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Test the Effect of Miana Leaf Ethanol Extract on Ureum and Creatinine Levels in Male White Rats

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Abstract

This study aims to determine the content of secondary metabolites in miana leaf ethanol extract, and to determine the effective dose of miana leaf ethanol extract in reducing urea and creatinine levels in male white rats. This study used 30 rats divided into 6 treatment groups, each group consisting of 5 test animals, namely normal group, negative control, positive control, dose of 150 mg/kg BW, dose 200 mg/kg BW, and dose 250 mg/kg. kg body weight. The data obtained will then be tested for normality and homogeneity to find out the data is normally distributed and homogeneous. If the data is normally distributed and homogeneous, then it is continued using One Way Anova statistical analysis at a 95% confidence level and further LSD test is carried out. If the data obtained is not normal and homogeneous, then it is analyzed using non-parametric statistics Kruskal-Wallis test and continued with Mann Whitney further test to determine the difference between all treatments. The results showed that the ethanolic extract of miana leaves contained secondary metabolites of alkaloids, flavonoids, saponins,and tannins; miana leaf ethanol extract has an effect on reducing urea and creatinine; Miana leaf ethanol extract at a dose of 250 mg/kg BW was an effective dose in reducing urea and creatinine with an average decrease of 18.8 mg/dl and 0.64 mg/dl.

Keywords: Miana leaves, Streptozotozin, Ureum and Creatinine

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1 Introduction

The development of the times and technology that so far has seen so many significant changes in modern human life, one of which is in Indonesia. Especially in a modern lifestyle, one of which is in determining food choices. There are so many foods that can cause various diseases, one of which is diabetes mellitus. Diabetes mellitus according to the World Health Organization (WHO) is a chronic disease caused by a lack of insulin produced by the pancreas, or by an ineffectiveness of insulin against its receptors [1].

Hyperglycemia that occurs in people with diabetes mellitus causes a state of oxidative

stress, between Reactive Oxygen Species (ROS) and antioxidants [2] Hyperglycemia that occurs will damage the blood vessels in the kidneys, causing interference with glomerular filtration as a blood filter. This makes the structure of the kidney change so that kidney function is disturbed, changes in kidney function can be seen from the increase in creatinine and urea levels [3]. Kidneys have a function to excrete metabolic substances. Metabolic waste substances excreted through the kidneys include urea and creatinine.

Urea is the end product of protein and amino acid catabolism produced by the liver and distributed through the intracellular and extracellular fluids into the blood and then filtered by the glomerulus. Measurement of serum urea can be used to evaluate kidney function, hydration status, assess nitrogen balance, assess progression of kidney disease, and assess hemodialysis results. Urea and other nitrogen-rich waste products are normally excreted from the blood vessels through the kidneys, so an increase in urea/BUN levels can indicate kidney function failure [4]

Creatinine is the result of the breakdown of muscle creatine phosphate, produced by the body constantly depending on muscle mass. Serum creatinine levels have been widely used to measure kidney function by measuring the glomerular filtration rate (GFR). Over the past 40 years, serum creatinine has become a common and inexpensive marker of kidney function. Creatinine levels are in a relatively constant state, making it a good marker of renal filtration. Creatinine is an ideal substance for measuring kidney function because it is a product of the body's metabolism that is produced constantly, filtered by the kidneys, not reabsorbed, and secreted by the proximal tubule. The diagnosis of renal failure can be made when the serum creatinine level rises above the normal reference value [5].

Miana plant is a plant that has the scientific name (*Coleus atropurpureus Benth)* grouped in the Lamiaceae family belonging to the Lamiales nation. The phytochemicals contained in miana include essential oils, tannins, flavonoids, eugenol, steroids, saponins, phytol, streptozotocin and quercetin. Miana is interpreted as being able to play a role in curing disease due to the pharmacological activity of its phytochemical content [6]. The benefits of the miana plant are as a poison neutralizer (antitoxic), cure hepatitis, reduce fever, inhibit bacterial growth (antiseptic), treat hemorrhoids, menstrual bullets, food indigestion, lung inflammation, overcome heartburn and diarrhea and as an antidiabetic[7].

Previous research on miana leaves conducted by [8] menyatakan bahwa ekstrak etanol daun miana dosis pada dosis 200 mg/kg BB dapat menurunkan kadar glukosa darah pada tikus dengan persentase 55,69%. Penelitian yang dilakukan olehstated that the ethanol extract of miana leaves at a dose of 200 mg/kg BW can reduce blood glucose levels in rats with a percentage of 55.69%. Research conducted by [9] stated that miana leaves contain flavonoid compounds that have antioxidant activity, based on the results of the analysis, the AEAC (Ascorbic Acid Equivalent Antioxidant Capacity) value was 98.53 mg AEAC/gram sample and IC50 was 324.80. The IC50 value is included in the weak level (in the range of 250-500 ppm). Another study conducted by [10] stated that miana leaves (*Coleus atropurpureus* Benth) can inhibit the growth of Escherichia coli with a concentration of 250

Previous research on creatinine and urea levels in ethanol extract of long bean leaves (*Vigna unguiculata* (L) Walp) at a dose of 300mg/kg BW gave an effect on creatinine and urea levels with an average of 0.76 mg/dl and 25.00 mg/dl [11]. Another research on urea and creatinine is the ethanol extract of red gendola leaves (*Basella alba* L.) t a dose of 200 mg/kg BW was effective in reducing creatinine and urea levels with an average of 0.70 mg/dl and 46.52 mg/dl [12] ethanol extract of red gedi leaves (*Abelmoscuschus manihot* L.) a dose of 50 mg/Kg BW, leaf extract of cat whiskers (*Orthosiphon stamineus* at a dose of 100 mg/Kg BW was effective as nephroprotective against creatinine and urea levels with an average of 0.76 mg/dl and 38.0 mg/dl [13].

Based on the description above, the researchers are interested in conducting further research on urea and creatinine using ethanol extract of miana leaves with various doses of 150 mg/kg BW, 200 mg/kg BW and 250 mg/kg BW and whether it has an effect on creatinine and urea levels on streptozotocin-induced male white rats. Then the normal and homogeneous

research data will be tested with the One Way Anova statistic with a 95% confidence level and Duncan's further test is carried out, and if the data obtained are not normal and not homogeneous, the Kruskal-Wallis test non-parametric statistics will be used and continued with further tests. Mann Whitney to determine the difference between all treatment groups.

2 Methods

2.1 Tool

Glassware (Pyrex), stirring rod, maceration vessel, porcelain cup, animal cage, rotary evaporator (Heidolph), centrifugation (Table Top Centrifuge Plc 03 Series), UV-VIS spectrophotometry (Evolution 201), oral probe (One Med Health care)), injection syringe (One Med Health care), rat drinking water, blood tube (Vacuntainer Plain), effendorph tube and analytical balance (Ohaus), water bath (Denville).

2.2 Materials

Distilled water, 70% alcohol, aluminum foil, 2N hydrochloric acid, Citrate-buffer saline, Dagenndrof LP, EDTA, 96% ethanol, miana leaf extract, FeCl3, Glibenclamid Filter paper, Magnesium, 0.5% Na CMC, Sodium hydroxide, Sodium chloride, sodium salicylate, sodium nitroprusside, sodium hyochlorite, sodium citrate, phosphate buffer, sodium hydroxide, streptozotocin, creatinine reagent kit, urea kit reagent and standard feed. Production of Miana Leaf Ethanol Extract

Miana leaf extract was made by maceration method. Miana leaf powder that has been sieved using a mesh sieve no. 40, weighed 1000 grams and then put into 2 maceration vessels of 500 grams each using 3 liters of 96% ethanol solvent as much as 1.5 liters each, closed, then allowed to stand for 3x24 hours protected from light while occasionally stirring. The extract was then filtered using filter paper to obtain the filtrate. Then it is concentrated using a Rotary Vacuum Evaporator at a temperature of 40-60°C then followed by evaporation using a water bath at a temperature of 60°C until a thick extract is obtained.

2.3 Glibenclamide Suspension Manufacturing

The dose of glibenclamide in adult humans is 5 mg per day, if converted to rats weighing 200 grams then multiplied by a conversion factor of 0.018 so that the dose of glibenclamide for rats is 0.45 mg/kg BW. Glibenclamide tablet powder was weighed equivalent to 3.6 mg then suspended in 0.5% Na CMC to 100 ml, then shaken until homogeneous.

2.4 Preparation Of Streptozotocin Solution (STZ)

Streptozotocin was weighed as much as 0.32 grams and then dissolved using citrate-buffer saline with a pH of 4.5, then induced in rats via intraperitoneal. The dose of streptozotocin is 40 mg/kg BW.

2.5 Data Analysis

The data obtained from the measurement of urea and creatinine levels were then tested for normality to determine if the data were normally distributed. If the data is normally distributed, then it is continued using One Way Anova statistical analysis at a 95% confidence level and Duncan's further test is carried out. If the data obtained is not normal or homogeneous, then it is analyzed using non-parametric statistics Kruskal-Wallis test and continued with Mann Whitney further test to determine the difference between all treatments. Data processing using SPSS software program.

3 Results and Discussions

Phytochemical screening test to determine the content of compounds contained in the ethanol of miana leaves (Coleus atropurpureus Benth). The results of the phytochemical screening test (Table 1) showed that the ethanolic extract of miana leaves (Coleus atropurpureus Benth) contained flavonoids, alkaloids, saponins, and tannins.

Table 1. Phytochemical Test Results of Miana Leaf Ethanol Extract (*Coleus atropurpureus* Benth)

No.	Secondary Metabolic Compound	Reactor	Results	
			Miana Leaf Ethanol Extract	Information
1.	Flavanoids	Magnesium and HCl	Formation of brick red color	+
2	Alkaloids	Reactor Dragendorf	Formation of a red-orange precipitate	+
3.	Tanins	$FeCl_3$	Formation of dark blue color	+
4.	Saponins	Aquadest	Foam builds up for 5 minutes	+

Note: (+) contains the class of compounds being tested

This study begins with measuring the initial urea level on (day 0) to determine the urea level before treatment (Table 2). The mean value of initial urea level measurement in normal control test animals was 16.6 mg/dl, negative control was 15.8 mg/dl, positive control was 16.6, the treatment group was 150 mg/kg BW was 16.6 mg/dl, the group was 16.6 mg/dl. the treatment dose of 200 mg/kg BW was 17.4 mg/dl, and the treatment dose of 250 mg/kg BW was 17.2 mg/dl, which means that the average creatinine level of the test animals used is within the normal range where the creatinine level is normal for mice is 15.0 – 21.0 mg/dl [14]

Table 2. Average Urea Level

Mean ± SD Ureum Level (mg/dl)							
Days to-	Normal Control	Negative Control	Positif Control	Dose 150 mg/kg BB	Dose 200 mg/kg BB	Dose 250 mg/kg BB	P
0	16,6 ± 1,1	15,8 ± 0,8	16,6 ± 0,5	16,6 ± 1,1	17,4 ± 0,9	17,2 ± 0,8	0,161(x)
7	18,2 ± 2,3	55,0 ± 11,6	48,2 ± 9,0	47,0 ± 9,7	49,4 ± 9,5	45,6 ± 10,4	0,017(x)
14	19,2 ± 2,0	54,8 ± 8,2	36,4 ± 5,1	45,2 ± 7,9	43,8 ± 11,0	43,6 ± 9,7	0,004(x)
21	17,2 ± 1,5	64,0 ± 14,0	20,0 ± 1,0	43,4 ± 9,0	39,4 ± 3,6	28,0 ± 3,0	0,000(y)
28	17,0 ±1,6	57,2 ± 11,0	16,0 ± 0,7	33,2 ± 7,6	33,0 ± 5,0	18,8 ± 2,6	0,000(x)

Note: P value < 0.05 = Significantly different and P value> 0.05 = Not significant difference

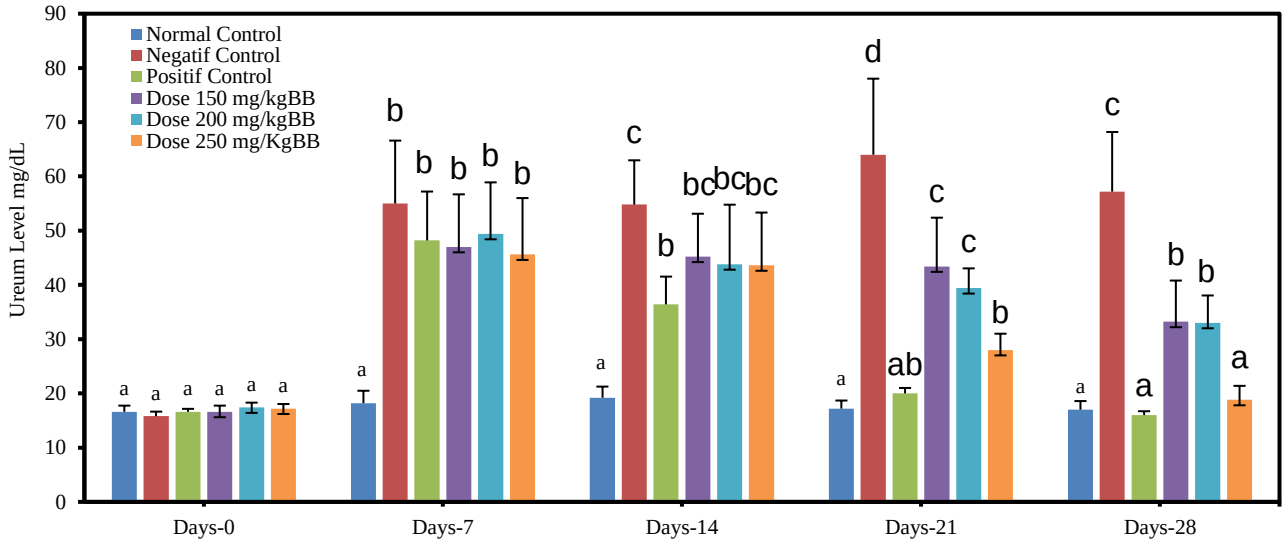

Figure 1. Ureum Level Profile of Male White Rats in Each Group On Day 0, Day 7 (After STZ Induction), Day 14, Day 21, Day 28 (After Administration of Miana Leaf Ethanol Extract)

The results of the Kruskal Wallis statistical test on day 0 showed that all treatment groups were not significantly different with a P value> 0.05 (P value = 0.161) which means that creatinine levels at the beginning of the study were homogeneous with normal levels.

The results of the Kruskal Wallis statistical test on day 7 showed that there was a significant difference in all treatment groups with a P value <0.05 (P value = 0.017). This means that on the 7th day there is an effect of giving streptozotocin so that it is continued with the

Man Whitney test to see the difference between all treatment groups. The results of the Mann Whitney test showed that the negative control, positive control, a dose of 150 mg/kg BW, a dose of 200 mg/kg BW and 250 mg/kg BW were significantly different from the normal group. This means that the test animals in this treatment group are sick or have increased urea levels. This is because the normal control was not given streptozotocin induction while the negative control, positive control and 3 treatment groups were induced by streptozotocin this is because streptozotocin can cause cell death resulting in an increase in blood sugar levels and cause an increase in Reactive Oxygen Species (ROS).), an increase in ROS can cause glomerulosclerosis so that urea levels increase [3]

The results of the Kruskal Wallis statistical test on day 14 showed that there was a significant difference in all treatment groups with a P value <0.05 (P value = 0.004), so it was continued with the Mann Whitney test to see the difference between all treatment groups. The results of the Mann Whitney test showed that the doses of 150 mg/kg BW, 200 mg/kg BW and 250 mg/kgBW were not significantly different from negative and positive controls, but significantly different from normal controls. This shows that the doses of 150 mg/kg BW, 200mg/kg BW and 250 mg/kg BW have not had an effect in reducing urea levels, therefore administration needs to be continued until the 28th day to see the long-term effect on reducing urea levels from administration. ethanol extract of miana leaves at a dose of 150 mg/kg BW, 200 mg/kg BW and 250 mg/kgBW.

The results of the one-way ANOVA test on day 21 showed that there was a significant difference in all treatment groups with a P value <0.05 (P value = 0.000), so that it was continued with the Post Hoc follow-up test. Post Hoc follow-up test results showed a dose of 150 mg. /kg BW and 200 mg/kg BW were significantly different with normal controls, negative and positive controls, the dose of 250 mg/kg BW was not significantly different with positive controls, but significantly different with normal and negative controls. This shows that a dose of 250 mg/kg BW has an effect but is not effective enough in reducing urea levels, therefore the administration needs to be continued until the 28th day to see the long-term effect on reducing urea levels from the administration of ethanol extract of miana leaves at a dose of 150 mg. /kg body weight, 200 mg/kg body weight and 250 mg/kg body weight.

The results of the Kruskal Wallis statistical test on day 28 showed that there was a significant difference in all treatment groups with a P value <0.05 (P value = 0.000), so it was continued with the Mann Whitney test to see the difference between all treatment groups. The results of the Mann Whitney test showed that the doses of 150 mg/kg BW and 200 mg/kg BW were significantly different from normal controls, negative controls and positive controls, doses of 250 mg/kg BW were not significantly different from normal controls and positive controls, but significantly different from controls. negative, meaning that the dose of 250 mg/kg BW is close to normal control and is comparable to positive control. This indicated that on day 28 the urea levels in male white rats decreased in the dose groups of 150 mg/kg BW, 200 mg/kg BW and 250 mg/kg BW. with a mean of 33.2 mg/dl; 33.0 mg/dl and 18.8 mg/dl. And the effective dose obtained is a dose of 250 mg/kg BW, the average value obtained is still within the normal value of 19 mg/dl. This is because the content of flavonoids with antioxidant activity that works as a diuretic increases the glomerular filtration rate so that urea levels decrease.

Table 3. Average Creatinine Levels

Mean ± SD Creatinine Level (mg/dl)							
Days to-	Normal Control	Negative Control	Positif Control	Dose 200 mg/kgBB	Dose 300 mg/kgBB	Dose 400 mg/kg BB	P
0	0,46 ±0,23	0,46 ± 0,22	0,46 ± 0,27	0,38 ± 0,22	0,54 ± 0,17	0,48 ± 0,23	0,875(x)
7	0,46 ± 0,18	1,38 ± 0,18	1,48 ± 0,19	1,54 ± 0,18	1,52 ± 0,22	1,42 ± 0,22	0,000(y)
14	0,50 ± 0,12	1,28 ± 0,20	1,18 ± 0,23	1,40 ± 0,14	1,44 ± 0,19	1,36 ± 0,24	0,008(x)
21	0,48 ± 0,18	1,28 ± 0,33	0,70 ± 0,12	1,20 ± 0,21	1,18 ± 0,29	0,94 ± 0,23	0,000(y)
28	0,48 ± 0,11	1,36 ± 0,17	0,40 ± 0,14	0,96 ± 0,26	0,92 ± 0,23	0,64 ± 0,30	0,001(x)

Note: P value < 0.05 = Significantly different and P value> 0.05 = Not significant difference

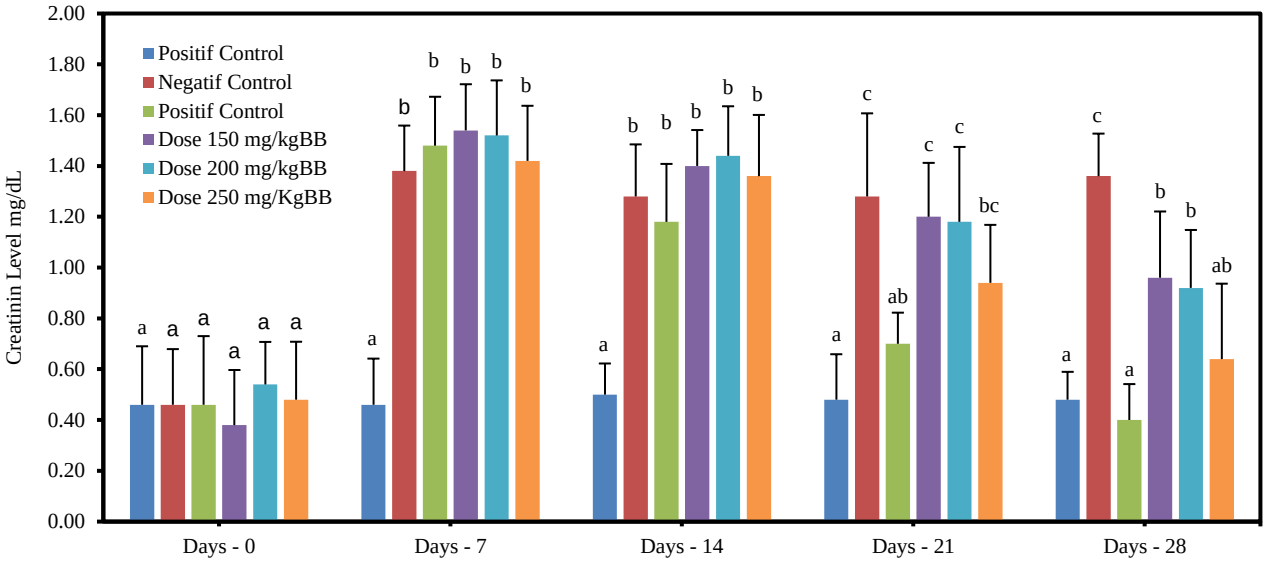

Figure 2. Creatinine Level Profile of Male White Rats in Each Group On Day 0, Day 7 (After STZ Induction), Day 14, Day 21, Day 28 (After Administration of Miana Leaf Ethanol Extract).

This study begins with measuring creatinine levels early on (day 0) to determine creatinine levels before treatment (Table 3). The mean value of the initial creatinine level measurement in normal control test animals was 0.23 mg/dl, negative control was 0.22 mg/dl, positive control was 0.27 mg/dl. The treatment group dose of 150 mg/kg BW was 0.22 mg/dl. dl, the treatment group at a dose of 200 mg/kg BW was 0.17 mg/dl, and the treatment group at a dose of 250 mg/kg BW was 0.23 mg/dl, which means that the average creatinine level of the test animals used is within the normal range, normal creatinine for rats is 0.2 – 0.8 mg/dl [14]

The results of the Kruskal Wallis statistical test on day 0 showed that all treatment groups were not significantly different with a P value> 0.05 (P value = 0.875) meaning that creatinine levels at the beginning of the study were homogeneous with normal levels.

The results of the one-way ANOVA test on day 7 showed that there was a significant difference in all treatment groups with a P value <0.05 (P value = 0.000), meaning that on day 7 there was an effect of giving streptozotocin so that it was continued so that it was continued with the test. Post Hoc continued the results of the Post Hoc follow-up test showed that the negative control, positive control, dose of 150 mg/kg BW, dose of 200 mg/kg BW and 250 mg/kg BW were significantly different from the normal group, meaning that the test animals in the treatment group were in a different condition. sick or experiencing an increase in creatinine levels caused by streptozotocin induction, causing hyperglycemia which can increase ROS production as a result, oxidative stress will occur so that it can disrupt the glomerular filtration rate and can reduce the function of renal filtration which causes creatinine levels in the blood to increase [15].

The results of the Kruskal Wallis statistical test on day 14 showed that there was a significant difference in all treatment groups with a P value <0.05 (P value = 0.008), so it was continued with the Mann Whitney test to see the difference between all treatment groups. The results of the Mann Whitney test showed that the negative control, positive control, dose of 150 mg/kg BW, 200 mg/kg BW and 250 mg/kg BW were significantly different from the normal group. This shows that the doses of 150 mg/kg BW, 200mg/kg BW and 250 mg/kg BW have not had an effect in reducing urea levels, therefore administration needs to be continued until the 28th day to see the long-term effect on reducing urea levels from administration. ethanol extract of miana leaves at a dose of 150 mg/kg BW, 200 mg/kg BW and 250 mg/kgBW.

The results of the one way ANOVA test on day 21 showed a significant difference in all treatment groups with a P value <0.05 (P value = 0.000), so that it was continued with the Post

Hoc follow-up test. Post Hoc follow-up test results showed a dose of 150 mg/day. kg BW and 200 mg/kg BW were not significantly different from negative controls, but significantly different from normal and positive controls, the dose of 250 mg/kg BW was not significantly different from positive and negative controls, but significantly different from normal controls. This shows that on the 21st day creatinine levels at a dose of 150 mg/kg BW and a dose of 200 mg/kg BW have not decreased, but there is a decrease at a dose of 250 mg/kg BW, this is due to the concentration being too small so the effect is very low. small compared to the dose of 250 mg/kg BW, this indicates that the larger the dose, the more active substances contained in the extract so that it can have an effect [16].

The results of the Kruskal Wallis statistical test on day 28 showed that there was a significant difference in all treatment groups with a P value <0.05 (P value = 0.001), so it was continued with the Mann Whitney test to see the difference between all treatment groups. The results of the Mann Whitney test showed that the dose of 150 mg/kg BW, 200 mg/kg BW was not significantly different from normal control, negative control and positive control, the dose of 250 mg/kg BW was not significantly different from normal control and positive control, but significantly different from negative control. This shows that on day 28 the creatinine levels in male white rats decreased in the dose groups of 150 mg/kg BW, 200 mg/kg BW and 250 mg/kg BW. with a mean of 0.96 mg/dl; 0.92 mg/dl and 0.64 mg/dl. And the effective dose obtained is a dose of 250 mg/kg BW, the average value obtained is still within the normal value of 0.64 mg/dl. Miana leaf extract at a dose of 250 mg/kg BW can be suspended properly so that the active substances contained in the ethanol extract of miana leaves can be perfectly absorbed by the receptor so that it has a good effect in lowering creatinine levels.

4 Conclusion

Based on the results of the study it can be concluded that:

1. The ethanolic extract of miana leaves (Coleus atropurpureus Benth) contains secondary metabolites, namely flavonoids, alkaloids, saponins, and tannins.

2. Ethanol extract of miana leaves (Coleus atropurpureus Benth) doses of 150, 200 and 250 mg/kgBW had an effect on reducing urea and creatinine levels in male white rats (Rattus norvegicus).

3. Ethanol extract of miana leaves (Coleus atropurpureus Benth) dose of 250 mg/kgBW is an effective dose in reducing urea and creatinine levels in male white rats with an average of 18.8

5 Konflik Kepentingan

Tidak ada konflik kepentingan.

6 Daftar Pustaka

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