

THE SUB-CHRONIC TOXICITY TEST OF MENIRAN (*Phyllanthus niruri* L.) AND PEGAGAN (*Centella asiatica*) EXTRACT IN WISTAR STRAIN RATS ON LIVER AND KIDNEY FUNCTION

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ABSTRACT

Meniran (*Phyllanthus niruri* L.) and Pegagan (*Centella asiatica* L.) was proven had activity that considered as an antioxidant. However, the safety was not confirmed. This research is intended to evaluate sub-chronic toxicity of standardized combination extract of meniran and pegagan on liver and kidney function. This research used post-test-control design. Twenty female and twenty male Wistar strain rats divided into 4 groups. The first group was controlled in dosage of CMC Na 0.5%. The others were given a combination of meniran and pegagan extract in ratio with different dosage (50:50; 250:250; and 1250:1250 mg/KgBW). Sub-chronic toxicity test of meniran and pegagan combination was given orally once a day for 28 consecutive days. On the 29th day, all the rats were sacrificed and blood samples were analyzed using automatic analyzer. SGOT, SGPT, BUN, and creatinine value were statistically analyzed using one way ANOVA with post hoc LSD ($p < 0.05$). The results show that treatment of meniran and gotu kola combination had no significantly different of SGOT and creatinine value of male and female rats, and SGPT value of male rats ($p > 0.05$). The treatment of meniran and gotu kola combination had significantly different of BUN value of male and female rats, and SGPT value of female rats ($p < 0.05$) but still within normal range. Based on this study, it can be concluded that orally administered of meniran and gotu kola extract combination at doses 50:50 mg/KgBW; 250:250 mg/KgBW; and 1250:1250 mg/KgBW had no affected on SGOT, SGPT, BUN and creatinine value of Wistar strain rats on sub-chronic administration for 28 consecutive days.

Keywords: *Phyllanthus niruri* L.; *Centella asiatica* L.; subchronic toxicity; liver and kidney function

INTRODUCTION

Meniran (*Phyllanthus niruri* L.) and *Pegagan* (*Centella asiatica* L.) are the most found plants in Indonesia as herbal or traditional cure. *Pegagan* has substances, comprising of triterpenoid saponin, flavonoid, essential oil, phytosterol and other active materials (Kristanti, 2010). Additionally, *Meniran* has many advantages derived from substances of various chemical substances, such as alkaloid (securinine),

flavonoid (quercetin, quercitrin, isoquercitrin, astragalin, niruri, rutine, leucodelphinidin, and galocatecine), and lignan (filantine and hipofilantine) (Mangunwardoyo *et al.*, 2009).

Utilization of both plants as traditional cure require further research to prove feasibility and security. A study of Fitrianiingsih (2017) postulated that combination of *meniran* and celery at dosage of 100:50 mg/KgBW can decrease significantly the extent of blood urea nitrogen (BUN) ($p > 0.05$), while, at

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dosage of 100:100 and 50:100 mg/KgBW, it has not decreased the level of BUN and creatinine of rats induced by gentamycin significantly ($p>0,05$). Other researches stated that there are components of *meniran* and *pegagan* having adverse effects on body's organ. Research performed by Praptiwi (2010) argued that saponin substance is main component of *pegagan* extract that can cause hemolysis and decrease surface pressure, so that it can result degeneration and sinusoid congestion, color changing and there is white spot in liver caused by cell destruction and leucocyte accumulation. Further, a study done by Mulyadi (2010) set forth that tannin substance in *meniran* can provide worse depiction of histopathology against mice's gastric and duodenum at dosage administer up to 2.000 mg/kgBW. Anfiandi (2013) then reported that infuse of *pegagan* leaves at dosage of 1.500 mg/kgBW can provide teratogenic effect against mice, such as physical defect, stunting, and hemorrhagic on mice's fetus. Therefore, it is necessary to design a test to acknowledge security from utilization of *meniran* and *pegagan* extract combination.

Sub-chronic toxicity testing of *meniran* extract at dosage of 2.000 mg/KgBW and 5.000 mg/KgBW showed that there is no significant difference against the content of *serum glutamic oxaloacetic transaminase* (SGOT) and *serum glutamic pyruvic transaminase* (SGPT) of rats after 14 days of administering (Asare *et al.*, 2011). While, Sujono *et al.* (2015) stated that administering of ethanol-*meniran* extract at dosage of 50 mg/KgBW and 250 mg/KgBW does not cause significant difference against decreasing SGPT level measured in the 0-day and 90-day at Sprague Dawley strain rats. Another research depicted that repeated dosage of *pegagan* extract at 9.07 mg/20 grams to mice or equivalent to 63.49 mg/200

grams of rats can cause changes of liver and kidney (Praptiwi, 2010).

Based on above description, this research is significantly to be performed aimed to analyze sub-chronic toxicity against liver and kidney function from both *meniran* and *pegagan* extract combination since both extracts have activity as anti-oxidant.

METHOD

Materials and Tools

Materials employed in this research were standardized dried *meniran* extract (number of bets 049PP02.2) and non-specifically standardized dried *pegagan* (number of bets 056PP01.2) obtained from PT. Industri Jamu Borobudur, *sodium carboxymethyl cellulose* (CMC Na) and aquadest derived from Laboratory of Pharmaceutical Technic of Ahmad Dahlan University, reagent tube obtained from Laboratory of Parahita, and male and female Wistar strain rats aged 2-3 months and weighted 100-300 grams obtained from Integrated Testing and Research Laboratory, Universitas Gadjah Mada, Yogyakarta.

In addition, tools used was measuring glass (*Pyrex*, Indonesia), volumetric flask (Iwaki, Indonesia), measuring pipette (Iwaki, Indonesia), beaker glass (*Pyrex*, Indonesia), spatula, orally injection needle, 5-cc syringe, analytic weight (Sartorius, Indonesia), electric stove, a series of surgery tools (nippers, scalpel, blade, scissor), flacon, vacutainer tube, and automatic analyzer (Sysmex XT-2000i).

Method

Designing 0.5 % of CMC Na

CMC Na with concentration 0.5 % was used to suspense dried *meniran* and *pegagan* extract. The manufacturing, 0.5% of CMC Na, was by weighting 0.5% of CMC Na as 0.5 grams and solved it little by little into 100,0 mL of heated aquadest. Such mixing was then

homogenously stirred until colorless liquid was obtained. Further, 0.5% solution of CMC Na utilized to suspend dried extract was always made freshly every time it would be used.

Designing of *Meniran* and *Pegagan* Suspension Extract

The design of suspension extract was always made freshly as it would be administered to test rats for each group. It was made from stock solution by concentration of 25% b/v. At dosage of 1250 mg/kgBW, it was made by weighing each extract of 12.5 grams. Next, it was suspended with 0.5% of CMC Na and 50.0 mL of ad, so that 25% b/v of concentration was obtained. Further, this design of suspension at dosage of 250 mg/kgBW and 50 mg/kgBW used following formulation:

$$V_1M_1 = V_2M_2 \dots \dots \dots (1)$$

Solution at dosage of 50 mg/kgBW was made by taking 1,0 mL of suspension stock and 25,0 mL of ad using 0,5% of CMC Na, so that 1% b/v of concentration was obtained. The design of suspension at dosage of 250 mg/kgBW was made by taking 5,0 mL of suspension stock and 25,0 mL of ad, using 0,5% of CMC Na, so that 5% b/v of concentration was obtained. As an example of calculation for dosage administered to every 200 grams of rat at dosage of 50 mg/KgBW, it can be seen in following equation:

$$\frac{\text{Dosage of extract (mg)}}{1000 \text{ grams}} = \frac{\text{Dosage given}}{200 \text{ grams}} \dots \dots \dots (2)$$

$$\frac{50 \text{ mg}}{1000 \text{ grams}} = \frac{\text{Dosage given}}{200 \text{ grams}}$$

Dosage given = 5 mg

As an example of calculation for administering volume for every 200 grams of rat at dosage of 50 mg/KgBW, it can be seen in following equation:

$$\text{Administering volume} = \frac{\text{Dosage} \left(\frac{\text{mg}}{\text{KgBB}} \right) \times 0,2 \text{ Kg}}{\text{Extract concentration}} \dots \dots (3)$$

$$\text{Administering volume} = \frac{50 \frac{\text{mg}}{\text{KgBB}} \times 0,2 \text{ Kg}}{1\% \text{ b/v}}$$

$$\text{Administering volume} = \frac{50 \frac{\text{mg}}{\text{KgBB}} \times 0,2 \text{ Kg}}{10 \text{ mg/mL}}$$

Administering volume = 1 mL

Treatment of Test Rats

The research was performed in the Laboratory of Faculty of Pharmacy, Ahmad Dahlan University, Yogyakarta. Administratively, this procedure had obtained letter of statement of Committee of Research Ethics, Ahmad Dahlan University under No. 011803043. This study, then, was according to Regulation of Head of Food and Drug Supervisory of the Republic of Indonesia Number 7 of 2014 on Manual of Non-Clinical Toxicity Test by In Vivo (Anonim, 2014). Wistar strain rats thus were selected randomly, and 5 rats were classified into male and female group, respectively. Test rats were previously adapted for 1 week prior to treatment process. Treatment of each test group can be seen in following Table I.

Table I. Treatment of Test Rats

No.	Group	Description
1.	Group I	Administered feed + drink and suspension of 0,5% of CMC Na
2.	Group II	Administered feed + drink and extract combination of <i>meniran</i> and <i>pegagan</i> at dosage of 50:50 mg/kgBW
3.	Group III	feed + drink and extract combination of <i>meniran</i> and <i>pegagan</i> at dosage of 250:250 mg/kgBW
4.	Group IV	feed + drink and extract combination of <i>meniran</i> and <i>pegagan</i> at dosage of 1250:1250 mg/kgBW

Clinically Bio-chemical Test

At the 29th day, sampling through *sinus orbitalis* was performed, which the blood was contained into vacutainer tube. It then was tested in the Laboratory of Parahita to know the value of SGOT, SGPT, BUN, and creatinine.

Data Analysis

The result of this research gained data comprising of the level of SGOT, SGPT, BUN, and creatinine for each group, respectively. Such data was statistically analyzed. Data analysis of clinically biochemical parameter employed SPSS (statistic product and service solutions). The first analysis was distribution test using the Shapiro Wilk test to examine data distribution, and the Levene test was aimed to see data homogeneity. If data was normally and homogeneously distributed, parametrically statistical test of one-way ANOVA was done using SPSS by reliable degree of 95% to acknowledge which group showed difference.

RESULT AND DISCUSSION

This study is aimed to know sub-chronic toxicity of *meniran* and *pegagan* extract combination against liver and kidney function during 28 days of orally

administering with various dosage levels. It utilized test rats of male and female Wistar strain as many as 40 rats.

SGPT was mostly found in liver, so that SGPT was more specific to detect disease than SGOT. The measurement result of SGPT for male and female can be seen in following Figure 1, and for female, it can be viewed from Figure 2.

According to Figure 1, the analysis result of one-way ANOVA depicts that there was no significant difference toward SGPT value of male rats, showed by its significant value of 0,105 ($p > 0,05$). Average value of SGPT from male rats in controlled group was 90.96 ± 24.22 U/L. The SGPT had consecutive decreasing value than controlling group did. The higher dosage of *meniran* and *pegagan* extract combination, the more decreasing the SGPT level of test rats. Based on such result, the extract combination of *meniran* and *pegagan* could prevent the increasing value of SGPT on male rats. It is probably because *meniran* and *pegagan* contain polyphenol and triterpenoid, having activity as antioxidant, so that it can decrease enzyme level produced by liver, as cell necrosis takes place (Hashim *et al.*, 2011; Hu, 2011).

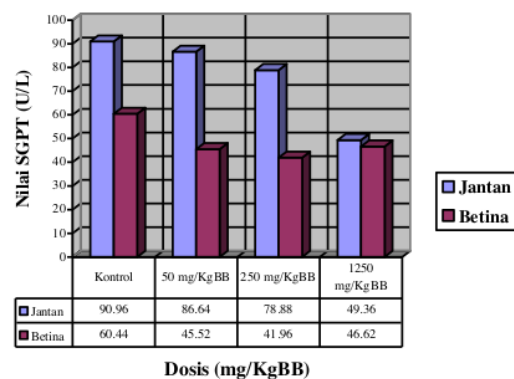


Figure 1. The average SGPT value of male and female rats after the administration of a combination of Meniran and Gotu kola extract for 28 days

Meanwhile, the analysis result of one-way ANOVA in the Figure 1 shows that there was no significant difference in the SGPT value of female rats, depicted by its significant value of 0,059 ($p>0,05$). Average SGPT value of female rats in the controlled group was 60.44 ± 15.45 U/L. The SGPT value of each group administered extract combination was lower than controlling group. However, such decreasing was in normal level of rats' SGPT, which was 35.9–81.6 U/L (Wicaksono, 2010). Based on such result, extract combination of *meniran* and *pegagan* could prevent increasing value of SGPT on female rats. Further, the decreasing value of SGPT in treatment group under administering of *meniran* and *pegagan* extract combination could happen since *meniran* contains filantine, having activity as antioxidant, so that it can protect liver from cell degeneration or impairment.

In detail, based on Figure 1, the SGPT value of male group was higher than female group. This was caused by physiology factor of those test rats. While, statistical result demonstrates that there was no significant difference on decreasing value of SGPT on male and female rats ($p>0,05$). Further, it can be said that administering of *meniran* and *pegagan* extract combination to male and female Wistar strain rats would not interfere the SGPT value.

Subsequently, SGOT is enzyme existed in body to promptly detect periphery circulation, if there is trauma or necrosis in certain tissue. Also, SGOT is greatly found in any tissue other than liver, such as heart. In general, changing level of SGOT is related to liver disease, but it is also possible that the SGOT changes also take place due to heart disease (Yuwono *et al.*, 2016). The

calculation result of SGOT for group of male rats is shown in Figure 2, while female rats is in Figure 2.

According to Figure 2, the analysis result of one-way ANOVA in the Figure 2 describes that there was no significant difference of the SGOT value of male rats, depicted by its significant value of 0.354 ($p>0,05$). Averagely, the rate value of SGOT from female rats in controlled group was 173.76 ± 34.87 U/L. Moreover, the SGOT value derived from administering of extract combination at dosage of 250:250 mg/kgBW was higher than controlling group, which was 180.48 ± 16.85 U/L. Nonetheless, such increasing was insignificant. Liver impairment can be seen from three folds increasing of SGOT and SGPT parameter from normally upper range (Maria, 2014). Then, the result obtained from the measurement of male's SGOT level (Figure 2) is that increasing of SGOT level had not reached more than three folds of normally upper range, so, as consequence, it can be said that there was no impairment of liver.

In addition, the analysis result of one-way ANOVA in the Figure 2 depicts that there was significant difference at the SGOT value of female rats, shown by its significant value of 0,026 ($p<0,05$). In average, the SGOT value of female rats under controlled group was 174.5 ± 23.37 U/L. The SGOT value in each group administered with extract combination was lower than controlling group, yet it was still under normal range (35.7-168 U/L) (Wicaksono, 2010). Additionally, significant difference existing between controlling group against group administered with *meniran* and *pegagan* extract at dosage of 1250:1250 mg/KgBW was shown by its significant value of 0.003 ($p<0,05$).

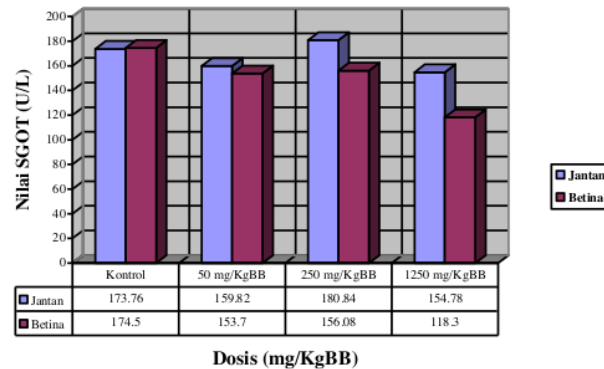


Figure 2. The average SGOT value of male and female rats after the administration of a combination of Meniran and Gotu kola extract for 28 days

Hence, according to such results, extract combination of *meniran* and *pegagan* could prevent increasing value of the SGOT at female rats. While, decreasing value of the SGOT was probably caused by polyphenol, contained in *pegagan* (Sutardi, 2016). Polyphenol has substance included in class of primary antioxidants, such as phenol substances enabling to cut off chain reaction of fatty-acid-free radical formation (Hu, 2011).

According to Figure 2, further, the SGOT value at male group was higher than female group was. It was probably caused that male rats had heavier muscle mass. Similarly, Tripathi and Hall (2016) argued that SGOT is mostly found in muscle, skeletal, heart, and brain. Therefore, the SGOT value of male rats is higher than female rats. Meanwhile, the statistical result demonstrates that there was no significant difference of the SGOT value found in male rats ($p=0.354$). Contrastingly, the statistical result of the SGOT value found in female rats had significant difference against controlling group ($p=0.026$). However, such decreasing was still in normal range, so that it can be concluded that administering of *meniran* and *pegagan* extract combination at male and female Wistar strain could not interfere the SGOT value.

Moreover, the level of BUN is final product from protein metabolism synthesized inside liver and secreted almost 75% through kidney without experiencing molecule changes. Increasing of BUN level in blood could show impairment of kidney function. The result of the BUN level derived from this research is then shown in following figures as attached.

Based on Figure 3, significant value from statistical test of one-way ANOVA was 0.025 ($p<0.05$), meaning that there was significant difference. This result depicts that average value of BUN at 14.20 ± 2.61 was lower than controlling group (0,5% of CMC Na), while the group III and IV demonstrated more significant increasing of BUN's average value than controlling group, which was 20.16 ± 4.23 and 19.00 ± 1.97 , respectively, with increasing value of BUN where was still under normal range. In addition, normal value of BUN on mice was 13.9-28.3 mg/dL (Anshar, 2015). Based on above result, increasing value of BUN was necessarily cautioned since it could show impairment of kidney function (Haryoto *et al.*, 2015). Main function of kidney is to regulate liquid and electrolyte balance and body's basal and acid to create figure environment for tissue and cell metabolism (Miriam and Wallace, 1998).

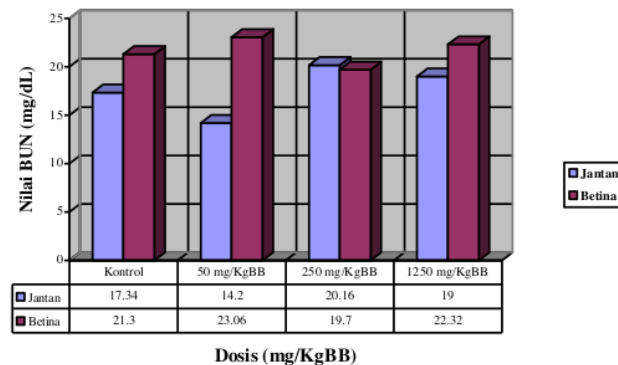


Figure 3. The average BUN value of male and female rats after the administration of a combination of Meniran and Gotu kola extract for 28 days

Figure 3 postulates that value of statistical for the $F_{1,1}$ BUN value on female rats was 0.031 ($p > 0.05$), meaning that there was significant difference. Thus, from Figure 3, it is known that group administered with *meniran* and *pegagan* at dosage of 250:250 mg/KgBW showed decreasing value of the BUN as 19.70 ± 0.52 rather than controlling group (0.5% of CMC Na), whereas the group II had BUN value of 23.06 ± 0.82 ; and the group IV had 22.32 ± 0.67 . Improvement of the BUN value was occurred on both groups than controlling group. Such increasing happened in the group II and IV of female rats, yet it was still in normal range.

Next, based on Figure 4, the analysis result of one-way ANOVA gained was significant value of 0.590 ($p > 0.05$). It means that there was no significant difference. Such result shows that there was increasing of creatinine value of three groups than controlling group (0.5% of CMC Na). The group II demonstrated creatinine's average value of 0.56 ± 0.07 ; the group III was 0.52 ± 0.09 ; and the group IV was 0.56 ± 0.08 . Creatinine's reference value of Wistar rats was 0.2-0.8 mg/dL and it was secured due to below normal range (Amir *et al.*, 2015).

Improvement of creatinine serum became impairment index and kidney disfunction. Kidney ability to filter non-protein nitrogen (NPN) (metabolism product of phosphate creatinine) is lessen during kidney disfunction. It was due to declining glomerulus filtration (Reddy *et al.*, 2012).

Lastly, based on Figure 4, it postulates that significance value of statistic $F_{1,1}$ test with one-way ANOVA as 0.181 ($p > 0.05$). It means that there was no significant difference. Moreover, the result depicts that the group II was more improving than controlling group (0.5% of CMC Na). Thus, average value of creatinine at the group II was 0.61 ± 0.08 , while the controlling group was 0.56 ± 0.09 . The average value of creatinine at the group III was 0.51 ± 0.03 , and the group IV was 0.56 ± 0.06 . Hence, there was decreasing occurred in the group III and IV, yet it was insignificant.

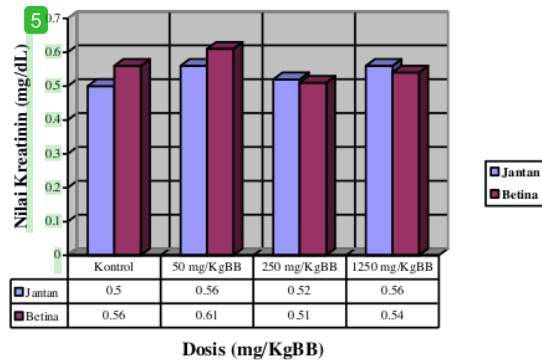


Figure 4. The average creatinine values of male and female rats after administration of a combination of Meniran and Gotu kola extract for 28 days

Any impairment of kidney function in determining minor, moderate, or major severity could be known from total value of glomerulus filtration (GFR) (Hutagaol, 2017). Also, other supporting impairment of kidney, such as kidney histopathology, usually depicted inflammation or focally lymphocyte cells infiltration and bleeding (Winarno and Sundari, 2011).

From above research's findings, administering of *meniran* and *pegagan* extract combination had not result adverse effect to liver and kidney function as seen in the level parameter of SGOT, SGPT, BUN, and creatinine, so it was secured and did not cause toxicity.

CONCLUSION

In sum up, according to research's findings, it can be concluded that orally administering of *meniran* and *pegagan* extract combination at dosage of 50:50; 250:250; and 1250:1250 mg/KgBW had not affected SGOT, SGPT, BUN, and creatinine value in Wistar strain rats after sub-chronic toxicity test, administered for 28 days.

It is further necessary to perform histopathology to acknowledge liver and kidney in detail and research using more variative dosages in *meniran* and *pegagan* extract combination.

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