**Jurnal Info Kesehatan**
Vol. 21, No. 3, September 2023, pp. 517-528
P-ISSN 0216-504X, E-ISSN 2620-536X
DOI: *10.31965/infokes.Vol21Iss3.1191*
Journal homepage:*http://jurnal.poltekeskupang.ac.id/index.php/infokes*

RESEARCH Open Access

# Acute Toxicity and Antipyretic Test of Ethanol Extract of Sterculia Quadrifida. R. Br. Leaves as Traditional Medicine

**Stefany S.A Fernandez[1a*], Dominus Mbunga[1b], Acacio Cardoso Amaral[2c], Lidia Lau[1d], Putriasa G Feoh[1e]**

[1] Department of Pharmacy, Politeknik Kesehatan Kementerian Kesehatan Kupang, Kupang, East Nusa Tenggara, Indonesia
[2] Universidade Nacional Timor Lorosa'e (UNTL), Republic Democratic of Timor Leste

[a] Email address: eztephanie88@gmail.com
[b] Email address: noezzb@gmail.com
[c] Email address: acacio.amaral@untl.edu.tl
[d] Email address: lidialau05889@gmail.com
[e] Email address: gfhputriasa@gmail.com

Received: 23 May 2023 Revised: 24 September 2023 Accepted: 28 September 2023

## Abstract

Sterculia quadrifida (SQ) is a plant which is also known as "faloak" by the people of East Nusa Tenggara. The secondary metabolite content of this plant has sufficient potential to be developed. Taking the bark of SQ which is not balanced with its preservation can threaten its survival. The use of SQ leaves as a new traditional medicine needs to be tested for its efficacy and safety.The aim of the study was to provide information about the efficacy and safety of SQ leaves in the development of new traditional medicines. The acute toxicity test used the fix-dose combination method according to the BPOM recommendation. A single oral dose of 2000 mg/KgBw of extract was given to five male mice at 24 h intervals. Animals were observed individually for any clinical signs of toxicity or mortality for 24 hours and 14 days. DPT (difteri, pertussis, tetanus)-Hb (Hepatitis-B) was used as a fever inducer in the antipyretic test of infusion and ethanol extract of SQ leaves. For acute treatment, the ethanol extract of Sterculia quadrifida (EESQ) did not reveal any signs of toxicity or mortality in any animal, during the observation period. The LD50 of extract was estimated to be greater than 2000 mg/KgBw. A dose of 2000 mg/KgBw in mice for 14 days showed significant side effects on the liver and spleen which were marked by organ weights that were significantly different from the control group. Paracetamol as positive control, infusion of Sterculia quadrifida leaves (ISQ) 100%, and EESQ 400 mg/KgBw showed a significant difference ($p<0.05$) with the negative control group. The results showed that SQ leaf has potential as an antipyretic, but liver function must be monitored, even though the LD50 value is above 2000 mg/KgBw.

**Keywords:** Sterculia Quadrifida, Faloak, Extract, Acut Toxicity, Antipyretic

***Corresponding Author:***

Stefany S.A Fernandez
Department of Pharmacy, Politeknik Kesehatan Kementerian Kesehatan Kupang, Kupang, East Nusa Tenggara, Indonesia
Email: eztephanie88@gmail.com

## 1. INTRODUCTION

Traditional medicine is derived from plant materials that have been used for generations for treatment with efficacy and safety. The affectivity and safety of the plant must be proven through pre and clinical trials. This is because one of the requirements for a plant to be developed as a medicinal plant must be proven safe for consumption. This safeness is proven through oral acute toxicity testing (BPOM, 2022).

Data from the Central Statistics Agency shows that there has been an increase in the number of people who treat themselves from 2020 to 2022 by 22.74%, it shows that public awareness in treating diseases is increasing (Badan Pusat Statistika, 2022). Data from the central statistics agency also shows that the percentage of residents who experienced health complaints but did not seek outpatient treatment during the last month was 69.76% who chose to treat themselves, 16.52% were still worried about being exposed to Covid-19, 11.62% felt it was not necessary and 2.10% for other reasons (Badan Pusat Statistik Nusa Tenggara Timur, 2022).

Sterculia quadrifida (SQ) is a plant which is also known as "faloak" by the people of East Nusa Tenggara to treat several diseases. These diseases include ulcers, typhoid, anemia, liver disease, rheumatism, backache, diarrhea, increase stamina and clean the blood after childbirth (Dillak, Kristiani, & Kasmiyati, 2019), Kidney disorders, bladder disorders and blood boosters (Siswadi, et al., 2016). The bark of SQ is an endemic plant of NTT, especially on the island of Timor. There are several benefits of this plant, which has been proven through pre-clinical trials. These benefits include antibiotic (Ranta, Pribadi, & Nawawi, 2011; Tenda, Lenggu, & Ngale, 2017), immunomodulatory (Winanta & Hertiani, 2019) and antioxidant (Dillak, Kristiani, & Kasmiyati, 2019). This plant as traditional medicine is safe because it has been proven through toxicity testing (Siswadi& Saragih, 2018; SP3T Provinsi Nusa Tenggara Timur, 2016). Epicatechin compounds have been successfully isolated from the bark of SQ stems. This compound was reported to have hepatoprotective activity against hepatitis C virus (Dean, Handajani, & Khotib, 2019).

In addition to efficacy and safety, bioavailability must also be considered in the development of traditional medicine. The phenomenon found shows that taking bark that exceeds the carrying capacity of the tree can cause the death of the tree, thus threatening the availability of this plant. In addition, the success of SQ development vegetatively is still very low, only around 15 - 25% (Rianawati & Siswadi, 2020). The part of the plant that is interesting to study is the leaf, although it is not used by the people of NTT as a traditional medicine, some evidence of phytochemical screening shows that SQ leaves contain secondary metabolites of flavonoids, phenols (Saragih & Siswadi, 2019), steroid, terpenoids and tannin (Akter, et al., 2016). Toxicity tests are carried out on animals as evidence of the safety of a drug candidate so that it can provide an overview of the possible risk of exposure when used by humans (BPOM, 2022). Phytochemical screening results can be an indication of the efficacy of a medicinal plant even though empirically it is not used by the public.

The content of flavonoid compounds in plants is known to inhibit the cyclooxygenase pathway resulting in the inhibition of prostaglandin synthesis which is a mediator of fever, pain, and inflammation (Masula et al., 2018; Nijveldt, et al., 2020). A recent study has shown that plants containing flavonoids are thought to have antipyretic effects such as sapodilla leaves (Chrysophyllum albidum) (Onyegbule, et al., 2020), gotu kola leaves (Centella asiatica (L.) Urban) (Saptarini & Kartikawati, 2021), *tarum leaves* (*Indigofera argentea)* (Javed, et al., 2020) *artemisia (Artemisia judaica* L) (Moharram et al., 2021), Fever is a sign of something happening in the body such as typhus (Levani & Prastya, 2020), Virus infection (Alvinasyrah, 2021), bacteria infection (Alvinasyrah, 2021), autoimmunity (Fitriany & Annisa, 2019),

hepatitis (NSW Government, 2017) and Coronavirus infection (Ai et al., 2021; Asare-Boateng, et al., 2020).

Fever can be caused by abnormalities in the brain or by toxic substances that affect the temperature regulation center which ends in heat stroke. To prove the efficacy of a new plant, it must first be supported by safety data. Empirical evidence for the use of the leaves of SQ has not been found in Indonesia, it is recorded that aboriginal people have been using faloak leaves since 1983 (Lassak, 1983). The content of active compounds in the leaves suspected of being antipyretic needs to be ensured for their safety and activity. Empirically the people in NTT use the stem bark. The aim of this research is to provide information to the public regarding the safety and efficacy of SQ as an antipyretic.

## 2. RESEARCH METHOD

The plant material used for the study was leaves of SQ obtained from Liliba, Kupang East of Nusa Tenggara determined by Jatinangor Herbarium Plant Taxonomy Laboratory Department of Biology, FMIPA Padjajaran University with identification letter No. 38/HB/02/2022. Chemical and reagent used include: Pentabio (PT. Biofarma), ethanol 96% (PT. Bratachem, Indonesia), aqua dest ( Bratacem, Indonesia), and Paracetamol (PT. Kimia Farma).

Fresh SQ leaves are taken and dried by air-drying. The dried simplicia is then divided for infusion and extraction using 96% ethanol. The infusion procedure is based on the BPOM Reference (BPOM, 2022) using 10% SQ leaf simplicia. The infusion process takes 15 minutes starting when the temperature reaches 90°C with occasional stirring. The extraction process are performed as follows 900g of the substance was weighed and placed in a maceration container before 9 L of 96% ethanol solvent was added. After that, the maceration container was sealed and kept for 24 hours away from direct sunlight while being intermittently stirred (Departemen Kesehatan Republik Indonesia, 2017). The materials were then filtered and separated between the dregs and the filtrate. After that, remaceration was performed by adding 4.5 L of 96% ethanol into the container containing the dregs. Then close and re- store the container during 24 hours. The ethanol filtrate obtained was collected and the liquid filter was evaporated using a rotary evaporator (Eyela N-1000) at a temperature of 50˚C to obtain a thick ethanol extract.

Identification of SQ leaf infusion (ISQ) and ethanol extract of SQ leaf (EESQ) were carried out by tube test and TLC (Thin Layer Chromatographty) test for alkaloids, flavonoids, tannins, saponins, and steroids. Alkaloid Test: Reaction with Mayer's reagent will form a white precipitate, Dragendorff's reagent will form an orange-red precipitate and Wagner's reagent will form a brown precipitate. Flavonoid Test: A positive test is indicated by the formation of a red, yellow, or orange color. Steroid Test: Steroid positive test if it produces a blue or green color. Saponin Test: If the foam formed remains stable for approximately 7 minutes, then the extract is positive for saponins. Tannin Test: Positive extract contains tannin when it produces a blackish green or blackish blue color (Harborne, 1996).

Extract characterization includes testing specific parameters (extract identity, organoleptics, water and ethanol soluble compound content using the gravimetric method) and non-specific parameters (determination of water content, ash content, and acid insoluble ash content) (Departemen Kesehatan Republik Indonesia, 2017).

Adult male Swiss webster albino mice were used for this study. They weighed 20 to 40 g and were all 6 to 12 weeks of age. The animals were obtained from the animal house of the Department of Pharmacology, Faculty of Pharmacy, Kupang Health Polytechnic Ministry of Health. They were housed in cages with soft wood shavings as beddings with 5 mice per cage. They were kept at room temperature and were allowed free access to clean water and food. They were acclimatized to normal laboratory conditions for 7 days. The animals were fed with Pellets and water ad libitum. All experimental procedures were conducted with the approval of

the Institutional Animal Ethics Health Polytechnic Ministry of Health Kupang (No.LB.02.03/1/0178/2022) for the care and use of animals and their guidelines were strictly followed throughout the study. The animals were starved for 18 h before the study and were only allowed access to water.

The toxicity test was carried out using the fixed dose method, the dose chosen was the dose that did not cause death, severe pain, or irritating/corrosive. The test animals used were 5 mice each for the test and control groups. Test animals were given multilevel doses using the fixed dose method, including doses of 300 and 2000 mg/KgBw orally. signs of toxicity and death were observed intensively for 24 hours. Observation of animal body weight and mortality was then monitored from the first day to the 14th day after administration. After 14 days, the animals were euthanized and observed for symptoms of toxicity in their vital organs by calculating the organ index based on the ratio of the weight of the organs of the brain, lungs, liver, heart, kidneys, stomach, and spleen to body weight (BPOM, 2022).

Antipyretic activity in mice was studied with fever induced by DPT-Hb (difteri, pertussis, tetanus)-Hb (Hepatitis-B) Vaccine. After measuring the rectal temperature of the mice by introducing a 1.5 cm of digital thermometer in the rectum, pyrexia was induced by injecting intra-muscular, 0.2 mL/20gBw DPT-Hb. After 60 minutes of pyrexia injection, mice that showed a rise in temperature of at least 0.6°C were taken for the study. The animals were divided into five treatment groups labeled ‘1ab to 5ab.

Group 1a,b: 1% aqueous suspension of CMC
Group 2a,b: Paracetamol (PCT) 65 mg/KgBw with 1% aqueous suspension of CMC
Group 3a: EESQ 100 mg/Kg with 1% aqueous suspension of CMC
3b: ISQ 50% (0.2 mL/20gBw)
Group 4a: EESQ 200 mg/KgBw with 1% aqueous suspension of CMC
4b: ISQ 75% (0.2 mL/20gBw)
Group 5a: EESQ 400 mg/KgBw with 1% aqueous suspension of CMC
5b: ISQ 100% (0.2 mL/20gBw)
(a: ISQ; b: EESQ)
All treatments were administered orally (0.2 mL/20gBw)

Rectal temperature was recorded every 30 minutes for 120 minutes after administration of drugs. The data were analyzed by Analysis of variance (ANOVA) to find differences between the test groups and to determine the LD50 value based on the fixed dose method.

## 3. RESULTS AND DISCUSSION

Based on identification letter No. 38/HB/02/2022, it shows that the Latin name of the Faloak leaf is *Sterculia quadrifida* R.Br. With family Sterculiaceae. The determination of Faloak was carried out at Jatinangor Herbarium, Plant Taxonomy Laboratory, Department of Biology, FMIPA Padjajaran University. Determination aims to ensure the identity of the plants used.

The results of the dry extract of SQleaves with 96% ethanol solvent were obtained as much as 68.43 grams, with an extract yield of 7.6%. The yield of the extract complies with the standards set by the Indonesian Herbal Pharmacopoeia, which is not less than 7.2% (Departemen Kesehatan Republik Indonesia, 2017). The habit of taking stem bark continuously and not accompanied by cultivation will be a threat to the extinction of a plant, prevention efforts that can be done are cultivation and identifying other plant parts that contain secondary metabolites that are qualitatively the same as SQ stem bark which is empirically used by the community NTT as a medicine for liver disease. SQ plants are also known to have been clinically tested to contain epicatechin compounds which can inhibit the replication of VHC JFH1 in the liver (Dean et al., 2019).

**Table 1.** Identification of ISQ and EESQ

| Identifiction | ISQ | | EESQ | |
|---|---|---|---|---|
| | Test Tube | TLC Test | Test Tube | TLC Test |
| Alkaloid | + | + | + | + |
| Flavonoid | + | + | + | + |
| Tannin | + | + | + | + |
| Saponin | - | - | + | + |
| Steroid | + | + | + | + |

*note: (+) detected ; (-) not detected*

Rf value in EESQ aims to calculate the speed of transfer from the mobile phase to the stationary phase. Compounds with the same or close Rf values can show that both have the same or similar characteristics (Rizki & Ferdinand, 2021).

**Table 2.** RF Value of EESQ

| Identifiction | RF Value | Standard |
|---|---|---|
| Alkaloid | 0.56 | 0.07 – 0.62 (Harborne, 1996) |
| Flavonoid | 0.97; 0.81; 0.61; 0.5 | 0.31 - 0.98 (Harborne, 1996) |
| Tannin | 0.5 | 0.29 – 0.85 (Harborne, 1996) |
| Steroid | 0.71 | 0,71 (Forestryana & Arnida, 2020) |

The identification of alkaloids obtained an Rf value of 0.56, this value is known to meet the standard Rf alkaloids with a value of 0.07 – 0.62. As well as flavonoids Rf values obtained consecutively 0.97; 0.81; 0.61; 0.5. All these Rf values meet the standard Rf values of flavonoids 0.31 - 0.98 (Harborne, 1996). The tannin Rf value is 0.5, this value also meets the standard Rf tannin value of 0.29 – 0.85. In the results, the Rf value of saponin compounds, which is suspected to be a saponin compound is an Rf value of 0.63 when compared to the reference standard for saponins, which is 0.66. In the steroid test, a spot was found with an Rf value of 0.71. This data is similar to previous research which produced the same Rf value of 0.71 and produced the same color (Blue-green) (Forestryana & Arnida, 2020). A good Rf value is 0.2 - 0.8 so the Rf value obtained is in the range of a good Rf value. Slightly different from the TLC test on leaf infusion, the RF value cannot be determined because there are no clear spots, this could be due to the secondary metabolite content being too small, a positive test result is stated based on the color change on the TLC plate after being sprayed using a stain spotter and observed below 254 nm UV light. Where the TLC on the flavonoid test showed brown-yellow spots, steroids appeared blue spots, and tannins appeared purple spots.

Extract characteristics test includes specific and non-specific parameters. Reference is needed as a standard to assess the feasibility of extracts. However, there is no official reference in standardizing the ethanol extract of SQ leaves published by the Ministry of Health or from other sources, so the research reference used is with general extract requirements which include non-specific parameters. Specific parameter testing includes extract identity, extract organoleptic, and soluble compounds in certain solvents (water and ethanol).

**Table 3.** Specific parameters of EESQ (*Sterculia quadrifida* R.Br)

| Paremeter | Result |
|---|---|
| Extract name | Ethanolic extract of SQ |
| Latin Name | *Sterculia quadrifida* R.Br |
| Plant parts | Leaf |
| Indonesian Name | Faloak |
| Organoleptic | Form : Dry extract<br>Colour : Dark green<br>Odor : not rancit, not specific |

| | |
|---|---|
| | Taste : Chelate; bit bitter |
| Water soluble compounds | 4,6 % |
| Ethanol soluble compounds | 11,26% |

The content of ethanol-soluble compounds is greater than the levels of water soluble compounds because ethanol is a universal solvent that can dissolve almost all substances that are polar to nonpolar. Determination of levels of soluble compounds in water and ethanol is carried out to provide an initial description of the number of chemical compounds that are polar (water-soluble) and semi-polar to non-polar (ethanol soluble) compounds (Saifudin, Tahayu, & Teruna, 2011). Determination of the content of the extract is very important, because it can provide an overview of the number of dissolved materials and is the part that is used as a medicinal ingredient.

Determination of water content in the extract of SQ was carried out using a Moisture Analyzer at a temperature of 105°C for 15 minutes. This test aims to ensure that the extract used meets the requirements (less than 5%). Determination of water content is carried out to determine the residual water after the drying process. Moisture content is a quality parameter related to the microbiological, enzymatic, and chemical processes of the extract. The high water content will affect the stability of the extract or preparation due to the growth of microbes.

**Tabel 4.** Non-spesifik Parameter of EESQ *(Sterculia quadrifida* R.Br)

| **Parameter** | **Result** |
|---|---|
| Water level | 0.42% |
| Total ash content | 3.1% |
| acid soluble ash content | 0.5% |

The total ash content aims to determine the internal and external mineral content of the extract, the higher the ash content of a material indicates the high content of toxic minerals such as mercury, lead, copper, cadmium, and strontium that can cause harmful effects to the body, the worse the quality of the material. The ash content should have a small value because this parameter indicates the presence of heavy metal contamination that is resistant to high temperatures. Heavy metals can accumulate and react directly to the body, causing toxic effects in various organs (Borowska & Brzóska, 2015).

Determination of acid insoluble ash content is done by dissolving the total ash with an acid solvent in the form of 10% dilute HCl acid insoluble minerals will be detected in the amount. The acid insoluble ash content test is related to the purity of the material, it is also a measure of the mineral content in a material. The presence of silicate contamination such as soil and sand is also interpreted as the value of acid-insoluble ash content.

The acute toxicity test used the fix-dose combination method according to the BPOM recommendation, the initial dose was started from 300mg/KgBw, and no toxic effects were found, so it was continued with a test dose of 2000mg/KgBw in 5 test animals (BPOM, 2022). In This study, the acute toxicity test used adult animals which is in the process of growth so that it can be seen the effect of the extract based on body weight parameters.

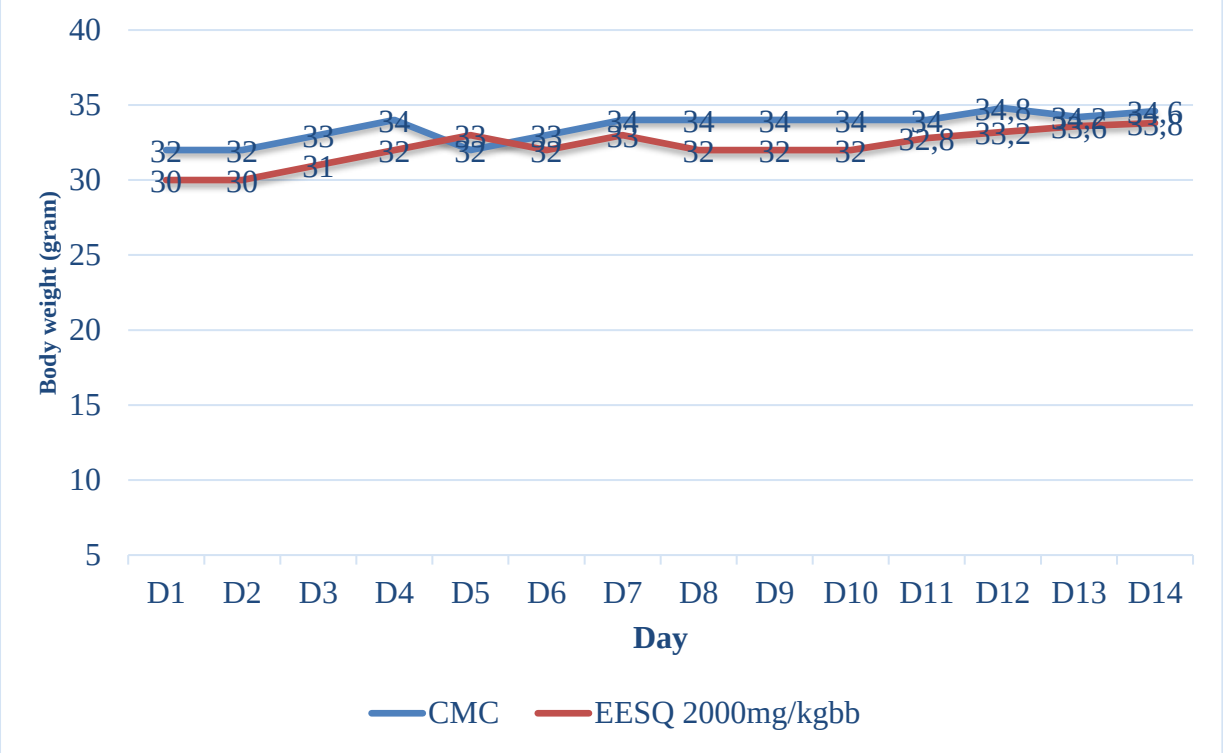


**Figure 1.** Body weight of test animals on day 1 to day -14

The results showed that the body weight of the test animals that received EESQ 2000mg/KgBw and CMC both showed a significant difference in body weight ($p<0.05$) between days 1 and 14. An increase in animal body weight is a normal process that commonly occurs when animals are in the process of growth (Haraguchi et al., 2022). Mice were observed individually for 24 hours after administration of EESQ 2000mg/KgBw and CMC 1%. No signs of toxicity were found based on observations of motor activity, straub, piloerection, ptosis, pineal reflex, corneal reflex, lacrimation, posture, retablishment, flexion, hafner, grooming, gastrointestinal effects, defecation, urination, salivation, vocalization and breathing at 4 hours first. No deaths occurred in any of the groups during the entire period of treatment of extract as well as 24h after treatment. Observations were continued until the 14th day, there were no signs of toxicity indicating that the test animals were in good health, but a chronic toxicity test was necessary to assess the safety of long-term use as well as histopathological tests to find the cause of weight gain in the liver and spleen organs of the test animals (Burgos-Pino et al., 2023).

In addition to the number of dead animals and symptoms of toxicity, macropathological data of vital organs on the 14th day can also be considered as a consideration for the level of toxicity of a preparation.

**Table 5.** Organ index of test animals on day 14

| Organ index (%) | CMC Group | EESQ 2000 mg/Kg BB |
|---|---|---|
| Brain | 1.1 ± 0.09 | 1.2 ± 0.06 |
| Heart | 0.6 ± 0.10 | 0.6 ± 0.01 |
| Lungs | 1.2 ± 0.17 | 1.1 ± 0.26 |
| Liver * | 6.0 ± 0.78 | 9.5 ± 2.30 |
| Spleen* | 0.8 ± 0.09 | 1.8 ± 0.63 |
| Stomach | 1.9 ± 0.42 | 1.4 ± 0.37 |
| Kidney | 1.6 ± 0.16 | 1.7 ± 0.14 |

*Significantly different from negative control ($P < 0.05$)

The purpose of the acute oral toxicity test is that in addition to detecting the intrinsic toxicity of a substance, it can also determine target organs, species sensitivity, and obtain hazard information after acute exposure of a substance, obtaining initial information that can be used to determine dose levels. Based on the results of the acute toxicity test, the antipyretic activity test was chosen at a dose below 2000mg/KgBw.

In this study, several parameters are thought to provide an important description of the conditions in the toxicity of a substance (Alkahtani, et al., 2022; Asare et al., 2012). Acute administration of SQ leaf does not showed death in a single dose of 2000 mg/KgBw, however these data could not yet describe indications of toxicity or mortality in the long term, but could suggest that the lethal dose of SQ leaves (LD50) was greater than 2000 mg/KgBw. Determination of relative organ weight is very important to know possible organ damage through exposure to the substance toxic properties. The level of toxicity of a substance can affect the organ weight of the test animals (Rosidah et al., 2009). In this study doses up to 2000 mg/KgBw caused weight changes in the spleen and liver when compared to controls. The use of SQ leaves may not be toxic to other organs, but it needs to be reviewed on the liver and spleen.

The results of the acute toxicity test of SQ leaves can give an idea to the public that traditional medicines with good pharmacological activity must still be tested for safety, this means that even traditional medicines can show side effects when used for a certain period of time and certain organs.

The infusion method is the most commonly used by the community. Empirical use in the community is limited to the bark, this action can threaten the extinction of the SQ tree. The infusion activity test is carried out as an initial stage of the antipyretic test, because fever is a symptom of a viral/bacterial infection or as a sign of illness in the body.

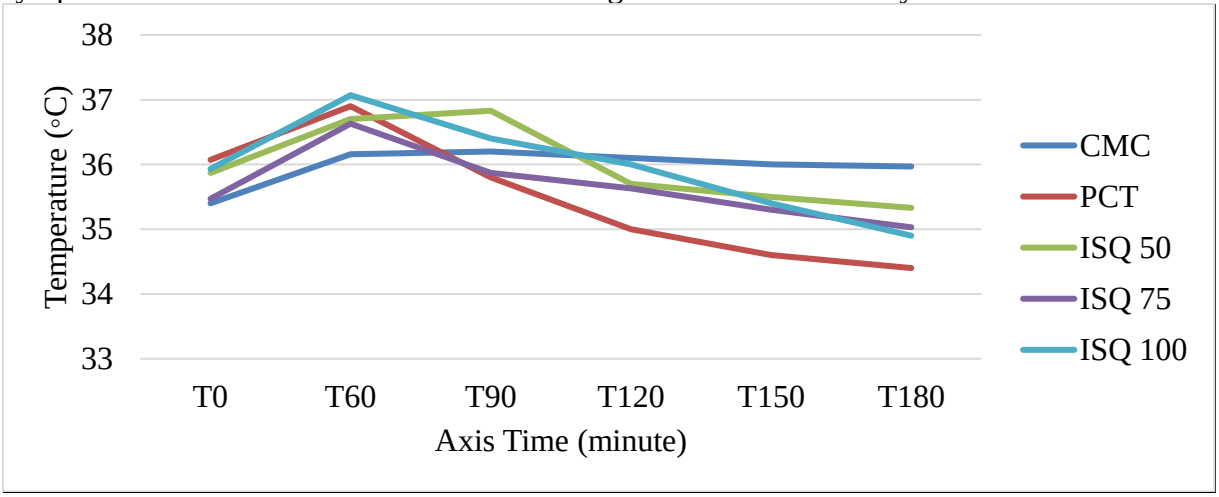


**Figure 2.** Changes in animal body temperature on ISQ administration

Figure 2 and 3 shows the temperature change every 30 minutes. DPT-Hb induction succeeded in increasing the body temperature of the test animals at 60 minutes with an average temperature increase of above 0.6°C (Quartey et al., 2020). Antipyretic activity was shown at 30 minutes after administration of the preparation, except for the CMC and ISQ groups at the lowest concentrations. It is known that the content of active substances in the infusion is directly proportional to the concentration of the infusion. One hour after administration of paracetamol has shown maximum antipyretic effect, followed by ISQ concentration of 100%, 75% and 50%. These results are in line with the data in table 5, where based on the results of statistical tests, ISQ concentration of 100% and Paracetamol group showed a significant difference ($p<0.05$) with the negative control group. Phytochemicals such as flavonoids (Nijveldt et al., 2020) and

tannins have been found to be responsible for many of the biological properties exhibited by plant extracts one of which is the antipyretic effect (Quartey et al., 2020).

**Table 6.** Antipyretic effect of ISQ

| Groups | ΔT (°C) |
|---|---|
| CMC | 1.6 ± 0.94 |
| PCT* | 7.5 ± 1.20 |
| ISQ 50 | 4.1 ± 0.18 |
| ISQ 75 | 4.8 ± 0.65 |
| ISQ 100* | 6.5 ± 0.24 |

*significantly different from negative control ($p < 0.05$)

There was no significant difference between the paracetamol and ISQ groups at 100% concentration. This shows that ISQ at a concentration of 100% has an antipyretic effect which is thought to be the same as paracetamol. The greater the value of ΔT , the higher the antipyretic effect.

The greatest value was in the paracetamol group, in accordance with the mechanism of action against prostaglandin synthesis inhibition in the central nervous system. ISQ and EESQ can significantly reduce body temperature in test animals induced by pyrexia when given the highest dose. The possible reason behind this mechanism is that it can block the prostaglandins in tissues, such as aspirin (Zhou et al., 2021).

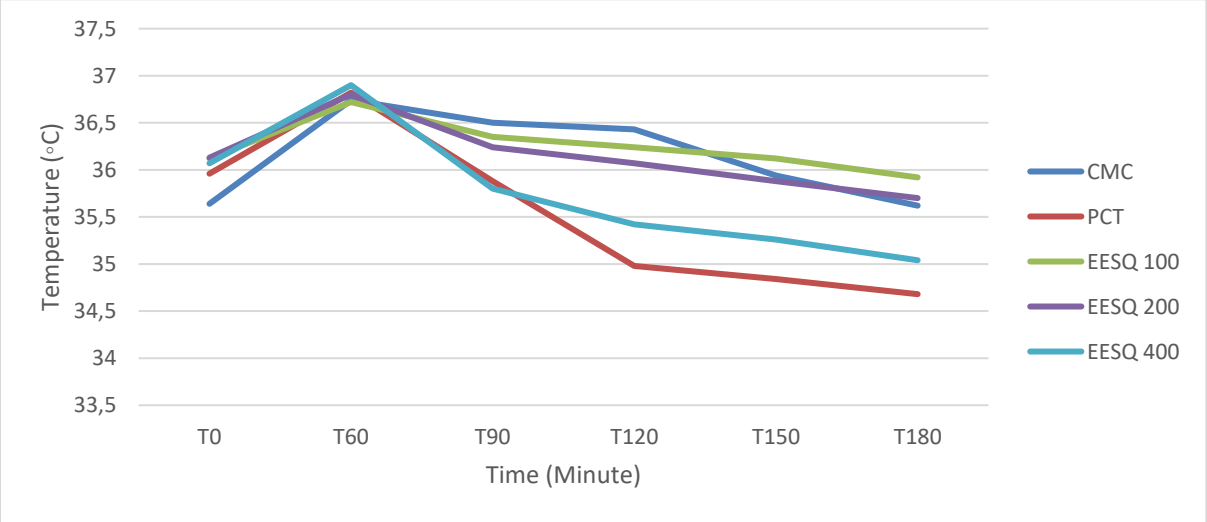


**Figure 3.** Changes in animal body temperature on EESQ administration

The statistical test showed that the preparations that were significantly different from CMC were only positive control and the test dosage form was 400mg/KgBw.

**Table 7.** Antipyretic effect of EESQ

| Groups | ΔT ( °C) |
|---|---|
| CMC | 5.6 ± 0.74 |
| PCT* | 10.7 ± 0.81 |
| EESQ 100 | 6.2 ± 0.62 |
| EESQ 200 | 6.4 ± 0.51 |
| EESQ 400* | 9.3 ± 0.85 |

*significantly different from negative control ($p < 0.05$)

The graph of the decrease in temperature of 400 mg/KgBw EESQ in Figure 3 works quickly at 30 minutes after administration of the preparation, in contrast to ISQ at a

concentration of 100% which tends to show an antipyretic effect longer although it is not significantly different from paracetamol.

Considering that the use of leaves is not common in society, even though acute toxicity testing has been carried out, chronic toxicity tests must also be carried out to see the effect on long-term use.

## 4. CONCLUSION

The research results show that SQ leaves have the potential to be an antipyretic, but liver function must still be monitored even if the LD50 value is above 2000mg/KgBw. Sub-chronic toxicity tests are needed to prove the safety of using leaves as an alternative treatment to SQ bark.

## REFERENCES

Ai, M., Li, T., Zhang, L., Xu, H., Mou, D., & Liang, L. (2021). Clinical Features and Prognostic Risk Factors of COVID-19 in Adults: a Retrospective Analysis of 93 Cases. *Chinese General Practice*, *24*(2), 196-204. Retrieved from https://pesquisa.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/resource/pt/covidwho-1034429

Akter, K., Barnes, E. C., Brophy, J. J., Harrington, D., Community Elders, Y., Vemulpad, S. R., & Jamie, J. F. (2016). Phytochemical profile and antibacterial and antioxidant activities of medicinal plants used by Aboriginal people of New South Wales, Australia. *Evidence-Based Complementary and Alternative Medicine*, 2016, 4683059. https://doi.org/10.1155/2016/4683059

Alkahtani, S., Hasnain, M. S., Algamdy, H., Aljarba, N. H., & AlKahtane, A. (2022). Acute and sub-acute oral toxicity Lagerstroemia speciosa in Sprague-Dawley rats. *Saudi Journal of Biological Sciences*, *29*(3), 1585-1591. https://doi.org/10.1016/j.sjbs.2021.11.005

Alvinasyrah, A. (2021). Nilai Trombosit dan Hematokrit dalam Manifestasi Perdarahan Pasien Demam Berdarah Dengue. *Jurnal Penelitian Perawat Profesional*, *3*(1), 153-158. https://doi.org/10.37287/jppp.v3i1.358

Asare, G. A., Gyan, B., Bugyei, K., Adjei, S., Mahama, R., Addo, P., ... & Nyarko, A. (2012). Toxicity potentials of the nutraceutical Moringa oleifera at supra-supplementation levels. *Journal of ethnopharmacology*, *139*(1), 265-272. https://doi.org/10.1016/j.jep.2011.11.009

Asare-Boateng, K., Mensah, Y. B., Mensah, N. A., Oliver-Commey, J., & Oduro-Mensah, E. (2020). A review of chest radiographic patterns in mild to moderate novel corona virus disease 2019 at an urban hospital in Ghana. *Ghana Medical Journal*, *54*(4s), 46-51. https://doi.org/10.4314/gmj.v54i4s.8

Badan Pusat Statistika. (2022). *Persentase Penduduk yang Mengobati Sendiri Selama Sebulan Terakhir*. Badan Pusat Statistika

Borowska, S., & Brzóska, M. M. (2015). Metals in cosmetics: implications for human health. *Journal of applied toxicology*, *35*(6), 551-572. https://doi.org/10.1002/jat.3129

BPOM. (2022). *Peraturan Badan Pengawas Obat Dan Makanan Nomor 10 Tahun 2022 Tentang Pedoman Uji Toksisitas Praklinik Secara In Vivo.* BPOM

Badan Pusat Statistik Nusa Tenggara Timur. (2022). *Statistik Kesehatan Provinsi Nusa Tenggara Timur*. Badan Pusat Statistik Nusa Tenggara Timur.

Burgos-Pino, J., Gual-Orozco, B., Vera-Ku, M., Loría-Cervera, E. N., Guillermo-Cordero, L., Martínez-Vega, P. P., ... & Gamboa-León, R. (2023). Acute oral toxicity in BALB/c mice of Tridax procumbens and Allium sativum extracts and (3S)-16, 17-

didehydrofalcarinol. *Journal of Ethnopharmacology*, *301*, 115840. https://doi.org/10.1016/j.jep.2022.115840

Dean, M., Handajani, R., & Khotib, J. (2019). Faloak (Sterculia quadrifida R. Br) stem bark extract inhibits hepatitis C virus JFH1. *Oriental Journal of Chemistry*, *35*(1), 430-435. https://doi.org/10.13005/ojc/350155

Departemen Kesehatan Republik Indonesia. (2017). *Farmakope Herbal Indonesia Edisi II*. Departemen Kesehatan Republik Indonesia.

Dillak, H. I., Kristiani, E. B. E., & Kasmiyati, S. (2019). Secondary metabolites and antioxidant activity of ethanolic extract of Faloak (Sterculia quadrifida). *Biosaintifika: Journal of Biology & Biology Education*, *11*(3), 296-303. Retrieved from https://journal.unnes.ac.id/nju/index.php/biosaintifika/article/view/20736

Fitriany, J., & Annisa, I. (2019). Demam Reumatik Akut. *AVERROUS: Jurnal Kedokteran dan Kesehatan Malikussaleh*, *5*(2), 11-25. https://doi.org/10.29103/averrous.v5i2.2078

Forestryana, D., & Arnida, A. (2020). Skrining Fitokimia Dan Analisis Kromatografi Lapis Tipis Ekstrak Etanol Daun Jeruju (Hydrolea Spinosa L.). *Jurnal Ilmiah Farmako Bahari*, *11*(2), 113-124. https://doi.org/10.52434/jfb.v11i2.859

Haraguchi, A., Yamazaki, T., Ryan, C., Ito, K., Sato, S., Tamura, K., ... & Shibata, S. (2022). Caffeine suppresses high-fat diet-induced body weight gain in mice depending on feeding timing. *Journal of Functional Foods*, *99*, 105307. https://doi.org/10.1016/j.jff.2022.105307

Harborne, J. B. (1996). Metode Fitokimia, penuntun dan cara modern menganalisis Tumbuhan. *Penerjemah: Padmawinata K dan Soediro I. Penerbit ITB Bandung*.

Javed, F., Jabeen, Q., Aslam, N., & Awan, A. M. (2020). Pharmacological evaluation of analgesic, anti-inflammatory and antipyretic activities of ethanolic extract of Indigofera argentea Burm. f. *Journal of Ethnopharmacology*, *259*, 112966. https://doi.org/10.1016/j.jep.2020.112966

Lassak, E. V., & McCarthy, T. (1983). Australian medicinal plants. New South Wales

Levani, Y., & Prastya, A. D. (2020). Demam Tifoid: Manifestasi Klinis, Pilihan Terapi Dan Pandangan Dalam Islam. *Al-Iqra Medical Journal: Jurnal Berkala Ilmiah Kedokteran*, *3*(1), 10-16. https://doi.org/10.26618/aimj.v3i1.4038

Masula, A. F., Puspitasari, D., SW, E. S., Ummah, K., Rokhmatin, D., Mubarrok, M. M., ... & Purnama, E. R. (2018). Docking Molekuler Senyawa Metabolit Sekunder Lantana camara Sebagai Antiinflamasi Terhadap Enzim COX-1. *Jurnal Biota*, *4*(2), 79-83. https://doi.org/10.19109/Biota.v4i2.2172

Moharram, F. A., Nagy, M. M., El Dib, R. A., El-Tantawy, M. M., El Hossary, G. G., & El-Hosari, D. G. (2021). Pharmacological activity and flavonoids constituents of Artemisia judaica L aerial parts. *Journal of Ethnopharmacology*, *270*, 113777. https://doi.org/10.1016/j.jep.2021.113777

Nijveldt, R. J., Van Nood, E. L. S., Van Hoorn, D. E., Boelens, P. G., Van Norren, K., & Van Leeuwen, P. A. (2001). Flavonoids: a review of probable mechanisms of action and potential applications. *The American journal of clinical nutrition*, *74*(4), 418-425. https://doi.org/10.1093/ajcn/74.4.418

NSW Goverment. (2017). Lembar Fakta Penyakit Menular Hepatitis A. *Hepatitis A - Indonesian*.

Onyegbule, F. A., Ezenwa, C. J., Bruce, S. O., & Umeokoli, B. O. (2020). Standardization, chemical composition and antipyretic evaluation of the methanol leaf extract and fractions of chrysophyllum albidum (Sapotaceae). *Tropical Journal of Natural Product Research*, *4*(6), 216–222. https://doi.org/10.26538/tjnpr/v4i6.1

Quartey, A. K., Jibira, Y., Forkuo-Donkor, A., Ayensu, I., Oduro-Kwarteng, A. A., Asuamah, S. E. R., & Noah, P. (2020). Hydroethanolic stem bark extract of Vernonia amygdalina

Del.(Asteraceae) suppresses yeast-induced pyrexia and Plasmodium berghei malaria in murine models. *Journal of Medicinal Plants Research*, *14*(6), 258-264. https://doi.org/10.5897/jmpr2020.6931

Ranta, F., Pribadi, E. S., & Nawawi, D. S. (2011). *Sifat Antimikroba Zat Ekstraktif Pohon Faloak ( Sterculia comosa Wallich ). Scientific Repository. IPB University*

Rianawati, H., & Siswadi, S. (2020). Effect of donor plants and rooting medium on stem cutting propagation of faloak (Sterculia quadrifida). *International Journal of Tropical Drylands*, *4*(2), 31-35. https://doi.org/10.13057/tropdrylands/t040201

Rizki, F. S., & Ferdinand, A. (2021). Isolasi Dan Identifikasi Senyawa Flavonoid Ekstrak Etanol Pandan Hutan Jenis Baru Freycinetia Sessiliflora Rizki. *Jurnal Insan Farmasi Indonesia*, *4*(1), 1-6. https://doi.org/10.36387/jifi.v4i1.642

Rosidah, Yam, M. F., Sadikun, A., Ahmad, M., Akowuah, G. A., & Asmawi, M. Z. (2009). Toxicology evaluation of standardized methanol extract of Gynura procumbens. *Journal of ethnopharmacology*, *123*(2), 244-249. https://doi.org/10.1016/j.jep.2009.03.011

Saifudin, A., Tahayu, V. & Teruna, H. Y. (2011). Standarisasi Bahan Obat Alam. Edisi Pertama. In *Standarisasi Bahan Obat Alam*. Yogyakarta : Graha Ilmu

Saptarini, N. M., & Kartikawati, E. (2021). Antipyretic activity of centella (Centella asiatica (l.) urban) herb in vaccine induced mice. *International Journal of Applied Pharmaceutics*, *13*(Special Issue 3), 76–78. https://doi.org/10.22159/IJAP.2021.V13S3.16

Saragih, G. S., & Siswadi, S. (2019). Antioxidant activity of plant parts extracts from Sterculia quadrifida R. Br. *Asian Journal of Pharmaceutical and Clinical Research*, *12*(7), 143-148.

Siswadi, S., & Saragih, G. S. (2018). Acute tocixity of Sterculia quadrifida R. br bark ethanol extract on sprague-dawley rats. *Majalah Obat Tradisional*, *23*(2), 127-134. https://doi.org/10.22146/mot.34871

Siswadi, S., Pujiono, E., Rianawati, H., & Saragih, G. S. (2016, April). Nilai Ekonomi Kulit Batang Pohon Faloak (Sterculia quadrifida R. Br.). *Proceeding of Mulawarman Pharmaceuticals Conferences*, 3, pp. 379-388. Retrieved from https://prosiding.farmasi.unmul.ac.id/index.php/mpc/article/view/137

SP3T Provinsi Nusa Tenggara Timur. (2016). *Inventarisasi, Penapisan Fitokimia Dan Penentuan Ld50 Tanaman Faloak (Sterculia Comosa Wallich) Yang Digunakan Sebagai Ramuan Tradisonal Oleh Masyarakat Dan Penyehat Tradisional (Hattra) Di Kabupaten Kupang Provinsi Nusa Tenggara Timur*. Kupang: SP3T Provinsi Nusa Tenggara Timur.

Tenda, P. E., Lenggu, M. Y., & Ngale, M. S. (2017). Uji Aktivitas Antibakteri Ekstrak Etanol Kulit Pohon Faloak (Sterculia sp.) Terhadap Bakteri Staphylococcus Aureus. *Jurnal Info Kesehatan*, *15*(1), 227-239. Retrieved from https://jurnal.poltekeskupang.ac.id/index.php/infokes/article/view/143

Winanta, A., & Hertiani, T. (2019). In vivo Immunomodulatory Activity of Faloak Bark Extract (Sterculia quadrifida R. Br). *Pakistan Journal of Biological Sciences: PJBS*, *22*(12), 590-596. https://doi.org/10.3923/pjbs.2019.590.596

Zhou, W., Dai, Y., Meng, J., Wang, P., Wu, Y., Dai, L., … Huo, H. (2021). Network pharmacology integrated with molecular docking reveals the common experiment-validated antipyretic mechanism of bitter-cold herbs. *Journal of Ethnopharmacology*, *274*, 114042. https://doi.org/10.1016/j.jep.2021.114042