ACUTE TOXICITY TEST OF RAMBUTAN HONEY ADHESIVE CREAM AGAINST SWISS WEBSTER MICE

(UJI TOKSISITAS AKUT KRIM PEREKAT MADU RAMBUTAN TERHADAP MENCIT *SWISS WEBSTER*)

Euis Reni Yuslianti[1]*, Florence Meliawaty[2], Afifah B. Sutjiatmo[3],Ariana Pradita[1]
[1] Department of Oral Biology, Faculty of Dentistry, Universitas Jenderal Achmad Yani, Cimahi, West Java, Indonesia
[2] Department of Oral Surgery, Faculty of Dentistry, Universitas Jenderal Achmad
Yani, Cimahi, West Java, Indonesia
3 Department of Pharmacology and Toxicology, Faculty of Pharmacy, Universitas Jenderal Achmad Yani, Cimahi, West Java, Indonesia

*Corresponding author
ery.unjani@yahoo.co.id

JHDS.unjani.ac.id/jite
Doi: 10.54052/jhds.

Article History
Received:22/05/2022
Accepted: 29/05/2022

ABSTRACT

Denture adhesive is indicated for conditions of poor retention and stabilization. Commercially available denture adhesives have side effects, thus requiring a safer alternative adhesive, one of which is rambutan honey adhesive cream. Rambutan honey is safe and does not cause toxic effects on test animals. This study aimed to observe the impact of acute toxicity of the orally administered rambutan honey adhesive cream on mice. The research method is an experimental laboratory method and was carried out using 24 male and female Swiss Webster mice. The subject was divided into four groups, one being the negative control group. Rambutan honey adhesive cream was given in three dose groups, namely 1250, 2500, and 5000mg/kg BW. Observations made were death, body weight, behavioural changes, and

relative organ weight in mice for fourteen days. The analysis test was carried out using the *one-way ANOVA* ($p < 0.05$). The results showed that rambutan honey adhesive cream did not cause death and toxicity symptoms in mice. There was no significant increase in body weight in male and female mice in the group. In the control group, the macroscopic necropsy analysis did not show any change in color and organ index of the heart, lung, liver, spleen, and kidney. This study concludes that the oral administration of rambutan honey adhesive cream on male and female Swiss webster mice is safe and is classified as practically non-toxic.

Keywords: *adhesive cream; acute toxicity test*

ABSTRAK

Perekat gigi tiruan diindikasikan untuk kondisi retensi dan stabilisasi yang kurang. Perekat gigi tiruan yang tersedia secara komersial memiliki efek samping, sehingga memerlukan alternatif perekat yang lebih aman salah satunya krim perekat madu rambutan. Madu rambutan terbukti aman dan tidak menimbulkan efek toksik terhadap hewan uji. Tujuan penelitian ini adalah untuk mengamati efek toksisitas akut krim perekat madu rambutan yang diberikan secara oral pada mencit. Metode penelitian adalah metode laboratorium eksperimental dan dilakukan dengan menggunakan masing-masing 24 ekor mencit Swiss webster jantan dan betina yang dibagi kedalam empat kelompok dengan satu kelompok sebagai kelompok kontrol negatif. Krim perekat madu rambutan diberikan dengan tiga kelompok dosis pada masing-masing kelompok yaitu 1250, 2500 dan 5000mg/KgBB. Pengamatan yang dilakukan yaitu kematian, berat badan, perubahan perilaku, dan berat organ relatif pada mencit yang dilakukan selama 14 hari. Uji analisis yang dilakukan menggunakan uji one way ANOVA (p<0,05). Hasil penelitian menunjukkan bahwa krim perekat madu rambutan tidak menyebabkan kematian dan gejala toksisitas pada mencit. Tidak terdapat peningkatan berat badan yang bermakna pada kelompok

mencit jantan dan betina. Analisis nekropsi secara makroskopik tidak menunjukkan adanya perubahan pada warna, dan indeks organ pada organ jantung, paru, hati, limpa, dan ginjal terhadap kelompok kontrol. Kesimpulan pada penelitian ini yaitu pemberian krim perekat madu rambutan secara oral pada mencit Swiss webster jantan dan betina aman dan termasuk klasifikasi praktis tidak toksik.

Kata kunci: *krim perekat; uji toksisitas akut*

INTRODUCTION

The prevalence of dental and oral problems based on Riskesdas in 2018 was still relatively high, 57.6%, with tooth loss cases of 1.3%1. Tooth loss can cause difficulty eating, communicating, and temporomandibular joint disorders. The installation of dentures can overcome this problem.[2,3] The use of dentures, both complete dentures and removable partial dentures. Removable partial dentures used by the public generally use hot polymerized acrylic resin or Polyvinylether methylcellulose/maleic acid (PMMA). Hot polymerized acrylic resins are widely used because of their easy processing, low cost, light weight, excellent aesthetics, low water absorption, low solubility, and ease to repair.[4] Commercially available denture adhesives have the side effect that they can affect the Acceleration of microbial growth, causing denture stomatitis due to Candida albicans microbes.[5] Also, commercially available denture adhesives have mostly dose-dependent cytotoxic effects on fibroblasts and keratinocytes, with poor cell recovery in older human fibroblasts.[6] One of the safer alternatives to natural ingredients is honey. Honey has hydrogen bonds that act as an oxidizing agent. This can increase the retention of denture adhesive. According to research by Chayati in 2012, rambutan honey has low water content and is very stable for microbial growth. Rambutan honey also has a high viscosity of 18,24. Rambutan honey can be used as a denture adhesive because of its low water content and high viscosity. Has higher the viscosity obtained, Rambutan honey strengthof the adhesive cream, so that the retention of the denture will be better.[8,9] In addition, honey has important factors like H_2O_2, low pH, levels of phenolic acids, and flavonoids. Other phytochemical factors such as tetracycline, peroxide, amylase, fatty acids, phenol,

carbonic acid, terpenes, benzyl alcohol, and benzoic acid make honey active against pathogenic bacteria and produce bacteriostatic/bactericidal properties.[7]

The development of herbal ingredients must consist of six stages: selection, screening of biological substances, toxicity tests, pharmacodynamic tests, development of drug formulations, and clinical trials on humans in the laboratory. The preclinical test is a toxicity test to determine the body's reaction to an ingredient and to measure the ability of honey to cause pathological changes in the body.[10]

Toxicity tests are divided into several types: acute oral toxicity, oral subchronic toxicity, and chronic oral toxicity. An acute oral toxicity test is carried out to detect intrinsic toxicity. It is used to obtain hazard information after acute exposure to a substance, obtain initial data that can be used to determine dose levels, and obtain the LD50 of a substance/preparation.[11,12] Previous research was carried out by Yuslianti et al. in 2016. They researched the toxicity test of rambutan honey on mice and proved that it is safe for consumption and does not cause toxic effects or death in mice but affects mice's body weight.[13] Rambutan honey has been proven safe. However, there has been no acute toxicity test study on rambutan honey as adhesive cream. As the interaction of adhesive cream ingredients with honey content can cause toxic effects or not, therefore it is necessary to do an acute toxicity test for rambutan honey adhesive cream. This study aimed to determine the toxic effect of the adhesive teeth cream rambutan honey in mice using rambutan honey as an herbal ingredient.

METHOD

The research was conducted at the Laboratory of Pharmacology and Therapy, Faculty of Medicine, Padjajaran University, Bandung. The research was done from September 2021 until January 2022. Ethical approval was obtained from the Research Ethics Committee of the Faculty of Medicine, Padjadjaran University, with the number 974 /UN6.KEP /EC/2021.

The research is an experimental laboratory with a completely randomized design. The sample used in this study was rambutan honey adhesive cream. The rambutan honey was obtained from Pusbahnas, stored in a dark bottle, and stored in a freezer box with a temperature of -20^0c. Rambutan honey adhesive cream is divided into three dose groups, namely 1250, 2500, and 5000 mg/Kg. The research subjects were 48 *Swiss webster* males and females calculated based on *Federer's formula*. Mice were obtained from the Laboratory of Pharmacology and Therapy

at the Faculty of Medicine, Padjajaran University. The mice were weighing 20-30 grams and 2-3 months old, healthy, and had no anatomical abnormalities. Mice were divided into four groups, with 1 group as the control group and each containing six mice. The Control group was not given rambutan honey adhesive cream and only food and drink. Group 2 was given rambutan honey adhesive cream at a dose of 1250 mg/Kg, group 3 was assigned a dose of 2500 mg/Kg, and group 4 was given a dose of 5000 mg/Kg given per day orally using an oral probe. Then, the mice were adapted for seven days before being given treatment in the laboratory with room temperature 22°±3°C, relative humidity 30-70%, lighting for 12 hours of light and 12 hours of darkness, and treated according to the 3R principle (replacement, reduction, refinement) and 5 Freedom for animal welfare (Freedom from hunger and thirst, freedom from discomfort, Freedom from pain, injury and disease, Freedom from fear and distress, Freedom to express natural behaviour).[13–15]

Observations were carried out 24 hours after being given rambutan honey adhesive cream until the 14th day, weighing from day 1 to day 14, and observations of changes in behaviour were carried out at minutes 0, 30, 60, 120, and 240 which include changes in motor activity, Straub phenomenon, piloerection, ptosis, corneal reflex, pineal reflex, flexion, Haffner, stretching, grooming, lacrimation, vasodilation, catalepsy, stupor, reestablishment, tremor, vocalization, salivation, defecation, and urination. The mice were then euthanized by cervical dislocation on the 15th day for an autopsy and then weighed on the heart, lungs, liver, spleen, kidneys, ovaries, uterus for female mice and organs of the heart, lungs, liver, spleen, kidney, testes, *vesica seminal* for male mice. The organs that have been weighed are then calculated relative organ weight (ROW) according to the formula:

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

Data analysis

The data obtained from the study results were statistically analyzed using SPSS. The analytical test was the ANOVA and Kruskal Wallis test, followed by a post hoc test using Mann Whitney with $p < 0.05$.

RESULT

Mortality: the administration of rambutan honey adhesive cream up to the highest dose of 5000 mg/Kg observed for

fourteen days did not show any mortality in the male and female mice groups.

Body weight: based on the study's results, the average body weight of male mice was found in the group given rambutan honey adhesive cream at 1250 mg/Kg. The highest average body weight in the female mice group was given rambutan honey adhesive cream 2500 mg/Kg, as shown in Figure 1.

Based on the results of the normality test using Shapiro Wilk showed that both data were normally distributed or had a p-value > 0.05 so it was continued.

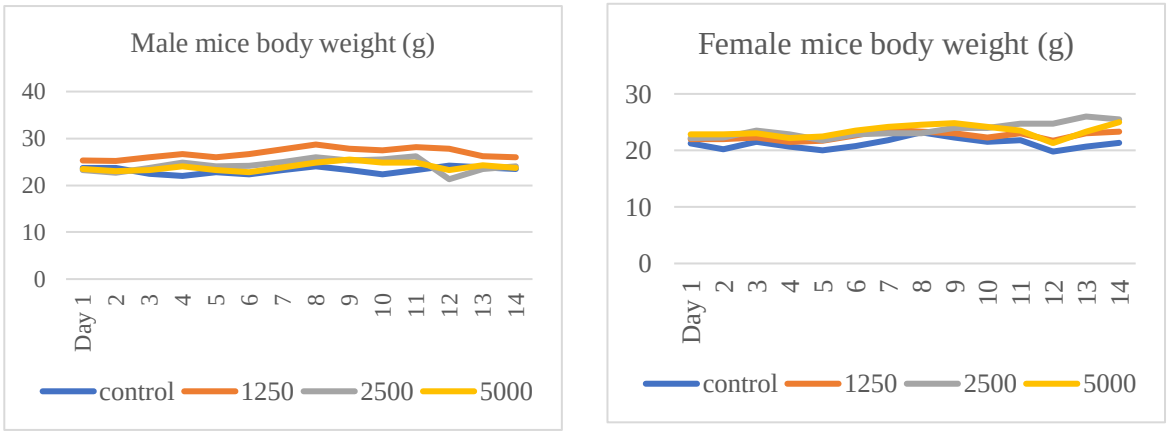

Figure 1. Changes in body weight of male and female mice after giving rambutan honey adhesive cream

The statistical analysis used the Kruskal Wallis test, as shown in Table 1. The results of statistical analysis with Kruskal Wallis showed no significant difference in body weight between male and female mice with a p-value > 0.05, so it was not followed up with a post hoc test using Mann Whitney

Table 1. Effect of rambutan honey adhesive cream on male and female mice's body weight

Group	Average ± SD	P value	Group	Average ± SD	P value
Male Mice			**Female Mice**		
Control	22.81 ± 1.84	0.077	Control	21.31 ± 1.54	0.335
1250 mg/Kg	27.16 ± 2.89		1250 mg/Kg	22.17 ± 1.97	
2500 mg/Kg	24.45 ± 1.43		2500 mg/Kg	23.52 ± 4.74	
5000 mg/Kg	23.64± 1.19		5000 mg/Kg	2241 ± 2.71	

Kruskal Wallis test, *p < 0.05 significant difference

Symptoms of toxicity: observations made at 30, 60, 120, and 240 minutes after administration of rambutan honey adhesive cream did not show any changes in the behaviour of mice in motor activity, Straub phenomenon, piloerection, ptosis, corneal reflex, pineal reflex, flexion, Haffner, stretching, grooming, lacrimation, vasodilation, catalepsy, stupor, reestablishment, tremor, vocalization, salivation, defecation, and urination.

Relative Organ Weight (ROW): based on the results of the study, administration of rambutan honey adhesive cream up to the maximum dose (5.000 mg/Kg) did not show any significant difference in the relative organ weight (ROW) of male and female mice in the heart, lungs, liver, spleen, kidneys, ovaries, uterus for female mice and organs of the heart, lungs, liver, spleen, kidney, testes, vesica seminal for male mice with $p>0.05$ as shown in Table 2 and Table 3. The effect of giving rambutan honey adhesive cream did not cause abnormalities in the shape, size, and colour of organs in male and female mice.

The statistical test for the relative organ weight of the male mice group was used the Kruskal Wallis test because, based on the normality test results, the data on the relative organ weight of the male mice were normally distributed, as shown in Table 3.

Table 2. The effect of rambutan honey adhesive cream on the organ index of male mice

Organs	Male Group				P value
	Control	1250 mg/KgBW	2500 mg/KgBW	5000 mg/KgBW	
Heart	0.62 ± 0.13	0.63 ± 0.19	0.74 ± 0.22	0.67 ± 0.22	0.709[a]
Pulmonal	1.61 ± 0.30	1.04 ± 0.18	0.99 ± 0.47	1.06 ± 0.14	0.969[a]
Spleen	1.67 ± 0.49	2.22 ± 0.88	1.44 ± 0.27	2.09 ± 0.32	0.07[a]
Hepar	7.32 ± 1.54	6.87 ± 1.95	6.99 ± 1.37	6.47 ± 1.37	0.64[b]
Kidneys	1.58 ± 0.22	1.76 ± 0.45	1.78 ± 0.58	1.69 ± 0.32	0.831[a]
Testicles	2.62 ± 0.56	2.15 ± 0.58	3.33 ± 0.77	3.25 ± 1.37	0.096[a]
Vesica Seminalis	0.57 ± 0.19	0.87 ± 0.34	0.95 ± 0.39	0.93 ± 0.28	0.146[b]

Anova test, *p < 0,05 significant difference

The statistical test for the relative organ weight of the mice female group has used the Kruskal Wallis test because, based on the normality test results, the weight data on the close organs of female mice were normally distributed, as shown in Table 3.

Table 3. The effect of rambutan honey adhesive cream on the organ index of female mice

Organs	Female Group				P value
	Control	1250 mg/KgBW	2500 mg/KgBW	5000 mg/KgBW	
Heart	0.76 ± 0.13	0.71 ± 0.25	0.52 ± 0.20	0.66 ± 0.27	0.281[a]
Pulmonal	1.07 ± 0.34	0.89 ± 0.43	0.99± 0.38	1.05 ± 0.21	0.812[a]
Spleen	1.52 ± 0.41	1.94 ± 0.38	1.49 ± 0.74	1.66 ± 0.32	0.406[a]
Hepar	6.94 ± 1.22	6.67 ± 1.59	5.79 ± 4.13	6.47 ± 0.75	0.206[a]
Kidneys	1.62 ± 0.53	1.79 ± 0.63	1.34 ± 0.077	1.60± 0.21	0.592[b]
Ovarium	1.16 ± 0.67	1.27 ± 0.53	0.94 ± 0.26	0.82 ± 0.40	0.354[a]
Uterus	0.62 ± 0.27	0.59 ± 0.24	0.47 ± 0.39	0.44 ± 0.21	0.362[a]

Anova test, *p <0.05 significant difference

Effect of giving rambutan honey adhesive cream not causing abnormalities in the shape, size, and colour of organs in male and female mice.

DISCUSSION

Rambutan honey has been proven to be safe and does not cause toxic effects such as death, behavioural changes, and organ indexes, but has a positive impact, namely increasingbody weight in groups of male mice, as in a study conducted by Yuslianti *et al.* (2016). They researched toxicity tests on acute rambutan honey in *Swiss webster mice.* Even though it is only used as an adhesive for dentures in the oral cavity, honey rambutan adhesive cream still needs to be tested for toxicity. It is because the requirements for the material to be used in the oral cavity must be biocompatible, including not containing toxic substances so as not to injure the oral mucosa when used.[16] This study was conducted to know the toxic effects of rambutan honey adhesive cream by determining the LD50 value by observing mortality and changes in body weight, behaviour, and organ indexes in male and female mice.

This study used mice aged 2-3 months because the test animals with a younger age tend to be more sensitive to the drug. Observation of the LD50 value carried out 24 hours to 14 days after administration of the rambutan honey adhesive cream showed that it did not cause death in experimental animals, which showed the LD50 value of rambutan honey adhesive cream > 5000 mg/kg BW. Based on the result, it could be categorized as practically not toxic. Observation of body weight of male and female mice from day 1 to day 14 showed no significant changes in groups of male and female mice. The increased body weight of mice can be caused by an increase in the consumption of mice feed, while the weight loss of mice can be caused by stress, hormones, and environmental conditions.

Observations on changes in the mice's behaviour were carried out at 0, 30,

60, 120, 240, and 480 minutes after administration of rambutan honey adhesive cream given orally to observe the pharmacology or description of the effect of the drug on the body of the mice. It was done by seeing the appearance or absence of toxic symptoms after giving rambutan honey adhesive cream.[17]

Pharmacological observations were made by observing behavioral changes in mice such as changes in locomotor activity, Straub phenomenon, piloerection, ptosis, corneal reflex, pineal reflex, lacrimation, vasodilation, catalepsy, hanging, reestablishment, flexion, Haffner stretching, grooming, tremor, vocalization, salivation, defecation, and urination.[18] Based on the study's results, oral administration of rambutan honey adhesive cream did not cause behavioural changes in mice. There were no changes in the locomotor activity of male and female mice compared to normal conditions. Mice also did not experience the Straub phenomenon where the mice's tails stood up or formed the letter "S", which means there were no abnormalities in the neuromuscular system and motor activity in mice. The study also did not show any piloerection or a condition in which the mice's fur became erect due to tension. This indicated that there were no abnormalities in the skin of the mice. Symptoms of ptosis, or a condition where the mice's eyes become swollen or the eyelids cover the mice's eyes, do not occur in mice, indicating any disturbance in the eye organs.

Catalepsy is a condition in which the mice experience seizures or lose consciousness and body muscles. Tremor, on the other hand, is a condition in which one or more parts of the mice's body tremble. The absence of catalepsy and tremor in mice indicates no disturbance in mice's central nervous system.

Corneal and pineal reflexes were performed by touching the tip of the cotton bud to the eye and earlobe of mice. Flexion and Haffner are the reactions of mice to pain when the legs and tail of mice are clamped using tweezers. There were no abnormalities in the corneal reflex, pineal reflex, flexion, and Haffner. The result indicated that there was no abnormality in the sensory nervous system of mice. No abnormality in the hanging and reestablishment test was found, which was seen by the way the mice were allowed to climb and hang on the wire or fall quickly. This indicates that the rambutan honey adhesive cream does not cause a pharmacological effect in the form of a sedative and relaxing effect on the muscles so that the mice can climb and hang on four

legs while holding on to the wire.

The study's results did not show any change in the frequency of grooming. If the frequency of grooming increased or decreased, it indicated an abnormality such as suppression or stimulation of the central nervous system and sympatholytic nerves. There were no abnormalities in salivation, lacrimation, and urination, indicating no abnormalities in the autonomic nervous system of mice. There were also no abnormalities in the digestive system of mice seen from the faeces that were excreted normally (not denser or more liquid and did not change colour).[19] Yuslianti et al. (2016) proved in their research that the administration of rambutan honey did not cause changes in the behaviour of male and female mice.[19]

Mice were observed for 14 days to monitor changes in body weight, changes in behaviour, and death. On the 15th day, surgery was performed for weighing, and then the organ index value of the mice was calculated. The organs that were weighed were the heart, lungs, liver, spleen, kidneys, ovaries, and uterus for female mice and organs of the heart, lungs, liver, spleen, kidney, testes, and *seminal vesicles* for male mice. There was no difference in colour or organ shape between the treatment and control groups. Based on the study's results, there was no significant difference in the organ index between all groups of male and female mice given rambutan honey adhesive cream with the control group. This shows that rambutan honey adhesive cream does not cause toxic effects on the organs of the mice, especially the liver and kidneys, which are the main targets for the toxic effect of a drug.

Based on the results and data analysis, it can be stated that the rambutan honey adhesive cream given orally to groups of male and female mice at the highest dose (5000 mg/kg BW) did not cause toxic effects and death in mice. It was included in the practically non-toxic classification.

CONCLUSION

Based on the results and discussion, it can be concluded that the administration of rambutan honey adhesive cream with doses of 1250, 2500, and 5000 mg/kg BW did not cause toxic effects on mice such as death, changes in behaviour, organ index. It had a positive effect by adding body weight in male mice. This indicates that the LD50 value of rambutan honey adhesive cream is > 5000 mg/kg BW and is practically non-toxic. Further research in the form of sub-chronic toxicity tests, chronic toxicity tests, and microscopic examination of the organs of mice is needed to see if there are changes in the structure of the tissues in the organs of mice.

CONFLICT OF INTEREST

We declare no conflict of interest in the scientific articles we write.

ACKNOWLEDGEMENT

We want to express our gratitude to Titta Hartyana S., S.Si., M.Sc, Apt Faculty of Pharmacy Universitas Jenderal Achmad Yani and LPPM Universitas Jenderal Achmad Yani.

REFERENCES

1. Badan Penelitian dan Pengembangan Kesehatan Kementerian Kesehatan Republik Indonesia. Laporan nasional riskesdas 2018. Jakarta: Balitbang Kemenkes RI; 2018.
2. Yin Z, Yang J, Huang C, Sun H, Wu Y. Eating and communication difficulties as mediators of the relationship between tooth loss and functional disability in middle-aged and older adults. J Dent. 2020 May;96(308):103331.
3. Sugiatno E, Th M, Tjahjanti E. Pengaruh kehilangan gigi posterior rahang atas dan rahang bawah terhadap gangguan sendi temporomandibula (Tinjauan klinis radiografi sudut inklinasi eminensia artikularis). J Kedokt Gigi. 2015;6(3):315–20.
4. Alla RK, KN RS, Vyas R, Konakanchi A, Rama Krishna Alla Scholar C, Krishna Alla R, et al. Conventional and contemporary polymers for the fabrication of denture prosthesis: part I-Overview, composition and properties. ~ 82 ~ Int J Appl Dent Sci. 2015;1(4):82–9.
5. Nomura T, Murakami T, Shimoyama Y, Kobayashi T, Furuya J, Sasaki M, et al. Effects of denture adhesives on growth and morphological transformation of Candida albicans. J Prosthodont Res. 2020;64(1):78–84.
6. Costa RTF, Barbirato D da S, Santiago Junior JF, Barros MCM de, Pellizzer EP, Moraes SLD. Toxicity potential of denture adhesives: A scoping review. J Prosthet Dent]. 2021 Apr.
7. Almasaudi S. The antibacterial activities of honey. Saudi J Biol Sci. 2021 Apr;28(4):2188–96.
8. Kano H, Kurogi T, Shimizu T, Nishimura M, Murata H. Viscosity and adhesion strength of cream-type denture adhesives and mouth moisturizers. Dent Mater J. 2012;31(6):960–8.
9. Yuslianti ER, M. Bachtia B, F. Suniart D, B. Sutjiat A. Antioxidant activity of rambutan honey: The free radical-scavenging activity in vitro and lipid peroxidation inhibition of oral mucosa wound tissue in vivo. Res J Med Plant. 2015 Jun 1;9(6):284–92.

10. Zulfiana D. Pengujian toksisitas akut oral dan dermal pada biolarvasida Metarhizium anisopliae terhadap tikus putih Spraque Dawley. J Biol. 2014;7(1):1–8.

11. Badan Pengawas Obat dan Makanan (BPOM). Pedoman uji toksisitas nonklinik secara in vivo. 2014.

12. Makiyah A, Tresnayanti S. Uji toksisitas akut yang diukur dengan penentuan LD50 ekstrak etanol umbi iles-iles (Amorphophallus variabilis Bl .) pada tikus putih Strain Wistar. MKB. 2017;49(3):145–55.

13. Yuslianti ER, Bachtiar BM, Suniarti DF, Sutjiatmo AB. Effect of rambutan honey (Nephelium lappaceum) acute administration on mortality, body weight, toxicity symptoms and relative organ weight of swiss websters mice. Res J Toxins. 2016;8(1–2).

14. Cheluvappa R, Scowen P, Eri R. Ethics of animal research in human disease remediation, its institutional teaching; and alternatives to animal experimentation. Pharmacol Res Perspect. 2017;5(4):1–14.

15. Susanto W, Gandha MV. Pusat edukasi tentang hewan peliharaan di Kelapa Gading. J Kaji Teknol. 2015;11(1):28–42.

16. Adam MA, Meizarini A. Sitotoksisitas pemutih gigi berdasarkan konsentrasi bahan. J Dentomaxillofacial Sci. 2010;9(2):116.

17. Nurfaat DL, Indriyati W. Uji toksisitas akut ekstrak etanol benalu mangga (Dendrophthoe petandra) terhadap mencit Swiss webster. 2016;3.

18. Caturizani DS, Fajriaty I, Sari R. Uji toksisitas akut ekstak etanol 96% daun pasir-pasir (ilex cymosa Blume) pada tikus betina galur wistar. 2016;14–6.

19. Yuslianti ER, M. Bachtia B, F. Suniart D, B. Sutjiat A. Effect of rambutan honey (Nephelium lappaceum) acute administration on mortality, body weight, toxicity symptoms and relative organ weight of Swiss Websters Mice. Res J Toxins. 2016 Mar 15;8(1):1–7.