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The effect of red guava juice (*Psidium guajava Linn.*) in decreasing uric acid and creatinine levels of hyperuricemic white mice (*Mus musculus*)

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ABSTRACT

Background: Uric acid is the final product of purine metabolism in humans. Increased uric acid production or decreased uric acid excretion can raise the blood creatinine level. Red guava (Psidium Guajava Linn.) contains a high amount of vitamin C, polyphenol, and flavonoids that serve as antioxidants. Empirically, red guava was used medicine for various diseases, one of which is secondary hyperuricemia.

Aim: This study aims to determine the effect of red guava juice on uric acid and creatinine levels of secondary hyperuricemic model in white mice (*Mus musculus*)

Method: The study used an experimental design with pretest-posttest control group method. Subjects were 48 two-months-old male, white mice BALB/C breed. The study subjects were categorized into 6 different groups, namely normal control (NC) group which were given standard feed; positive control (PC) group which were induced by potassium oxonate and were given standard feed; intervention 1 (I1) group which were induced by potassium oxonate, were given standard feed and allopurinol 0.26mg/Kg mice body weight/day; and intervention 2, 3, 4 (I2, I3, I4) groups which were induced by potassium oxonate, were given standard feed and red guava juice with the dose of 5 ml/Kg mice body weight/day, 10ml/Kg mice body weight/day, and 20ml/Kg mice body weight/day, respectively. The blood uric acid level of the mice was measured by an enzymatic method using FS TBHBA uric acid reagent. The blood creatinine level was measured by Jaffe method using Creatinine FS reagent. The data was then analyzed using One Way ANOVA and were considered significant if p-value < 0.05.

Results: Based on statistical analysis, red guava juice with the dose of 5 ml/Kg mice body weight/day, 10 ml/Kg mice body weight/day, and 20 ml/Kg mice body weight/day can lower the uric acid level and creatinine level significantly ($p < 0,05$). The reductions in uric acid level dose 5 ml/ Kg mice body weight/day were 4.90 ± 0.35 mg/dl ($p=0.001$), dose 10 ml/Kg mice body weight/day were 5.80 ± 0.39 mg/dl ($p=0.001$), dose 20 ml/Kg mice body weight/day were 6.71 ± 0.47 mg/dl ($p=0.001$). The reductions of blood creatinine level dose 5 ml/Kg mice body weight/ day were 0.55 ± 0.07 mg/dl ($p=0.001$), dose 10 ml/Kg mice body weight/day were 1.67 ± 0.16 mg/dl ($p=0.001$), dose 20 ml/Kg mice body weight/day were 2.12 ± 0.14 mg/dl ($p=0.001$).

Conclusion: The administration of red guava juice dose of 5 ml/Kg mice body weight/day, 10 ml/Kg mice body weight/day, and 20 ml/ Kg mice body weight/day were significant can lower the uric acid and creatinine levels of mice (*Mus musculus*). The most effective dose on lowering uric acid and creatinine levels of hyperuricemic white mice (*Mus musculus*) was 20 ml/Kg mice body weight/day.

Keywords: red guava (Psidium guajava linn.), uric acid, creatinine

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INTRODUCTION

Uric acid is the final byproduct of nucleic acid or purine metabolism in human body.[1] The normal uric acid level are 3,5 – 7,0 mg/dL in males and 2,6 – 6,0 mg/dL in females.[2] The prevalence of hyperuricemia in human population is quite high. Based on Basic Health Research (Riset Kesehatan Dasar) in Indonesia on 2013, the prevalence of joint disease in Indonesia is 11.9% according to health care personnel diagnosis and 24.7% according to diagnosis or symptoms.[3] An American study in 2011 showed that the prevalence of hyperuricemia was 21.2% and 21.6% among men and women, respectively.[4] In 2012, a study of Japanese population showed that the prevalence of hyperuricemia was 30% in men.[5]

Factors that contribute to the development of hyperuricemia are increases in metabolic production of uric acid and decreases in urinary uric acid excretion by the kidney.[6] Hyperuricemic conditions may lead to an increase in blood creatinine level.[7,8] This increase in blood creatinine level may indicate the decrease in renal function by decreasing glomerular filtration rate.[9] Advanced hyperuricemia may prompt to gout diseases. Gout is a group of heterogeneous disease as a result of deposition of monosodium urate (MSU) crystals in tissues due to hyperuricemic metabolic disorders.[10]

Red guava (*Psidium guajava linn.*) contains various nutritional contents including vitamin C, vitamin A, vitamin B1, B2, B3, B6, B9, B12, B15, minerals, oxalic acid, malic acid, saponins, polyphenols, flavonoids, and quercetin.[11] Several studies showed that antioxidant feature on nutrients such as vitamin C, polyphenols, flavonoids, and mineral compounds such as magnesium and calcium

have antihyperuricemic and anti-inflammation properties.[8,12]

Currently, there are not many studies investigating the effect of red guava (Psidium guajava linn.) on uric acid and creatinine levels due to hyperuricemic conditions. Based on the description above, the authors are interested in examining the effect of red guava (Psidium guajava linn.) juice to the blood uric acid and creatinine level of white mice (Mus musculus) model of hyperuricemia.

MATERIAL AND METHOD

The present study used true experimental design with pre-test-post-test control group design, which was conducted on BALB-C strain white mice (Mus musculus) as the study object. The study only included male mice due to the lack of estrogen hormones in their body. This study used 48 male mice, which were randomly distributed into six different groups with different treatments on each group. The feed is used in this research is the standard feed *Comfeed*. Standard feed and drinking water are given *ad libitum*. The different treatments conducted to the mice groups were as follow:

NC = normal control (standard feed , aquadest)
PC = positive control (standard feed, aquadest, potassium oxonate)
I1 = drug intervention (standard feed, aquadest, potassium oxonate, allopurinol)
I2 = red guava juice (RGJ) intervention dose 1 (standard feed, aquadest, RGJ of 5 ml/Kg mice body weight/day)
I3 = red guava juice (RGJ) intervention dose 2 (standard feed, aquadest, RGJ of 10 ml/Kg mice body weight/day)
I4 = red guava juice (RGJ) intervention dose 3 (standard feed, aquadest, RGJ of 20 ml/Kg mice body weight/day)

Hyperuricemia Induction

The increase in blood uric acid and creatinine level of the mice was induced by intraperitoneal potassium oxonate administration with a dose of 250 mg/kg mice body weight/day. Potassium oxonate is a reagent that inhibits urate oxidation, and thus the administration of potassium oxonate lead to hyperuricemic state.[7,13]

Preliminary Study to the Study Sample

Prior to the study, the mice were adapted for one week and were given standard feeding. The first test was a preliminary test to induce hyperuricemic model at the mice. A total of 6 male, white mice were weighed and divided into two groups of three mice each, namely:

1. Hyperuricemic group (7 days): were given potassium oxonate 250 mg/Kg mice body weight/day for 7 days
2. Hyperuricemic group (14 days): were given potassium oxonate 250 mg/Kg mice body weight/day for 14 days

The potassium oxonate inductions were done during the accumulation of uric acid, which was between 09.00 and 10.00 AM. Blood sampling was performed when the uric acid level was at the highest point, that is, 150 minutes after potassium oxonate induction.[14]

The administration of potassium oxonate with a dose of 250 mg/Kg mice body weight/day for seven days can cause hyperuricemic model in the mice, marked by elevated blood levels of uric acid and creatinine.[13] The administration of potassium oxonate on the preliminary study was done for seven days and fourteen days. The difference in the duration of potassium oxonate induction was made to determine the highest uric acid and creatinine levels achieved.

Uric Acid Level Measurement

The blood uric acid level was tested by an enzymatic reaction using FS* TBHBA uric acid reagent. The sample solution was prepared by taking 20 µl of serum plus 1000 µl of mono-reagent (4 parts of Reagent 1 and 1 part of Reagent 2). The homogeneously mixed serum with FS* TBHBA uric acid Reagent was then incubated for 6 to 8 minutes at 37°C. Next, the sample solution, standard and the label were interpreted using StartDust FC* 15 spectrophotometers at 546nm wavelength.[15]

Creatinine Level Measurement

The blood creatinine levels were determined by the Jaffe method, that is, a complex reaction of creatinine-pikrat using Creatinine FS reagent. Blood was contained in 1,5 mL microtube with heparin, centrifuged at 8000rpm for 10 minutes. The test material was then taken using a micropipette and inserted into the test tube.[16]

Data Analysis

Obtained data were then analyzed using SPSS computer program version 22. The data normality test was done using Shapiro-Wilk test. Data is normally distributed if $p>0.05$. Next, we perform data homogeneity test using Levene test and the p value>0.05 which indicate that the data distributed homogeneously.

The different effect of six different intervention groups was analyzed using One Way ANOVA parametric test if the data were normally and homogeneously distributed, continued with Post Hock test

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using Tukey High Significant Difference (HSD). If data were normally distributed but was not homogenous, the next test to be done was Games Howell test to see the difference between the six intervention groups. If the data were not normally distributed, Kruskal Wallis parametric test would be used. The difference in blood level of uric acid and creatinine before after intervention were examined using Paired T-test. The difference was significant if p-value < 0.05.

RESULT

Preliminary Test Result

The preliminary test was done to induce hyperuricemic model on the mice by administering potassium oxonate with a dose of 250mg/Kg mice body weight/day intraperitoneally between 09.00 and 10.00 AM.[14] The dose used in this study was based on the dose used in previous study.[7]

The preliminary study showed that administration of potassium oxonate with a dose of 250mg/ Kg mice body weight/day for 7 and 14 days lead to increase in uric acid level. The duration of administration of potassium oxonate in the white mice affects the blood level of uric acid and creatinine. Administration of potassium oxonate for 7 days resulted in the uric acid level of 8.76 mg/dL and creatinine level of 3.13 mg/dL, while administration for 14 days resulted in the uric acid level of 9.21mg/ dL and creatinine level of 3.9mg/dL.

The normal uric acid level for male white mice is 1.10 mg/dL to 4.12 mg/dL, while the normal creatinine level for male white mice is 0.19 mg/dL to 0.84 mg/dL.[17]

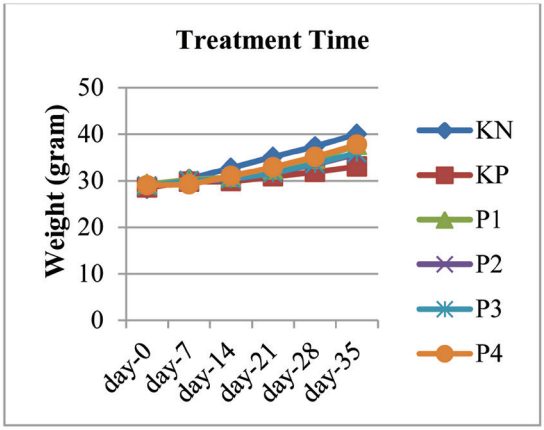

Figure 1 Mice Weight Progress in every intervention group

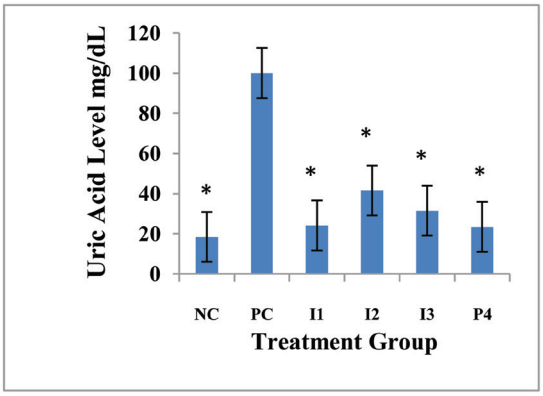

Figure 2 The mean uric acid level in groups treated with PO, RGJ with various dose and medication compared with PC group. *) Shows intervention groups compared to positive control group

White Mice Weight Progress

The white mice were weighed six times during the study, that is on day-0, day-7, day-14, day-21, day-28, and day-35. (Figure 1)

From Figure 1, we can see the weekly weight progress of the mice. The mice experienced both weight gain. The smallest weight gain in all groups occurred at week 1 and week 2 that is day-7 and day-14 caused by an external factor such as stress due to the treatment of animal model of hyperuricemia. Increased Weight gain normal mice might be due to the effort of the mice to maintain their health and therefore increased their appetite.

The weight gain of mice in the NC group was 7.25±0.70 grams, in the PC group was 3.12±0.64 grams, in the I1 group was 6.87±0.35 grams, in the I2 group was 5.50±0.92 grams, in the I3 group was 5.62±0.74 grams, and in the I4 group was 6.75±0.70 grams.

The Effect of Guava Juice in Reducing Uric Acid Level

The uric acid level of mice was examined 3 times during this study; at the beginning of the study, before administration of RGJ (*Pre-test*), and after administration of RGJ (*Post-test*). The measurement data of the mice uric acid level was tested for normality using *Shapiro-Wilk* test and tested for its homogeneity using *Levene test*. Based on ANOVA test, there was a significant difference in the mean of the uric acid level before and after treatment. The effect of RGJ administration on each group can be seen in Table 1.

From Table 1 it can be seen that the administration of RGJ with a dose of 5ml/Kg mice body weight/ day (I2), 10ml/Kg mice body weight/ day (I3), and 20ml/Kg mice body weight/day (14) allowed for a decrease in blood uric acid level. The administration of allopurinol (I1) also decreased uric acid level significantly. Nonetheless, there was a significant difference on the NC and PC group due to an increase in blood uric acid level between *pre-test* and *post-test*.

Table 1 The effect of RGJ administration on each group

Group	Pre-Test Mean±SD	Post-Test Mean±SD	Delta (Δ)	P)*
NC	1.58±0.17	1.62±0.15	+0.04±0.02	0.003*
PC	8.70±0.31	8.79±0.33	+0.08±0.06	0.005*
I1	8.61±0.40	2.12±0.15	-6.48±0.41	0.001*
I2	8.56±0.42	3.65±0.13	-4.90±0.35	0.001*
I3	8.58±0.30	2.77±0.19	-5.80±0.39	0.001*
I4	8.77±0.42	2.06±0.09	-6.71±0.47	0.001*

*) significant difference (p<0.05)

Table 2 The effect of red guava juice on blood creatinine level

Group	Pre-Test Mean±SD	Post-Test Mean±SD	Delta (Δ)	P)*
NC	0.66±0.02	0.68±0.03	+0.16±0.00	0.002*
PC	3.29±0.15	3.92±0.16	+0.09±0.06	0.003*
I1	3.20±0.15	0.92±0.04	-2.28±0.14	0.001*
I2	3.22±0.08	2.67±0.12	-0.55±0.07	0.001*
I3	3.31±0.12	1.63±0.10	-1.67±0.16	0.001*
I4	3.28±0.14	1.16±0.08	-2.12±0.14	0.001*

*) significant difference (p < 0,05)

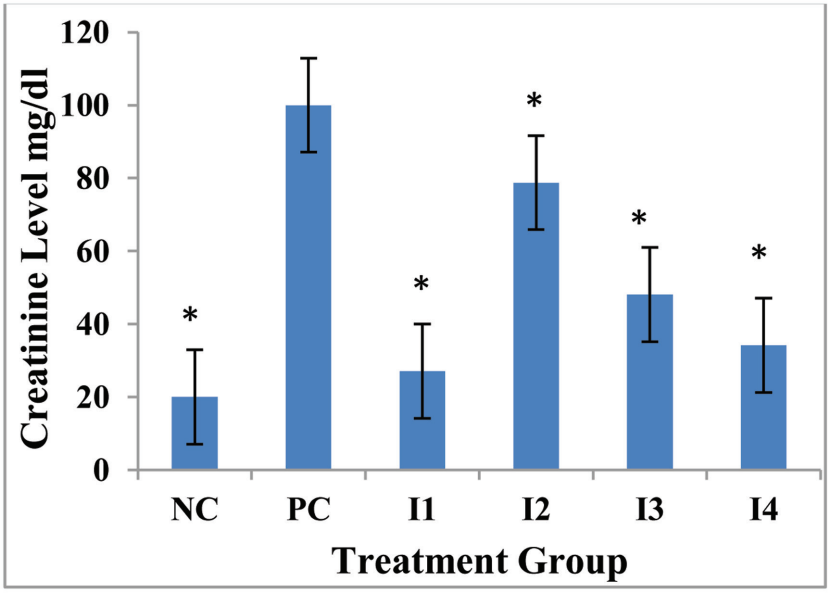

Figure 3 The mean increase in creatinine level with mice groups given potassium oxonate, red guava juice, and allopurinol. *)shows intervention groups compared to positive control (PC) group

Figure 2 shows the comparison of uric acid levels after treatment with the uric acid level in the PC group normalized as 100%. Based on Figure 2, it can be seen that there was a decrease in uric acid level after treatment compared with the PC group. The uric acid level in I1 group decreased to 24.11%, on the I2 group decreased to 41.52%, on the I3 group decreased to 31.51%, and on I4 group decreased to 23.43%. However, the uric acid level in NC group increased to 18.43%.

The Effect of Guava Juice in Reducing Creatinine Level

The effect of RGJ on blood creatinine level in each group can be seen in Table 2.

Based on table 2 be known there are meaningful differences (P < 0.05) between the NC and the PC, treatment of RGJ with a dose of 5ml/ Kg mice body weight/day (I2), 10ml/Kg mice body weight/ day (I3), and 20ml/Kg mice body weight/ day (14).

Treatment of RGJ with a dose of 5ml/Kg mice body weight/day (I2), 10ml/Kg mice body weight/ day (I3), and 20ml/Kg mice body weight/day (14) give effect in lowering blood levels of uric acid. Drug treatment of allopurinol (I1) also gives the effect of lowering uric acid levels significantly. While the NC and the PC there is a meaningful difference (p < 0.05) due to an increase in the levels of blood uric acid between pre-test and post-test.

Decreased blood creatinine levels occurred at drug treatment group (I1) of 2.28 ± 0.14 mg/dl, the group RGJ with a dose of 5ml/Kg mice body weight/day (I2) of 0.55 ± 0.07 mg/dl, group RGJ with a dose of 10ml/Kg mice body weight/day (I3) of 1.67 ± 0,16 mg /dl, and group RGJ with a dose of 20ml/Kg mice body weight/day (14) of 2.12 ± 0.14 mg/dl.

Creatinin levels after treatment with potassium oxonate, JJBM variation, dose and Allopurinol compared to KP can be seen pictures 3

Figure 3 shows the comparison of blood creatinine level after intervention with the blood creatinine level on PC group normalized as 100%. The decrease in blood creatinine level after intervention on group I1 was 27.13%, on group I2 was decreased to 78.76%, on group I3 was decreased to 48.08, and on group I4 was decreased to 34.21%. Contrarily, the creatinine level of the NC group increased to 20.05%.

DISCUSSION

The average mice body weight tended to increase from the beginning until the end of the study. Nevertheless, there was a decrease in the mice's weight on the second week, either in the control groups or in the intervention groups. This phenomenon might be due to the mice experienced stress because of the treatment that was given as well as decreased intake of food. During the second week, the mice were given potassium oxonate to induce

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increases in uric acid and creatinine level, which also lead to renal histopathologic structure changes in hyperuricemic model mice. Besides, increase and decrease in mice body weight is influenced by several factors such as stress, genes, environmental conditions, and food intake.[18]

Male mice were selected for this study based on the consideration that male mice are lack of estrogen. In addition, the stress level in female mice is higher than that of male mice; a factor that might be disruptive during the study period.[13]

The administration of potassium oxonate in mice was to induce hyperuricemia because potassium oxonate could act as a competitive uricase inhibitor to increase uric acid and creatinine level by preventing the conversion of uric acid into allantoin. Allantoin is water soluble and excreted in the urine. Thus uricase inhibition by potassium oxonate will accumulate uric acid, increase creatinine and not eliminated through the urine.[7]

Positive control in this study is the drug allopurinol, which is an antigout drug; acting by inhibiting purine formation through inhibition of xanthine oxidase.[19]

The measurement of uric acid level in this study showed that uric acid levels in hyperuricemic model mice in the PC group were higher compared to RGJ intervention. The analysis showed that the uric acid level in intervention groups experienced significant difference ($p<0.05$).

A significant decrease of uric acid levels occurred in all intervention groups with different doses in group I2 (5ml/Kg mice body weight/day), group I3 (10ml/Kg mice body weight/day), and group I4 (20ml/Kg mice body weight/day). There was a significant increase in the mean uric acid level between each intervention group ($p<0.05$).

To determine the potency of RGJ in lowering blood uric acid level, we can see the percentage of the decrease in uric acid level compared to the PC group (Figure 2). Based on this percentage comparison, administration of RGJ to the intervention groups lowered the uric acid level of the mice within normal limits. The optimal dose in reducing blood uric acid level in hyperuricemic mice is the dose of 20ml/Kg mice body weight/day because it has the same potential with allopurinol in lowering uric acid level.

The measurement showed that the creatinine level of hyperuricemic mice in the PC group was higher compared to hyperuricemic mice on the RGJ intervention groups. Analysis showed that the creatinine level of the intervention groups experienced a significant decrease ($p<0.05$). The significant decrease occurred in all RGJ intervention with all doses.

Based on the test results the average difference of group treatment RGJ dose of 5ml/Kg mice body weight/day (I2), dose of 10 ml/Kg mice body weight/day (I3) and dose of 20 ml/Kg mice body weight/day (I4) there are meaningful differences (p 0.05 >).

Dose in lowering blood levels of creatinine at a dose of 20 ml/Kg mice body weight/day (I4), due to decreased levels of creatinine with a dose of 20 ml/Kg mice body weight/day is the highest loss compared doses 5 ml/Kg mice body weight/day (I2) and doses 10 ml/Kg mice body weight/day (I3).

Decreased blood creatinine levels approaching the normal limit that is RGJ treatment group dose 20 ml/Kg mice body weight/day with a large decrease of 2.12 ± 0.14 mg/dl. To know the magnitude of the potential Red guava juice (RGJ), can use the percentage decrease in the levels of creatinine by comparing positive control group (CP) (Figure 3). Based on the results of the percentage of all treatment groups were able to decrease the creatinine levels of hyperuricemia mice.

This ability of red guava (Psidium guajava Linn.) in Indonesia is used as an alternative medicine to cure certain diseases. This phenomenon was based on the result of several studies exhibiting the activity of red guava as an anti-rheumatic agent, as an anti-inflammatory agent, in reducing oxidative stress, reducing blood pressure, and lowering lipid profile.[12,20,21]

Based on several studies in the medical field, red guava has the potential as an antioxidant (because of its vitamin C, vitamin E, β-carotene, zinc, polyphenols, and flavonoids content) and acts as a phytonutrient which is scientifically proven through various studies.[22]

Active compounds in red guava that play a role in lowering uric acid level are vitamin C, polyphenols, and flavonoids.[7] Vitamin C has a uricosuric effect, which enacts a major mechanism in reducing blood uric acid level.[23] Vitamin C also increases glomerular filtration rate by reducing glomerular microvascular and improving afferent arteriole dilatation during reabsorption and excreted through urine.[24]

Vitamin C can reduce creatinine level because vitamin C has antioxidant property. Acting as an antioxidant, vitamin C serves as a hydrogen ion donor, which converts peroxyl radical into less reactive tocopheryl. This event prevents the radical from damaging the tissue and suppresses the effects of lipid peroxidation, thus decreases kidney damage. Vitamin C also induces tissue proliferation

and cell regeneration to replace damaged cells and forms new tissue. The proliferation and regeneration of new tissue will restore kidney function.[8]

Polyphenols and flavonoids can lower uric acid level as they act as an antioxidant and inhibit free radicals, inhibit several enzymes, including xanthine oxidase, cyclooxygenase, and lipoxygenase.[25] Flavonoids and polyphenols are substrates of xanthine oxidases, which generally oxidize xanthine to uric acid. This substrate competition will lead to a decrease in uric acid production because the xanthine oxidase tends to oxidize flavonoids and polyphenols rather than xanthine.[26]

After observing the development of mice body weight during the study and evaluating two parameters—blood uric acid and creatinine levels—we can comprehend that the most effective RGJ administration was at the dose of 20 ml/Kg mice body weight/day. This assertion was based on the decrease in uric acid and creatinine levels with the dose of 20 ml/Kg mice body weight/day were equivalent to drug (allopurinol) effect.

Based on this event, patients should be encouraged to consume more red guava to lower blood levels of uric acid and creatinine. Red guava contains more complex antihyperuricemic substances compared with other medicinal plants, and also relatively palatable and widely available.

CONCLUSION

The administration of RGJ with the dose of 5ml/ Kg mice body weight/day, 10ml/Kg mice body weight/ day, and 20ml/Kg mice body weight/ day decrease blood uric acid and creatinine levels of hyperuricemic model mice. The higher the RGJ dose given, the greater the decrease in blood uric acid and creatinine level. The administration of RGJ with a dose of 20ml/Kg mice body weight/day is shown to be the most effective dose in lowering blood uric acid and creatinine levels of white mice.

This study also provided information about the implication of the RGJ potential with its antioxidant content as an inhibitor of xanthine oxidase formation and free radical chain breaker, which consequently, prevents an increase of blood uric acid and creatinine level. Further research is needed to explain more about the mechanism of RGJ in the human body as an antihyperuricemic agent.

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