index of lipid peroxidation. *Methods Enzymol*,186: 421-431.

Efiong, E.E., Igile, G. O., Mgbeje, B.I.A., Out, E.A. and Ebong, P.E. (2013) Hepatoprotective and anti-diabetic effect of combined extracts of M. oleifera oleifera and Vernonia amygdalina in streptozotocin-induced diabetic albino Wistar rats, *J.Diab. Endocrinol.*, 4(4): 45-50.

Eid, W.A., Azab, D., EL.S. and Negm, S.H. (2025). Characterization of a novel date energy bar fortified with *Moringa oleifera* leaves powder. *Journal of Future Foods*. 5 (3) 266-275.

El-Gindy, Y.M.; Zeweil, H.S. and Hamad, M. (2017). Effects of moringa leaf as a natural antioxidant on growth performance, blood lipid profiles and immune response of rabbits under moderate heat stress. *Egypt. J. Poult. Sci.*, 37: 333-344.

El-Shehawi, A.M., Alkafafy, M., El-Shazly, S., Sayed, S., Farouk, S., Alotaibi, S., Madkour,
D.A., Khalifa, H.K., Ahmed, M.M. (2021) *Moringa oleifera* leaves ethanolic extract ameliorates high fat diet-induced obesity in rats. *J. King Saud Univ.- Sci*. 33(6): 101552.

Ezeigwe, O. and Francis, E. (2020). Antidiabetic and modulatory effect of ethanol extract of Neem leaf on some essential biochemical parameters of streptozotocin-induced diabetic rats. *Inter. J. Biochem. Res. Rev*. 7(3):1-11.

Fossati, P and Praneipe, L. (1982). Serum triglycerides determined colorimetrically with an enzyme that produces hydrogen peroxide. *Clin Chem*. 28(10):2077-80.

Frimpong, E. K., Thembane, N., Hlatshwayo, S., Ngcobo, M. and Gqaleni, N. (2024). Indigenous Medicinal Plants Used in the Management of Diabetes in Africa: 5 Years (2019–2024) in Perspective. *Plants*, *13*(14), 1898.

Fruchart, GG. (1982). LDL-cholesterol determination after separation of low-density lipoprotein. *Rev. Fr. Des. Laboratories*. 103(7):117.

Ghasemi, A., and Jeddi, S. (2023) Streptozotocin as a tool for induction of rat models of diabetes: a practical guide. *Exp. Clin. Sci. J.* 22:274-294.

Govindappa, M. (2015). A review on role of plant(s) extracts and its phytochemicals for the management of diabetes. *J. Diabetes Metab. 6*, 1000565.

Gupta NK, Srivastva N, Puri S, Bubber P. and Puri V. (2017). Neuroprotective potential of Azadirachtaindica leaves in diabetic rats. *Asian J Pharm Clin Res.* 10:243–248.

Helmy, S.A., Morsy, N.F.S., Elaby, S.M., and Ghaly, M.A.A. (2017) Hypolipidemi effect of *Moringa oleifera* LAM leaf powder and its extract in diet induced hypercholesterolemic rats. *J Med Food.*, 20(8):755–762.

Hossain MA, Al-Toubi WAS, Weli, AM, Al-Riyami QA. And Al-Sabahi JN. (2023). Identification and characterization of chemical compounds in different crude extracts from leaves of Omani neem: *Journal of Taibah University for Science*, 7(4):181-188.

Ibrahim, R. E., Ghamry, H. I., Althobaiti, S. A., Almalki, D. A., Shakweer, M. S., Hassan, M. A. and Ahmed, S. A. (2022). *Moringa oleifera* and *Azadirachta indica* Leaves enriched diets mitigate chronic oxyfluorfen toxicity induced immunosuppression through disruption of pro/anti-inflammatory gene pathways, alteration of antioxidant gene expression, and histopathological Alteration in Oreochromis niloticus. *Fishes*, *8*(1), 15.

International Diabetes Federation Diabetes (IDF), (2023) "Facts & figures" available in Diabetes Facts and Figures | International Diabetes Federation (idf.org) *Retrieved 2023-08-10.*

International Diabetes Federation Diabetes. Atlas, 9th ed.; (IDF): Brussels, Belgium, (2019). Available online: https://diabetesatlas.org/upload/resources/material/20200302_133351_IDFATLAS9e-final-web.pdf (*accessed on 25 March 2024).*

Isdadiyanto, S., Mardiati, S.M., and Sitasiwi, A.L. (2021) Blood-glucose levels of rats given high-fat diets after administration of Neem leaf ethanolic extract. *Biosaintifika* 13(2): 142-148.

Islas, J.F., Acosta, E., G-Buentello, Z., Delgado-Gallegos, J.L., Moreno-Trevino, M.G., Escalante, B., Moreno-Cuevas, J.E. (2020) An overview of Neem (*Azadirachta indica*) and its potential impact on health. *J. Funct. Foods*, 74:104171.

Jani, D.K., and Goswami, S. (2017) Screening of the herbal extracts to compare and investigate effect on glucose lowering and anorexic activity in wistar rats. *Asian J Pharm Clin Res.* 10:160–165.

Jelodar, G.A., Maleki, M., Motadayen, M.H. and Sirus, S. (2005). Effect of fenugreek, onion and garlic on blood glucose and histopathology of pancreas of alloxaninduced diabetic rats, *Indian Journal of Medical Sciences*.Vol. 59: 64-69.

Kaur, Y.; Dhawan, A.; Naveenkumar, B.; Tyagi, A. and Shanthanagouda, A. (2020). Immunostimulatory and antifertility effects of neem (*Azadirachta indica*) leaf extract on common carp (*Cyprinus carpio* Linnaeus). *Indian J. Anim. Res, 54*, 196–201.

Kianbakht, S. and Dabaghian, F.H. (2013). Improved Glycemic Control and Lipid Profile in Hyperlipidemic Type 2 Diabetic Patients 576 Consuming *Salvia Officinalis* L. Leaf Extract: A Randomized Placebo. Controlled Clinical Trial. *Complement. Ther. Med*, 57*21*, 441-446.

Kifle, Z.D.; Yesuf, J.S. and Atnafie, S.A. (2020). Evaluation of in vitro and in vivo anti-diabetic, anti-hyperlipidemic and antioxidant activity of flower crude extract and solvent fractions of *Hagenia abyssinica* (rosaceae). *J. Exp. Pharmacol. 12*, 151–167.

Koksal B. (2015). Effect of streptozotocin on plasma insulin levels of rats and mice: A meta-analysis study. *Open Access Maced. J. Med. Sci*. 3(3):380-383.

Kota, S. K., Meher, L. K., Jammula, S., Kota, S. K., Krishna, S. V. S. and Modi, K. D. (2012). Aberrant angiogenesis: The gateway to diabetic complications. *Indian journal of endocrinology and metabolism*, *16*(6), 918-930.

Latif, M. J., Hassan, S. M., Mughal, S. S., Aslam, A., Munir, M., Shabbir, N. and Perveiz, S. (2020). Therapeutic potential of *Azadirachta indica* (neem) and their active phytoconstituents against diseases prevention. *J Chem Chem Sci*, *10*(3), 98-110.

Liu, Q.; Xie, Y.; Qu, L.; Zhang, M and Mo, Z. (2019). Dyslipidemia involvement in the development of polycystic ovary syndrome. *Taiwanese J. Obstet. Gynecol.* 58(4):447-453.

Mc Calla, G., Parshad, O., Brown, P.D., Gardner, M.T. (2016) Beta Cell Regenerating Potential of Azadirachta indica (Neem) Extract in Diabetic Rats. *West Indian Med. J*. 65(1): 13.

Metwally, F.M., Rashad, H.M., Ahmed, H.H., Mahmoud, A.A., Raouf, E.R and Abdalla, A.M. (2017). Molecular mechanisms of the anti-obesity

potential effect of *Moringa oleifera* in the experimental model. *Asian Pac. J. trop. Biomed.*, 7(3), 214-221.

Mohamed MA., Ahmed MA. and El-Sayed RA. (2019). Molecular effects of Moringa leaf extract on insulin resistance and reproductive function in hyperinsulinemic male rats. *J. Diabetes Metab Disord*. 18: 487-494.

Mohammed, A., Kumar, R., Ashfaq, F., Alsayegh, A. A., Al Areefy, A. A. E. H., Khan, M. I. and Rizvi, S. I. (2023). Young and mature leaves of *Azadirachta indica* (neem) display different antidiabetic and antioxidative effects. *Egy. J. Basic Appl. Sci.*, *10*(1), 316-328.

Mthiyane FT, Dludla PV, Ziqubu K, Mthembu SXH, Muvhulawa N, Hlengwa N, Nkambule BB. and Mazibuko-Mbeje SE. (2022). A Review on the Antidiabetic Properties of *Moringa oleifera* Extracts: Focusing on Oxidative Stress and Inflammation as Main Therapeutic Targets. *Front Pharmacol*. 13:940572.

Mwamatope, B.; Tembo, D.; Chikowe, I.; Kampira, E. and Nyirenda, C. (2020). Total phenolic contents and antioxidant activity of Senna singueana, Melia azedarach, Moringa oleifera and Lannea discolor herbal plants. *Sci. Afr. 9*, e00481.

Negm, S. H. (2019). Effect of soybean, virgin coconut and *moringa oleifera* seed oils on the propylthiouracil induced hypothyroidism in rats. *Alexandria Science Exchange Journal*, 40, 649-659.

Negm, S. H. (2023). Gut Microbiota and Obesity. *Chapter 8.* Book *The Gut Microbiota in Health and Disease*, First published: 87-97. https://doi.org/10.1002/9781119904786.ch8

Negm, S. H. (2023a). Novel Therapeutic Strategies Targeting Gut Microbiota to Treat Diseases. *Chapter 12.* Book *The Gut Microbiota in Health and Disease*, First published: 133-142. https://doi.org/10.1002/9781119904786.ch12

Negm, S.H. (2020). Study of Glycemic Control by Ketogenic Diet Supplemented with Different Oils in Type II Diabetic Rats. *J. Home Econ*. 36 (2), 21-40.

Pareek, A., Pant, M., Gupta, M.M., Kashania, P., Ratan, Y., Jain, V., Pareek, A. and Chuturgoon, A.A. (2023) *Moringa oleifera*: An Updated Comprehensive Review of Its Pharmacological Activities, Ethnomedicinal, Phytopharmaceutical Formulation, Clinical, Phytochemical, and Toxicological Aspects. *Int. J. Mol. Sci.* 24(3):2098.

Pashapoor, A., Mashhadyrafie, S. and Mortazavi, P.(2020). Ameliorative effect of Myristica fragrans (nutmeg) extract on oxidative status and histology of pancreas in alloxan induced diabetic rats. *Folia Morphol.* (Warsz);79(1):113-119.

Perry, B.D., Caldow, M.K., Brennan-Speranza, T.C., Sbaraglia, M., Jerums, G., Garnham, A., Wong, C., Levinger, P., Asrar, U.l., Haq, M., Hare, D.L., Price, S.R. and Levinger, I. (2016). Muscle atrophy in patients with Type 2 Diabetes Mellitus: roles of inflammatory pathways, physical activity and exercise. *Exerc Immunol Rev*. 22:94-109.

Pingali, U., Ali, M. A., Gundagani, S. and Nutalapati, C. (2020). Evaluation of the effect of an aqueous extract of Azadirachta indica (Neem) leaves and twigs on glycemic control, endothelial dysfunction and systemic inflammation in subjects with type 2 diabetes mellitus–a randomized, double-blind, placebo-controlled clinical study. *Diabetes, Metab. Syndr. Obes.*, 4401-4412.

Pratiwi, R.Y., Elya, B., Setiawan, H., Solawati, A., Rosmalena (2021) Alterations in body weight, blood glucose levels, and lipid profiles in high-fat diet-low dose streptozotocin-induced diabetic rats. *Pharmacogn J*. 13(6)Suppl: 1562-1567.

Reeves, P.G., Nielson F.H. and Fahmy G.C. (1993): AIN-93 purified diets for laboratory rodents: final report of the American Institute of Nutrition ad hoc writing committee on the reformulation of the AIN-76A rodent diet. *J. Nutri.,* 123(11):1939-1951.

Seriana, I., Akmal, M., and Darusman, D. (2021) Neem Leaf (*Azadirachta indica* A. Juss) Ethanolic Extract on the Liver and Kidney Function of Rats. *The Scientific World J*. 2021(5): 1-7.

Shewasinad, A.; Bhoumik, D.; Zero Hishe, H. and Masresha, B. (2018). Antidiabetic activity of methanol extract and fractions of *Thymus schimperi* Ronniger leaves in normal and streptozotocin induce diabetic mice. *Iran. J. Pharmacol. Ther. 16*, 1–8.

Somani, RS. and Singha,i AK.(2008). Hypoglycaemic and antidiabetic activities of seeds of myristica fragrans in normoglycaemic and alloxan-induced diabetic rats. Asian J Exp Sci. 22(1): 95‑102.

Spitz, D.R and Oberley, L.W. (1989). An assay for superoxide dismutase activity in mammalian tissue homogenates. *Anal Biochem*; 179:8- 18.

Udofia, P., Ojimelukwe, P. C., Ukom, A., Olaoye, O. and Ekanem, M. (2024). Establishing the anti-hyperglycemic potency of ethanol extract of *Moringa Oleifera* leaf on albino rat: Focusing on optimization of biomarkers of Type 2 Diabetes. *Adv Nutr Food Sci*, *9*(2), 1-9.

Ugbaja, R., Akinloye, D., Akamo, J., Ilesanmi, O.O., Tytler, O., Ogunbona, M., and Ademuyiwa, O. (2016) Ameliorative effects of aloe vera gel extract on circulatory and tissue lipid profile status in streptozotocin-induced diabetic rats, *Bangl. J. Med. Biochem*. 9 (1):11–26.

Umar, S. Z., Osibemhe, M. and Ganiyu, A. I. (2024). Antidiabetic Potential of *Azadirachta indica* Aqueous leaves Extract on Streptozotocin-Induced Diabetic Wistar Rats. *Bulletins of Natural and Applied Sciences, 1*(2), 129-137.

Verma, A. R., Vijayakumar, M., Mathela, C. S. and Rao, C.V. (2009). Phyto-chemistry of Moringa oleifera. *Food Chem. Toxicol*., 47(9): 2196-3001.

Vidhya Rekha U., Anita, M., Bhuminathan, S. and Sadhana, K. (2022). Known data on the therapeutic use of *Azadiracta indica* (neem) for type 2 diabetes mellitus. *Bioinformation*. 18(2):82-87.

Villarruel-Lopez, A., Lopez-de la Mora, D.A., Vazquez-Paulino, O.D., Puebla-Mora, A.G., Torres-Vitela, Ma R., Guerrero-Quiroz, L.A., and Nuno, K. (2018) Effect of *Moringa oleifera* consumption on diabetic rats. *BMC Complement. Altern*. Med. 18: 127.

Vongsak B, **Sithisarn P, Mangmool S, Thongpraditchote S, Wongkrajang Y, and Gritsanapan W. (2013)** Maximizing total phenolics, total flavonoids contents and antioxidant activity of *Moringa oleifera* leaf extract by the appropriate extraction method. *Ind Crop Prod.* **44**:566–571.

World Health Organization (WHO), "The top 10 causes of death". available in https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death. Retrieved in 7 August 2024

Yarmohammadi F., Mehri S., Najafi N., Salar Amoli S. and Hosseinzadeh H. (2021). The protective effect of *Azadirachta indica* (neem) against metabolic syndrome: A review. *Iran J Basic Med Sci*. 24(3):280-292.

Yassa HD. and Tohamy AF. (2014). Extract of *Moringa oleifera* leaves ameliorates streptozotocin-induced Diabetes mellitus in adult rats. *Acta Histochem*. 116: 844-854.

Youssef, E., Abuelsaoud, A.M., Moghazee, M.M., and Marie, O.M. (2024)

Ethanolic extract of orange leaves ameliorates dyslipidemia in streptozotocin-induced diabetic rats. Advances in Environ. *Life Sci*. 5(1): 35-41.

Zafar, M. and Nagvi, S.M.H. (2010) Effects of STZ-induced diabetes on the relative weights of kidney, liver and pancreas in albino rats: A comparative study. *Int. J. Morpho*l. 28(1):135-142.

الملخص العربي

داء السكرى ,وبالأخص السكرى من النوع الثانى, يعتبر من أحد أهم المشاكل الصحية على مستوى العالم، يتميز داء السكرى بارتفاع مستويات الجلوكوز أو الأنسولين في الدم.

تهدف هذه الدراسة إلى استكشاف تأثير المستخلص الايثانولى المائى لأوراق المورينجا أوليفيرا و مستخلص أوراق النيم على الفئران البالغة المصابة بمرض السكري الناتج عن الحقن بمادة الستربتوزوتوسين.

تم استخدام ستة وخمسين فئران ألبينو ذكر بالغ في الدراسة الحيوية. حيث تم تقسيم الفئران إلى سبع مجموعات على النحو التالي: المجموعة (١) عملت كمجموعة ضابطة طبيعية غير مصابة بداء السكري (ND)، بينما تم إدخال المجموعات الثانية إلى السابعة في حالة مرض السكرى عن طريق الحقن داخل الصفاق بمادة الستربتوزوتوسين (٤٠ مللجم / كجم وزن الجسم). المجموعة (٢) تركت مصابة بالسكري بدون علاج كمجموعة ضابطة إيجابية (D)؛ المجموعتين (٣) و (٤) فئران مصابة بالسكرى تم معاملتها بالمستخلص الايثانول لأوراق المورينجا عن طريق الأنبوب المعدى بتركيزى ٢٥٠ و ٥٠٠ مللجم / كجم وزن الجسم، على التوالي. في حين المجموعتين (٥) و (٦) فئران مصابة بالسكرى تم معاملتها بالمستخلص الايثانول لأوراق النيم بالأنبوب المعدى بتركيزى ٢٥٠ و ٥٠٠ مللجم / كجم، على التوالي. أخيرًا، المجموعة (٧) فئران مصابة بالسكري تم معاملتها بمزيج من المستخلص الايثانولى لأوراق المورينجا والنيم بتركيز ٢٥٠ مللجم / كجم من كل مستخلص. بعد أربعة أسابيع تجريبية، تم تسجيل وزن الجسم والعلف المستهلك وتقدير مستويات الجلوكوز والأنسولين ونمط الدهون ومؤشرات مضادات الأكسدة الذاتية في مصل الدم. أظهرت النتائج انخفاضًا ملحوظًا

($P \leq 0.05$) في نسبة كفاءة التغذية (FER) ونسبة زيادة وزن الجسم (BWG %) في فئران المجموعة (٢) مقارنة بفئران NDمجموعة (١).

و كشفت النتائج أن الفئران المصابة بمرض السكري في المجموعة (٢) أظهرت انخفاضًا كبيرًا (P <0.05) في مستوى الأنسولين في المصل ومؤشرات مضادات الأكسدة الذاتية وكوليسترول ليبوبروتين عالى الكثافة، بينما أظهرت زيادة ملحوظة (P <0.05) في مستوى جلوكوز مصل ومستوى مركب المالوندىألدهيد وأنواع نمط الدهون باستثناء الكوليستروا ليبوبروتين عالى الكثافة مقارنة بفئران مجموعة (١). وجد أن مجموعة (٧) التي عوملت مزيج من مستخلصى أوراق المورينجا والنيم أظهرت تحسن ملحوظ (P <0.05) في جميع المؤشرات السابق ذكرها. علاوة على ذلك، أظهرت مجموعة (٧) تحسن واضح في التغيرات المرضية الضارة التي تم اكتشافها بشكل ملحوظ في أنسجة الكبد والبنكرياس في فئران مجموعة (٢) والتحسن في تلك المجموعة وصل الى الحد المماثل لمجموعة (١).

الاستنتاج: أظهر المستخلص الإيثانولى من أوراق نبات المورينجا ونبات النيم تأثيرًا خافضًا ملحوظا لمستوى الجلوكوز وتحسن في مستويات الانسولين ومضادات الاكسدة الداخلية ونمط الدهون وتحسن في النسيج الكبدى والبنكرياسى في مصل الفئران المصابة بمرض السكري الناجم عن الحقن بمادة الستربتوزوتوسين.

الكلمات المفتاحية

نبات المورينجا – نبات النييم – داء السكرى – القدرة على خفض جلوكوز الدم