Acute Toxicity Test of Sarang Semut (Myrmecodia Pendens) Ethanol Extract in Male Wistar Rats (Rattus Norvegicus) as Periodontal Pocket Irrigation Therapy

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Acute Toxicity Test of Sarang Semut (*Myrmecodia Pendens*) Ethanol Extract in Male Wistar Rats (*Rattus Norvegicus*) as Periodontal Pocket Irrigation Therapy

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Abstract

Root canals that are potentially contaminated with microorganisms when the gingiva is inflamed require periodontal pocket therapy to eliminate or reduce the microbial population and biomechanically remove necrotic tissue in the root canal system. Sarang Semut (Myrmecodia pendens) extract has the effectiveness as an antibacterial containing chemical compounds from the flavonoid and tannin groups. In many cases, flavonoids can act directly as antibiotics by interfering with the function of bacterial or viral microorganisms. The high rate of failure of periodontal treatment caused by the activity of several anaerobic and aerobic bacteria and there has been no research on the Sarang Semut plant used as a material for periodontal pocket irrigation and mouthwash, so a study was conducted to determine the acute toxicity of the Sarang Semut extract (Myrmecodia pendens) as a base material. Irrigation therapy for periodontal pockets and gingivitis.

Data were analyzed using ANOVA test and regression test. The type of research conducted is experimental laboratory. Acute toxicity test of ethanol extract of Sarang Semut (Myrmecodia pendens) in Wistar Male rats (Rattus Norvegicus) at a dose of 0.1 g/kg BW on histology of the liver and kidneys had minimal toxic effect 7 days after application with minimal inflammatory cell infiltration. This dose can be used as a basic reference for periodontal pocket irrigation therapy. Further research is needed to formulate Myrmecodia pendens extract at lower dose yet effective for mouthwash preparations or for liquid periodontal pocket irrigation materials.

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Introduction

The gingiva is a part of the oral mucosa that has a role in supporting the teeth, protecting the alveolar bone and periodontal ligament from microbial attack. Infected gingiva is caused by a microorganism that plays an important role in the occurrence of necrosis of the dental pulp tissue and the formation of periapical abnormalities such as abscesses, granulomas and cysts. Treatment of periodontal pockets on infected gingiva aims to eliminate or reduce the microbial population and biomechanically dispose of necrotic tissue in the root canal system where this canal is a medium for microbial growth and prevent reinfection by closing the canal space tightly.

Indonesia is a tropical country that has abundant plant diversity that must be utilized properly. One of the medicinal plants from the Packagemantan forest that has great potential is the Sarang Semut (*Myrmecodia pendens*). Its epiphytic nature is beneficial for its use as a medicinal plant because its exploitation does not harm the ecosystem.[1] Sarang Semut (*Myrmecodia pendens*) the stems are rarely branched, if there are only one or a few branches. There are even some species that do not have the same set of branches. The trunk is thick and internodal very close, except at the base of the Sarang Semut of some species. The leaves are thick like leather. Some species have leaves that are narrow and long. Stipule (support) large, persistent, split and opposite the petiole, and form like 'ears' in clipeoli. Sometimes it continues to develop into wings around the top of the clipeus. The benefits of the Sarang Semut plant include treating various systemic diseases such

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as leukemia, liver disease, tuberculosis, kidney, prostate dysfunction, various allergies, migraine, hemorrhoid rheumatism, infectious diseases, and infections that cause dental caries. [2]

The active compounds contained in the Sarang Semut include phenolic acid which functions as an antioxidant, eliminates free radicals, and improves blood flow in blood vessels; flavonoids function to protect cell structure, treat cancer, weaken HIV/AIDS and herpes viruses, prevent osteoporosis, increase the effectiveness of vitamin C, as an antibiotic, and anti-inflammatory; tannins function as *astringents* that bind and precipitate proteins in the body to treat hemorrhoids/hemorrhoids, stop nosebleeds and bleeding; polyphenol serves to lower blood sugar levels and antimicrobial; Tocopherol functions as a scavenger of free radicals.[3]

The ability of the Sarang Semut extract (*Myrmecodia pendens*) to be effective as an antibacterial is also supported by the active substances contained in this plant. Based on the phytochemical analysis, in addition to containing nutrients that are important for the body, the Sarang Semut plant (*Myrmecodia pendens*) also contains chemical compounds from the flavonoid and tannin groups. In many cases, flavonoids can act as antibiotics by interfering with the function of bacterial or viral microorganisms and also can form a cell defense mechanism against free radical damage as an antioxidant[4]

Inhibition mechanism of flavonoids on bacterial growth is thought to be due to the ability of these compounds to form complexes with extracellular proteins, activate enzymes, and damage cell membranes. In general, flavonoid compounds can inhibit the growth of gram-positive and gram-negative bacteria.[5]

Toxicity testing is the determination of the potential hazards that may be produced by the test substance and characterization of its action, most of the toxicity testing is carried out on experimental animals. Toxicity testing is very important in screening newly developed drugs before they can be used in humans.[6] The advantages of using animal models in toxicity testing are enormous. These advantages include the possibility of a clearly defined genetic constitution and its ease of controlled exposure, duration of controlled exposure, and the possibility of detailed examination of all tissues after necropsy. The information obtained can serve as a basis for hazard classification and labeling of chemicals in trade. The point of toxicity testing is not just to check how safe a test substance is but to characterize the possible toxic effects it produces. The toxic effects of drugs can range from negligible to severe to prevent further development of the compound. All toxicity studies are supported by; clinical analysis, autophytic analysis, haematological and haematochemical analysis, histopathological analysis and statistical presentation and interpretation of data.

Due to the high failure rate of periodontal treatment caused by the activity of several anaerobic and aerobic bacteria and there has been no research on the Sarang Semut plant which is used as a material for making periodontal pocket irrigation and mouthwash, the researchers are interested in conducting research on the extract of Sarang Semut (*Myrmecodia pendens*) as a basic material for irrigation for periodontal pocket therapy and gingivitis for acute toxicity tests.

So the researchers are interested in conducting research on "Acute Toxicity Testing of Sarang Semut (*Myrmecodia Pendens*) Ethanol Extract In Male Wistar Rats (*Rattus Novergikus*) As Periodontal Pocket Irrigation Therapy".

Materials and methods

The subjects of this study were white Wistar rats (*Rattus Norvegicus*), male, aged 4-6 months, weighing 100-200 grams. The rats were in good health and adapted to the laboratory atmosphere for 3 days. The Sarang Semut used in this study were obtained from Kalimantan. The samples were dried by drying and then mashed. A total of 1000 grams of powder is macerated with a 96% ethanol filter for 5 days. The ethanol fraction obtained was concentrated with *a rotary evaporator* to obtain a thick extract. In addition, 1% NaCMC solution was used to be given to the control group. This research has been approved for ethical feasibility by the ethics committee of the Faculty of Medicine, Mulawarman University No.82/KEPK-FK/IX/2021.

This study used a completely randomized design with 20 rats as test animals which were devided into 4 groups, each consisting of 5 rats. Group I: given 1 ml of 1% NaCMC solution, Group II: given ethanol extract of 0.1 g/kgBW Sarang Semut, Group III: given ethanol extract of

Sarang Semut 1 g/kgBW, Group IV: given ethanol extract of Sarang Semut 2.5 g/kgBB. The test material for all groups was given orally in a single dose. All group of rats were previously fasted for 8 hours. The test material was given at the appropriate dose for each group. Observations were carried out intensively in the first 3 hours of giving the test material. The number of test animals that died in the first 24 hours was counted and recorded. Test animals that died were autopsied to be examined both macroscopically and microscopically. This observation was continued for 7 days including physical observations and the number of dead animals.

Calculation The LD50

Determination was carried out using the Thompson-Weil method with a 95% confidence level. LD50 is calculated using the following formula:

Log LD50 = Log D + d(f+1)

D = smallest dose used

d = logarithm of multiples

f = Factors in table R

df = look up in table R

Results

This study used a completely randomized design with 20 rats as test animals which were devided into 4 groups, each consisting of 5 rats. There were 4 groups that were given to each of the 5 rat organs, namely the control group which was given a solution of *sodium carboxymethyl cellulose* (CMC-Na), the intervention group with a dose of 0.1 gram/kg of body weight Sarang Semut extract, the intervention group with a dose of 1 Sarang Semut extract. gram/kg body weight and the intervention group with a dose of extract Sarang Semut 2.5 grams/kg body weight. The percentage of each group is 25%.

The distribution of the incidence of inflammation in all samples experienced inflammation of the liver organ with the majority experiencing inflammation (55%), then 30% had minimal inflammation and the other 15% had moderate inflammation. In all the interventions given to the sample, the majority of samples did not experience necrosis of the liver, while 30% of the samples had necrosis of the liver. Histology of the liver with inflammation is present in Figure 1.

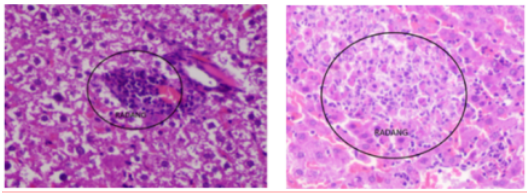

Figure 1. Histology of the liver with inflammation (*radang-Indonesian*), as indicated by circle. Under a microscope with 400x magnification.

All of the interventions given to the sample, the majority of samples did not experience necrosis of the liver, while 30% of the samples had necrosis of the liver. Histology of inflammation of the liver with necrosis present in Figure 2.

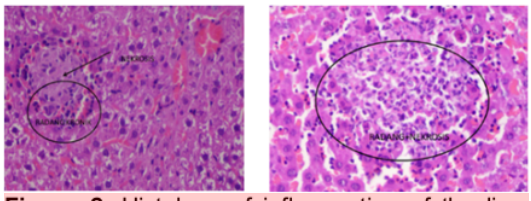

Figure 2. Histology of inflammation of the liver with necrosis, as indicated by arrow. Under a microscope with 400x magnification.

All interventions given to the sample, the majority of samples experienced sinus dilatation, namely liver sinusoid widening by 70% and the other 30% had no sinus dilatation effect. Histology of the liver organs with sinus dilation is present in Figure 3.

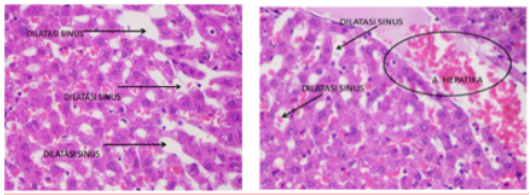

Figure 3. Histology of Liver Organs with Sinus Dilation, as indicated by arrow. Under a microscope with 400x magnification.

All interventions given to the sample, the majority of samples experienced vacuolization in the liver organ, namely the cytoplasm of the liver cells formed a vacuolization of 75%. Meanwhile, the other 25% did not experience vacuolization. Histology of vacuolized liver organs is present in Figure 4.

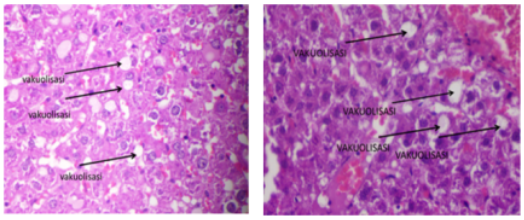

Figure 4. Histology of Vacuolized Liver Organs, as indicated by arrow. Under a microscope with 400x magnification.

Differences in the effect of inflammation occurred in the kidney organs, namely not all samples experienced inflammation. There were 15% of normal samples from the four intervention groups. The majority of the samples also only had minimal inflammation, i.e. 80% and 5% had inflammation. Histology of inflammatory kidney organs is present in Figure 5.

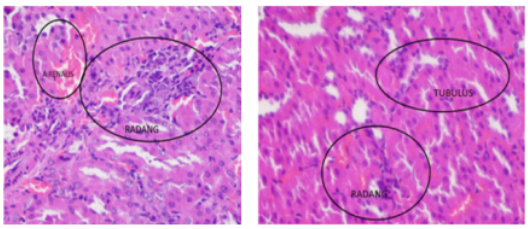

Figure 5. Histology of inflammatory kidney organs, as indicated by circle. Under a microscope with 400x magnification.

There was no incidence of renal necrosis in all samples. This is different from the liver, where 30% of the samples were necrotic. The whole control group and the group that was given the intervention of Semut Semut extract at different doses did not experience the effect of necrosis on the kidney organs. Meanwhile, the difference in effects or cross tabulation of each given intervention on the effects that appear in each sample is shown in the next table.

All samples in the control group, which were given the addition of Na-CMC in the liver, had minimal inflammation. Meanwhile, the intervention group with a dose of Sarang Semut extract per kilogram of body weight given 0.1 grams of the majority experienced inflammation (80%) and the group that was given 1 gram all experienced inflammation (100%). Furthermore, the group with the intervention of 2.5 gram/kg Sarang Semut extract had moderate inflammation (30%) and inflammation (40%).

Group		Minimal inflammation	Moderate inflammation	Inflammation	Total
Control (Na-CMC)	N	5	0	0	5
	%	100%	0%	0%	100%
0.1gr/kgBB	N	1	0	4	5
	%	20%	0%	80%	100%
1 gr/kgBB	N	0	0	5	5
	%	0%	0%	100%	100%
2.5gr/kgBB	N	0	3	2	5
	%	0%	60%	40%	100%
Total	N	6	3	11	20
	%	30%	15%	55%	100%

Table 1. Cross tabulation of the sample group with the incidence of inflammation in the liver.

Group		No	Yes	Total
I. Control (Na-CMC)	N	5	0	5
	%	100%	0%	100%
II. 0.1gr/kgBB	N	4	1	5
	%	80%	20%	100%
III. 1 gr/kgBB	N	4	1	5
	%	80%	20%	100%
IV.2.5gr/kgBB	N	1	4	5
	%	20%	80%	100%
Total	N	14	6	20
	%	70%	30%	100%

Table 2. Cross tabulation group samples with the incidence of necrosis in the liver.

Table 2 shows that the majority of the control group and the intervention group in the liver did not experience necrosis except in the intervention group which was given 2.5 grams of Sarang Semut extract, 80% of them experienced necrosis. As for each group that did not experience necrosis, namely the control group which was given Na-CMC solution (100%), the group that was given 0.1 gram and 1 gram of Sarang Semut extract, 80% each did not experience necrosis.

Table 3 illustrates that the control group that was given Na-CMC solution did not experience sinus dilatation in the liver (60%) and 40% had sinus dilatation. Meanwhile, all samples that were given 0.1 gram Sarang Semut extract experienced sinus dilatation. Furthermore, the group that was given the Sarang Semut extract 1 gram and 2.5 grams the majority experienced

sinus dilatation in the liver organs, namely 60% and 80%, respectively.

Group		No	Yes	Total
Control (Na-CMC)	N	3	2	5
	%	60%	40%	100%
0.1gr/kgBB	N	0	5	5
	%	0%	100%	100%
1 gr/kgBB	N	2	3	5
	%	40%	60%	100%
2.5gr/kgBB	N	1	4	5
	%	20%	80%	100%
Total	N	6	14	20
	%	40%	70%	100%

Table 3. Cross tabulation of sample groups with sinus dilatation on the liver.

Group		No	Yes	Total
Control (Na-CMC)	N	3	2	5
	%	60%	40%	100%
0.1gr/kgBB	N	1	4	5
	%	20%	80%	100%
1 gr/kgBB	N	1	4	5
	%	20%	80%	100%
2.5gr/kgBB	N	0	5	5
	%	0%	100%	100%
Total	N	5	15	20
	%	25%	75%	100%

Table 4. Cross tabulation of sample groups with hepatic vacuolization.

Table 4 illustrates that the control group given Na-CMC solution experienced hepatic vacuolization (40%) and the rest did not experience hepatic vacuolization. Furthermore, the entire intervention group that was given the Sarang Semut extract respectively 0.1 gram, 1 gram and 2.5 gram underwent liver vacuolization respectively, namely 80%, 80% and 100%.

The interventions given to the kidneys

The control group that was given Na-CMC solution was mostly normal or not inflamed (60%) and 40% of this group only had minimal infiltration of inflammatory cells. Meanwhile, the intervention group that was given 0.1 gram Sarang Semut extract experienced minimal inflammation (80%) and inflammation (20%). Furthermore, the group with the intervention of 1 gram and 2.5 grams of Sarang Semut extract all experienced minimal infiltration of inflammatory cells.

Discussion

Experimental animals treated were 20 male Wistar rats (*Rattus norvegicus*) which had the same weight and were adapted to the laboratory environment for 3 days. Furthermore, on day 7 all rats were sacrificed and an autopsy was performed on 20 male wistar rats, then two rats organs were removed and further examination was carried out in the form of tissue histology examination. The two organs are the liver and kidneys. The effects that can occur in each given intervention are the following effects:

1. Inflammation of the lymphocyte and neutrophil cells that may occur in the liver and kidneys
2. Necrosis of necrotic tissue surrounded by inflammatory cells kidney
3. Sinus dilatation, i.e. widening of hepatic sinusoids
4. Vacuolization, i.e. the cytoplasm of liver cells forms vacuolization.

Observations were made under a microscope with a magnification of 400x. Materials used for the manufacture of histopathological preparations with HE staining (*Haematoxylin-Eosin*), 70% alcohol, 80% alcohol, 90% alcohol, 96% alcohol, absolute alcohol, toluene, and paraffin.[7] Observations were made and in general all rats did not die and did not show signs of poisoning, such as restlessness, walking left and right without direction, seizures. During the observation period, it was found that the behavior of the mice was active, there were no abnormalities in the eyes and hair loss. Appetite to eat and drink is also good.

Animals that were treated were 20 male Swiss rats (Mus musculus), which were divided into 5 groups; 1 control group was given 1% NaCMC and 4 experimental groups were given the ethanol extract of Anth's Nest (Myrmecodia pendens) respectively 0.1, 1, 10 and 100g/Kg BW. Evaluation of toxic clinical symptoms and mortality was carried out within 24 hours and 14 days for the viability of mice. The test resulted in

the LD50 of the ethanol extract of Anth's Nest which was 3,162g/Kg body weight. All mice in the 10 and 100g/kg body weight groups died within one hour of giving the extract and showed toxic clinical symptoms such as hyperactivity and seizures. Histopathological examination of the kidneys of dead mice showed inflammatory cell infiltration and diffuse congestive tubules. Sarang Semut ethanol extract is a substance that is slightly toxic to Swiss male mice based on Hodge and Sterner criteria.[8]

Sarang Semut's Aceh ethanol extract has the potential for acute toxicity. This is related to the four compounds that have been chemically identified in the Sarang Semut, namely phenolic groups, saponins, triterpenoids, and steroids. These four groups of compounds play a role in causing the death of *Artemia salina* Leach larvae. This is due to the different types (species) of the two plants. The location of growth and differences in growing climate will greatly affect the composition and levels of active compounds possessed by similar plants (the same genus).[9]

Besides, several previous studies have stated that *Myrmecodia pendens* has antimicrobial effects against *Candida albicans*, *Shigella dysentriae*, *Enterococcus faecalis*, *Streptococcus mutans*, and *Streptococcus sanguis.*[10] There is a relationship between 25% concentration of Sarang Semut plant extract and 50% concentration as root canal irrigation material that can inhibit the growth of *Enterococcus faecalis*. [11] The growth of *Fusobacterium nucleatum* was inhibited by 20%, 40%, 60%, and 80% of the ethanol extract of the Sarang Semut plant.[12] Sarang Semut extract of *Myrmecodia pendens* with a concentration of 25% and a concentration of 50% also effective in inhibiting the bacteria *Porphyromonas gingivalis.*[13]

Histopathological results of test animal organs given test preparations and autopsied 24 hours after treatment showed abnormalities in the form of renal tubular epithelial degeneration, peribronchiolitis, perivasculitis, and hydropic degeneration of the liver. Histopathological results of test animals that were autopsied on the 14th day after treatment showed inflammation of the liver.[14]

Liver function as an organ is to detoxify foreign materials that enter and are harmful to the body. When the dose of Sarang Semut extract was increased to 375 mg/kg BW, liver disorders began to appear and resulted in midzonal degeneration which was marked by the formation of vacuoles in the liver cell tissue. This happens because of the buildup and increase in toxic materials in the liver and cause disruption of the process of formation of nutrients from digestive venous blood. The next impact is the accumulation of toxicants and is harmful to liver cells. With a dose of 3750 mg/kg BW, more and more toxic substances accumulate and cannot be processed by the liver and can cause necrosis or cell death in the liver and kidneys. Liver cell necrosis is characterized by changes in the nucleus and cytoplasm of the cells. When the plasma membrane of liver cells is damaged, enzymes from the cytosol will be released into the bloodstream and become a quantitative sign of widespread liver cell damage. The detoxification process carried out by *hepatic microsomal* can also cause harmful substances to become more toxic and cause cell damage. Doses of 3750 mg/kg BW can interfere with the detoxification process of *microsomal* so that necrosis occurs and continues to kidney tissue and can trigger immune reactions and affect cell biochemical reactions. Severe liver damage can occur and may hinder the regeneration process and may leave scars even after the liver has recovered. In severe poisoning, liver function can fail and if it continues it can cause death in just 12-24 hours. Meanwhile, at a dose of 3750 mg/kg BW, necrotic conditions can occur until day 12 and on day 26, vacuolization will appear with infiltration of macrophage and neutrophil cells. This dose did not cause death in test animals so that the use of Sarang Semut extract at that dose was quite safe and had the potential to be used as a pharmaceutical drug.[15]

Conclusions

Acute toxicity test of Sarang Semut (*Myrmecodia pendens*) ethanol extract in male Wistar rats (*Rattus Norvegicus*) at a dose of 0.1 g/kg BW on histology of liver and kidney had minimal toxic effect 7 days after application with minimal inflammatory cell infiltration. This dose can be used as a basic reference for periodontal pocket irrigation therapy. Further research is needed to formulate *Myrmecodia pendens* extract at lower dose yet effective for mouthwash preparations or for liquid periodontal pocket irrigation materials.

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Declaration of Interest

The authors report no conflict of interest.

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