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Effectiveness of Durian Fruit Seed Extract (Durio Zibethinus) on Kidney Function and Histopathology of Rats Induced by Wistar Streptozotocin

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Abstract: Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia due to impaired insulin secretion or action. Diabetic nephropathy, a microvascular complication of type 2 DM, causes damage to kidney function due to progressive hyperglycemia. This study analyzed the potential of durian seed extract in reducing blood sugar levels (KGD) and improving kidney function and histopathological features in streptozotocin (STZ)-induced Wistar rats. Rats were divided into six groups: normal,

positive control (STZ + metformin), negative control (STZ), and three treatment groups with durian seed extract doses of 150, 300, and 450 mg/kgBB. The extract was given for 14 days, followed by examination of kidney function and histopathology. The results showed that a dose of 450 mg/kgBB was most effective in reducing KGD, equivalent to metformin, which could improve kidney function and histopathology. Durian seed extract 450 mg/kgBB has the potential as an effective antidiabetic in reducing kidney damage.

Keywords: *Antidiabetes, Durian Seeds, Streptozotocin, Kidney Function, Histopathology*

INTRODUCTION

Diabetes mellitus has become one of the growing global health challenges and is becoming increasingly worrisome. Although the overall prevalence of diabetes mellitus has increased rapidly, the burden is not only felt in physical health, but also in social and economic aspects. According to the World Health Organization (WHO), by 2020, around 9% of the world's total population will have been diagnosed with diabetes, a figure that shows how widespread the impact of this disease is. The consequences of diabetes mellitus go far beyond mortality, which amounts to about 4% of deaths caused by non-communicable diseases. More alarmingly, 80% of these deaths occur in low- and middle-income countries, indicating that this group is most vulnerable to the serious complications of diabetes, including disability, amputation and blindness caused by the disease.[1] Diabetes also causes a huge economic burden, both in the form of long-term medical care costs, hospitalizations, and lost productivity due to disability or premature death. These costs have a major impact on healthcare systems, especially in countries with limited medical resources. The WHO estimates that by 2030, diabetes mellitus will rank seventh as the world's leading cause of death, a projection that adds urgency to finding innovative and effective solutions to diabetes, especially in low- and middle-income countries.[2] In Indonesia, this situation is particularly striking. According to the latest report

[1] WHO, "Constitution of the World Health Organization 49th Edition." (2020, n.d.), https://doi.org/ISBN 978-92-4-000051-3.

[2] Fatmawati Fatmawati, Andi Suswani, and Nurlina Nurlina, "Comparison of the Rate of Depression in Early and Late Elderly Women with Diabetes Mellitus," *Journal of Science Education Research* 9, no. 7 (2023): 5329-5332.

from the International Diabetes Federation (IDF), Indonesia ranks fifth in the world with 19.47 million people with diabetes, and a prevalence of 10.6%, with the majority of cases being type 2 diabetes. This figure shows the enormous impact of diabetes mellitus in Indonesia, and emphasizes the need for a more aggressive approach to prevention and treatment. In this context, there is an urgent need to raise public awareness and strengthen the healthcare system to effectively address the burden of this disease. With increasing prevalence and worse projections in the future, diabetes mellitus requires urgent attention from the government, health organizations, and the public at large so that its impact can be minimized and the quality of life of patients can be improved.[3]

Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia, caused by impaired insulin secretion, insulin resistance, or both.[4] DM consists of type 1, type 2, and gestational, with type 2 being the most common form. Type 2 DM results from insulin resistance caused by pancreatic beta cell dysfunction and an unhealthy lifestyle, such as physical inactivity.[5] Lack of physical activity reduces the number of insulin receptors and the activity of GLUT-4, which plays a role in glucose transportation into cells.[6] As a result, blood glucose remains high, triggering damage to body tissues such as blood vessels, eyes, kidneys, heart and nerves. Hyperglycemia also inhibits GLUT-4 transport to the plasma membrane, so cells fail to take up glucose for energy, worsening the condition of type 2 DM.[7]

Diabetic nephropathy is a microvascular complication that occurs in type 2 diabetes mellitus (DM), caused by changes in kidney function. These changes begin with progressive hyperglycemia, which stimulates renal cell hypertrophy, extracellular matrix synthesis, and changes in capillary permeability.

[3] Dianna J Magliano et al., *IDF Diabetes Atlas 10 TH Edition*, *Diabetes Research and Clinical Practice*, vol. 102, 2, 2021.

[4] Ibid.

[5] I Putu Dedy Arjita, I Putu Bayu Agus Saputra, and Dhika Juliana Sukmana, "Noni (Morinda Citrifolia) Ethanol Extract Lowered Blood Glucose Levels, Increased Glutathione Peroxidase Activity, and Decreased Malondialdehyde in White Rats Model of Diabetes," *Journal of Science Education Research* 9, no. 12 (2023): 10698-10704.

[6] Veranyca Chiuman et al., "Oral Ulcer Healing Activity of Lemon Pepper Ethanol Extract Gel in Streptozotocin-Induced Diabetic Wistar Rats," *Bandung Medical Magazine* 52, no. 2 (2022): 80-88.

[7] Afiat Berbudi et al., "Type 2 Diabetes and Its Impact on the Immune System," *Current Diabetes Reviews* 16, no. 5 (2019): 442–449.

Hyperglycemia also causes non-enzymatic glycation of amino acids and proteins, leading to the formation of advanced glycation end products (AGEs). The formation of these AGEs leads to thickening of the glomerular basement membrane and tubulointerstitial fibrosis, which ultimately contributes to renal sclerosis. The accumulation of this damage impairs glomerular filtration and leads to microalbuminuria, which, if left untreated, can progress to diabetic nephropathy (Hendromartono, 2020). [8]

Streptozotocin is a compound often used to experimentally induce diabetes mellitus due to its toxic properties to pancreatic β-cells. This compound has a high affinity for the GLUT-2 transporter, which is found in the plasma membrane of pancreatic β-cells, as well as in liver and kidney tissues. As a result, these organs can also be damaged. Upon entry into β-cells via GLUT-2, streptozotocin causes oxidative stress and DNA damage, which triggers apoptosis or death of β-cells. This process results in pancreatic dysfunction, characterized by tissue swelling, β-cell degeneration in the islets of Langerhans, and decreased insulin production. The accumulation of this damage contributes to the development of hyperglycemia that characterizes diabetes mellitus.[9]

Diabetes mellitus is a chronic disease that cannot be cured but can be managed by keeping blood glucose levels stable through nonpharmacological and pharmacological therapies. Nonpharmacologic therapies include dietary management, physical activities such as exercise, as well as the use of herbal ingredients as treatment support. On the other hand, pharmacological therapy involves the administration of medications such as oral hypoglycemics, antihyperglycemic agents, or insulin. Although pharmacological therapy is effective in controlling blood glucose levels, its use is often accompanied by side effects, such as swelling in peripheral areas, which can reduce patients' comfort and quality of life.[10]

[8]S. O. Kolset, F. P. Reinholt, and T. Jenssen, "Diabetic Nephropathy and Extracellular Matrix," *Journal of Histochemistry & Cytochemistry* 60, no. 12 (December 2012): 976–986.

[9] Hans Pangestu Simarmata et al., "Effectiveness of PRP on Changes in Blood Lipid Profile of Male White Rats (Rattus Norvegicus) Diabetes Mellitus Induced by Streptozotocin," *Biospecies* 14, no. 1 (2021): 10-17.

[10] Ni Luh Kade Arman Anita Dewi et al., "Review: Utilization of Plants as Phytotherapy in Diabetes Mellitus," *Usadha* 2, no. 1 (2022): 31-42.

Indonesia has very abundant biodiversity, including various types of plants that have been widely utilized by the community. Herbs and spices are often used as traditional medicine because they are considered safe and do not cause harmful side effects to the human body. There are around 30 thousand types of flora that grow in Indonesia, making it one of the countries with the largest flora diversity in the world. The utilization of plants as traditional medicine is a cultural heritage that has been carried out for generations. Apart from being used as medicinal materials, these plants are also used for food, cosmetics, beverages, and medicinal products.[11]

One plant that is widely used by Indonesians as a traditional medicine to help treat diabetes is durian (Durio zibethinus Murr). Durian, which is abundant in Indonesia, has a complete nutritional content, such as potassium, magnesium, iron, phosphorus, omega-3, omega-6, and vitamins B and C. In addition, durian contains antioxidants that are beneficial to protect the body from free radicals. In addition, durian contains antioxidants that protect the body from free radicals. This content has the potential to prevent and reduce the risk of developing diseases such as cancer, diabetes, and cataracts. Durian seeds contain various bioactive compounds such as alkaloids, triterpenoids, phenolics, and flavonoids, which provide significant health benefits. Flavonoids in durian seeds have various properties, including being antioxidant, antibacterial, antiviral, anti-inflammatory, antiallergic, and anticancer. These compounds work by capturing free radicals, acting as natural antioxidants, and helping to repair damaged kidney tissue. In addition, durian seeds can also lower blood sugar levels. Flavonoids have been shown to have antidiabetic activity, which can stimulate the regeneration of cells in the islets of Langerhans, the part of the pancreas responsible for insulin production. This increased insulin production helps lower blood glucose levels, providing benefits in the management of diabetes.

Research conducted by Muh. Nur Amir et al. (2020) with the title Anti Diabetes Mellitus Activity of Durian Plants (Durio zibethinus Murr.) on Fasting Blood Glucose Levels of Alloxan-Induced Mice, showed that durian extract has a significant antidiabetic effect. In the study, administration of durian extract to alloxan-induced mice successfully reduced fasting blood glucose levels, which

[11] A. Hadian Pratama Hamzah et al., "Ethnobotanical Identification of Medicinal Plants Used by the Sangihe Tribe in Sangihe Archipelago District, North Sulawesi," *Journal of Science Education Research* 9, no. 7 (2023): 5765-5772.

signaled the potential of durian as a natural treatment for diabetes.[12] This study aims to evaluate the effectiveness of durian (Durio zibethinus Murr.) seed extract in reducing blood sugar levels, as well as to determine the histopathological picture of the kidneys in streptozotocin-induced Wistar rats, a compound used to trigger diabetes in experimental models.[13]

THEORETICAL BASIS

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia due to impaired insulin secretion or function. This disorder leads to decreased glucose utilization by body cells, increased fat metabolism, and decreased protein metabolism. There are three main types of diabetes mellitus: type I, type II, and gestational diabetes. Type I occurs due to the destruction of insulin-producing pancreatic beta cells, often due to genetic or autoimmune factors. Type II diabetes, which is more common in adults, is associated with insulin resistance, where the body does not respond well to insulin. Gestational diabetes occurs during pregnancy and usually goes away after the birth of the baby. Symptoms of diabetes mellitus often include weight loss, fatigue, frequent urination, excessive thirst, and constant hunger due to an imbalance in glucose levels in the body. In addition, diabetes can also lead to other complications such as visual impairment, neuropathy, and increased susceptibility to infections. The disease has a major impact globally, both in terms of health and economy, especially in developing countries. Diabetes affects individuals' quality of life, causes physical disability, and increases the burden on the healthcare system. Therefore, early detection and effective management are essential to prevent long-term complications and lower mortality rates due to the disease.[14]

Durian (Durio zibethinus Murr) is a tropical fruit that is very popular in Southeast Asia and is known for its distinctive taste and smell. In addition to its delicacy, durian also has great potential in traditional medicine. The plant thrives

[12] Muh. Nur Amir et al., "Anti Diabetes Mellitus Activity of Durian Plants (Durio Zibethinus Murr.) Against Fasting Blood Glucose Levels of Alloxan-Induced Mice," *Pharmacy and Pharmacology Magazine* 23, no. 3 (2020): 75-78.

[13] Charoenphun and Klangbud, "Antioxidant and Anti-Inflammatory Activities of Durian (Durio Zibethinus Murr.) Pulp, Seed and Peel Flour."

[14] Ade Dwi Karisma Maharani, Puguh Santoso, and Ni Nyoman Wahyu Udayani, "Efek Ekstrak Etanol Buah Dewandaru (Eugenia uniflora L) terhadap Penurunan Kadar Glukosa Darah dan Perbaikan Sel Beta Pankreas pada Mencit yang Diinduksi Aloksan," *Usadha* 2, no. 2 (April 30, 2023): 39–44.

in Indonesia and is characterized by tall trees, with large and sharply spiked fruits. Durian fruits contain a variety of active compounds with potential health benefits, including alkaloids, flavonoids, tannins, saponins, and terpenoids. These compounds are known to have various therapeutic effects, such as anti-inflammatory, antioxidant, and lowering blood sugar levels. Durian seed extract, obtained through various extraction methods, may also provide benefits in the treatment of certain diseases, including diabetes mellitus, due to its ability to increase insulin secretion and lower blood glucose levels. In traditional medicine, durian has long been used to treat health problems, including metabolic disorders, and further research into its therapeutic potential is needed.

The pathophysiology of type II diabetes mellitus involves a disturbance in the balance of hormones that regulate blood glucose levels, particularly insulin resistance and impaired insulin secretion. Insulin, which is produced by beta cells in the pancreatic islets of Langerhans, functions to lower blood glucose levels, while other hormones such as glucagon, cortisol, and growth hormone act to increase glucose levels. In type II diabetes, insulin fails to work effectively due to insulin resistance, which is the inability of cells to respond properly to insulin, resulting in impaired glucose metabolism.[15] This resistance occurs in the muscles and liver, where insulin cannot stimulate glucose uptake optimally, while the failure of pancreatic beta cells to meet insulin demand causes blood glucose levels to rise. In addition, various other organs contribute to metabolic disturbances, such as fat tissue that increases lipolysis, the gastrointestinal tract with incretin deficiency, pancreatic alpha cells that cause hyperglucagonemia, kidneys that increase glucose reabsorption, and the brain with insulin resistance. This combination of disorders leads to metabolic impairment and impaired glucose tolerance that characterizes type II diabetes mellitus.[16]

Complications of diabetes mellitus are divided into macrovascular and microvascular complications. Macrovascular complications include cardiovascular diseases (CVD) such as coronary heart disease, peripheral vascular disease and cerebrovascular disease. Meanwhile, microvascular

15 Amir et al., "Aktivitas Anti Diabetes Mellitus Tanaman Durian (Durio Zibethinus Murr.) Terhadap Kadar Glukosa Darah Puasa Mencit Yang Diinduksi Aloksan."

16 Flora Sijabat, Rinco Siregar, and Marthalena Simamora, "The Effect of Binahong (Anredera Cardifolia) Leaf Decoction on Blood Sugar Levels in Elderly Dm Type Ii at the Datar City Health Center," *PREPOTIF: Journal of Public Health* 6, no. 1 (2021): 204-213.

complications include disorders that affect the kidneys, retina and nervous system. One of the major microvascular complications is diabetic nephropathy, which is a deterioration in kidney function due to progressive hyperglycemia that stimulates renal cell hypertrophy, extracellular matrix synthesis and changes in capillary permeability.[17] These conditions trigger the formation of advanced glycation end products (AGEs), leading to thickening of the glomerular basement membrane, tubulointerstitial fibrosis, and eventually renal sclerosis. The process impairs glomerular filtration, causes microalbuminuria, and leads to diabetic nephropathy. In advanced stages, diabetic nephropathy can progress to terminal kidney disease characterized by proteinuria, hypertension, and decreased renal function. Uncontrolled hyperglycemia is a major factor in kidney damage, affecting hemodynamics, metabolism, endothelial function, and triggering inflammation and changes in vascular expression. The kidney, a kidney bean-shaped organ located on both sides of the upper back of the body, has an important function in regulating body fluids, minerals and salts. Fluid imbalance or consumption of certain medications can increase the risk of kidney stones, which are formed from chemicals such as calcium, uric acid and phosphate in the urine. Untreated damage to kidney function can worsen the quality of life for people with diabetes mellitus.[18]

This study aims to investigate the effect of durian seed extract on blood glucose levels, kidney function, and histology of streptozotocin-induced diabetic rats, and determine the optimal dose. Diabetes mellitus is an increasing global health problem, with limitations of current therapies, such as side effects and high costs. Durian, which is rich in bioactive compounds, has the potential to be a natural alternative for managing diabetes and its complications. This research is expected to support the development of safer and more effective natural ingredient-based therapies.

RESEARCH METHODS

This study used a post-test only controlled group design with Wistar rats as experimental animals, taking place at the Pharmacology Laboratory of the

[17] Abdul Basit et al., "Prevalence of Diabetes, Pre-Diabetes and Associated Risk Factors: Second National Diabetes Survey of Pakistan (NDSP)," *BMJ Open* 8, no. 8 (2018).

[18] Chiuman et al., "Oral Ulcer Healing Activity of Lemon Pepper Ethanol Extract Gel in Streptozotocin-Induced Diabetic Wistar Rats."

Faculty of Pharmacy, University of North Sumatra and the Anatomical Pathology Laboratory of Royal Prima Hospital, Medan, from April to June 2024. The research protocol was approved by the Health Research Ethics Committee of Prima Indonesia University (No. 057/KEPK/UNPRI/III/2024). The rats were housed in 22-25°C cages with a 12-hour light-dark cycle, given standard feed and water ad libitum, and monitored daily to ensure welfare. Euthanasia was performed using an overdose of ketamine-xylazine anesthesia to minimize suffering, as per ethical guidelines. Sample size was determined statistically, and rats were randomly divided into five groups: negative control with 1% Na CMC solution, positive control with 500 mg/KgBB metformin, and treatment with 150 mg/KgBB, 300 mg/KgBB, and 450 mg/KgBB durian seed extract. This procedure was designed to maintain ethical standards and ensure valid results.

This study used materials such as 96% ethanol solution, durian seeds, filter paper, ketamine, Hematoxylin-Eosin (HE), metformin, and Streptozotocin (STZ). The tools used include rotary evaporator, scalpel, dropper, mask, and gloves. The study began with the extraction process of durian seeds (*Durio zibethinus* Murr) using the maceration method with 96% ethanol solvent. A total of 1.5 kg of durian seeds were washed, thinly sliced, and dried in an oven at 40°C for one week. After drying, durian seeds were pulverized into powder and extracted through maceration method with stirring until homogeneous. The maceration process was followed by evaporation using a vacuum rotary evaporator to produce a solvent-free thick extract. The thick extract of durian seeds was then subjected to phytochemical screening to determine the content of secondary metabolites, including alkaloid test, terpenoid/steroid test, flavonoid test, tannin test, and saponin test.

Phytochemical screening tests were conducted to detect the presence of bioactive compounds in thick extracts of durian seeds using various methods. The alkaloid test was carried out by adding 1 mL of HCl and 3 mL of distilled water to the extract, then the solution was heated on a water bath for two minutes, cooled, and filtered. After that, 2 drops of Dragendorff reagent were added. The color change to orange indicates the presence of alkaloid compounds. Saponin test is done by mixing 1 mL of extract with 10 mL of distilled water in a test tube, then shaken. If the foam formed lasts for one minute, the results are positive for saponins. Tannin test is done by adding 2 drops of 5% $FeCl_3$ solution into the

extract. The formation of a blackish green color indicates the presence of tannin compounds. For flavonoid test, a little magnesium (Mg) metal powder and a few drops of concentrated HCl were added to the extract. The formation of a reddish orange color indicates the presence of flavonoid compounds.[19]

Blood sampling was performed through heart dissection of Wistar rats to obtain more blood volume compared to the method of collecting from the tail or eyes of rats. Prior to the procedure, rats were fasted for 12 hours and then euthanized until they lost consciousness. The rats were placed in a supine position on a surgical tray, with the legs tied using a needle to maintain the position. An incision was made along the midline of the abdominal wall muscle from the tip of the sternum to the symphysis pubis, taking care to avoid damaging the diaphragm and preventing pneumothorax. The heart is found on the left side of the chest, between the 3rd and 4th ribs. The syringe is inserted into the heart at an angle of 25-30° to the chest surface to a depth of 5 mm. A total of 5 ml of blood was drawn using a syringe and collected in a vacutainer.

Test animals in each group were placed in the same cage. Groups IV to VI were given durian seed extract (Durio zibethinus Murr) orally according to the specified dose, while the negative control group was given 1% Na CMC solution, the positive control group was given 500 mg/KgBB metformin, and the normal group was only given food and drink without treatment. Grouping of test animals consisted of: Group I (normal, without treatment), Group II (negative control, given 1% Na CMC), Group III (positive control, given metformin 500 mg/KgBB), Group IV (given durian seed extract dose 150 mg/KgBB), Group V (given durian seed extract dose 300 mg/KgBB), and Group VI (given durian seed extract dose 450 mg/KgBB). Blood sugar checks were carried out on day 0, then the rats were fed for 8 hours. On day 1, rats were induced streptozotocin intraperitoneally at a dose of 45 mg/KgBB and checked blood glucose levels on day 3. Rats were declared to have hyperglycemia if blood glucose levels reached ≥ 135 mg/dL. Urea levels and creatinine levels were examined on day 28.

[19] Tcanty Indrianti, Ali Napiah Nasution, Evelyn Angie, Clarissa Lister, & Veranyca Chiuman. (2024). The Effect Of Ethanol Extract Of Ziziphus Mauritiana Lam. Leaf On Alloxan-Induced Rat. *International Journal of Islamic Education, Research and Multiculturalism (IJIERM)*, *6*(2), 741–762. https://doi.org/10.47006/ijierm.v6i2.348

In this study, histopathologic assessment of the kidneys was performed systematically to observe the extent of tissue damage. Kidney samples were taken from the test animals on day 28, then cleaned and fixed in 10% buffered formalin solution for at least 24 hours.[20] After fixation, samples were dehydrated using graded alcohols, cleared with xylol, and embedded in paraffin. The resulting paraffin blocks were cut to 5 µm thick using a microtome and stained with the Hematoxylin-Eosin (HE) method, which allows detailed visualization of tissue structure. This stain works by binding the acidic cell nucleus with hematoxylin so that it appears blue, while the alkaline cytoplasm is stained red by eosin.[21] Histopathological observations were made using a microscope with 400x magnification, and tissue damage was assessed based on scoring. A score of 0 indicates no kidney damage in one field of view, score 1 indicates 1-20% damage, score 2 for 21-50% damage, score 3 for 51-75% damage (mild damage), and score 4 for more than 75% damage (severe damage). Assessment criteria included glomerular hypertrophy, tubular necrosis, and interstitial fibrosis. Each sample was observed in multiple field of view to ensure accuracy, and scoring was performed by two independent observers to improve inter-rater reliability. This approach is designed to provide accurate, standardized and reliable results in evaluating kidney damage.[22] The study data were analyzed using the SPSS program. To analyze the kidney damage scoring data, the Kruskal-Wallis test was used, followed by the Mann-Whitney test to identify differences between all treatment groups

[20] Winda Irawati Zebua et al., "Histopathological Evaluation of Green Betel Leaf Extract Ointment on Incision Wounds Infected with Staphylococcus Aureus in Wistar Rats," *Jurnal Teknologi Laboratorium* 2 13, no. April (2024): 71–82.

[21] Joni Tandi et al., "Effectiveness Test of Mangrove Leaf (Rhizophora Apiculata) on Decreasing Blood Glucose Levels and Pancreas Histopatology Streptozotocin Induced Male White Rats," *Jurnal Penelitian Pendidikan IPA* 9, no. 6 (2023): 4596–4604.

[22] E. Setiadi, E. Peniati, and R. Susanti, "The Effect of Aloe Vera Skin Extract on Blood Sugar Levels and Histopathological Features of the Pancreas of Rats Induced by Alloxan," *Life Science 9* 9 (2), no. 2 (2020): 171–185.

RESULTS AND DISCUSSION

Results

1. Phytochemical content of ethanol extract of durian (Durio zibethinus Murr) fruit seeds

Table 1. Phytochemical test of ethanol extract of durian fruit seeds

Secondary Metabolite Compounds	Reagents	Results
Alkaloids	Bouchardart	+
	Maeyer	+
	Dragendroff	+
	Wagner	+
Steroids and Triterpenoids	Salkowsky	-
	Lieberman-Burchad	-
Saponins	Aquadest+96% Alcohol	+
Flavonoids	FeCl3 5%	+
	Mg(s)+ HCl (p)	+
	10% NaOH	-
	H2O 4(p)	+
Tannins	FeCl3 1%	+
Glycosides	Mollish	+

The results of phytochemical testing on durian seed extract showed the presence of alkaloid compounds, saponins, flavonoids, tannins, and glycosides, which were detected positively using various reagents. However, steroidal and triterpenoid compounds were not detected in durian seed extract with the reagents used.

2. Measurement of blood sugar levels

Tabel 2 Mean and standard deviation of KGD

Group	Before	After	14 Days	Difference
	Mean±SD	Mean±SD	Mean±SD	Mean±SD
N	86,8±9,55	125,6±2,88	118,0±8,19	7,6±6,69

K+	83,6±5,32	381,4±57,39	136,6±12,10	244,8±53,28
K-	83,6±6,99	309,8±68,11	390,6±111,22	-80,8±72,88
P1	86,0±11,07	304,6±12,54	161,0±11,38	143,6±21,33
P2	88,6±7,89	282,2±18,23	189,8±13,70	92,4±28,30
P3	95,4±9,07	281,8±20,28	237,8±16,13	44,0±30,68

The mean blood glucose level (KGD) in the positive control group (K+) showed a significant increase, with a difference of 244.8 ± 53.28 mg/dL between after treatment and day 14. The negative control group (K-) experienced an increase that continued to increase until day 14, with a negative difference of -80.8 ± 72.88 mg/dL. Meanwhile, the P1, P2, and P3 treatment groups showed a more moderate decrease in blood glucose levels, with a difference of 143.6±21.33 mg/dL, 92.4±28.30 mg/dL, and 44.0±30.68 mg/dL on day 14, respectively. The normal group (N) showed little change with a difference of only 7.6±6.69 mg/dL.

3. Measurement of creatinine levels

Table 3. Creatinine mean and standard deviation

Group	Average	Standard deviation
N	0,54	0,064
K+	0,77	0,074
K-	1,38	0,100
P1	0,88	0,021
P2	0,91	0,007
P3	0,93	0,011

The results showed that the mean and standard deviation of creatinine in groups N, K+, K-, P1, P2, and P3 were 0.54±0.064; 0.77±0.074; 1.38±0.100; 0.88±0.021; 0.91±0.007; and 0.93±0.011. Group P1 is the group that has the smallest mean creatinine value compared to groups P2 and P3.

4. Measurement of ureum levels

Table 4. Mean and standard deviation

Group	Average	Standard deviation
N	30,0	2,550

K+	45,8	2,683
K-	55,4	3,209
P1	46,8	2,683
P2	49,0	1,225
P3	49,8	0,837

The results showed that the mean and standard deviation of ureum in groups N, K+, K-, P1, P2, and P3 were 30.0 ± 2.550; 45.8 ± 2.683; 55.4 ± 3.209; 46.8 ± 2.683; 49.0 ± 1.225; and 49.8 ± 0.837. Group P1 is the group that has the smallest mean ureum value compared to groups P2 and P3.

5. Histopathologic analysis of the kidney

Table 5. Mean and standardized kidney

Group	Average	Standard deviation
N	0	0
K+	0,2	0,447
K-	1,6	0,548
P1	0,2	0,447
P2	0,4	0,548
P3	0,6	0,548

The results showed that the mean and standard deviation of glomerular hypertrophy in groups K+, K-, P1, P2, and P3 were 0.2±0.447; 1.6±0.548; 0.2±0.447; 0.4±0.548; and 0.6±0.548, while group N showed no glomerular hypertrophy. Group P1 had the smallest mean glomerular hypertrophy compared to groups P2 and P3. There were significant differences in glomerular hypertrophy between group N and group K-, group K+ and group K-, and group K- and groups P1, P2, and P3 ($p<0.05$). However, between the other two groups no significant differences were found ($p>0.05$). Based on the results of the study, it can be concluded that P1 is the most effective treatment concentration in reducing glomerular hypertrophy, with the ability comparable to the K+ group ($p = 0.000$; $p>0.05$).

DISCUSSION

The results of phytochemical tests on durian (Durio zibethinus Murr) seed extract showed the presence of flavonoid and alkaloid compounds that have great potential in diabetes management. Flavonoids in durian seeds can improve insulin sensitivity by increasing insulin receptor expression and modulating insulin signaling pathways in target tissues, such as muscle and liver. In addition, flavonoids also protect pancreatic beta cells from oxidative stress and apoptosis through antioxidant activity, which plays an important role in preventing progressive damage due to hyperglycemia. This mechanism supports cell regeneration in the islets of Langerhans, allowing for increased insulin secretion. Alkaloids in durian seeds also have significant effects on blood sugar control. These compounds work by inhibiting the alpha-glucosidase enzyme in the intestinal mucosa, slowing the breakdown of complex carbohydrates into monosaccharides, thereby reducing postprandial blood glucose spikes. This effect also slows the absorption of glucose into the blood, keeping glucose levels stable.

In type 2 diabetes, chronic uncontrolled hyperglycemia often contributes to complications such as diabetic nephropathy. Hyperglycemia can lead to renal cell hypertrophy, increased synthesis of extracellular matrix, and formation of advanced glycation end products (AGEs). These AGEs trigger glomerular basement membrane thickening, tubulointerstitial fibrosis, and increased renal capillary permeability, ultimately leading to decreased glomerular filtration function and microalbuminuria. Flavonoids and alkaloids in durian seeds have the potential to mitigate these effects by suppressing oxidative stress, inflammation, and AGE formation. Several studies support these benefits. For example, research by Muh. Nur Amir et al. demonstrated the ability of durian seeds to significantly lower blood glucose levels in a diabetic rat model. Other studies have also shown antioxidant activity and alpha-glucosidase inhibition by durian extract, strengthening scientific evidence of its potential as an antidiabetic agent. Thus, the active compounds in durian seeds not only target blood glucose management, but also have the potential to protect against diabetic complications, making it a strong candidate for natural ingredient-based therapies.

The results showed that before the intervention, the mean and standard deviation of blood glucose levels (KGD) in groups N, K+, K-, P1, P2, and P3 were 86.8±9.55; 83.6±5.32; 83.6±6.99; 86.0±11.07; 88.6±7.89; and 95.4±9.07, respectively. After STZ administration, all groups experienced an increase in KGD that exceeded normal limits (<126 mg/dL). After 14 days, groups K+, P1, P2, and P3 showed a decrease in KGD that was close to normal, while KGD in group K- still increased. The P1 group showed the greatest decrease in KGD compared to P2 and P3. The analysis showed that the treatment of durian seed extract at a dose of 450 mg/KgBB had a significant effect on reducing KGD after 14 days, although it was not significantly different from the positive control (STZ + Metformin). Durian seed extract proved effective in reducing KGD, with a dose of 450 mg/KgBB providing the best results compared to the control group and other treatments. Overall, the effect of durian seed extract treatment on KGD was significant after 14 days compared to before and after induction. The results of this study are in line with the findings reported by Erina (2020) in her research entitled "Durian Seed Ethanol Extract as a Free Radical Repressor of Pancreatic Histology in Wistar Rats Model of Diabetes Mellitus." In the study, durian seed extract at a dose of 300 mg/kgBB proved effective in reducing blood sugar levels (KGD), with the highest dose providing more significant effectiveness against KGD, which supports the findings that durian seed extract can have a positive impact in the management of diabetes mellitus.

The results showed that the mean and standard deviation of creatinine in groups N, K+, K-, P1, P2, and P3 were 0.54±0.064; 0.77±0.074; 1.38±0.100; 0.88±0.021; 0.91±0.007; and 0.93±0.011. Group P1 had the smallest mean creatinine value compared to groups P2 and P3. Based on Dunnet's post-hoc test, P1 proved to be the most effective treatment group concentration in reducing creatinine. In addition, the mean and standard deviation of ureum in the same group were 30.0±2.550; 45.8±2.683; 55.4±3.209; 46.8±2.683; 49.0±1.225; and 49.8±0.837. Group P1 again showed the smallest mean ureum value compared to groups P2 and P3. Based on Dunnet's post-hoc test, P1 also proved to be the most effective concentration in reducing ureum.

CONCLUSION

Durian fruit seed extract has been shown to reduce fasting blood sugar levels, which plays a role in reducing the risk of complications such as diabetic nephropathy. In addition, durian seed extract can also reduce serum creatinine

and ureum levels in the kidneys. A high dose of durian seed extract (450 mg/kgBB) provided better effectiveness in reducing blood sugar, serum creatinine, and ureum levels, compared to lower doses. Furthermore, the highest dose of durian seed extract showed significant results in reducing blood sugar levels (BG) and improving kidney function, as seen from the decrease in ureum and creatinine values, as well as a reduction in histopathological kidney damage.

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