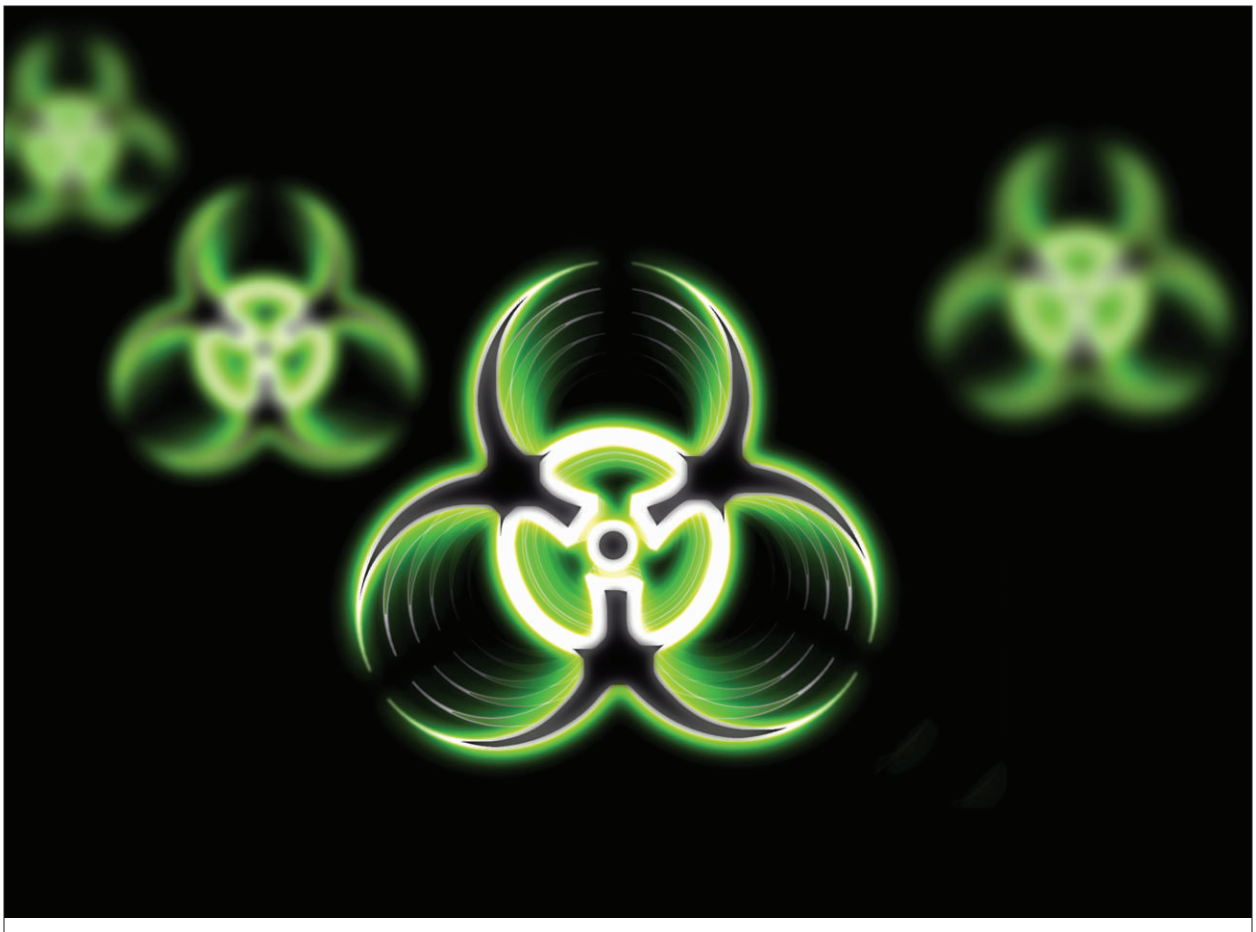

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Research Article
Effect of Rambutan Honey (*Nephelium lappaceum*) Acute Administration on Mortality, Body Weight, Toxicity Symptoms and Relative Organ Weight of Swiss Websters Mice

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Abstract
Rambutan honey is honey from rambutan flowers nectar (*Nephelium lappaceum*) and known as a traditional medicine which can accelerate the oral mucosa wounds. Scientific evidence for its efficacy is widely studied, but systemic studies are still lacking. It is essential to study the impact of consumption of honey on the health. The objective of this research is to observe the effect of acute administration (14 days) of rambutan honey on male and female Swiss webster mice. The research method was an acute oral toxicity study with minor modification. Rambutan honey were administered at 625, 1250, 2500 and 5000 mg kg^{-1}. Animals were observed for mortality, body weight changes, toxicity symptoms and relative organ weight for the next 14 days and analyzed with paired t-test and ANOVA, Tukey's $p<0.05$. The results showed rambutan honey did not exhibit any abnormal signs or deaths. There was a significant increase in male mice body weight. There were no toxicity symptoms in mice. The gross necropsy analysis did not reveal changes of the organs. The conclusions of rambutan honey acute administration were safe and practically non-toxicon male and female Swiss webster mice.

Key words: Acute administration, rambutan honey

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Honey has been known to have medicinal properties at both preventives and curative levels since ancient times. It has been known to have antibacterial, antioxidant and wound healing constituents (Kassim *et al*., 2012). Wound is missing or partial destruction of body tissue. In the human body, wound is often occurred including in the oral mucosa (Peterson, 2003). If a wound is not treated immediately and properly, it will lead to a long healing time, discomfort, complications such as bleeding and infections. This condition will lead to chronic wound that can degrade the quality of life. Good management and control on wound healing is very important to avoid the occurrence of chronic wounds and to prevent complications (Sjamsuhidajat and de Jong, 2010). Naturally, wounded tissue has been programmed to heal them through the process of tissue repair through wound healing. Wound healing is a coordinated process involving complex relationships between cellular factors. Wound healing process occurs in three phases; the inflammatory, the proliferative and the remodeling (Kumar *et al*., 2009).

Some studies reveal that honey serves as an antiseptic, anti-inflammatory, antioxidant and immunomodulatory (Perez *et al*., 2006; Suranto, 2007). Honey is effective as a debridement solution, topical antimicrobial treatment of the skin, treatment of burns, ulcers and stimulates wound infection (Seckam and Cooper, 2013; Vandamme *et al*., 2013). Honey is useful in disease infection treatment because it has antibacterial and anti-inflammatory activity. Honey also has antioxidant activity that has been proven *in vitro*. Venezuelan honey proved to reduce hydroperoxide lipid and MDA level (Perez *et al*., 2006). In the early stages of research, the result has been carried out *in vitro* examination on antioxidant potency against blood plasma induced by $CuCl_2$ using rambutan honey squeeze centrifugation (Yuslianti, 2014).

Rambutan honey is one of natural medicine that often used in wound treatment. By means of smeared and drink, honey empirically is used to treat mouth burns, skin lesions and sores. In some health service, doctors use honey in patient's wound treatment. Indonesian community and government are trying to develop all the potential of the nature, including the proceeds of tropical fruit trees for example flower nectar and fruit. This effort is to support the repertoire of natural herbal remedy (Depkes, 2007). Rambutan honey is produced by *Apis mellifera*, a honey bee, from *Nephelium lappaceum* trees and collected from a beekeeping farm. Rambutan honey is known by Indonesian communities which empirically have been reported to heal wounds including oral mucosa wounds. With appropriate WHO quality standards, traditional medicine must meet several requirements including quality, safety and efficacy. The validity of safety/toxicity test is influenced by factors such as dosage test, preparation of dosage test, animals testing, doses, technique, national and international standardized testing procedures (Bpom, 2014). Only a few studies to date have taken cognizance of the possible consumption effects of honey. For instance, Kassim *et al*. (2012) documented acute analysis of gelam honey on mice and rabbits at doses of 10, 60, 300 and 600 mg kg^{-1} and Samat *et al*. (2014) documented an acute study of gelam honey and acacia honey with doses of 2000 mg kg^{-1}. However, an acute administration study of rambutan honey on Swiss webster mice according to BPOM guidelines has not been carried out. Therefore, this study aims to observe the effect of acute administration (14 days) of rambutan honey on male and female Swiss webster mice. Observations were made include the effect on behavior, weight and manner of death and relative organ weight after administration of single dose samples of rambutan honey.

MATERIALS AND METHODS

The research was conducted at the Laboratory of Pharmacology of the Faculty Pharmacy and Biochemistry, Faculty of Medicine, General Ahmad Yani University, Cimahi, which was held from May until June 2015.

Sample collection: Rambutan honey samples were obtained from Indonesia National Beekeeping Center (Pusbahnas) and isolate pure samples were obtained with pharmaceutical standard sterile technique. The sample was then kept at -20°C and in dark bottles.

Experimental animal husbandry: Ethical approval was obtained from the research ethic commission team of Hasan Sadikin Hospital Bandung No. 140/UN6.C1.3.2/KEPK/PN/2015. Ethical aspect of the research was based on three principal of Russel and Burch in Guide for the care and use of laboratory animal, they were reduction, replacement and refinement. The experimental animals were taken from the population of Swiss webster male and female mice which were obtained from center laboratory of Biological Sciences Bandung Institute of Technology Indonesia. At the commencement of study, each mice was six week old and weighed between 20 and 30 g. Mice previously was adapted in the laboratory cages for seven days at ambient conditions (temperature of 22±3°C, 30-70% relative humidity, with a 12 h dark/light cycle), with the same maintenance techniques and strict supervision were done

during stage (Bpom, 2014). Mice divided randomize into 5 groups, each consisting of 5 mice. The control group (C) were given only distilled water, the treatment group 1 (P1) were given the dosage of rambutan honey with a dose of 625 mg kg^{-1}, the treatment group 2 (P2) received the dosage at a dose of 1250 mg kg^{-1}, the treatment group 3 (P3) were given the dosage at a dose of 2500 mg kg^{-1}, while for the treatment group 4 (P4) were given the highest dose of 5000 mg kg^{-1}.

Acute administration test: The test preparation was administered orally with only one administration at the beginning of the study period. The calculation of the dose in this research was based on BPOM guidelines with slight modifications on dose toxicity test for traditional materials (Generally Recognized As Safe/GRAS) by the level of toxicity of 5 for the honey that is a dose of 5 g kg^{-1} that mean the calculation is practically non-toxic. The dosage was given orally in experimental animals, once during the test (Bpom, 2014).

Mortality analysis: The observations of experimental animals against toxic symptoms were carried out every day until day 14 to see whether there were mice died. Mice that died when there was immediately it dissected to examine the cause of death.

Body weight analysis: The body weight of each mouse was recorded every day until day 14. The data of average weight changes was created in tables and graphs to see the effect of the test material on the development of body weight.

Toxicity symptoms analysis: The behaviors of mice were observed for 2 min before being given the test material. The effects which were observed include the number locomotors activity, motoric activity, straub phenomenon, piloerection, ptosis, corneal reflex, pineal reflex, lacrimation, vasodilatation, catalepsy, to hang on, reestablishment, flexion, haffner, stretching, grooming, tremor, vocalization, salivation, body attitude, defecation and urination. After acute administration, the effects were observed in the 0th, 30th, 60th, 120th and 240th min. The effects observed which include pharmacological observations on central nervous, autonomic nervous, respiratory, digestive and the excretory system.

Relative Organ Weight (ROW): On day 15 mice were terminated, a comprehensive gross observation was carried out on the internal organs, such as the liver, spleens, pulmonary, heart, kidneys, vesicaseminalis and the testis. They were observed for any signs of abnormality and for the presence of lesion owing to any effect of the rambutan honey administration (Lakmichi *et al*., 2010). The organs were then carefully dissected, cleaned of any fats and weighed (Soemardji *et al*., 2002).

The Relative Organ Weight (ROW) of each organ was then calculated according to the following equation (Samat *et al*., 2014):

$$\text{ROW} = \frac{\text{Absolute organ weight (g)}}{\text{Body weight of mice on sacrifice day (g)}} \times 100$$

Statistical analysis: The data obtained was quantitative and qualitative data. The amounts of dead animal data was analyzed to determine the value of LD_{50} that was calculated according to the Indonesian Pharmacopoeia 3rd edition. This method was used to evaluate the acute isolate toxicity potential of pure rambutan honey. Data on toxic symptoms appearances on vital functions was qualitatively used to evaluate the arising of toxic effects, mice weight loss and weight index of vital organs. The weight data before and after treatment was analyzed by paired t-test while rambutan honey effect data on ROW use ANOVA analysis followed by Duncan's *post hoc* test. Prior to the ANOVA, the data distribution should be checked for the normality. This data normality test used the Shaphiro-Wilk test because the size of sample was $\leq$50. If the results of normality and homogeneity data were not normal, then the alternative tests would be used which was the Kruskal-Wallis test followed by Mann-Whitney *post hoc*.

RESULT

Mortality: The observation for fourteen days treatment indicated there were no treatment-related deaths (both male and female) in the control group and the treatment group. The acute study showed that mice administered with rambutan honey did not result in any mortality; thus we cannot determine LD_{50} from the study.

Body weight: From the normality Shapiro Wilk test on male mice weight data, the value obtained for the weight before treatment $p = 0.196$ and weight after treatment are $p = 0.258$ where $p>0.05$. The result indicated that the data had a normal distribution. Male mice weight observations before and after administration of rambutan honey with paired t-test were significantly increased ($p<0.05$). Female mice weight data

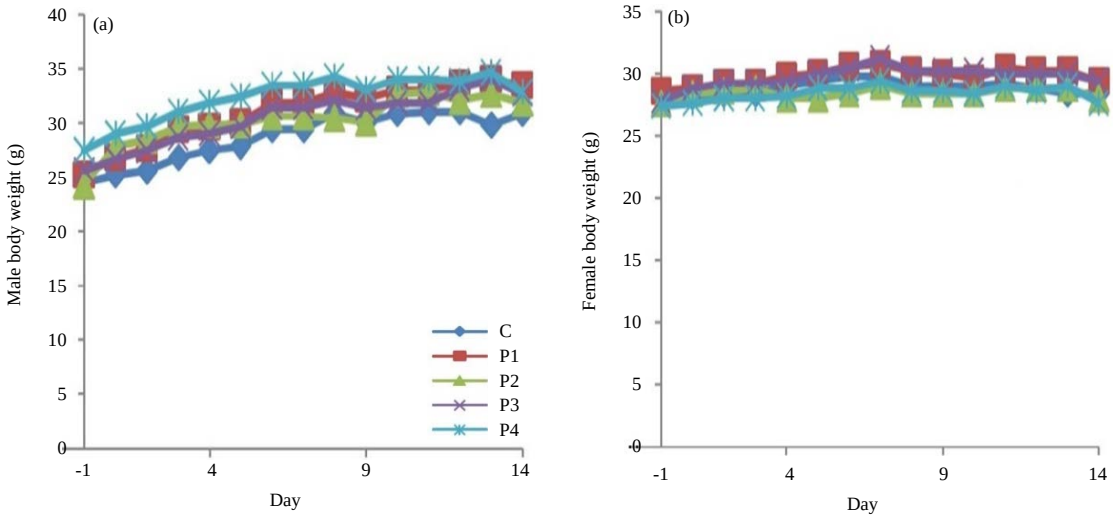

Fig. 1(a-b): Dosing effect of rambutan honey 625 mg kg^{-1} (P1), 1250 mg kg^{-1} (P2), 2500 mg kg^{-1} (P3), 5000 mg kg^{-1} (P4) and control (C) in (a) Body weight of male and (b) Female mice for 14 days

Table 1: Distribution mice body weight mean value and standard deviation before and after rambutan honey treatment

	Male weight (g)			Female weight (g)		
Groups	Before	After	p-value	Before	After	p-value
P1	25.2±3.70	33.4±3.21	0.02*	28.60±2.07	29.40±1.82	0.554
P2	24.2±4.15	31.8±3.03	0.05*	27.60±2.97	28.00±2.35	0.099
P3	25.6±2.07	32.6±2.07	0.12*	27.80±2.28	29.40±1.95	0.587
P4	27.4±3.95	32.8±3.27	0.035*	27.40±2.70	27.60±3.44	0.749

Paired t-test, *p<0.05 significant difference

from the normality Shapiro Wilk test before treatment were obtained p = 0.777 and weight after treatment are obtained p = 0.103, where p>0.05. In female mice body weight observation before and after the test treatment with paired t-test were not differences significantly (p>0.05) as shown in Table 1. There was a difference between the weight of control group (C) and the treatment group P2, P3, P4 where p<0.05. In the treatment group, only between P1 and P3 there were significant difference (p = 0.016). Dosing effect of rambutan honey groups and control group to body weight can be seen in Fig. 1.

Toxicity symptoms: Throughout the 14 day study, no apparent differences in physical activity or other behaviors, no significant changes in the nature of stool, urine and eye color of any mice, no diarrhea, salivation, convulsion, sleep or coma (which are signs associated with oral toxicity) and no significant loss of fur or skin lesions were observed. Pharmacological observation in experimental animals after treatment showed there were not toxic symptoms significantly that arise after the administration of pure rambutan honey in the 30th, 60th, 120th and 240th min as shown in Fig. 2.

Relative Organ Weight (ROW): The effect of rambutan honey treatment on male and female mice relative organ weight was analyzed using the Kruskal Wallis. The result of abnormality in normality test (p<0.05) was not homogenous. The relative organ weight of the isolated hearts, spleens, kidneys, pulmonal, hepars, vesicaseminalis and testis from the groups were recorded and calculated. There was no significant change in relative organ weight in either male or female mice as shown in Table 2. Figure 3 shows the effect of rambutan honey on shapes, sizes and colors organs in male and female mice. There were not abnormalities or within normal limits.

DISCUSSION

Honey has been used for medicinal purposes in many cultures since ancient times (Aljadi and Kamaruddin, 2004). It

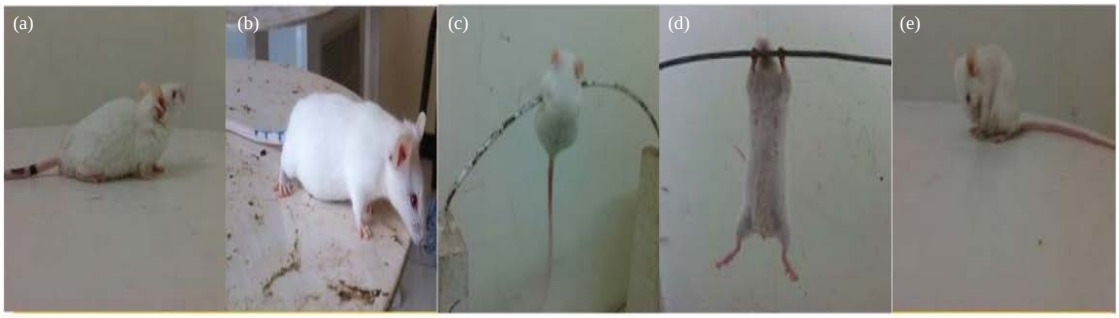

Fig. 2(a-e): Observation of mice behaviour, (a) Locomotor activity up, (b) Locomotor activity down, (c) Reestablishment, (d) To hang down and (e) Grooming

Fig. 3: Male and female mice organs

Table 2: Effect of rambutan honey 625 mg kg^{-1} (P1), 1250 mg kg^{-1} (P2), 2500 mg kg^{-1} (P3), 5000 mg kg^{-1} (P4) and administration of distilled water (C) to the relative organ weights of male and female mice

	Male					Female				
	C	P1	P2	P3	P4	C	P1	P2	P3	P4
Hepar	2.02±0.71	1.75±0.23	1.58±0.20	1.70±0.25	1.75±0.15	1.23±0.26	1.34±0.17	1.35±0.30	1.28±0.17	1.19±0.34
Pulmo	0.13±0.02	0.12±0.01	0.12±0.01	0.15±0.03	0.16±0.04	0.09±0.02	0.07±0.03	0.10±0.02	0.10±0.02	0.10±0.01
Heart	0.22±0.06	0.20±0.03	0.18±0.02	0.24±0.09	0.22±0.02	0.15±0.03	0.16±0.01	0.14±0.03	0.15±0.03	0.16±0.05
Kidneys	0.38±0.04	0.41±0.04	0.38±0.07	0.43±0.08	0.39±0.11	0.21±0.04	0.21±0.02	0.22±0.03	0.23±0.05	0.22±0.08
Spleens	0.42±0.20	0.24±0.05	0.32±0.07	0.33±0.10	0.36±0.12	0.21±0.18	0.21±0.03	0.22±0.07	0.18±0.06	0.21±0.14
Ovarium (F)						0.03±0.05	0.02±0.01	0.02±0.01	0.02±0.02	0.01±0.01
Testis (M)	0.18±0.03	0.19±0.05	0.17±0.03	0.19±0.01	0.19±0.03					
Tuba palopi (F)						0.03±0.03	0.06±0.05	0.09±0.08	0.04±0.03	0.02±0.01
Vesika Seminalis (M)	0.15±0.07	0.12±0.03	0.13±0.03	0.13±0.04	0.18±0.06					

Results of the mean and standard deviation (n = 5), *Meaningful ($p<0.05$) compared to control

is one of the oldest and the most enduring substances used in wound management. Scientific evidence for its efficacy has been widely studied but the systemic safety studies were very limited (Al-Waili *et al*., 2011). Study of acute administration was essential ensure the impact of consumption of rambutan honey on health. Rambutan honey was selected because it is extensively consumed in Indonesia. The test animals were aged 5-6 weeks because animals generally at young age are more sensitive to drugs. The test using male and female mice are to know toxic symptoms differences that occur in each test animals, time the onset of toxic symptoms and long-occurrence of toxic (Bpom, 2014; Soemardji *et al*., 2002).

The results reveal that oral administration of rambutan honey pure isolate on male and female mice over 14 days did not cause any mortality. This shows that oral administration of a single dose of rambutan honey pure isolates up to a

maximum dose could be given. Technically in test animals (5000 mg kg^{-1}), or about 200 times, the dose that was commonly used in humans does not cause mortality in experimental animals. Thus, we cannot determine LD_{50} from the study, i.e., the LD_{50} value would be greater than 5000 mg kg^{-1}. According to the criteria, these results have toxicological significance. This was meant that acute toxicity of rambutan honey non-toxicity nature of test material. Rambutan honey at the highest doses did not leave a toxic effector that was categorized NOAEL (No Observed Adverse Effects Level) (Bpom, 2014).

Weighing on test animals was performed daily for 14 days to determine the changes in body weight of test animals. There were changes in male mice body weight before and after treatment, while there were differences the female mice but statistically not significant. Body weight gain of the male mice fed with rambutan honey showed a significant increase (Fig. 1 and Table 1). Weight gain could be ascribed to the nutritive compounds in rambutan honey and its androgenic properties, since androgens exhibit anabolic activity (Chepulis, 2007). However hormonal factors in female mice consider playing a role in the study and required further investigation.

Oral administration of doses of rambutan honey did not cause abnormal or alter any behavioral or physiological states of the mice. Observation of the presence of toxic symptoms on organs and systems were affected by the dosage. Toxic symptoms were characterized by behavioral changes in test animals. Toxic symptoms on the central nervous system were observed in sedation, convulsions and tremors. Toxic symptoms on the sensory nervous system were observed in corneal reflex, reflex pineal, flexion and haffner. Observation of the autonomic nervous system was observed in salivation, lacrimation and urination. Observation of the neuromuscular system and the motor activity was observed in Straub phenomena. Observation of the digestive system was observed in defecation. Ptosis was a symptom that occurs in the eyes and piloerection organ was symptoms on the skin organ. Result from the study reveal that the oral administration of rambutan honey pure isolate did not cause abnormality or alterity in any behavior or physiological state of the mice in the acute tests. Observations were made at T0, T30, T60, T120 and T240 min with duration for 2 min for each time point except for to hang down, reestablishment, corneal reflex, pineal reflex, flexion and haffner. The observations are generally seen not affect corneal reflex, pineal reflex, flexion and haffneron male and female test animals. This means that rambutan honey pure isolate does not affect the central nervous system. In experimental animals that were given the dosage of rambutan honey pure isolate there is an increasing umber of locomotors activity on male mice at platform ranging from doses 625 mg kg^{-1} at T30, T60, T120 and T240 min, which showed an increasing in mice curiosity whereas in female mice there were no change in the number locomotors activity. Dosage administration of rambutan honey pure isolate on male mice compared to control defecation causes symptoms but it did not occur diarrhea (stool color black/normal and feces remain solid) whereas in female mice cause no symptoms compared to control defecation and diarrhea (stool color blackish brown and feces remain solid). Dosage administration on male and female mice show there were no urination symptoms compared with control. This means that rambutan honey did not create symptoms in the digestive and excretions system. Dosage administration of 5000 mg kg^{-1} in male and female mice grooming was given because a decrease in symptoms compared to the control. Grooming symptoms that may occur due to the nature of central nervous system depression, especially in female mice because it was seen a decrease in body posture.

After 14 days of observation, the test animals from each group were further dissected. The dissection were including cardiac, pulmonal, liver, kidney, spleen and reproductive organs test is seminal vesicles (males), ovary and uterus (females) observations. The weighing of organs were carried out; this was done to determine the toxic effects of the test preparation rambutan honey pure isolates of the organ systems in test animals. Toxic effects caused to the organs in test animals are usually characterized by changes in color, size and shape. The relative organ's increment in weight of male and female mice considers normal. There no differences were observed between the control and the treatment groups in terms of relative organ weight and structure (Table 2 and Fig. 3). Organs in male and female mice were given a dosage of rambutan honey at all doses are found no changes in color, size and shape as compared to the control group. There were not changes in size or not there was a significant difference compared to control in liver, pulmonal, heart, kidneys, spleens, vesicaseminalis and the testis weight index in the male group of test animals at variety of doses. This means that rambutan honeys did not have toxic effect on vital organs, especially to the liver and kidneys as the main target of the toxic effect. Organs of male and female mice that were given a dosage of rambutan honey at all doses were found no changes in color, size and shape as compared with the control group. Weight index in liver, pulmonal, heart, kidney, spleen, vesicaseminalis and the testes in the male group of test animals at variety of doses were not changes in size and there were a significant difference compared to control. A rambutan honey did not

have toxic effect on vital organs, especially the liver and kidneys as the main target of the toxic effect. Organs in female mice which were the heart, kidneys, pulmonal, liver, spleen, uterus and ovaries unchanged (normal) and showed no significant difference compared to the control group in the administration of the test preparation isolate pure rambutan honey at every level dose.

The results showed that up to of 5000 mg kg^{-1} dose of rambutan honey pure isolate did not cause toxic effects and did not lead to mortality during the 14 days of observation. This indicates that pure isolates of rambutan honey until 5000 mg kg^{-1} dose was safe for use in accordance with the limits issued safety testing of BPOM. Based on these results, it also can be seen the degree of toxicity of rambutan honey pure isolate as practical non-toxic material.

CONCLUSION

Rambutan honey has positive effect on male body weight, did not have toxicity symptoms in physical activity or other behaviors and were no significant change in relative organ weight. The LD_{50} of rambutan honey was greater than 5000 mg kg^{-1}, indicating the safety. Further studies are needed to determine whether rambutan honey pure isolate can standardize as a pharmaceutical grade and safely can be applied for human wound healing.

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