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The Effect of Ethanol Extract of Ziziphus Mauritiana Lam. Leaf on Alloxan-Induced Rat

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Abstract: Bidara (Ziziphus mauritiana Lam.) or Indian jujube or ber is one Indonesian endemic plant which widely used as a traditional remedy in Indonesia and other Asian countries. Bidara leaves are commonly used as a remedy for diarrhea, liver diseases, and diabetes. This study aims to determine the effect of ethanol extract of bidara leaves (Z. mauritiana Lam.) on alloxan-induced male Wistar strain rat's (Rattus norvegicus) liver. This is an experimental study with a randomized pretest-posttest with a control group design. This study involved 24 male Wistar strain rats (R. norvegicus) which were divided into 6 separate groups induced with alloxan and each group received a different intervention accordingly. Data in this study shows that ethanol extract of bidara leaves contains alkaloids, saponins, flavonoids, and glycoside compounds. This study also found that ethanol extract of bidara leaves at doses as low as 150 mg/kgBW managed to decrease the blood glucose, SGOT, and SGPT levels better than negative control and as effective as metformin. Escalation of SOD activity was also found to be

directly proportional to dose increase, however, the highest concentration of MDA was also found in the highest dose of ethanol extract of bidara leaves. It can be concluded that ethanol extract from bidara leaves has anti-hyperglycemic ($p<0.001$) and hepatoprotective ($p<0.05$) effects, but the antioxidant properties cannot be determined according to this study's data

INTRODUCTION

Data from The Global Burden of Disease 2021 found that around 525 million people across the globe have diabetes mellitus, of which 24 million were newly diagnosed in 2021 [1]. Meanwhile, the International Diabetes Federation (IDF) projected that by 2045, the number of people living with diabetes mellitus will exceed 780 million [2]. Diabetes mellitus, a condition of constant high blood glucose [3] promotes oxidative stress across all cells in the body, from cells in the blood vessels to cells of specific organs like the liver [4]. This oxidative stress is possible to manage either by controlling the blood glucose level, hence preventing oxidative stress promotion; or by introducing antioxidants into the system [5].

[1] GBD 2021 Diabetes Collaborators, "Global, Regional, and National Burden of Diabetes from 1990 to 2021, with Projections of Prevalence to 2050: A Systematic Analysis for the Global Burden of Disease Study 2021," *Lancet* 402, no. July (2023), https://doi.org/10.1016/S0140-6736(23)01301-6.

[2] International Diabetes Foundation, *IDF Diabetes Atlas*, 10th ed. (Brussels: International Diabetes Foundation, 2021).

[3] Roshan Kumar et al., "A Review on Diabetes Mellitus: Type 1 & Type 2," *World Journal of Pharmacy and Pharmaceutical Sciences* 9, no. 10 (2020): 838–50, https://doi.org/10.20959/wjpps202010-17336.

[4] Eleftheria Papachristoforou et al., "Association of Glycemic Indices (Hyperglycemia, Glucose Variability, and Hypoglycemia) with Oxidative Stress and Diabetic Complications Eleftheria," *Journal of Diabetes Research* 2020 (2020), https://doi.org/10.1155/2020/7489795; Andrés García-sánchez, Alejandra Guillermina Miranda-díaz, and Ernesto Germán Cardona-muñoz, "The Role of Oxidative Stress in Physiopathology and Pharmacological Treatment with Pro- and Antioxidant Properties in Chronic Diseases," *Oxidative Medicine and Cellular Longevity* 2020 (2020), https://doi.org/10.1155/2020/2082145.

[5] Barinta Widaryanti, Nur Khikmah, and Nunung Sulistyani, "Efek Rebusan Sereh (Cymbopogon Citratus) Terhadap Respon Stress Oksidatif Pada Tikus Wistar Jantan (Rattus Norvegicus) Diabetes," *Life Science* 10, no. 2 (2021): 173–81, https://doi.org/10.15294/lifesci.v10i2.54457; Sema Demirci-Çekiç et al., "Biomarkers of

Diabetes treatment involves various approaches, both through conventional medical therapy and the use of natural or herbal medicines. One alternative treatment that is starting to be recognized is the use of *Ziziphus mauritiana Lam. Ziziphus mauritiana Lam.* leaf extract has been studied to have hypoglycemic effects, which is the ability to lower blood sugar levels[6]. *Ziziphus mauritiana Lam.* fruit ethanol has been found to have inhibitory activity against α-glucosidase enzyme, which makes it potentially useful as an antidiabetic agent. The α-glucosidase enzyme is an enzyme that plays a role in the process of carbohydrate digestion into glucose in the intestine. By inhibiting this enzyme, the absorption of glucose into the blood can be slowed down, which ultimately helps to lower blood sugar levels after meals [7].

Based on its antioxidant content, *Ziziphus mauritiana Lam.* has the potential to help manage diabetes mellitus by reducing oxidative stress and helping regulate blood sugar levels[8]. This study aimed to evaluate the antidiabetic effect of ethanol extract of *Ziziphus mauritiana Lam.* leaves in alloxan-induced rats. Although research in Indonesia has investigated the phytochemical properties of *Z. mauritiana Lam*., studies focusing on the antidiabetic effect are still limited[9].

Oxidative Stress and Antioxidant Defense," *Journal of Pharmaceutical and Biomedical Analysis* 209 (2022): 114477, https://doi.org/https://doi.org/10.1016/j.jpba.2021.114477.

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[7] Pratiwi, N. (2023). Aktivitas Antidiabetes Ekstrak Etanol Buah Bidara Ziziphus Mauritiana Lam. Secara In Vitro Melalui Penghambatan α–Glukosidase (Tesis, Fakultas Sains dan Teknologi, UIN Syarif Hidayatullah Jakarta). Retrieved from https://repository.uinjkt.ac.id/dspace/handle/123456789/72905

[8] Nur Syamsi Dhuha, Haeria Haeria, and Hardiyanti Eka Putri, "Toksisitas Akut Ekstrak Etanol Daun Bidara (Ziziphus Spina-Christi L.) Berdasarkan Gambaran Morfologi Dan Histologi Hati Mencit," *Ad-Dawaa' Journal of Pharmaceutical Sciences* 2, no. 1 (2019), https://doi.org/10.24252/djps.v2i1.6706.

[9] Elsya Nurul Mauludiyah, Fitrianti Darusman, and Gita Cahya Eka Darma, "Skrining Fitokimia Senyawa Metabolit Sekunder Dari Simplisia Dan Ekstrak Air Daun Bidara Arab (Ziziphus Spina-Christi L.)," *Prosiding Farmasi* 6, no. 1 (2020), https://doi.org/10.29313/.v6i2.24325; Farida Iriani et al., "Analisis Fitokimia Buah Bidara Arab (Ziziphus Mauritiana) Pada Lahan Tropika Basah Kota Bandung," *Gunung Djati*

THEORETICAL BASIS

Diabetes mellitus is a chronic non-communicable disease that is the result of the inability of the pancreas to secrete enough insulin and/or when the cells cannot utilize the insulin effectively [10]. American Diabetes Association defined diabetes mellitus as a complex chronic disease marked by hyperglycemia due to a disorder in insulin secretion, action, or both [11]. This chronic hyperglycemia in turn linked to multiple organ dysfunction and failure, especially in the eyes, kidneys, nerves, heart, and blood vessels [12]. This chronic hyperglycemia in turn disrupts multiple metabolisms in the body, among them are lipid and carbohydrate metabolism [13]. One of the reasons why hyperglycemia induces many complications is because glucose is an aldohexose, which is a moderately reactive oxygen species (ROS), hence moderately propagating oxidative stress in the body [14].

Several experimental studies found that diabetes-induced liver damage physiologically, histologically, and anatomically and found that diabetes mellitus and non-fatty liver disease are linked through interactions among hepatic inflammation, oxidative stress, and free-fatty acids accumulation; all of which is the result of metabolic disruption due to

Conference Series 38 (2024); Titik Dwi Sulistiyawati and R Adharyan Islamy, "Phytochemical Characteristics and Antimicrobial Activity of Medical Plant Zizyphus Mauritiana against Pseudomonas Fluorescens," *Ecology, Environment & Conservation* 27, no. November Suppl. (2021); Ami Febriza et al., "Antibacterial Effects of Ziziphus Mauritiana Lam Leaf Extract Against Vibrio Cholerae," *Herb-Medicine Journal* 5, no. 3 (2022): 9–13.

[10] Dhanny E P Lagarense, Windy M V Wariki, and Aaltje E Manampiring, "Analisis Faktor Risiko Yang Berhubungan Dengan Kejadian Diabetes Melitus Tipe 2 Di Kabupaten Morowali Utara," *Jurnal Kesehatan Tambusai* 4 (2), no. 4 (2023): 1587–97.

[11] American Diabetes Association, "Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetesd2021," *Diabetes Care* 44, no. January (2021): 15–33, https://doi.org/10.2337/dc21-S002.

[12] Lagarense, Wariki, and Manampiring, "Analisis Faktor Risiko Yang Berhubungan Dengan Kejadian Diabetes Melitus Tipe 2 Di Kabupaten Morowali Utara."

[13] Wahyu Widowati et al., "Antidiabetic and Hepatoprotection Effect of Butterfly Pea Flower (Clitoria Ternatea L.) through Antioxidant, Anti-Inflammatory, Lower LDH, ACP, AST, and ALT on Diabetes Mellitus and Dyslipidemia Rat Wahyu," *Heliyon* 10, no. 8 (2024): e29812, https://doi.org/10.1016/j.heliyon.2024.e29812.

[14] Patricia Gonzalez et al., "Hyperglycemia and Oxidative Stress: An Integral, Updated and Critical Overview of Their Metabolic Interconnections," *International Journal of Molecular Sciences* 24, no. 9352 (2023).

insulin resistance or hyperglycemia [15]. The study also found that hyperglycemia propagates oxidative stress which in turn damages the β cell of the pancreas. This process induced the activation of protein kinase C and NK-κB which resulted in peroxide overexpression and further increased lipid peroxidation [16].

Diabetes treatment can be through conventional medical therapy or the use of natural or herbal medicines. One alternative treatment that is starting to be recognized is the use of *Ziziphus mauritiana Lam.*. *Ziziphus mauritiana Lam*. leaf extract has several bioactive compounds, such as flavonoids, saponins, and phenolics, which can reduce blood glucose levels through various mechanisms. These compounds can increase insulin sensitivity, so that body cells are more efficient in absorbing glucose from the blood. In addition, the saponins in Bidara leaves inhibit the α-glucosidase enzyme, which slows the absorption of glucose in the intestines and prevents blood sugar spikes after meals [17]. *Ziziphus mauritiana Lam*. leaf extract can also stimulate insulin secretion from the pancreas, helping the body manage blood glucose levels. The antioxidant and anti-inflammatory properties of flavonoids and phenolics also play a role in reducing oxidative stress and inflammation, which are associated with insulin resistance. Bidara leaf extract works through various pathways to help lower blood

[15] Chengyu Shi et al., "Diabetes Induces Hepatocyte Pyroptosis by Promoting Oxidative Stress-Mediated NLRP3 Inflammasome Activation during Liver Ischaemia and Reperfusion Injury," *Annals of Translational Medicine* 8, no. 12 (2020): 1–12, https://doi.org/10.21037/atm-20-1839; Sylwia Ziolkowska et al., "The Interplay between Insulin Resistance, Inflammation, Oxidative Stress, Base Excision Repair and Metabolic Syndrome in Nonalcoholic Fatty Liver Disease," *International Journal of Molecular Sciences* 22, no. 11128 (2021); Margalida Monserrat-mesquida et al., "Metabolic Syndrome Is Associated with Oxidative Stress and Proinflammatory State," *Antioxidants* 9, no. 236 (2020).

[16] Widowati et al., "Antidiabetic and Hepatoprotection Effect of Butterfly Pea Flower (Clitoria Ternatea L.) through Antioxidant, Anti-Inflammatory, Lower LDH, ACP, AST, and ALT on Diabetes Mellitus and Dyslipidemia Rat Wahyu."

[17] Siregar, M. (2020). Berbagai manfaat daun bidara (Ziziphus mauritiana Lamk) bagi kesehatan di Indonesia: Meta-analisis. Jurnal Pandu Husada, 2(1), 75-81. https://doi.org/10.30596/jph.v1i2.4415

sugar levels, but its use must be medically supervised to ensure its safety and effectiveness [18].

Ziziphus mauritiana Lam. leaf extract, as a natural product, offers advantages such as fewer side effects and the ability to work through multiple mechanisms, including improving insulin sensitivity and inhibiting glucose absorption. However, its effectiveness may vary due to lack of standardization and limited research. In contrast, conventional antidiabetic drugs such as metformin and sulfonylureas have been clinically tested at standardized doses, providing more consistent blood sugar control and can be medically monitored. Nonetheless, these drugs can cause significant side effects and may be expensive. *Ziziphus mauritiana Lam.* leaf extract can be a useful complementary therapy, but the use of conventional drugs remains more reliable for effective and safe diabetes management [19].

Although *Ziziphus mauritiana Lam.* leaf extract has potential as an antidiabetic therapy with benefits such as fewer side effects than conventional drugs, it is important to pay attention to potential side effects, especially if used long-term. The use of this extract may cause allergic reactions in some individuals, such as rashes or hives, and may cause gastrointestinal disturbances such as nausea or diarrhea if taken in high doses. In addition, Bidara leaf extract may interact with other diabetes medications, which risks increasing side effects or causing hypoglycemia. Therefore, it is important to use *Ziziphus mauritiana Lam.* leaf extract with proper medical supervision to monitor the body's reaction and ensure safe and effective therapy [20]

[18] Hermawati, I. N., Nursape'i, N. D., Maharani, S., Astriani, T., Kusniasih, N., & Harun, N. (2022). Podcast (Potency of Bidara (Ziziphus mauritiana) special plant as a destroyer of COVID-19). Jurnal STIKES Muhammadiyah Ciamis: Jurnal Kesehatan, 9(1), 6-15.

[19] Sabela, V., Farida, I., & Yuliastuti, C. (2023). Efektivitas wound cleansing daun bidara Arab (Ziziphus spina-christi L.) terhadap penyembuhan diabetic foot ulcer. Jurnal Ilmiah Keperawatan STIKES Hang Tuah Surabaya, 9(1), 135-143.

[20] Wahyudi, W., Putri Hsb, H. L., Hasanah, N., & Sitorus, R. A.-H. (2022). Studi literatur: Daun bidara (Ziziphus mauritiana) sebagai herbal Indonesia dengan berbagai kandungan dan efektivitas farmakologi. Farmanesia, 9(1), 22-27.

Ziziphus mauritiana Lam. leaf extract showed a dose-dependent blood sugar level lowering effect in male Wistar rats, with significant results observed at various concentrations. The study showed that increasing doses of *Ziziphus mauritiana Lam.* leaf extract were associated with greater reductions in blood glucose levels, indicating that higher doses of the extract provided more effective blood sugar lowering effects. These findings indicate the potential of *Ziziphus mauritiana Lam.* leaf extract as an antidiabetic therapy, but further studies in humans are needed to confirm its overall safety and effectiveness [21].

RESEARCH METHODS

This study is an experiment study with the post-test only with a control group design. This study aims to determine the anti-hyperglycemic and hepatoprotective properties of *Z. mauritiana Lam* leaves. The design and protocol employed in this study have been reviewed and approved by the Research Ethics Committee of Prima Indonesia University. This study uses rats (*Rattus norvegicus*) as the experiment subjects. The number of rats used in this study was 24 rats (calculated using Federer's formula). This experiment subject was divided into six groups of four consisting of two control groups and four groups that received *Z. mauritiana Lam*. leaves ethanol extract (ZLEE) with different dosages. The material used in this study consists of leaves of *Z. mauritiana Lam.* known locally in North Sumatera as bidara, ethanol, NaCMC, metformin, and alloxan.

The torbangun leaves extraction process began with adding 100 grams of powdered *Z. mauritiana Lam* leaves in a container followed by 1 liter of 96% ethanol. This mixture was mixed continuously for 6 hours, and stored in a dark chamber for 18 hours. After 18 hours, the mixture passed through a filter, producing the first filtrate and residue. The residue was then reused for the second maceration, adding only 0.5 liters of 96% ethanol,

[21] Pratiwi, N. (2023). Aktivitas Antidiabetes Ekstrak Etanol Buah Bidara Ziziphus Mauritiana Lam. Secara In Vitro Melalui Penghambatan α–Glukosidase (Tesis, Fakultas Sains dan Teknologi, UIN Syarif Hidayatullah Jakarta). Retrieved from https://repository.uinjkt.ac.id/dspace/handle/123456789/72905

producing the second filtrate. Both filtrates were then mixed and the ethanol was removed by evaporation using a rotary evaporator at 40^{o}C temperature, ended with thick and high concentration *Z. mauritiana Lam.* leaves extract. This extract was then qualitatively screened for its phytochemical contents.

During this study, all experiment subjects were kept in polypropylene containers with a controlled environment. Before alloxan was administered to all experiment subjects, the blood glucose of every experiment subject was measured and documented. Alloxan was administered intraperitoneally with 130 mg/kgBW dosage and the blood glucose was measured three days after alloxan administration. After the hyperglycemia condition was established, all experiment subjects received intervention according to their group: the first group (negative control) received 1% NaCMC, the second group (positive control) received metformin with 500 mg/kgBW dosage, and the last four groups each receive ZLEE with 50, 150, 300, and 500 mg/kgBW dosage, respectively.

The blood glucose of every experiment subject was measured and documented regularly every three days. After the final measurement and documentation on the 28th day, the experiment subject was euthanized. After the euthanasia, a final biological sample of blood. This blood was collected for biochemical study of SGOT and SGPT levels, along with SOD and MDA study. Data analysis in this study was conducted using ANOVA.

RESULTS AND DISCUSSION

Z. mauritiana Lam. is a species from the Rhamnaceae family which native to Africa, South Asia, South East Asia, China, and Australia [22]. *Z. mauritiana Lam.* is an evergreen shrub that can grow up to 15 meters tall, with jagged leaves [23]. *Z. mauritiana Lam.* also has a small flower with color ranging from yellow, white, or greenish-white, which if pollinated develops

[22] Deepak Jha et al., "Ziziphus Mauritiana : An in-Depth Review of Its Medicinal Attributes and Pharmacological Activities," *Intelligent Pharmacy*, no. December (2023), https://doi.org/10.1016/j.ipha.2023.12.001.

[23] Jha et al.

into an oblong-shaped fruit with color ranging from red, yellowish-brown, or white with a distinctive smell [24].

Table 1 *Z. mauritiana Lam.* Qualitative Phytochemical Analysis

Compounds	Reagent	Result
Alkaloids	Bouchardath	Not Detected
	Mayer	Not Detected
	Dragendroff	Detected
	Wagner	Detected
Steroids	Salkowski	Not Detected
Triterpenoids	Lieberman-Burchard	Not Detected
Saponins	Aquadest + Alcohol 96%	Detected
Flavonoids	$FeCl_3$ 5%	Detected
	$Mg_{(s)} + HCl_{(p)}$	Not Detected
	NaOH 10%	Not Detected
	$H_2SO_{4(p)}$	Not Detected
Tannins	$FeCl_3$ 1%	Detected
Glycosides	Molisch	Detected

The phytochemical analysis of *Z. mauritiana Lam.* leaves performed by the Organic Chemistry Laboratory of the Faculty of Mathematics and Natural Sciences of North Sumatera University found that *Z. mauritiana Lam.* leaves contain alkaloids, saponins, flavonoids, tannins, and glycosides compounds (Table 1). Multiple phytochemical studies found that *Z.* mauritiana Lam. contains flavonoids, alkaloids, terpenoids, pectin, terpenoids, and saponins in multiple parts of the plants; leaves, roots, bark, and fruit [25].

[24] Jha et al.

[25] Safaet Alam et al., "Antidiabetic Potential of Commonly Available Fruit Plants in Bangladesh : Updates on Prospective Phytochemicals and Their Reported MoAs," *Molecules* 27, no. 8709 (2022): 1–45, https://doi.org/10.3390/molecules27248709; Om Prakash and Ruchi Singh, "A Panoramic View on Phytochemical, Nutritional, and Therapeutic Attributes of Ziziphus Mauritiana Lam.: A Comprehensive Review," *Phytotherapy Research*, no. January (2020): 1–15, https://doi.org/10.1002/ptr.6769; Syed Zameer Hussain et al., *Fruits Grown in Highland Regions of the Himalayas: Nutritional and Health Benefits* (Cham: Springer Nature Switzerland, 2021); Sarah T Sakna et al., "Phytochemical Diversity and Pharmacological Effects of Triterpenes from Genus Ziziphus : A Comprehensive Review," *Phytochemistry Reviews* 22 (2022): 1611–36, https://doi.org/10.1007/s11101-022-09835-y; Mohan Kumar, Yamini Dhayanandamoorthy, and Shiyam Sundar, "HPLC-ESI-QqQ Based Standardization,

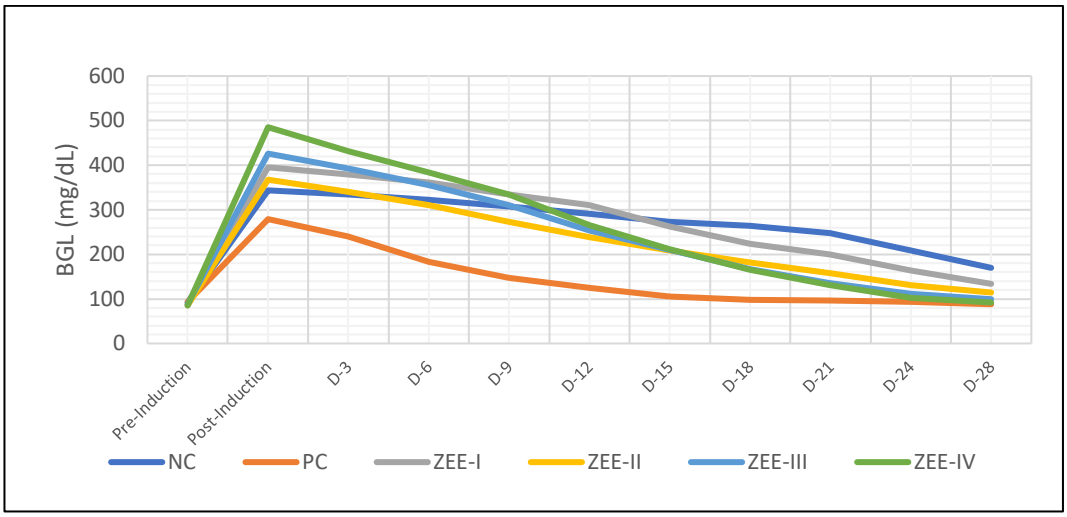

Figure 1 Blood Glucose Level Change During the Experiment (BGL: Blood Glucose Level; NC: Negative Control; PC: Positive Control; ZLEE-I: *Z. mauritiana Lam* leaves ethanol extract 50 mg/kgBW; ZLEE-II: *Z. mauritiana Lam* leaves ethanol extract 150 mg/kgBW; ZLEE-III: *Z. mauritiana Lam* leaves ethanol extract 300 mg/kgBW; ZLEE-IV: *Z. mauritiana Lam* leaves ethanol extract 500 mg/kgBW)

All experiment subjects were found to develop hyperglycemia on the third day following the administration of alloxan. After receiving its respective intervention, the blood glucose level appears to constantly

Mutagenic and Genotoxic Potential of Methanol Extract of Ziziphus Mauritiana Lam Leaves," *Journal of Ethnopharmacology* 246, no. August 2019 (2020): 112216, https://doi.org/10.1016/j.jep.2019.112216; Jha et al., "Ziziphus Mauritiana : An in-Depth Review of Its Medicinal Attributes and Pharmacological Activities"; Chardin Seri et al., "Saponins and Flavonoid Glycosides from the Leaves of Ziziphus Mauritiana Lam. Native of a Forest Area of Ivory Coast," *Phytochemistry Letters* 37, no. November 2019 (2020): 5–9, https://doi.org/10.1016/j.phytol.2020.03.001; S M Kamrul Hasan et al., "Proximate Composition, Minerals, Phytochemicals, and Functional Activities of Jujube Fruits Grown in Bangladesh," *Journal of Agriculture and Food Research* 8, no. March (2022): 100302, https://doi.org/10.1016/j.jafr.2022.100302; Tajudeen Owolarafe et al., "Toxicological Investigation of Aqueous Extract of Ziziphus Mauritiana Leaves on Wistar Rats," *International Journal of Traditional and Complementary Medicine Research* 3, no. 2 (2022): 91–100, https://doi.org/10.53811/ijtcmr.1056770; Ezzouhra El Maaiden et al., *Genus Ziziphus: A Comprehensive Review on Ethnopharmacological, Phytochemical and Pharmacological Properties*, *Journal of Ethnopharmacology* (Elsevier B.V., 2020), https://doi.org/10.1016/j.jep.2020.112950; Shumaila Zulfiqar Butt, Shabbir Hussain, and Khurram Shahzad Munawar, "Phytochemistry of Ziziphus Mauritiana: An Overview of Its Nutritional and Pharmaceutical Potential," *Scientific Inquiry and Review* 5, no. 2 (2021), https://doi.org/https://doi.org/10.32350/sir/52.

decreasing (Figure 1). Analysis of the data found that blood glucose data has a normal distribution and is homogenous ($p>0.05$), hence, ANOVA assumptions were fulfilled. Through ANOVA it was found that a significant difference in blood glucose level only appeared after the sixth day ($p<0.05$), so only data from the sixth day onward was included in the post-hoc test. Post-hoc test found that a significant difference with the negative only began to appear on the 12th day on the positive control ($p<0.05$). The significant difference only began to appear between the negative control and the extract on the 21st day for the 300 and 500 mg/kgBW dosage and on the 24th day for the 150 mg/kgBW ($p<0.05$); while the 50 mg/kgBW did not show any significant difference with the negative control to the 28th day ($p>0.05$). Beginning on the 21st day, the extract with 300 and 500 mg/kgBW dosage also has no difference with the positive control ($p>0.05$), while for the 150 mg/kg dosage it was at the 24th day; this can be interpreted as at this dosage, the extract performs as good as metformin in reducing blood glucose level.

This finding is in line with various studies that have found that *Z. mauritiana Lam.* leaf extract has anti-hyperglycemic or anti-diabetic effects [26]. Several experimental studies using either fruits, seeds, or leaves of *Z. mauritiana Lam.* plants, have found that the extracts have anti-hyperglycemic effects in models using alloxan-induced white rats at a minimum dose of 100 mg/kgBB (seed ethanol extract), 400 mg/kgBB (fruit

[26] Alam et al., "Antidiabetic Potential of Commonly Available Fruit Plants in Bangladesh : Updates on Prospective Phytochemicals and Their Reported MoAs"; Hasan et al., "Proximate Composition, Minerals, Phytochemicals, and Functional Activities of Jujube Fruits Grown in Bangladesh"; Sakna et al., "Phytochemical Diversity and Pharmacological Effects of Triterpenes from Genus Ziziphus : A Comprehensive Review"; Jha et al., "Ziziphus Mauritiana : An in-Depth Review of Its Medicinal Attributes and Pharmacological Activities"; Maaiden et al., *Genus Ziziphus: A Comprehensive Review on Ethnopharmacological, Phytochemical and Pharmacological Properties*; Saif Ali Siddiqui et al., "A Review on Ziziphus Mauritiana Plant," *World Journal of Pharmaceutical Research* 12, no. 22 (2023): 133–45, https://doi.org/10.20959/wjpr202322-30233; Khokon Miah Akanda and A. H. M. Nazmul Hasan, "Characterization of Pharmacological Properties of Methanolic Seed and Stem Bark Extracts of Ziziphus Mauritiana (BAU Kul) Using in-Vitro and in-Vivo Animal (Swiss Albino Male Mice) Model," *Clinical Phytoscience* 7, no. 8 (2021).

extract), or 300 mg/kgBB (leaf extract) [27]. Another study using mice (*Mus musculus*) showed that increasing the dose of *Z. mauritiana Lam.* bark extract and *Z. mauritiana Lam.* seed extract increased hypoglycemic activity in experimental animals characterized by a higher percentage reduction in blood sugar levels at higher doses [28]. This anti-hyperglycemic effect is probably produced by the content of alkaloid, flavonoid, and saponin compounds contained in the ethanol extract of *Z. mauritiana Lam.* leaves [29]. Compounds in these groups are known to have anti-hyperglycemic effects through various mechanisms either by inhibiting or stimulating the expression of various metabolic molecules such as AMP-Activated Protein Kinase (AMPK), Glucose Transporter 4 (GLUT4), Glycogen Synthase Kinase-3 (GSK3), Sterol Regulatory Element Binding Proteins 1 (SREBPl), Glucokinase (GK), Glucose-6-Phosphatase, Acetyl-CoA Carboxylase (ACC), Peroxisome Proliferator-Activated Receptor (PPAR) and Protein of Tyrosine Phosphatase-1B (PTPIB) [30].

Table 2 Post-Hoc Test of Blood Glucose Level Among All Groups

		p-value							
		D-6	D-9	D-12	D-15	D-18	D-21	D-24	D-28
NC	PC	0.424	0.116	0.031*	0.010*	0.005*	0.001*	0.001*	0.000*

[27] Prakash and Singh, "A Panoramic View on Phytochemical, Nutritional, and Therapeutic Attributes of Ziziphus Mauritiana Lam.: A Comprehensive Review"; Alam et al., "Antidiabetic Potential of Commonly Available Fruit Plants in Bangladesh : Updates on Prospective Phytochemicals and Their Reported MoAs."

[28] Akanda and Hasan, "Characterization of Pharmacological Properties of Methanolic Seed and Stem Bark Extracts of Ziziphus Mauritiana (BAU Kul) Using in-Vitro and in-Vivo Animal (Swiss Albino Male Mice) Model."

[29] Raghad Khalid Al-ishaq et al., "Flavonoids and Their Anti-Diabetic Effects: Cellular Mechanisms and E Ff Ects to Improve Blood Sugar Levels," *Biomolecules* 9, no. 430 (2019); Ijaz Muhammad et al., "Antidiabetic Activities of Alkaloids Isolated from Medicinal Plants," *Brazilian Journal of Pharmaceutical Sciences* 57, no. e19130 (2021), https://doi.org/10.1590/s2175-97902020000419130; Kushagra Dubey et al., "Anti-Diabetic and Antioxidant Potential of Saponin Extract of Leaves of Ziziphus Mauritiana," *Journal of Drug Delivery and Therapeutics* 9, no. 2-A (2019): 75–77.

[30] Al-ishaq et al., "Flavonoids and Their Anti-Diabetic Effects: Cellular Mechanisms and E Ff Ects to Improve Blood Sugar Levels"; Muhammad et al., "Antidiabetic Activities of Alkaloids Isolated from Medicinal Plants"; Dubey et al., "Anti-Diabetic and Antioxidant Potential of Saponin Extract of Leaves of Ziziphus Mauritiana."

	ZLEE-1	1.000	1.000	1.000	1.000	1.000	1.000	0.689	0.142
	ZLEE-II	1.000	1.000	1.000	1.000	0.593	0.110	0.025*	0.005*
	ZLEE-III	1.000	1.000	1.000	1.000	0.269	0.020*	0.003*	0.000*
	ZLEE-IV	1.000	1.000	1.000	1.000	0.247	0.016*	0.001*	0.000*
PC	NC	0.424	0.116	0.031*	0.010*	0.005*	0.001*	0.001*	0.000*
	ZLEE-1	0.106	0.039	0.012*	0.020*	0.049	0.045	0.063	0.026*
	ZLEE-II	0.654	0.461	0.373	0.321	0.577	0.836	1.000	0.671
	ZLEE-III	0.128	0.107	0.190	0.298	1.000	1.000	1.000	1.000
	ZLEE-IV	0.044*	0.038*	0.103	0.283	1.000	1.000	1.000	1.000

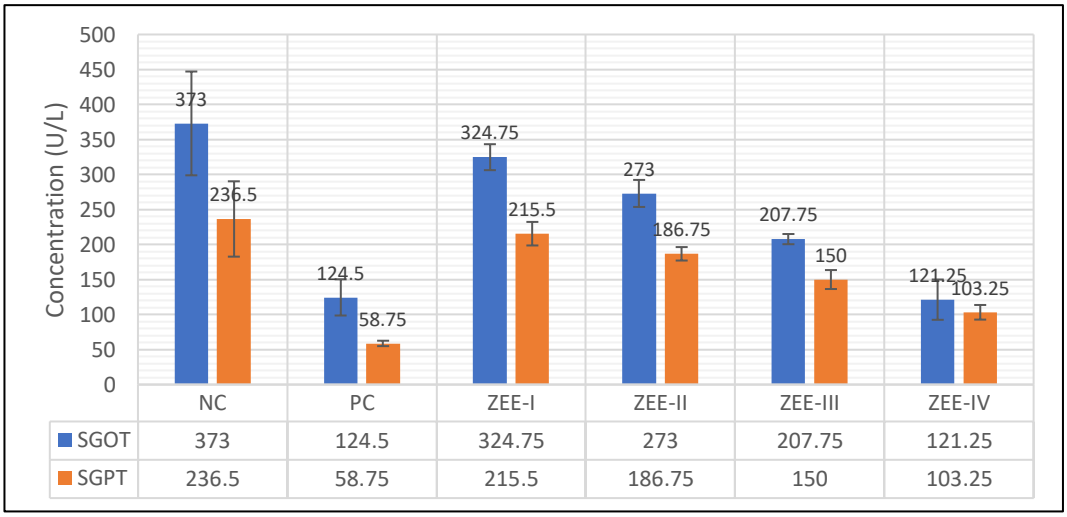

Figure 2 Liver Function Comparison Among All Groups

Graphically, all SGOT and SGPT levels across all extract groups were lower compared to the negative control although not as low as the positive control; the SGOT and SGPT levels were lower at higher extract dosages (Figure 2). On post-hoc tests, significant differences were only found between the SGOT level of positive control and extract with 500 mg/kgBW dosage with the negative control. Meanwhile, on the SGPT level,

except for the 150 mg/kgBW dosage, all other dosages showed significant differences with the positive control ($p<0.05$) but no difference with the negative control ($p>0.05$); since SGPT is more liver-specific than SGOT, the hepatoprotective property of ethanol extract of *Z. mauritiana Lam. leaves* cannot be determined.

In male rats (*R. norvegicus*), the normal value of SGOT is 74 to 143 IU/L, while the normal value of SGPT is 18 to 45 IU/L [31]. In the negative control group, the average SGOT concentration was 373 IU/L and SGPT was 236 IU/L, while in the positive control, the average SGOT concentration was 124.5 IU/L and SGPT was 58.75 IU/L. In the ZLEE groups, the average concentration of SGOT was between 121.25 to 324.75 IU/L and SGPT was between 103.25 to 215.5 IU/L. The findings in this study showed an increase in SGOT and SGPT concentrations in all experimental groups, regardless of the treatment each group received. This hepatotoxicity effect may be due to the induction of alloxan which is known to have selective toxic effects on the liver [32]. However, the hepatoprotective effect was also evident from the lower concentrations of SGOT and SGPT in the group that received ZLEE compared to the negative control group. Several studies suggest that *Z. mauritiana Lam.* extract has hepatoprotective properties through the effect of preventing oxidative stress and is characterized by improvements in biochemical markers such as SGOT, SGPT, MDA, SOD, LDH, and GSH-Pα [33]. Prakasha and Singh (2020) suggested tannins, saponins, and phenolic content of *Z.mauritiana Lam. are* most likely responsible for this hepatoprotective activity [34]. However, some studies show that *Z. mauritiana Lam.* extract has hepatotoxicity effects that can

[31] David M. Kurtz and Gregory S. Travlos, *The Clinical Chemistry of Laboratory Animals*, 3rd ed. (Boca Raton: CRC Press, 2018).

[32] Srikanta Guria and Madhusudan Das, "Diabetogenic Action of Alloxan on Liver Histopathology," *The Experiment* 28, no. 2 (2014): 1906–12.

[33] Hussain et al., *Fruits Grown in Highland Regions of the Himalayas: Nutritional and Health Benefits*; Prakash and Singh, "A Panoramic View on Phytochemical, Nutritional, and Therapeutic Attributes of Ziziphus Mauritiana Lam.: A Comprehensive Review"; Jha et al., "Ziziphus Mauritiana : An in-Depth Review of Its Medicinal Attributes and Pharmacological Activities."

[34] Prakash and Singh, "A Panoramic View on Phytochemical, Nutritional, and Therapeutic Attributes of Ziziphus Mauritiana Lam.: A Comprehensive Review."

cause inflammation [35]. Just like in this study, the *Z. mauritiana Lam.* leaves extract used in the study of Owolarafe and Kailani (2023) used ethanol as a solvent in the extraction process, where ethanol is known to have toxic properties to the liver [36].

Although there was an increase in SGOT and SGPT levels in all groups of test animals, histopathological examination of the liver tissue of all test animals did not show significant abnormal conditions, and there were no differences between all treatment groups. In the study of Owolarafe et al. (2022), *Z. mauritiana Lam.* leaves extract with distilled water solvent, at doses of 200 mg / kgBB and 400 mg / kgBB showed signs of inflammation and mild degeneration, but at doses of 100 mg / kgBB, 600 mg / kgBB, and 1000 mg / kgBB there were no significant pathological conditions in the liver tissue of the rats tested [37].

Table 3 Post-Hoc Test of Liver Functions, and Antioxidant and Lipid Peroxide Activities Among All Groups

		p-value			
		SGOT	SGPT	SOD	MDA
NC	PC	0.022*	0.033*	0.715	0.861
	ZLEE-1	0.792	0.963	0.494	1.000
	ZLEE-II	0.296	0.567	0.175	1.000
	ZLEE-III	0.093	0.201	0.101	0.162
	ZLEE-IV	0.020*	0.067	0.051	0.002*
PC	NC	0.022*	0.033*	0.715	0.861
	ZLEE-1	0.000*	0.001*	0.992	1.000
	ZLEE-II	0.001*	0.476	0.349	1.000
	ZLEE-III	0.028*	0.002*	0.116	1.000
	ZLEE-IV	1.000	0.009*	0.038*	0.861

[35] Maaiden et al., *Genus Ziziphus: A Comprehensive Review on Ethnopharmacological, Phytochemical and Pharmacological Properties*; Owolarafe et al., "Toxicological Investigation of Aqueous Extract of Ziziphus Mauritiana Leaves on Wistar Rats"; Tajudeen Alowonle Owolarafe and Salawu Kailani, "Identification and Toxicity Profiling of Column Fractions of Ethanol Leaf Extract of Ziziphus Mauritiana," *Biology, Medicine, & Natural Product Chemistry* 12, no. 2 (2023): 651–62, https://doi.org/10.14421/biomedich.2023.122.651-662.

[36] Ubaid Ullah et al., "Hepatoprotective Effects of Melatonin and Celecoxib against Ethanol-Induced Hepatotoxicity in Rats," *Immunopharmacology and Immunotoxicology* 42, no. 3 (May 3, 2020): 255–63, https://doi.org/10.1080/08923973.2020.1746802.

[37] Owolarafe et al., "Toxicological Investigation of Aqueous Extract of Ziziphus Mauritiana Leaves on Wistar Rats."

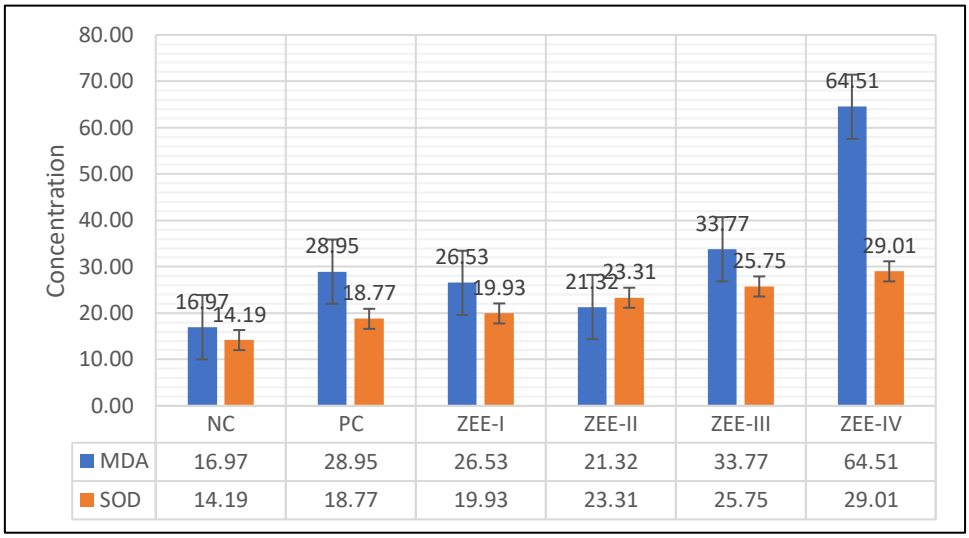

Figure 3 Comparison of Oxidative Stress Marker (MDA) and Antioxidant Marker (SOD) Levels Among All Groups

Analysis of the SOD found that there is a significant difference between groups ($p<0.001$). The further post-hoc test found that the only significant difference was between the positive control and the extract with 500 mg/kgBW dosage ($p<0.05$), however, there was no difference with the negative control ($p>0.05$). This means that the 500 mg/kgBW dosage of the *Z. mauritiana Lam.* dosage does not perform as well as the metformin, but is rather comparable to the placebo. Meanwhile, the Kruskall-Wallis analysis of MDA data found that there was a significant difference in MDA level across categories of groups ($p<0.005$). The further post-hoc test found that extract with 500 mg/kgBW dosage has a significant difference with the negative control ($p<0.005$), and no significant difference with the positive control ($p>0.05$). This high SOD activity explains the hepatoprotective effect of *Z. mauritiana Lam.* against oxidative stress that occurs in the liver [38]. Other studies have also

[38] Maaiden et al., *Genus Ziziphus: A Comprehensive Review on Ethnopharmacological, Phytochemical and Pharmacological Properties*; Jha et al., "Ziziphus Mauritiana : An in-Depth Review of Its Medicinal Attributes and Pharmacological Activities"; Xia Jiang and Bin Zhao, "International Journal of Complementary and Internal Medicine Biostatistical and Mathematical Analysis on Liver Disease during Covid-19 Pandemic," *International Journal of Complementary and Internal Medicine* 1, no. 2 (2022); Prakash and Singh, "A Panoramic View on Phytochemical, Nutritional, and Therapeutic Attributes of Ziziphus Mauritiana Lam.: A Comprehensive Review."

shown that increasing the dose of the extract also increases SOD activity in animal models [39].

In this study, the concentration of malondialdehyde (MDA) showed differences between each group, but the relationship between doses was not found. The highest MDA concentration was found in the ZLEE group with 500 mg/kgBB dosage, which reached 64.51 nmol/ml. However, significant differences were only found between the negative control and ZLEE at the highest dose, while the positive control did not differ from the negative control. The findings in this study contradict various studies that found that *Z. mauritiana Lam.* extract has an antioxidant effect that results in a decrease in MDA levels compared to placebo [40]. This anomaly may be explained by the use of ethanol as a solvent in the extraction process which resulted in increased oxidative stress in the liver, thus explaining the high MDA concentration at the highest extract dose. Metabolism of ethanol generally occurs through three different enzyme pathways namely alcohol dehydrogenase (ADH), CYP2E1, and catalase; where the majority of metabolism is performed by ADH. Regardless of the enzyme involved, this process will produce hydrogen peroxide (H_2O_2) and superoxide ion (O_2-); which are reactive oxygen species (ROS); resulting in oxidative stress, resulting in increased MDA concentrations[41].

CONCLUSION

According to all findings in this study, it can be concluded that ethanol extract of *Z. mauritiana Lam.* leaves, especially at 300 and 500 mg/kgBW dosage performs as anti-hyperglycemic as well as metformin. *Z.*

[39] Nourhan Hisham Shady et al., "Wound Healing and Antioxidant Capabilities of Zizyphus Mauritiana Fruits: In-Vitro, In-Vivo, and Molecular Modeling Study," *Plants* 11, no. 1392 (2022), https://doi.org/10.3390/plants11111392.

[40] Owolarafe et al., "Toxicological Investigation of Aqueous Extract of Ziziphus Mauritiana Leaves on Wistar Rats"; Jha et al., "Ziziphus Mauritiana : An in-Depth Review of Its Medicinal Attributes and Pharmacological Activities"; Hussain et al., *Fruits Grown in Highland Regions of the Himalayas: Nutritional and Health Benefits*; Maaiden et al., *Genus Ziziphus: A Comprehensive Review on Ethnopharmacological, Phytochemical and Pharmacological Properties*.

[41] L Moraes et al., "Evaluation of Oxidative Stress Markers in Ethanol Users," *Brazilian Journal of Medical and Biological Research* 56, no. e12465 (2023): 1–8, https://doi.org/10.1590/1414-431X2023e12465.

mauritiana Lam. leaves ethanol extract at 500 mg/kgBW also have better antioxidant activities compared to lower dosage.

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