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GC-MS ANALYSIS AND EVALUATION OF ANTIOXIDANT, ANTICANCER, CYTOTOXICITY, AND HYPOGLYCEMIC PROPERTIES OF THE LIBYAN *MORINGA OLEIFERA* LEAF EXTRACT ON ALLOXAN-INDUCED DIABETES IN MICE

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Moringa oleifera has been identified as a plant with numerous health benefits, including nutritional and medicinal properties including amino acids, carotenoids, and nutraceutical components. Methanol was used to extract Libyan M. oleifera leaves, and the antibacterial, antioxidant, anti-inflammatory, and anticancer properties of the bioactive components were determined using gas chromatography mass spectrometry (GC-MS). M. oleifera showed antioxidant activity at an IC50 of 11.53 µg/mL. The viability of the Wi38 cell line declined with increasing concentrations of M. oleifera extract, whereas cytotoxicity increased with an IC50 of 393.41±7.77 µg/mL. Alloxan-induced diabetes model in Swiss albino mice was implemented. Three different doses (100, 200, or 300 mg/kg of mice body weight) of M. oleifera's extract were evaluated for their effects on blood sugar concentration and the histology of the pancreatic islets. The normoglycemic group did not experience hypoglycemia as a result of the extract intake. Blood glucose levels were noticeably lower at 200 and 300 mg/kg, especially with the 300 mg/kg dose. The 300 mg/kg dose considerably decreased the fasting blood sugar by the fourth week without endangering hypoglycemia. Giving 100 and 200 mg/kg of M. oleifera extract to the diabetic control group resulted in varied alloxan attack recovery and regeneration of islet and acin. The morphology and acini of the pancreatic islets underwent a significant modification following the ingestion of 300 mg/kg of M. oleifera extract. They were notably bigger and more revitalized, and the number of β-cells that adopted a spherical shape significantly increased. The current findings support the concept of employing this plant as a nutritious supplement or ingredient in food preparation.

Keywords: *antimicrobial; antioxidant; anticancer; diabetic; Moringa*

INTRODUCTION

Diabetes is a potentially fatal metabolic disease that is characterized by a relative or complete lack of insulin secretion as well as abnormalities in the metabolism of fat, protein, and carbohydrates. These abnormalities lead to hyperglycemia, which is the main cause of diabetic complications, including retinopathy, nephropathy, and neuropathy. Over 150 million people worldwide have been diagnosed, and by

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2025, this figure is predicted to rise to 300 million[1,2]. According to estimates, the prevalence of diabetes worldwide was 9.3% (463 million) in 2019. This number is predicted to increase to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045 [3]. In Libya, the diabetes affects 13.7% of people according to WHO. The cost of treating diabetes patients in health care systems around the world, including many primary health care clinics, is high and keeps rising annually. The announcement that insulin and anti-diabetic medications are running low in Libya underscores the need to research the effectiveness of traditional medicinal plants in treating prediabetes patients, as 5 to 10% of those with prediabetes will go on to develop diabetes mellitus annually[4].

Many traditional medicinal plants from various nations have been used effectively to treat a variety of pathological disorders; these plants are also known to be less poisonous, to have very few side effects, and to be reasonably inexpensive [5]. Among the members of the *Moringa* genus, the most well-known and extensively utilized is *M. oleifera*, one of these plants[6,7]. Humans have traditionally eaten all of the edible components of the *Moringa* tree[8,9]. Nutraceuticals and vital nutrients can be found mostly in the leaves and seeds of the plant [10]. It is a well-known medication with several uses in Asia and Africa, attributed to the diverse sections of the plant that are also utilized in a variety of ways [11].

Moringa oleifera presents a great variety of biological activities evidenced in in vitro experiments, showing potent anti-oxidative, analgesic, cytoprotective, anti-ulcer, anti-hypertensive, immunomodulatory actions, and an inhibitory effect on proinflammatory mediators[12,13], as well as antimicrobial effect on some strains of human pathological bacteria [14]. The leaf is the most used plant part for therapeutic purposes. The main phytochemical compounds extracted from the leaves of *M. oleifera* include glucosinolates, flavonoids and phenolic acids that have a protective effect against chronic diseases (arterial hypertension, diabetes mellitus, cancer, metabolic syndrome and overall inflammation) [15]. The hypoglycemic effect of the *M. oleifera* leaves has also been associated with their fiber content and the presence of flavonoids and phenolic compounds. *In vitro* experiments have provided evidence that these molecules play a role in reducing the risk of developing diabetes and improving glucose levels in prediabetes and diabetic patients [16,17]. Consequently, this study aimed at identification of the active ingredients of the Libyan *M. oleifera* leaf extract's, which include antimicrobial, antioxidant, anti-inflammatory, and anticancer properties, and ascertain whether three dosages of the *M. oleifera* leaf extract—100, 200, and 300 mg/kg of mice body weight—could enhance the histology of the pancreatic islets and decrease blood glucose levels.

MATERIALS AND METHODS

Plant Material and Extraction Procedures

Moringa oleifera mature leaves were gathered at a farm in Tripoli, Libya. The leaves were cleaned with tab water and dried in an oven for 24 hours at 60 °C. The dehydrated leaves were crushed and put through a 35 mesh sieve. Until they were used, the powdered leaves were stored in dark, sealed receptacles. A 150 g of the powdered leaves were separately treated to three distinct extraction procedures, each requiring 500 mL of methanol using the maceration extraction technique [18,19]. The extract was filtered using Whatman No. 3 filter paper. The extract was then concentrated under vacuum in a rotating evaporator at 40 °C. The leftover methanol might be removed by letting the extract sit at room temperature for the full following day and obtaining the extract residue.

Gas Chromatography-Mass Spectroscopy (GC-MS) Analysis

The analysis was conducted at the Analytical Chemistry Unit, Faculty of Science, Assiut University (55PC+X4V); Egypt. After dissolving the residue of *M. oleifera* extract in CH_2Cl_2, it was added to a GC-MS device (7890A-5975B; USA). A DB 5-MS Capillary Standard nonpolar column measuring 30 mm × 0.25 mm ID × 0.25 μm film is part of the apparatus. As a carrier gas, helium is used at a flow rate of 1.0 mL/min. The mass range (m/z) of the detector was 20–440, the injector temperature was 250°C, the split ratio was 1/20, and the injection volume was 0.2 μL. The temperature of the GC oven was programmed to rise to 300°C at a rate of 6°C/min for two minutes, and then it was maintained there for 10 minutes. The entire GC-MS run took 70 minutes. The National Institute of Standard and Technology (NIST) [20]) library and the WILEY

09 database were used to interpret the mass spectrum of the extract's components.

DPPH Radical Scavenging Activity of the *M. oleifera*'s Extract

Following [21], instructions, a newly-made methanol solution containing 0.004% (w/v) of the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical was refrigerated at 10 °C overnight. The pure sample was prepared using the following concentrations: 100, 50, 25, 12.5, 6.25, 3.125, 1.56, and 0.78 µM methanol, in that order. Using 3 mL of the DPPH solution and 40 µL of the sample-containing methanol solution, the absorbance at 515 nm was detected (Milton Roy, Spectronic 1201; Canada). Data for 16 mines were collected every minute until the absorbance stabilized, which was then continually monitored [21]. Ascorbic acid, a reference molecule, and the DPPH radical's absorbance in the absence of an antioxidant were both assessed. Equation (1) was used to measure the percentage inhibition (PI) of the DPPH radical. Where AT is the sample absorbance + DPPH at time 16 minutes, and AC is the control absorbance at time zero.

$$PI = (AC - AT) \times 100 \quad (1)$$

To determine the concentration required to inhibit the DPPH radical by 50% (IC50), dose-response curve graphic plots were utilized. Three duplicates of the experiment were conducted.

Cytotoxicity Test of the *M. oleifera*'s Extract

The test was conducted in the Science Way for Scientific Researches and Consultations Company at Al-Moqattam, Cairo, Egypt. The assay utilized wi38 cells and followed the protocols described in publications [22,23]. A 96-well tissue culture plate was seeded with 1×10^5 cells/mL (100 µL/well) and allowed to establish a monolayer sheet for 24 hours at 37°C. After a confluent sheet of cells had grown, the growth material was removed from the 96-well micro titer plates, and the cell monolayer was twice washed using wash media. In RPMI medium containing 2% serum, two-fold dilutions of the examined *M. oleifera* extract were prepared (maintenance media). Each dilution was examined in a separate well with 0.1 ml, leaving three wells as the control group that received only maintenance media. Plate was inspected after being incubated at 37°C. Physical indicators of toxicity, such as shrinkage, rounding, granulation, or partial or whole loss of the monolayer, were examined in the cells. Cells without *M. oleifera* extract were considered a negative control and the effect *M. oleifera* extract on cell viability was calculated relative to the negative control.

MTT Assay

The assay was carried out in accordance with the pertinent procedures [24]. The MTT solution (5 mg/mL in PBS; BIO BASIC CANADA INC.) was made. To fully mix the MTT into the media, 20 µL of the MTT solution was added to each well and shook at 150 rpm for five minutes. After that, the plate was incubated for four hours at 37°C with 5% CO2 to enable the metabolism of the MTT. After emptying the media, the plate was dried on paper towels to see if any residue remained. After that, formazan, the MTT metabolic product, was suspended in 200 µL dimethyl sulfoxide (DMSO) and agitated for five minutes at 150 rpm to fully combine the formazan and solvent. At 560 nm, the optical density was measured, and at 620 nm, the subtract background. There was a direct correlation between cell amount and optical density. A ratio to the reference values was used to determine the cell viability. Equation (2) was utilized to ascertain the relative viability %, and the dose-response curve was utilized to obtain the IC50 [25].

$$\% \text{ Cell viability} = \frac{\textbf{Absorbance of the treated cells}}{\textbf{Absorbance of the control cells}} \times 100 \quad (2)$$

Animal Model and Application of Alloxan

The Zawia Medical Research Center's animal house provided the study's animals. They were male Swiss albino mice (*Mus musculus*), weighing between 30 and 35 grams, and were housed in cages at the ideal temperature, humidity, and light levels [26]. The mice were divided into four smaller groups, each of which had six mice, after the two main groups—a normal, healthy group and a diabetic group—each of which contained 24 mice. Per kg of body weight, four treatments were administered orally using an oral gavage needle. In addition to 100, 200, and 300 mg of the *M. oleifera* extract (n=6 each), 3 mL

distilled water (n=6) was employed as a negative control in each major group.

Protocol of Diabetes Induction

Alloxan monohydrate, which was used to cause experimental diabetes, was acquired from Sigma Chemical Company (St. Louis, Missouri, USA). In order to ensure the occurrence of diabetes, all animals were kept on a 24-hour fast. The diabetic subjects were then intraperitoneal injected with 150 mg/kg body weight of Alloxan monohydrate dissolved in phosphate buffer saline (PBS). Two additional doses of Alloxan were then administered: 100 mg/kg two days after the first dose and 150 mg/kg two days after the second dose. The study included an animal with a fasting blood glucose level between (150-200 mg/dl) as a diabetes subject [27].

Experimental Procedures

Weight and blood glucose levels were assessed at 0, 7, 14, 21, and 30 days using the Accu-check equipment. Following a 30-day trial period, each animal was chloroformed-anesthetized, and blood samples were taken from the aorta into sterilized tubes for further research. The pancreas was preserved in formalin for additional histological examination.

Histological Analysis

Samples were sliced up and put in a plastic container at the end of the experiment. Over the course of a day, the samples were dehydrated using various alcohol concentrations. Sections embedded in paraffin wax, measuring 4 µm in thickness, were consistently made following the fixation of pancreatic tissues using 10% neutral buffered formalin. The tissue sections were then stained with hematoxylin and eosin in order to assess the cell morphology. Using a digital camera and an optical microscope, histological images were captured [28].

Statistical Analysis

The data were statistically analyzed with the statistical analysis system MSTAT-C (Version 2.1) and subjected to ANOVA. Comparison among treatment means was done by the least significance difference (LSD) test at $P \leq 0.05$ [29].

RESULTS AND DISCUSSION

Results

GC-MS analysis of the *M. oleifera* Extract

The current results showed fifteen peaks based on the most prominent compounds' retention time, molecular weight, and fragmentation pattern. According to **Table 1** and **Fig. 1**, these had retention durations ranging from 6.43 to 66.90 minutes.

Antioxidant Activity of the M. oleifera Extract

The DPPH test was employed to examine *M. oleifera*'s potential for hydrogen scavenging, and the IC_{50} value was obtained for the free radical scavenging activity. The findings showed that when sample concentration rose, DPPH activity rose as well **(Fig. 2A)**. The ascorbic acid activity value of 2.85 µg/mL was less than the IC_{50} value of 11.53 µg/mL for the *M. oleifera* extract **(Fig. 2B).**

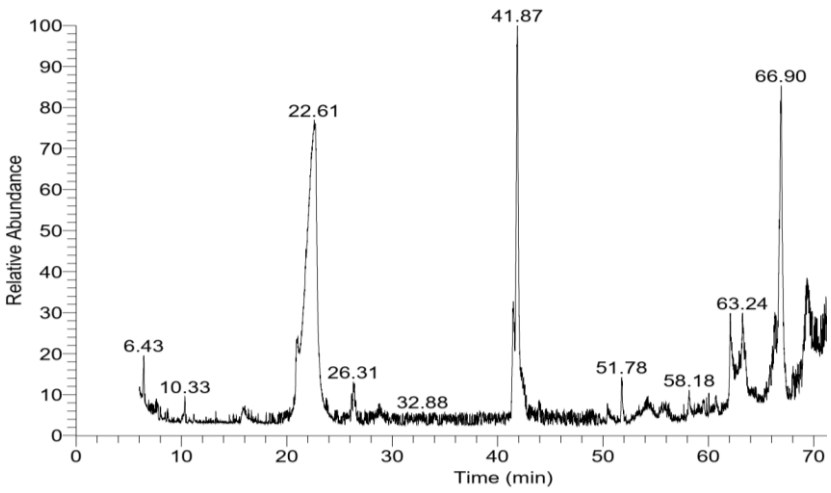

Fig. 1: Chromatogram of GC–MS spectral analysis of *M. oleifera* methanol leaf extract.

Table 1: GC–MS spectral analysis of the chemical compounds detected in the *M. oleifera* methanol leaf extract.

RT (min)	Compound name	Molecular weight	Chemical Formula	Area %	Biological activity
6.43	Acetic acid	60.05	$C_2H_4N_2$	1.13	ND
7.69	Acetic acid hydrazide	74.08	$C_2H_6N_2O$	0.43	Antimicrobial, Anti-inflammatory, antituberculosis [30-32]
10.33	2,2-Dimethoxybutane	118	$C_6H_{14}O_2$	0.52	Antimicrobial [33]
20.92	Dibutyl trisulfide	210.4	$C_8H_{18}S_3$	2.26	Anticancer [34]
22.61	Glycerin	92.09	$C_3H_8O_3$	16.87	ND
26.16	Acetyl valeryl	128.169	$C_7H_{12}O_2$	0.62	Antioxidant [35]
26.42	Acetin	134.13	$C_5H_{10}O_4$	0.42	Anti-adipogenic, antimicrobial, antioxidant, antidiabetic [36,37]
41.87	Undecylenic acid	184.27	$C_{11}H_{20}O_2$	11.87	Antifungal [38]
49.07	3-hydroxypropanehydrazide	104.11	$C_3H_8N_2O_2$	0.42	Anti-inflammatory, analgesic, antimicrobial, anticancer [39,40]
50.42	9,9-Dimethoxybicyclo[3.3.1]nona-2,4-dione	212.24	$C_{11}H_{16}O_4$	0.41	Antiradical, antimicrobial [41]
51.78	Linolenyl alcohol	264.4	$C_{18}H_{32}O$	1.40	Antibacterial, antiviral [42,43]
58.18	1-Pentadecyne	208.38	$C_{15}H_{28}$	0.81	Insecticidal [44]
62.08	Palmitic acid	256.42	$C_{16}H_{32}O_2$	2.82	Antidyslipidemia, antihyperglycemia [45]
63.24	10-Undecenoyl chloride	202.72	$C_{11}H_{19}ClO$	2.32	ND
66.90	13-Hexyloxacyclotridec-10-en-2-one	280.4	$C_{18}H_{32}O_2$	7.63	Antimicrobial, antioxidant, anti-inflammatory, antidiabetic [46,47]

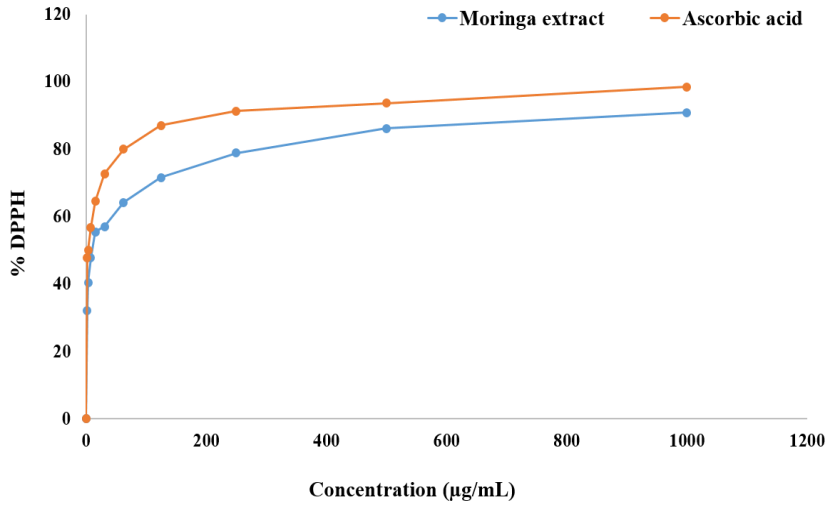

Fig. 2: (A), Antioxidant activity (% DPPH). **(B),** IC50 of the *M. oleifera* extract compared to the standard ascorbic acid.

Cytotoxicity (MTT Assay) and Effect of the M. oleifera Extract on Cell Viability

MTT test was used to determine the cytotoxic activity of *M. oleifera* extract against wi38 cells. If 50% inhibition was seen at the tested concentration, the material is deemed cytotoxic. According to the present investigation, the viability of the wi38 cells reduced and the cytotoxicity increased with an increase in sample concentration **(Fig. 3-4).** The proliferation of wi38 cells was reduced with IC 393.41±7.77 µg/mL when the cells were treated with *M. oleifera* extract.

Effect of *M. oleifera* Leaf Extract on Blood Glucose Level in Healthy Mice

When 100, 200, and 300 mg/kg of the *M. oleifera* extract were used, there was no discernible difference in blood glucose levels in the control group ($p>0.05$). The blood glucose levels on days 0, 7, 14, 21, and 30 were 122±12.3, 125±10.7, 124±7.6, 124±11.2, and 121.6±1.6 mg/dL, respectively, when utilizing a dosage of 100 mg/kg. Using 200 mg/kg of the extract, the fasting blood glucose (FBG) was found to be within the normal range at 122±17.5, 125±16.3, 123±9.3, 122±6.7, and 120±2.8 mg/dL, respectively. Additionally, at day 30, the blood glucose levels were 121±17.5, 124±16.3, 124±9.3, 121±6.3, and 120±2.8 mg/dL, respectively, with the dose of 300 mg/kg of the extract. Hence, utilizing these doses has no hypoglycemic impact ($p>0.05$) on the glucose level **(Fig. 5)**.

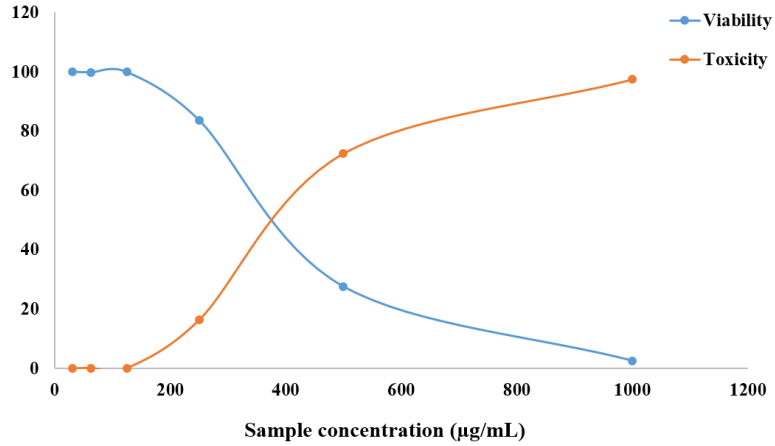

Fig. 3: Cytotoxicity and cell viability of wi38 human cell line as a response to different concentrations of *M. oleifera* leaf extract.

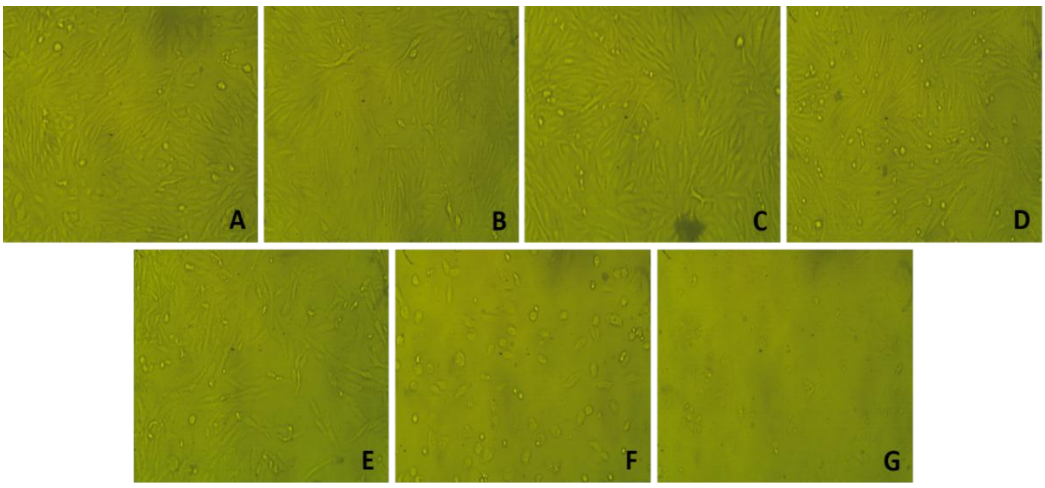

Fig. 4: Viability of wi38 human cell line as a response to different concentrations of *M. oleifera* leaf extract. (A), Control (B), 31.25 µg/mL (C), 62.5 µg/mL (D), 125 µg/mL (E), 250 µg/mL (F), 500 µg/mL (G), 1000 µg/mL.

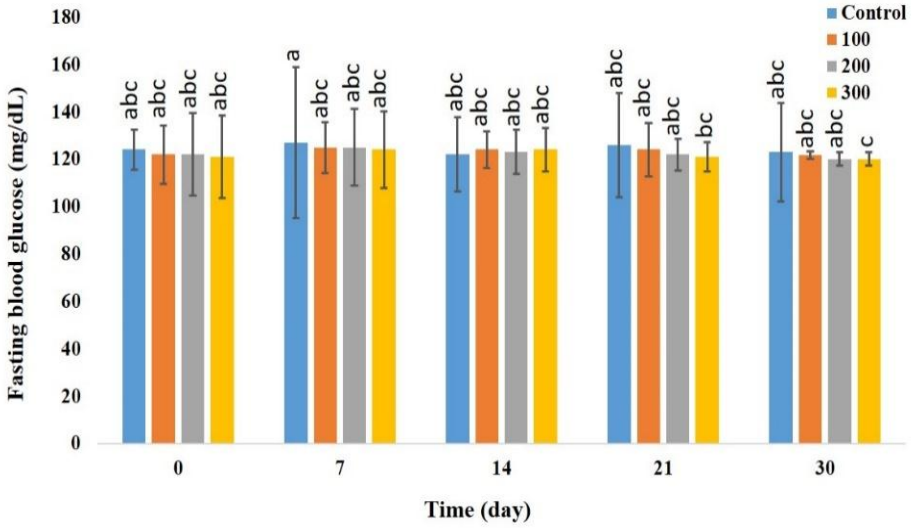

Fig. 5: Effect of different doses (100, 200, and 300 mg/kg of body weight) of *M. oleifera*'s methanol extract on the fasting blood glucose level of the healthy mice. Mean values (±SD) on bar graphs with different letters are significantly different ($p > 0.05$; $n = 6$).

Effect of *M. oleifera* Leaf Extract on the Fasting Blood Glucose Level in Diabetic Mice

On days 0, 7, 14, 21, and 30 after the creation of diabetes in the group of Alloxan-induced diabetic mice treated with *M. oleifera* extract, FBG levels were highly significantly lowered ($P = 0.00$) when extract doses of 200 and 300 mg/kg were applied. When compared to the control group, the blood glucose level with the 200 mg/kg dose decreased from 175.0±8.1 mg/dL on day 0 to 150.8±2.6 mg/dL on day 21, and finally, on the last day of the experiment, reached 138.1±7.5 mg/dL. The blood sugar reduction was more pronounced and evident at 300 mg/kg. On day 0, the FBG level was 185.0±17.5 mg/dL; on day 21, it was 130.1±7.2 mg/dL; and on day 30, it was 120.2±25.7 mg/dL, when compared to the control group **(Fig. 6)**.

It has demonstrated that, the FBG did not significantly drop in the healthy mice group when higher doses of 200 and 300 mg/kg were used ($p>0.05$); however, there was a clear hypoglycemic effect in the diabetic group when doses of 200 and 300 mg/kg were given. The FBS significantly decreased on day 30 ($p<0.05$), suggesting that the 300 mg/kg dosage was the appropriate for the diabetic group.

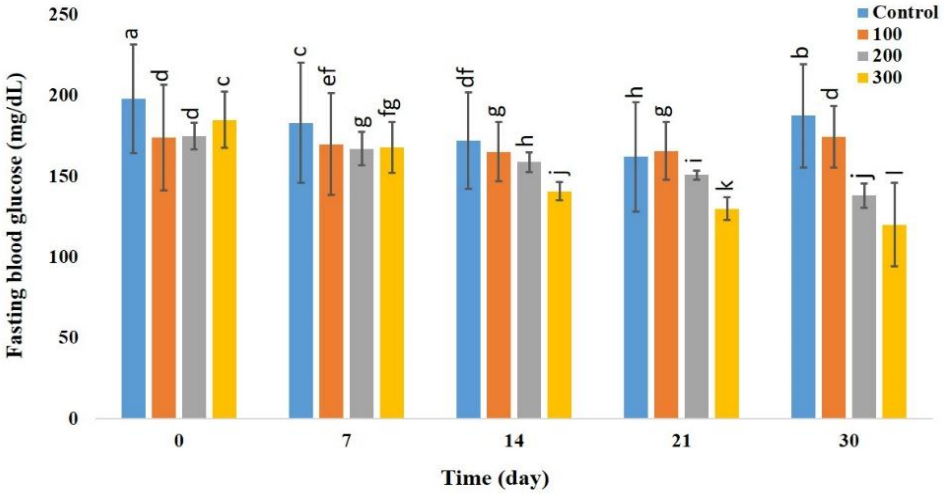

Fig. 6: Effect of different doses (100, 200, and 300 mg/kg of body weight) of *M. oleifera*'s methanol extract on the fasting blood glucose level of the Alloxan-induced diabetic mice. Mean values (±SD) on bar graphs with different letters are significantly different ($p < 0.05$; $n = 6$).

Effects of *M. oleifera* Extract on the Pancreatic Histopathology of Mice

Examining the pancreatic tissues in Alloxan-induced diabetic mice showed differences in histological structure between the various treated groups: diabetic control (100, 200, and 300 mg/kg), and healthy control (100, 200, and 300 mg/kg), in comparison to both negative and positive control groups. According to the current findings, the control healthy group had normal histological architecture of pancreatic islets and acini that was well clustered. Additionally, the islet cells were well-clustered and there was no evidence of necrosis or vacuolation within the islet or its surrounding exocrine pancreatic cells. The serous acini showed a prominent cytoplasm with Centro acinar cells and there was no evidence of necrosis or vacuolation within the **(Fig. 7 A&B).**

On the other hand, the pancreas of alloxanized diabetic mice (diabetic mice without treatment) displayed atrophy and degeneration of the islets, disruption of the islet cells with the presence of vacuolation and necrotic areas within islets, as well as an observational decrease in the size and number of pancreatic islets **(Fig. 8 A&B).**

Comparing the groups receiving 100 and 200 mg/kg of *M. oleifera* extract to the diabetic control group, however, revealed varying degrees of recovery from the Alloxan assault along with a little evidence of islet and acin regeneration **(Fig.s 9 A&B)**. However, after receiving 300 mg/kg of the *M. oleifera* extract, there was a significant difference ($p<0.05$) in the morphology and acini of the pancreatic islets, as well as a marked improvement in their size and rejuvenation. Regular islet cells also had a significant increase in the number of β-cells, most of which had returned to their rounded shape, and serous acini were completely normal. The islets that cover the connective tissue have also mostly retained their form and returned to their original texture **(Fig. 9 C)**.

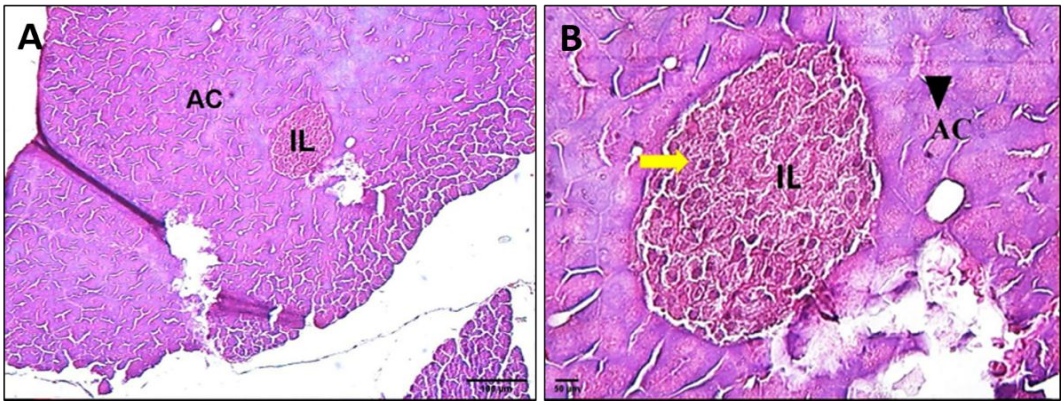

Fig. 7: (A-B), Photomicrograph of pancreatic section of the healthy mice showing prominent cytoplasm in Islet cells within islets of Langerhans (IL) and in serous acini cells with clear basal basophilia and apical acidophilia (AC).

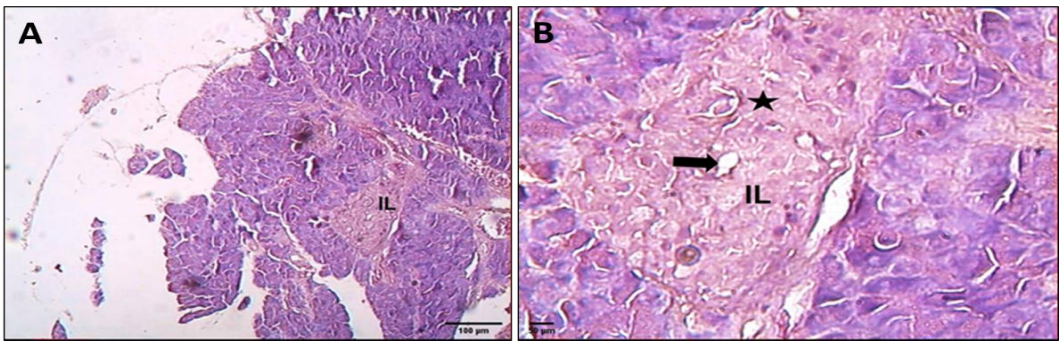

Fig. 8: (A-B), Photomicrograph of pancreatic section of diabetic mice showing degeneration and atrophy islets of Langerhans (IL), disruption of the Islet cells, and presence of necrotic areas, vacuolated cells within the islets.

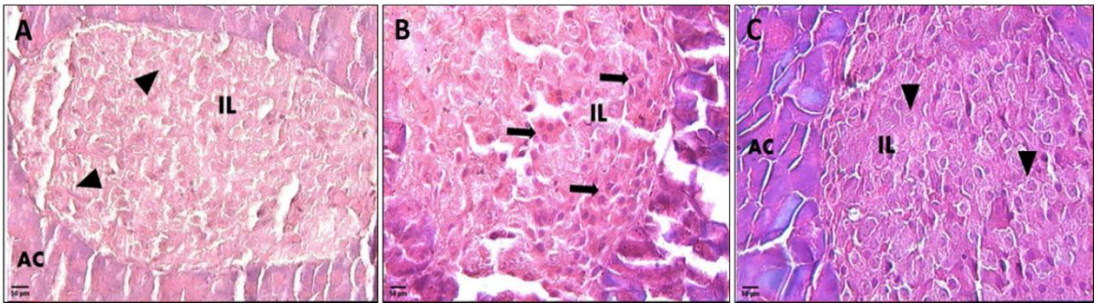

Fig. 9: Photomicrograph of *Moringa*-treated mice pancreatic section **(A),** Atrophy and degeneration of islets (IL) with minimization of the vacuolation and necrosis, and slight increase of cells with abundant eosinophilic cytoplasm and central small nuclei. **(B),** Absence of atrophy of islets of Langerhans (IL) and recovery of most normal acinar cells (AC), increased number of cells with abundant eosinophilic cytoplasm and central small nuclei, and islets size and covering connective tissue sheet was relatively restored (IL). **(C),** Increased number and abundant eosinophilic cytoplasm and central small nuclei, most of these cells restored their rounded shape, serous acini are completely normal. The islets covering connective tissue also relatively stored and regain its normal texture restored islets shape.

Discussion

The main goal of diabetes management is to get blood glucose levels back within normal limits. For this reason, there are several hypoglycemic drugs available; however, the majority of them have severe side effects. As a result, some diabetics frequently go back to medicinal plants and foods that have antidiabetic action but little or no side effects, and others combine traditional anti-diabetic medications with anti-diabetic herbs for improved glycemic control [48]. In a therapeutic context, more potent novel drugs with demonstrated pan-target efficacy and long-term safety could be very beneficial for patients with concomitant relevant lipid and glucose metabolic problems. These findings open the door to the development of medications to treat long-term multigene metabolic and cardiovascular diseases, for which there is now little to no therapy [49].

A significant potential for counterbalancing metabolic disruptions is provided by the phytochemicals found in plant products. There have been reports of several phytomolecules derived from different plant sources that are strong hypoglycemic agents. These include flavonoids, phenolic compounds, alkaloids, glycosides, saponins, glycolipids, dietary fibers, polysaccharides, peptidoglycans, sugars, and amino acids. In this study, the GC-MS analysis revealed a diverse group of widely distributed secondary metabolites that detected in *M. oleifera* extract, of which the most abundant fifteen compounds have been demonstrated a wide range of medical activities, such as antimicrobial, anti-inflammatory, anticancer, antioxidant, antidiabetic, anti-adipogenic, antidyslipidemia, antiradical, antihyperglycemia [30,33-36,39-41,45,47].

The GC-MS analysis in this work revealed detection of Acetyl valeryl, Acetin, and 13-Hexyloxacyclotridec-10-en-2-one. These compounds have been reported as antioxidant compounds [35-37,47]. The *M. oleifera* extract exhibited IC50 value of 11.53 µg/mL in this investigation. When in moderate amounts, reactive oxygen species (ROS) have beneficial effects for the body. However, when ROS production reaches a certain level, it leads to oxidative stress [50]. Protection against ROS damage can be obtained through the expression of the body's antioxidant systems or by supplementing with antioxidants from the outside [51]. The body uses ROS from regular cell redox activities, such as superoxide anion, hydroxyl radicals, nitric oxide, and hydrogen peroxide, to protect itself from additional harm during infections, inflammation, and several other diseases [52,53]. Plant-derived natural extracts and chemicals can be supplemented to enhance the regulation of ROS defense. Reports have indicated that a number of therapeutic plants can serve as external antioxidant sources, included among them is *M. oleifera*.

This study examined the histological impact on the pancreatic islets as well as the antidiabetic efficacy of different dosages of the methanol extract of Libyan *M. oleifera* leaves.

The results demonstrated that, in a dose- and time-dependent way, the methanol extract of *M. oleifera* leaves significantly reduced the blood glucose level in Alloxan-induced hyperglycemic mice. These results may be attributed to the presence of some compounds such as Acetin, Palmitic acid, and 13-Hexyloxacyclotridec-10-en-2-one, which have been detected in the GC-MS analysis. These compounds have been reported as antidiabetic, antidyslipidemia, and antihyperglycemia [36,45]. This is consistent with the findings of other researchers who have methodically shown that plant extracts (leaves, flowers, and seeds) have anti-diabetic qualities [54].

In a managed investigation with untreated type 2 diabetes patients (T2DM), William et al. [55] reported the anti-hyperglycemic activity of the *M. oleifera* leaves. The hypoglycemic effect of *M. oleifera* leaf dietary consumption in T2DM patients was also examined [56], and the glucose level has been significantly reduced after a 40-day period. The comparatively high antioxidant activity of the leaves, flowers, and seeds of *M. oleifera* has been linked to the medicinal effects of the plant [10,57]. Quercetin and kaemferol, in particular, are two of the potent antioxidant phytochemicals have been detected in *M. oleifera* leaves [58,59]. Many medicinal plants' kaemferol derivatives have been shown to exhibit hypoglycemic action[60,61].

These antioxidants in the extract may have contributed to the regeneration of the beta cell, which resulted in the release of insulin and a decrease in blood sugar levels, by scavenging and blocking the free radicals produced by alloxan. The extract may have also inhibited the ATP-sensitive potassium channels in the membrane of the remaining beta cells, which would have resulted in the release of insulin and anti-hyperglycemic action. Moreover, the extract may have enhanced the ability of insulin to promote the absorption and use of glucose by many tissues, including the skeletal muscle, adipose tissue, and liver. In this work, it became apparent that the *M. oleifera* methanol extract's antihyperglycemic effect in alloxan-induced diabetic mice was dose- and time-dependent. The antihyperglycemic impact of the 300 mg/kg dosage was greater than that of the 100 mg/kg low dose. The diabetic group was administered the *M. oleifera* leaf extract on several occasions until their blood sugar levels stabilized. Furthermore, the glycemic state was preserved and there was no hypoglycemia impact from the *Moringa* extract in the healthy mice with normal blood sugar. These findings are consistent with a research by Tende et al. [62], which found that *M. oleifera* alone causes hypoglycemia in diabetic rats induced with streptozotocin, but not in rats with normal blood sugar levels.

Alloxan destroys the ß-cells in the islets of Langerhans, which results in a significant decrease in the secretion of insulin. The chemical components of different plants, such as carbohydrates, phenolics, flavonoids, alkaloids, saponins, and glycosides, help the islet recover and increase the amount of insulin secreted by the pancreas from the Langerhans islet [63]. In this research, the histopathological pancreatic sections of non-diabetic control mice revealed normal histological architecture of pancreatic islets and acini. Langerhans islets were seen amid pancreatic acini as compact spherical to oval masses with well grouped Islet cells, the lack of necrosis and vacuolation inside it and its surrounding exocrine pancreatic cells. On the other hand, sections from alloxanized-diabetic group showed atrophy and degeneration of islets, as well as disruption of the islet cells with the presence of vacuolation and necrotic regions inside the islet, and the size and quantity of pancreatic islets were seen to be reduced. These findings are consistent with previously results [64,65].

The groups treated with MO extract showed variable degrees of healing from the Alloxan attack on pancreatic islets, according to the histological study in the present work. Notably, the islet cell volume density, proportion of β cells, and size all revealed significant histoarchitectural reversal of damage in the groups that received plant extracts. This observation may be construed as indicative of both regeneration and β-cell restoration, perhaps leading to elevated insulin release and adjusted blood glucose levels. The pancreatic acinar cells and islets of Langerhans exhibited shrinkage and degeneration in the low dose treatment group (100 mg/kg); nevertheless, there was a slight improvement in the minimizing of vacuolated islets cells. This is illustrated by using all dosages; however, larger doses generally result in better outcomes. The outcomes align with the research conducted by Nada et al. [66].

The group receiving treatment at an intermediate dose of 200 mg/kg showed no signs of islets of Langerhans atrophy and

recovered most of the normal acinar cells. Additionally, there was an increase in the number of abundant eosinophilic cytoplasm and central small nuclei cells, and the size and covering connective tissue sheet of the islets were relatively restored. These results are compatible with that reported by [66,67]. They stated that in terms of the pancreatic tissue of diabetic rats, there was no discernible improvement in the groups treated with 190 and 225 mg/kg. In contrast, the high dose treatment group (300 mg/kg) in this trial showed notable improvement and rejuvenation, with regular islet cells and a considerable rise in the number of β-cells as well as restored pancreatic islet size.

Conclusions

Methanol was used to extract Libyan *Moringa oleifera* leaves, and the bioactive components were evaluated by GC-MS analysis. *M. oleifera* demonstrated antioxidant activity in comparison to ascorbic acid and anticancer activities against the wi38 human lung cell line. The antidiabetic activity of *M. oleifera* extract was tested using an Alloxan-induced diabetes model in Swiss albino mice to determine its effect on blood sugar concentration and pancreatic islet histology. The study stated that the extract did not cause hypoglycemia in the group of normoglycemic mice. Blood glucose levels were significantly lower at 200 and 300 mg/kg, with the 300 mg/kg dose being particularly effective. Moreover, consuming the extract on a daily basis reduced blood sugar levels. The high dose of 300 mg/kg resulted in a significant decline in fasting blood sugar by the end of the fourth week, without endangering hypoglycemia. The recovery from the Alloxan assault, as well as some signs of islet and acin regeneration, were determined. After eating 300 mg/kg of *M. oleifera* extract, the shape and acini of the pancreatic islets changed noticeably. Notably, they were larger and more regenerated, with a considerable rise in the quantity of round-shaped β-cells. The current research supports the idea of using this plant as a healthy supplement or ingredient in food preparation.

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تحليل GC-MS وتقييم خصائص مضادات الأكسدة والسرطان والسمية الخلوية ونقص السكر في الدم لمستخلص أوراق المورينجا الليبية على مرض السكري الناجم عن الألوكسان في الفئران

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تم تحديد المورينغا أوليفيرا كنبات له فوائد صحية عديدة، بما في ذلك الخصائص الغذائية والطبية مثل الأحماض الأمينية والكاروتينات والمكونات الغذائية. تم استخدام الميثانول لاستخراج أوراق المورينغا أوليفيرا الليبية، وتم تحديد الخصائص المضادة للبكتيريا، ومضادات الأكسدة، والمضادة للالتهابات، والمضادة للسرطان للمكونات النشطة بيولوجيا باستخدام قياس الطيف الكتلي للغاز اللوني (GC-MS). أظهرت المورينغا أوليفيرا نشاطًا مضادًا للأكسدة عند IC50 قدره ١١.٥٣ ميكروغرام/مل. انخفضت صلاحية خلايا Wi38 مع زيادة تركيزات مستخلص المورينغا أوليفيرا ، في حين زادت السمية الخلوية مع IC50 بقيمة ٣٩٣.٤١ ± ٧.٧٧ ميكروغرام / مل. تم تنفيذ نموذج مرض السكري الناجم عن الألوكسان في الفئران البيضاء السويسرية. تم تقييم ثلاث جرعات مختلفة (١٠٠، ٢٠٠، أو ٣٠٠ ملغم/كغم من وزن جسم الفئران) من مستخلص المورينغا أوليفيرا لتأثيرها على تركيز السكر في الدم وأنسجة البنكرياس. لم تعاني المجموعة ذات مستوى سكر الدم الطبيعي من نقص السكر في الدم نتيجة تناول المستخلص. انخفضت مستويات الجلوكوز في الدم بشكل ملحوظ عند ٢٠٠ و ٣٠٠ ملغم / كغم، خاصة عند تناول جرعة ٣٠٠ ملغم / كغم. أدت الجرعة ٣٠٠ ملغم/كغم إلى انخفاض كبير في نسبة السكر في الدم أثناء الصيام بحلول الأسبوع الرابع دون تعريض نقص السكر في الدم للخطر. أدى إعطاء ١٠٠ و٢٠٠ ملغم/كغم من مستخلص المورينغا أوليفيرا إلى مجموعة مراقبة مرضى السكري إلى تعافي متنوع من هجوم الألوكسان وتجديد الجزر والحويصلات. خضع مورفولوجيا وعنيبات الجزر البنكرياسية لتعديل كبير بعد تناول ٣٠٠ ملغم/كغم من مستخلص المورينغا أوليفيرا. وكانت أكبر حجمًا وأكثر تنشيطا بشكل ملحوظ، كما زاد عدد خلايا بيتا التي اتخذت شكلا كرويًا بشكل ملحوظ. تدعم النتائج الحالية مفهوم استخدام هذا النبات كمكمل غذائي أو عنصر في إعداد الطعام.