Effectiveness of Sonification of Ketumbar Tip (*Coriandrum Sativum L.*) for Diabetes Melites Complications on the Gynels with Manly Wistar Rats (*Rattus Norvegicus*) as Aloksan Induced Coal Animals

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Abstract

The most common microvascular complication is diabetic nephropathy. Coriander is traditionally used as a stimulant, carminative, anticonvulsant, diuretic and antirheumatic, antiemetic and has potential as an antioxidant. Thus, the authors were interested in exploring the effectiveness of coriander seed sonification (Coriandrum sativum L.) on complications of diabetes mellitus in alloxan-induced male rats as experimental animals, especially on kidney micro-vascularization. This study was an experimental study. In this study, sonification of coriander seeds was carried out using a sonicator. All rats in this study were induced by injection of 5% alloxan, then grouped into 5 different groups including: control (Na-CMC), standard (metformin), coriander seed sonification 200 mg/kgBW, 400 mg/kgBW, and 800 mg/kgBW. The measured parameters in this study were GFR and uACR. The results revealed that the coriander seed sonification in this study significantly increased the GFR value and reduced uACR in line with the increase in the administered dose of coriander sonification (p value < 0.05). Hence, it can be concluded that coriander seed sonification has a protective effect against kidney damage due to diabetes.

Keywords: *Sonification, coriander seeds, GFR, uACR.*

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A. INTRODUCTION

Diabetes Mellitus (DM) is a group of metabolic disorders that occur due to abnormalities in insulin secretion, insulin action, or both, characterized by blood glucose levels that exceed normal (hyperglycemia) due to the body's lack of insulin, both absolute and relative.(Brata & Pratiwi, 2019). Diabetes is divided into two types, type 1 diabetes and type 2 diabetes. Type 1 diabetes is caused by damage to the beta cells of the pancreatic islets which causes an increase in glucose levels in the blood. Meanwhile, type 2 diabetes is caused by increased blood sugar due to loss of sensitivity to insulin (Bulqis et al., n.d., 2020).

According to the International Diabetes Federation (IDF), there were 463 million diabetes patients aged 20-79 years in the world in 2019, accounting for 9.3% of the total population of the same age. IDF estimates the prevalence of diabetes by gender in 2019 at 9% for women and 9.65% for men. The prevalence of diabetes is estimated to increase as the population ages to 19.9% or 111.2 million people aged 65-

79 years. This number is expected to continue to increase, reaching 578 million in 2030 and 700 million in 2045 (Jais & Susanti, 2021).

In Southeast Asia in 2016, the development of diabetes has reached 96 million people, of which 90% are type 2 diabetes, but half of them are a source of complications that lead to death. IDF (International Diabetes Federation) revealed that in Asia, Indonesia is the 7th country with diabetes prevalence (8.5 million), and the number of diabetes sufferers in Indonesia is expected to increase to 14.1 million in 2035 (Irwansyah & Kasim, 2021).

From the 2018 Riskesda results, the prevalence of diabetes in the age group ≥ 15 years in Indonesia reached 2%. According to gender, the prevalence of diabetes in women is 1.78%, and in men it is 1.21%. For prevalence by age group, the highest incidence is in the 55-64 year age group with a range of 6.3%(Azizah et al., n.d., 2022).

The hyperglycemia situation in type 2 DM triggers the formation of Reactive Oxygen Species (ROS) which exceeds the antioxidant capacity, resulting in oxidative stress in the tissue which causes various macrovascular and microvascular complications (Putra, S. O., 2020). The most common microvascular complication is diabetic nephropathy. Coriander is traditionally used as a stimulant, carminative, anticonvulsant, diuretic and antirheumatic, antiemetic and has potential as an antioxidant. Apart from that, coriander can have antibacterial and antifungal properties in vitro. Phytochemical screening of coriander stated that coriander contains carbohydrates, protein, phenolic compounds, tannins and flavonoids. (Yulia et al., n.d., 2020). The ability of flavonoids as antioxidants can reduce oxidative stress and reduce ROS. It can have a protective effect on pancreatic beta cells and increase insulin receptor sensitivity (Panjaitan et al., n.d., 2018).

Based on this background description, it is important to find effective traditional medicines at affordable prices with local resources and relatively safe side effects, one of which is coriander seeds (Coriandrum sativum L.) which are rich in phytochemical compounds such as flavonoids. This compound acts as an antioxidant which can improve oxidative stress in the body. Several studies show that coriander has pharmacological effects, including diuretic, antioxidant, antispasmodic, sedative, antimicrobial, antidiabetic, antimutagenic and anthelmintic (Dersing et al., 2020). However, no previous research has explored the effectiveness of sonification of coriander seeds (Coriandrum sativum L.) on complications of diabetes mellitus. So, researchers are interested in exploring the effectiveness of coriander seed nanoparticles (Coriandrum sativum L.) against complications of diabetes mellitus in male mice as an alloxan-induced experimental animal.

B. METHOD

This research is an experimental study with a Post Test Only Control Group Design research design which aims to assess differences in kidney function in each group of mice. This research was conducted at the Integrated Research Laboratory, Faculty of Medicine, Prima Indonesia University, Medan, from February 2023 to June 2023. This research has passed the Health Research Ethics Committee (KEPK) of

Prima Indonesia University with number 016/KEPK/UNPRI/I/2023. In this study, 30 white rats (Rattus norvegicus) were used that met the inclusion criteria, namely male, 2-3 months old, body weight 180-200 grams, no anatomical defects and blood sugar levels within normal limits. (Nazira, Selvester Thadeus, et al., 2020). Based on Federer's formula, the results The result obtained was 4.75 so rounded up to 5 mice in each group. The sample size required is a minimum of 25 mice, however, to avoid dropouts, 1 mouse was added to each group, so the sample size in this study was 30 mice. (Nazira, Selvester Thadeus, et al., 2020).After the test animals arrive, the test animals must first go through an acclimatization or adaptation process. This process was carried out for ± 7 days to adapt the experimental animals to their environmental conditions and avoid stress in the experimental animals. After the acclimatization process, the experimental animals were divided into 5 treatment groups(Iskandar et al., 2017).

The tools used in this research were a blender, plastic jar, oven, 60 mesh sieve, glass beaker, stirring rod, water bath, rotary evaporator, Branson 450 digital sonifier, glucometer, glucose strips, experimental animal cage, 3 cc injection syringe, injection syringe 1 cc, handgloves, analytical balance (Mahran et al., 2019).The materials used in this research were coriander seeds, 96% ethanol, 0.5% Na-CMC, white rat, alloxan, and metformin(Iskandar et al., 2017).

The work procedure in this research consists of several stages, namely identification and collection of samples, making sonification extracts (making simplicia and making extracts), phytochemical screening examinations (triterpenoid and steroid tests, tannin tests, flavonoid tests, alkaloid tests, saponin tests), making oral suspension (making Na-CMC 0.5%, making extract suspension, and making metformin suspension), preparing experimental animals, alloxan induction (making 5% alloxan solution, definition and dosage of diabetic rats), antidiabetic treatment and testing of samples, examination blood sugar levels, taking urine samples, taking blood samples, and ending with data processing.

Observational data on GFR and uACR levels obtained were analyzed using the Statistical Package for Social Sciences (SPSS) computer program. The results of the analysis were carried out to see whether the distribution was normal or not statistically using the Shapiro-Wilk test because the number of samples was n≤50 and the homogeneity test used the Leaven test ($p>0.05$). Normally distributed data ($p>0.05$) is followed by the parametric One-way Analysis of Variant (ANOVA) test with a confidence level of 95% ($p<0.05$) but if the data is not normally distributed or not homogeneous then the Kruskal test is carried out afterwards. -Wallis. Then proceed with the Post Hoc Test Least Significant Difference (LSD) to see the differences between treatment groups.

C. RESULTS AND DISCUSSION

Initial Body Weight

Table 1. Distribution of Initial Body Weight Data with Shapiro-Wilk

Parameter	Treatment Group	P value	Data Distribution
Initial Body Weight	Metformin	0.480	Normal
	Control	0.820	Normal
	Sonification of Coriander Seeds 200 mg/ kgBB	0.033	Abnormal
	Sonification of Coriander Seeds 400 mg/ kgBB	0.167	Normal
	Sonification of Coriander Seeds 800 mg/ kgBB	0.421	Normal

From the table data above, it can be seen that one of the initial body weight data for mice has an abnormal data distribution, this is reflected in the p value < 0.05. Therefore, the analysis was then continued with a non-parametric test in the form of Kruskal-Wallis and the results of the Kruskal-Wallis analysis can be seen in the following table.

Table 2. Comparison of Initial Body Weight of All Treatment Groups

Treatment Group	Initial Body Weight (Grams)			P value
	Median	Min	Max	
Metformin	145.00	143.00	148.00	
Control	162.50	161.00	164.00	
Sonification of Coriander Seeds 200 mg/ kgBB	154.50	153.00	158.00	< 0.001
Sonification of Coriander Seeds 400 mg/ kgBB	157.00	156.00	158.00	
Sonification of Coriander Seeds 800 mg/ kgBB	147.00	146.00	149.00	

From the table data above, it can be seen that there are significant differences in initial body weight in all treatment groups, this is reflected in the P value < 0.001. Where the body weight of the mice in this study ranged from 143 grams to 164 grams.

Glomerular Filtration Rate (GFR)

This study aims to evaluate the effect of sonifying coriander seeds on the kidney tissue of alcosan-induced diabetic rats. To determine the effect of sonication of coriander seeds on kidney tissue, this study evaluated two parameters of kidney function including glomerular filtration rate and the ratio of albumin to creatinine in urine. The glomerular filtration rate as one of the parameters evaluated in this study was initially analyzed for data distribution and the results of the data distribution analysis can be seen in the following table.

Table 3. Distribution of Glomerular Filtration Rate (GFR) Data with Shapiro-Wilk

Parameter	Treatment Group	P value	Data Distribution
Glomerular Filtration Rate	Metformin	0.058	Normal
	Control	0.007	Abnormal
	Sonification of Coriander Seeds 200 mg/ kgBB	0.275	Normal
	Sonification of Coriander Seeds 400 mg/ kgBB	0.291	Normal
	Sonification of Coriander Seeds 800 mg/ kgBB	0.159	Normal

From the table data above, it can be seen that one of the glomerular filtration rate data has an abnormal data distribution, this is reflected in the P value < 0.05. Therefore, the analysis was then continued with the Kruskal-Wallis test to compare glomerular filtration rates between treatment groups and the comparison of glomerular filtration rates in all treatment groups can be seen in the following table.

Table 4. Comparison of Glomerular Filtration Rate (GFR) in All Treatment Groups

Treatment Group	GFR (µL/min)			P value
	Median	Min	Max	
Metformin	71.80	47.62	111.11	
Control	18.92	9.47	44.44	
Sonification of Coriander Seeds 200 mg/ kgBB	30.02	22.22	66.67	0.004
Sonification of Coriander Seeds 400 mg/ kgBB	43.00	15.15	45.45	
Sonification of Coriander Seeds 800 mg/ kgBB	51.59	18.18	62.50	

From the table data above, it can be seen that there are significant differences in GFR across treatment groups, this is reflected in the P value < 0.05 (P value: 0.004). Where the tendency for the highest glomerular filtration rate value was found in the metformin group, namely 71.80 µL/minute, followed by the coriander seed sonification group 800 mg/kgBW, coriander seed sonification 400 mg/kgBW (43 µL/minute), coriander seed sonification 200 mg / kgBW (30.03 µL/minute), and the lowest was the control group, namely 30.02 µL/minute.

Albumin-Protein Ratio in Urine/Urine Albumin-Creatinine Ratio (uACR)

Another parameter that was also evaluated in this study was uACR, namely the ratio of albumin to creatinine in urine. All uACR data was first analyzed for data distribution with Shapiro-Wilk and the results of the uACR data distribution analysis can be seen in the following table.

Table 5. Data Distribution of Albumin-Protein Ratio in Urine/Urine Albumin-Creatinine Ratio (uACR) in All Treatment Groups

Parameter	Treatment Group	P value	Data Distribution
Albumin-Protein Ratio in Urine	Metformin	0.424	Normal
	Control	0.148	Normal
	Sonification of Coriander Seeds 200 mg/ kgBB	0.662	Normal
	Sonification of Coriander Seeds 400 mg/ kgBB	0.139	Normal
	Sonification of Coriander Seeds 800 mg/ kgBB	0.017	Abnormal

From the table data above, it can be seen that one of the uACR data has an abnormal data distribution, this is reflected in the P value < 0.05. Therefore, data analysis was then continued with the Kruskal-Wallis test and the results of this analysis can be seen in the following table.

Table 6. Comparison of the Albumin-Protein Ratio in Urine/Urine Albumin-Creatinine Ratio (uACR) in All Treatment Groups

Treatment Group	uACR (mg/g)			P value
	Median	Min	Max	
Metformin	0.72	0.65	0.75	
Control	0.95	0.79	1.24	0.004
Sonification of Coriander Seeds 200 mg/ kgBB	0.91	0.86	0.96	

Sonification of Coriander Seeds 400 mg/ kgBB	0.93	0.89	0.96
Sonification of Coriander Seeds 800 mg/ kgBB	0.86	0.80	0.92

From the table data above, it can be seen that there are significant differences in uACR values in all treatment groups, this is reflected in the P value < 0.05 (P value: 0.004). Where the tendency for the highest uACR value was found in the control group, namely 0.95mg/g, followed by the coriander seed sonification group 400 mg/kgBW (0.93 mg/g), coriander seed sonification 200 mg/kgBW (0.91 mg/g), sonification of seeds coriander 800 mg/ kgBW (0.86 mg/ dl), and the lowest was in the metformin group, namely 0.72 mg/ g.

The results of this research clearly show that sonification of coriander seeds contains several phytochemical compounds in the form of alkaloids, saponins, flavonoids and tannins. Where sonification of coriander seeds in this study significantly increased the GFR value and reduced uACR in line with the increase in the dose of sonification of coriander extract given (P value < 0.05). There is still limited research evaluating the effects of sonication of coriander seeds on kidney function parameters, especially GFR and uACR.

Several previous studies that have been conducted are limited to the effectiveness of coriander extract as an antidiabetic. Dersing et al. (2020) reported that ethanol extract of coriander seeds showed a significant reduction in blood sugar levels after 14 days of treatment, where an increase in the extract dose would be followed by a decrease in blood sugar levels. Dersing et al. reported that the average blood sugar level of a group of mice that received coriander seed extract at a dose of 5 mg/ml was 317.80 mg/dl, while at a higher dose, namely 7 mg/ml, the group of mice showed an average blood sugar level of 265.20 mg/dl, and the group of mice that received the largest extract dose, namely 9 mg/ml, showed the lowest blood sugar levels, namely 267.40 mg/dl (Dersing, Rusmini and Triwahyuni, 2020) .

Other research conducted by Naquvi et al. (2012) reported research results that were not much different. Where Naquvi et al. reported that water extract from coriander seeds could significantly reduce blood glucose levels, especially at doses of 250 mg/kgBW and 500 mg/kgBW in male Wistar rats induced with streptozotocin after 7 days of administering the extract (P value <0.01). Similar research was also conducted by Das et al. (2019) who reported that water extract from coriander seeds could significantly reduce blood sugar levels when compared to the control group after 14-28 days of administering the extract to a group of streptozotocin-induced diabetic mice, even water extract from coriander seeds could reduce HbA1C levels. after 28 days of extract administration. However, the effect of reducing blood sugar levels and HbA1C from water extract from coriander seeds is still not better or superior to the standard drug, namely metformin (Naquvi et al., 2011) .

The antidiabetic effect of coriander seed extract in this study cannot be separated from the presence of phytochemical compounds in coriander seed extract. Kajal and Singh (2019) reported that coriander seed extract contains several phytochemicals such as linalool, ascorbyl palmitate, petroselinic acid, docosahexanoic acid, linoleic acid, and oleic acid. Of the various phytochemical contents, the

phytochemical content that may be useful in reducing serum glucose levels is linalool. Apart from that, other compounds such as terpenes and terpenoids are also reported to reduce oxidative stress, hyperglycemia and hyperlipidemia, and can improve insulin secretion levels through tissue regeneration of pancreatic beta cells. Thus, coriander seed extract can improve the stimulation of insulin secretion and act like insulin on insulin receptors. Furthermore, coriander seed extract increases glucose transport, glucose oxidation, and glycolysis which is comparable to insulin preparations with a concentration of 10-8 M. This antidiabetic effect resembles the effect of oral antidiabetic drugs, namely sulfonylureas (Kajal and Singh, 2019; Dersing, Rusmini & Triwahyuni, 2020).

Diabetes mellitus is a metabolic disease that is often encountered and its prevention is important because of its complications and high prevalence. This long-term hyperglycemic state can cause significant changes in kidney tissue, leading to kidney failure. This damage can cause several abnormalities in the histological structure of kidney tissue, including accumulation of extracellular matrix, thickening of the glomerular membrane, and glomerular sclerosis (Patschan & Müller, 2016).

There are various parameters that can be used to assess kidney function. One of the commonly used kidney function examination modalities is urea and creatinine. Ureum is the final product with nitrogen atoms from the catabolism of proteins and amino acids, while creatinine is the breakdown product of creatine phosphate in muscles and is excreted by the kidneys. Urea is a parameter to measure kidney function indirectly because urea levels in the blood are directly related to kidney excretion function. Meanwhile, creatinine examination is usually used to diagnose kidney function disorders and measure creatinine phosphate in the blood. Based on the urea and creatinine values, kidney physiology or function can be measured using physiological parameters including GFR and uACR (Sadick et al., 2011; Besseling et al., 2021).

Glomerular Filtration Rate (GFR) is one of the parameters of kidney function which is estimated through creatinine levels in the blood and is the best test to measure the level of kidney function, especially in determining the stage of kidney disease (Veronika and Hartono, 2019). Meanwhile, uACR is the ratio of the amount of albumin in the urine to creatinine in the urine, where an increase in the uACR value indicates diabetic nephropathy. An albumin to creatinine ratio > 30 mg/g serves as a reference value (Tombokan et al., 2022). In this study, the trend of GFR and uACR values significantly decreased as the dose of coriander seed nanoparticles increased. This indicates that in line with the increase in the dose of coriander seed sonification, it will be followed by improvements in kidney function, especially in the excretory function of various physiological parameters including urea, creatinine and albumin in diabetic rats induced with alloxan.

The improvement of kidney function by sonification of coriander seeds in alloxan-induced diabetic rats is related to the antidiabetic and antioxidant effects of coriander seed extract. Phytochemical compounds such as phenolic acids and flavonoids have antioxidant effects with the activity of scavenging various free

radicals, thus preventing a decline in kidney function. Flavonoids together with other polyphenol molecules are reported to have antioxidant effects by neutralizing various free radicals that exist by donating electrons to unstable free radical molecules through the hydroxyl group (-OH) in polyphenol compounds. In addition, flavonoids and various other phytochemical compounds reduce the production of free radicals from prolonged hyperglycemic states in diabetes patients, thereby preventing the production of new free radicals. All of these effects can cumulatively increase kidney protection from damage due to prolonged hyperglycemic conditions (Dersing, Rusmini and Triwahyuni, 2020; Chiuman et al., 2021; Sari, Ginting and Yulizal, 2021).

D. CONCLUSION

There was a significant difference in GFR between all treatment groups, this was reflected in the P value < 0.05 (P value: 0.004). Where the tendency for the highest glomerular filtration rate value was found in the metformin group, namely 71.80 µL/minute and the lowest was in the control group, namely 30.02 µL/minute. The difference in uACR values was significant across treatment groups, this was reflected in the P value < 0.05 (P value: 0.004). Where the tendency for the highest uACR value was found in the control group, namely 0.95mg/g and the lowest was in the metformin group, namely 0.72 mg/g.

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