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Acute Toxicity of Bajakah Tampala (*Spatholobus littoralis* Hassk) Ethanolic Extract on The Microanatomy of Rat Spleens

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Abstract. *The utilization of bajakah tampala (Spatholobus littoralis Hassk) as a herbal medicine has been passed down through generations within the community in Kalimantan. However, no comprehensive studies have investigated the effects of consuming this herbal medicine without a standardized safe dose. This study aimed to determine the spleen microanatomy after administration of an acute dose of S. littoralis stem ethanolic extract. The stems of S. littoralis utilized in this study were obtained from the Sungai Ambawang Forest in Kubu Raya, West Kalimantan. These stems underwent maceration with 96% ethanol solvent. This study used a completely random design with four treatments, which included distilled water and S. littoralis stem ethanolic extract at three doses: 300; 2000; and 5000 mg/kg BW. Each treatment had five replicates. The results showed that the administration of extract doses above 2000 mg/kg BW caused a significant decrease in the diameter of the splenic white pulp, and the spleen's microanatomy revealed that the boundary between the periarteriolar lymphoid sheaths (PALS) and the lymphoid follicles disappeared, as well as lymphoid follicles that shrank in size. This shows that the administration of extract doses above 2000 mg/kg BW causes symptoms of damage to the spleen microanatomy of experimental animals.*

Keywords: *acute toxicity, extract, Spatholobus littoralis, spleen*

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INTRODUCTION

The local community presently utilizes plants as traditional medicines for their daily lives. Many people believe that herbal medicines are free from side effects, making them widely used for treating various diseases (Syafruddin et al., 2022). Bajakah tampala (*Spatholobus littoralis* Hassk) is one of the plants found in Kalimantan, recognized for its applications in herbal medicine (Hasna et al., 2021). *S. littoralis* stem extract is used by the Dayak community as a therapeutic agent for various ailments due to its rich composition of advantageous secondary metabolites (Syafruddin et al., 2022). The ethanol extract of *S. littoralis* stems contains secondary metabolites such as phenolics, tannins, and saponins (Ayuchecaria et al., 2020). According to (Rousdy et al., 2022), ethanol extract of *S. littoralis* stems at a dose of 2.5 mg/kg BW has potential anti-inflammatory activity by inhibiting carrageenan-induced edema formation in rats. *S. littoralis* stem extract at a dose of 100 mg/kg BW can induce the efficiency of the immune system and antibodies by increasing the number of leukocytes in mice (Susanto & Zayani, 2021). This plant has been empirically utilized as a herbal medicine within the community and has not been based on scientific evidence regarding its safety for human health (Abdulrahman et al., 2021). According to Jitareanu et al. (2023), inappropriate use of herbal medicines can pose several risks due to their side effects. Several types of potential risks from inappropriate use of herbal medicines, including plant metabolites toxic reactions, adverse reactions, adulteration, and adverse drug-herbal interactions.

Any substances in traditional herbal medicines commonly consumed by the community will the body and enter the bloodstream. This blood is transported to the spleen, where the body's immune response to chemical compounds in the blood takes place. Chemical compounds can stimulate the proliferation of T lymphocytes and B lymphocytes. (Noh et al., 2019). As a result of the proliferation activity of T and B lymphocytes in the splenic white pulp, the level of proliferation of T and B lymphocytes will be in line with the size of the diameter of the splenic white pulp (Rousdy et al., 2017). The spleen is the second largest lymphatic organ, so its blood flow plays a vital role in immunology and has relevant implications for toxicity testing of herbal medicines (Khayal et al., 2022).

Research on the toxicity test of plant extract administration to the spleen has been conducted previously. For instance, Ren et al. (2021) found that *Ageratina adenophora* extract has a specific dose for ethnopharmacological uses but can also cause spleen immunotoxicity at higher doses. As demonstrated by the study of Nalimu et al. (2022), Aloe vera leaf extract at a specific dose can manage several ailments. However, at higher concentrations, the extract can cause spleen damage.

The effects of *S. littoralis* extract on various organs have been studied. Still, studies on the spleen have been particularly limited. In contrast, consuming *S. littoralis* extract without the proper dose is prevalent among Indonesians due to its claimed health effects. This shows the importance of toxicity tests on *S. littoralis* stem extracts before being used as standardized herbal medicines and phytopharmaceuticals. Therefore, this study must be conducted to determine the safety of its use as herbal medicine. This study has the potential to contribute new insights into the effects of administration of an acute dose extract, especially in the spleen. In addition, this study can provide a reference for the microanatomical condition of the spleen after administration of an acute dose extract. Furthermore, it can

provide a reference for determining the dose in toxicity tests at a more advanced level.

MATERIALS AND METHODS

Study Duration and Location

This research was conducted from January to August 2023 at the Zoology Laboratory, Faculty of Mathematics and Natural Sciences, Tanjungpura University, Pontianak City, West Kalimantan.

Preparation of Materials

Bajakah tampala stems (*Spatholobus littoralis* Hassk) were collected from Sungai Ambawang Forest, Kubu Raya Regency, West Kalimantan. The stems are yellowish-brown and have a hard, slightly porous texture. The experimental animals were female Wistar strain (*Rattus norvegicus* Berkenhout) in nulliparous/virgin conditions aged ±8 weeks and weighed ±150 g. This study has obtained ethical approval from the Health Research Ethics Committee of the Faculty of Health Sciences, Respati University Yogyakarta (approval no. 0203.3/FIKES/PL/IX/2023). The experimental animals were acclimated for 7 days to a room temperature ranging from 22±3°C, relative humidity 40-60%, and 12 hours each for light and dark (Ren et al., 2021). The experimental animals were provided with ad libitum access to a commercial feed and distilled water.

Extraction of *S. littoralis* Stem

Extraction of *S. littoralis* stems using the maceration method (Ayuchecaria et al., 2020). The sundried stems of 2.8 kg were cleaned and ground into 8 mesh-sized simplisia. Simplisia was then macerated at room temperature with 96% ethanol solution, the ratio of simplisia and solvent 1:10. Maceration was conducted for 3×24 hours, and every 24 hours, the macerate was filtered with filter paper and vacuum filter, then added with a new solution. The macerate was evaporated with a rotary evaporator at a temperature range of 40-60°C to obtain a concentrated extract.

Phytochemical Screening of *S. littoralis* Ethanolic Extract

S. littoralis stem ethanolic extract was examined for its secondary metabolite content using Harborne's method, encompassing alkaloids, phenolics, flavonoids, saponins, terpenoids, and steroids (Rahminiwati et al., 2023). The alkaloid test was executed by adding Mayer's reagent, which formed a white-to-yellowish precipitate within the test tube, indicating a positive response. The phenolic test was conducted by adding a 1% $FeCl_3$ solution, yielding a blackish-green or blackish-blue coloration indicative of the presence of phenol, hydroquinone, or tannin. The flavonoid test used the Wilstatter reagent, and positive results were indicated by the formation of a red, yellow, or orange precipitate. The terpenoid and steroid tests proceeded by adding the Liebermann-Burchard reagent to the test tube containing the extract. Positive results for steroids were indicated by the appearance of a blue or green color, while a red or purple color indicated positive results for terpenoids. The saponin test was executed by adding hot water to the test tube containing the extract, then cooling and shaking vigorously for 10 seconds until stable bubbles characterized effervescent and positive results for ±10 minutes.

Acute Oral Toxicity Method

The experimental design was a completely randomized design (CRD) using four treatments and five replications. The first

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treatment was a control animal without stem extract, while the second, third, and fourth treatments were given 300, 2000, and 5000 mg/kg BW of stem extract, respectively. The extract was dissolved in 2 ml of 0.5% CMC (stabilizer solution) and delivered to animals using a gastric sonde.

Preparation of Spleen Microanatomy

The experimental animals were weighed before treatment on day 0 and after treatment with *S. littoralis* stem ethanolic extract on days 7 and 14. All experimental animals were narcotized using chloroform and dissected on day 14. The spleens were collected in the left abdominal cavity, and the organs were initially weighed. Then, the organs were washed with 0.9% NaCl (Rousdy et al., 2017). The organs were cut using a razor blade with a size of 0.5 × 0.5 cm and inserted into the embedding cassette. Then, the organ pieces were fixed in 10% NBF solution. The relative weights of the spleen organs were determined using the following formula:

$$\text{Relative Weight of Organ (\%)} = \frac{\text{organ weight (g)}}{\text{body weight (g)}} \times 100\%$$

Spleen microanatomy was prepared using paraffin (Ren et al., 2021). The tissue was fixed using a 10% NBF solution and a dehydration process using an ethanol solution in graded (70- 100%). The clearing stage of the process involved xylol, and each organ was embedded into paraffin blocks and sectioned using a microtome with a thickness of 6 µm. The tissue sections were made into ten object glasses, each containing five series sections.

Tissue sections were stained with Hematoxylin-Eosin (HE) method (Ren et al., 2021). The tissue samples were dewaxed using Xylol, then rehydrated using an ethanol grade (96 - 70%), and rinsed with running water. The tissue sample was stained with the hematoxylin and eosin solutions, followed by dehydration using ethanol in graded (70 - 100%). The final stage consisted of clearing the tissue in xylol, followed by dry mounting and labeling.

Spleen Microanatomy Examination

Spleen microanatomy was examined using a light microscope ranging from 100× to 400× with magnifications. The quantitative parameter measured was the diameter of the white pulp in the spleen, which was calculated using an ocular micrometer (Rousdy et al., 2017). The qualitative parameters were determined by observing the quality of the spleen white pulp structure (Noh et al., 2019).

Statistical Analysis

Statistical analysis was conducted to assess the data's normality of distribution and homogeneity. The relative weight of the spleen and the diameter of the splenic white pulp were examined using the Shapiro-Wilk test and the Levene test, respectively. These tests were carried out with SPSS 2.6, and the results were subsequently analyzed using one-way Analysis of Variance (ANOVA) at the 95% confidence level. If the analysis revealed a statistically significant effect between treatments, the study proceeded with Duncan's further post-hoc analysis test to determine the differences between groups ($p< 0.05$). Data representing the quality of the spleen white pulp structure are presented in images, while the results of the data analysis are displayed in tabular form.

RESULTS AND DISCUSSION

The extraction of 2.8 kg of *S. littoralis* stems using the maceration method yielded 43.6 g of extract.This extract was subjected

to qualitative phytochemical screening, including alkaloid, flavonoid, phenolic, terpenoid, steroid, and saponin tests. The phytochemical screening results indicated that the extract contained alkaloids, flavonoids, phenolics, terpenoids, and saponins (Table 1).

Table 1. Phytochemical Screening Test Results of *S. littoralis* Stem Ethanolic Extract

Metabolic Compounds	Reagen	Result
Alkaloid	Mayer	+
Flavonoid	Mg and Amyl Alcohol	+
Phenol	$FeCl_3$	+
Terpenoid	Lieberman-Burchard	+
Steroid	Lieberman-Burchard	-
Saponin	Hot Water	+

(+) contains the tested secondary metabolites; (-) did not contain the tested secondary metabolites

The results of the phytochemical screening (Table 1) indicate differences in alkaloid content compared to the previous research conducted by Rahminiwati et al. (2023), who used plants from Central Kalimantan. Additionally, the research by Ayuchecaria et al. (2020), which used plants from Central Kalimantan, also did not contain alkaloids and saponins. The difference in results obtained in this process shows that internal and external factors cause the difference in results. Cell type, growth rate, and physiological changes are internal factors that play a role. In contrast, external factors that have an effect are pressure from environmental changes, which determine the expression of plant genes in the production of secondary metabolite compounds (Li et al., 2020). This can be seen from the difference in characteristics between *S. littoralis* stems from West Kalimantan and Central Kalimantan. *S. littoralis* stem from Central Kalimantan is round, blackish-brown, with red and watery sap inside (Oliver et al., 2022), while from West Kalimantan it is round, brownish with yellowish inner skin (Wahyudi et al., 2023).

The experimental animal's body weight was weighed on day 0 before treatment, day 7, and day 14 after treatment. Measurement results were analyzed by ANOVA and continued with the Duncan Multiple Range Test. The results of body weight measurements are presented in Table 2. Changes in experimental animal body weight are used as assessment parameters in evaluating the therapeutic effect of extract administration. Oral induction of acute doses of *S. littoralis* stems ethanolic extract showed an increase in body weight from day 0 to day 14 in all experimental animals (Table 2). Compared to the standard control group, the observed increase in body weight among subjects treated with *S. littoralis* stems ethanolic extract indicates that the extract accumulation in the experimental animal's body did not affect their appetite.

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Table 2. Experimental Animal Body Weight in Each Treatment (N=20)

Treatments	Experimental animal Body Weight (g)		
	Day-0	Day-7	Day-14
Normal Control	132.4 ± 6.6[a]	129.4 ± 6.3[a]	148.6 ± 8.4
Extract Dose of 300 mg/kg BW	145.8 ± 9.8[b]	150.4 ± 9.8[b]	160.6 ± 13.3
Extract Dose of 2000 mg/kg BW	151.6 ± 7.9[b]	157.8 ± 9.6[b]	166.6 ± 12.8
Extract Dose of 5000 mg/kg BW	153.8 ± 12.5[b]	153.4 ± 15.05[b]	168.4 ± 13.3

[a,b)] significant at $p<0.05$

Table 3.Measurement Results of Experimental Animal Spleen Relative Weight and Spleen White pulp Diameters in Each Treatment (N=20)

Treatments	Spleen Relative Weight (%)	Spleen White Pulp Diameters (mm)
Normal Control	0.3 ± 0.05	0.36 ± 0.01[b]
Extract Dose of 300 mg/kg BW	0.31 ± 0.05	0.34 ± 0.05[b]
Extract Dose of 2000 mg/kg BW	0.3 ± 0.05	0.29 ± 0.01[a]
Extract Dose of 5000 mg/kg BW	0.33 ± 0.03	0.28 ± 0.02[a]

[a,b)] significant at $p<0.05$

Spleen weight was measured on day 14 after treatment to determine the relative weight of the organ. The diameter of the splenic white pulp was also observed to show damage after the administration of *S. littoralis* stems ethanolic extract.Measurement results of spleen relative weight and the diameter of the splenic white pulp are presented in Table 3.

The administration of *S. littoralis* stem ethanolic extract showed no significant difference between treatments in the spleen relative weight parameter. Relative organ weights are important for toxicity assessment because the normal ratio of spleen weight to total body weight is relatively constant (Al Chusna et al., 2024). This indicates that the extract administration does not induce toxic effects on macroscopic organs. Furthermore, the observation of experimental animals did not record any mortalities. This is in line with the research of Setiawan et al. (2021), which states that after giving an acute dose of 300 mg/kg BW of *Carica papaya* leaves ethanolic extract, there is no significant difference in the weight and spleen relative weight.

Analysis of the mean diameter of the splenic white pulp in the extract treatment group indicated that administration of *S. littoralis* stem ethanolic extract at an acute dose significantly decreased the size of the splenic white pulp diameters between treatments. The mean diameter of the splenic white pulp of white rats treated with 300, 2000, and 5000 mg/kg BW was 0.34 ± 0.05 mm, 0.29 ± 0.01 mm, and 0.28 ± 0.02 mm, respectively (Table 3). Furthermore, the analysis results of the average diameter of the splenic white pulp in the treatment group of extract dose of 300 mg/kg BW showed no significant difference with the normal control group (Table 3), while in the treatment group, extract dose of 2000 and 5000 mg/kg BW showed significantly differ-

ent values from the normal control group. This shows that the higher the dose of extract, the smaller the diameter of the splenic white pulp of the experimental animals. This in line with the study of El-Sebaey et al. (2019), administration of garlic extract at a dose of 300 mg/kg BW has immunomodulatory and antioxidant effects without structural organ damage.

The administration of *S. littoralis* stems ethanolic extract at doses of 2000 and 5000 mg/kg BW induced toxic symptoms in the spleen, as evidenced by a decrease in the mean diameter of the splenic white pulp compared to the normal control. This is in line with the study of Amira et al. (2023), that the administration of *Acorus calamus* rhizome extract at doses of 250 and 500 mg/kg BW have a healing impact on splenic white pulp shrinkage in size. However, at dose of 750 mg/kg BW made a difference to the mean diameter of splenic white pulp. Research conducted by Makiyah & Wardhani (2017), showed that administration of *Citrullus lanatus* ethanolic extract at a dose of 700 mg/kg BW has an effect as immunosuppression which is characterized by a decrease in the diameter of the splenic white pulp when compared to the treatment groups of 175 and 350 mg/kg BW. The observed decrease in the diameter of the splenic white pulp may be attributed to the presence of flavonoid secondary metabolite compounds in the extract, which have been shown to suppress lymphocyte proliferation in spleen white pulp (Makiyah & Wardhani, 2017). Flavonoid is classified as a phenol compound and has been demonstrated to possess antioxidant properties that contribute to its capacity to function as an anti-inflammatory and anti-oxidative agent. These antioxidants have been shown to protect cells from reactive oxygen's damaging effects and affect inflammatory signal transduction (Amira et al., 2023).

Secondary metabolites of the terpenoid group have also been reported to induce immunosuppression. Research by Kulyar et al. (2021) has indicated that the extract of *Nigella sativa*, which contains a significant amount of terpenoid compounds, can inhibit the regulation of cytokines involved in pro-inflammatory responses. These terpenoid compounds help reduce inflammation by inhibiting mRNA expression. This leads to decreased gene expression that produces cytokines associated with inflammatory responses, particularly in lymphocyte proliferation (Kulyar et al., 2021). This phenomenon is evidenced by the mean diameter of the splenic white pulp in the treatment groups at the 2000 and 5000 mg/kg BW doses, which show a significant decrease. This reduction was statistically significant when compared to the 300 mg/kg BW treatment group and was also significantly different from the normal control group.

The qualitative parameter observed was the quality of the splenic white pulp structure. Figure 1 presents the spleen microanatomical images of each experimental animal after treatment. Spleen microanatomical analysis of experimental animals in the treatment group revealed that administering of *S. littoralis* stems ethanolic extract at a dose of 300 mg/kg BW did not lead to any toxic effects. This observation is evidenced by the structure of the splenic white pulp, which maintains the same arrangement as the normal control group (Figure 1). It is considered that the dose of 300 mg/kg BW remains within the safe dose range and does not cause damage to the spleen microanatomy. This is in line with the research of Okafor et al. (2020), that the administration of *P. oleracea* methanolic extract at a dose of 400 mg/kg BW has a protective effect against the experimental animals' splenic white pulp structural damage. Spleen microanatomical observations of the experimental animals in the treatment group

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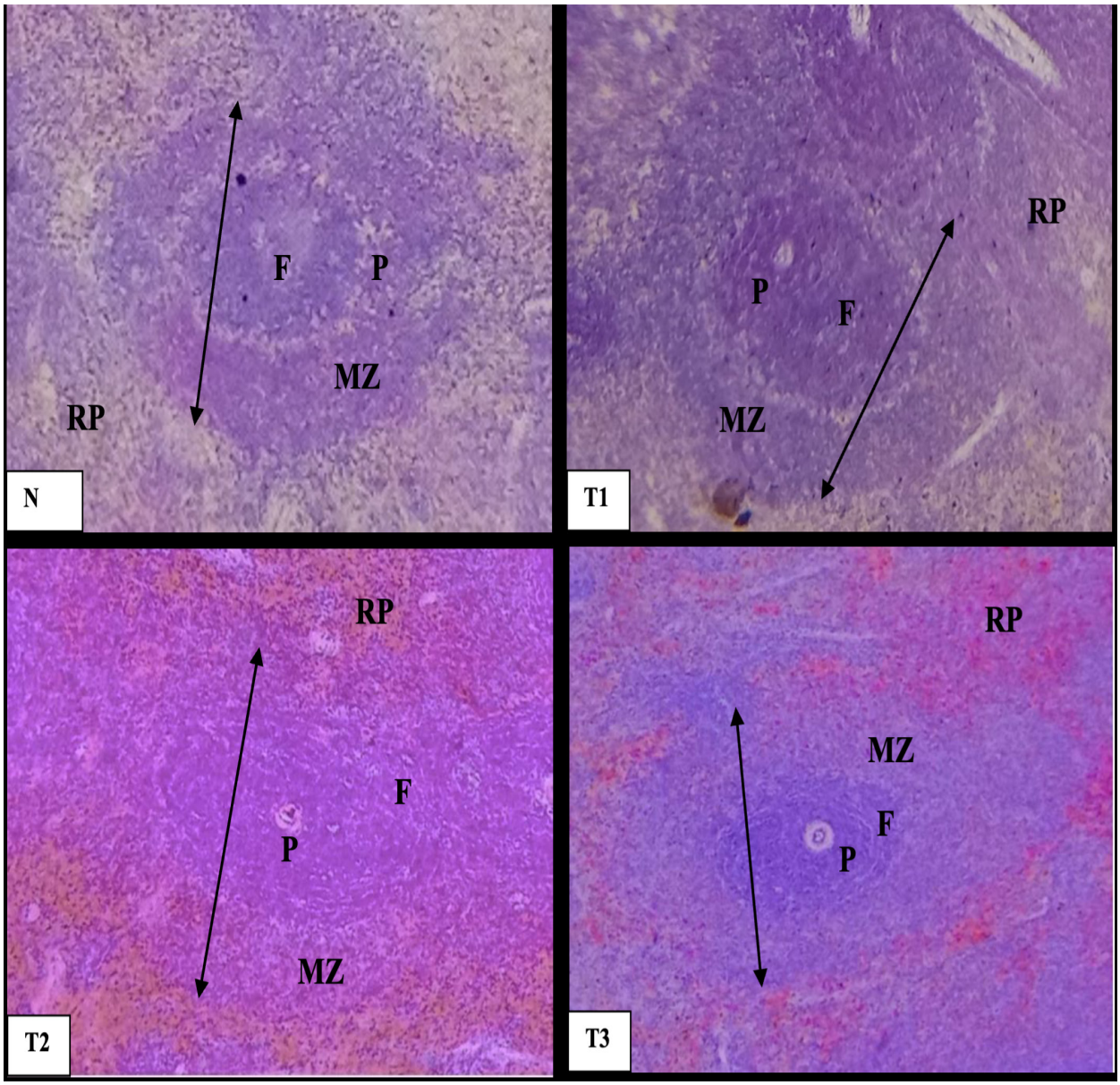

Figure 1. Spleen Microanatomy of Experimental Animal (Magnification 100×). Description; N) Normal Control; T1) Treatment of Extract Dose 300 mg/kg BW; T2) Treatment of Extract Dose 2000 mg/kg BW; T3) Treatment of Extract Dose 5000 mg/kgBW;RP) Red Pulp; Black Arrow)White Pulp; P)PALS; F)Follicles; MZ)Mantel Zone

of *S. littoralis* stem ethanolic extract doses of 2000 mg/kg BW and 5000 mg/kg BW caused toxic symptoms in the spleen microanatomy. This can be seen in Figure 1, which shows a difference in the structure of the splenic white pulp when compared to the normal control group, namely the barrier between PALS and lymphoid follicles of the white pulp is not clear and the follicles are out of shape or shrinking. This indicates that the doses of 2000 and 5000 mg/kg BW have caused toxic symptoms to the spleen microanatomy of the experimental animals. The white pulp contains B and T lymphocytes critical for recognizing and attacking pathogens, so damage to this area can disrupt the normal immune response process (Hermida et al., 2018).

Further research suggestions include using doses in the range of 2000 - 5000 mg/kg BW to see the effect of extracts in this range. Further research can also increase the dose and time of administration in chronic toxicity tests to see the effects of long-term consumption of extracts.

CONCLUSION

Due to its rich composition of advantageous secondary metabolites, Dayak community widely utilized S. littoralis stem extract as a therapeutic agent for various ailments. This study showed that the administration of ethanolic extract of S. littoralis stems at a dose of 2000 mg/kg BW and 5000 mg/kg BW caused toxic symptoms in the spleen of experimental animals, which can be seen from the decrease in the diameter of the splenic white pulp and the boundary that is not visible between PALS and lymphoid follicles in the white pulp of the spleen. The administration of an extract dose at 300 mg/kg BW did not cause toxic symptoms in the spleen of experimental animals because there was no damage to the spleen microanatomy. Therefore, it is recommended that the habitual consumption of *S. littoralis* extract by the Dayak people should not exceed a dose of 300 mg/kg BW per day.

AUTHOR CONTRIBUTION

A.M. collected and analyzed the data and wrote the manuscript, **D.W.** collected the data and supervised all the processes, **E.R.** collected the plants and supervised all the process.

CONFLICT OF INTEREST

The authors declared that there is no conflict of interest in this research and publication.

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