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Research Article

Description of Ciplukan Toxicity (*Physalis angulata* L.)

Ruqiah Ganda Putri Panjaitan[1,*], Titin[1], Yohanes Gatot Sutapa Yuliana[2]

ABSTRACT

Introduction: Ciplukan (*Physalis angulata* L.) is a plant used by Indonesian people as traditional medicine. Drug sanitization needs to be carried out to guarantee the use and availability of scientifically safe traditional medicines. This study aims to provide information and enrich knowledge about the safety of consuming ciplukan roots and stems. **Methods:** This study used 8 male mice as test animals, divided randomly into 4 treatment groups, namely mice treated with a dose of 0.56 mg/20 g body weight; mice treated with a dose of 5.6 mg/20 g body weight; mice treated with 56 mg/20 g body weight; and mice treated with 560 mg/20 g body weight. Treatment was given once and then observed for 24 hours to observe the number of deaths of the test animals. Then follow-up observations were carried out in 3 days on individuals who were still alive. **Results:** Within 24 hours all individuals at the treatment dose of 0.56 mg/20 g body weight survived, whereas all individuals at the treatment dose of 5.6; 56; and 560 mg/20 g body weight died. The observations on individuals treated at a dose of 0.56 mg/20 g body weight showed that the animals were in good condition, with sleeping and eating activities, moving a lot, having clean and nice fur, and not showing toxic symptoms such as disturbances in physical activity, impaired balance, and refusal to eat. **Conclusions:** The administration of the test extract below is less or equal to 0.56 mg/20 g body weight is relatively safe.

Key words: Acute toxicity, Ciplukan, Condition, Dosage, Traditional medicine.

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INTRODUCTION

Indonesian people use plants as traditional medicine for generations with the aim of being preventive, promotive, rehabilitative and palliative.[1] The use of medicinal plants as traditional medicine is more desirable because the price is relatively cheap, the processing is also relatively easy, the raw materials for medicine usually grow in yards, gardens, although some are wild plants, more than that traditional medicines are considered relatively safe.[2,3] Plants used as medicine can be in single form or in combination. In order to guarantee the use of traditional medicinal plants and increase the availability of safe traditional medicines, medicine is scientifically proven through research.[1] Several studies were conducted as a scientific proof step for plants that are used as traditional medicine, including testing the acute toxicity of the methanol extract of lempuyang wangi rhizome (*Zingiber aromaticum* Val.) which stated that LD_{25} value of lempuyang wangi rhizome methanol extract of 866.96 mg/kg body weight of mice and this value is in the moderate toxic category.[4] In another study, namely the acute toxicity test of the ethanol extract of kirinyuh leaves (*Euphatorium odoratum* Linn.), based on the test results, the LD_{50} value of the ethanol extract of kirinyuh leaves was 14.1416 g/kg body weight of mice and this value was included in the mild toxic category.[5]

Ciplukan (*Physalis angulata* L.) is an annual herb belonging to the Solanaceae family. This plant is widely used to treat various diseases such as overcoming digestive disorders, hypercholesterolemia, malaria, and inflammation, preventing diabetes mellitus, increasing the immune system and endurance, and helping cell regeneration.[6] Traditional Japanese society uses ciplukan for antipyretic purposes,[7] ciplukan fruit is cultivated by the American people for food, while traditional Chinese people use the ciplukan to treat acne.[8]

As a traditional medicine by people in Indonesia, the parts of the ciplukan plant that are commonly used are the roots, stems, fruit, and leaves.[2] The medicinal power possessed by these plants is related to the content of secondary metabolites, among others, ciplukan leaves are reported to contain saponins, alkaloids, and steroids. The ciplukan stems are reported to contain steroid, alkaloid, saponin, and flavonoid compounds. Ciplukan fruit is reported to contain saponins, alkaloids, and triterpenoids,[9] while ciplukan roots were reported to contain alkaloid group compounds.[10] Results of literature review by Panjaitan *et al.*[11] showed that the ethanol extract of ciplukan stems contained alkaloid, phenolic, flavonoid, saponin, and terpenoid group compounds. Ciplukan fruit contains alkaloids, saponins, flavonoids, and phenolic compounds, while ciplukan leaves contain flavonoids.

Related to activity in medicine, among others, that ciplukan leaves have potential anti-diarrheal activity,[12] antioxidants,[9,13-15] antibacteria,[16] analgesic,[17] and anti-mycobacterium tuberculosis.[18] Ciplukan stems are reported to have potential anti-inflammatory activity,[19] antioxidant,[9] and antihypercholesterolemia.[20] Ciplukan fruit is reported to contain potential antioxidant activity,[9,21] antihypercholesterolemia,[20] and antibacterial.[22] Ciplukan root is also reported to have potential antifungal and antibacterial activity,[23] anti-inflammatory,[24] and antibacterial.[25] In addition, from the results of a literature review by Panjaitan *et al.*[11] it is known that ciplukan has potential as an anti-inflammatory, antioxidant, antidiarrheal, antihypercholesterolemia, and immunomodulator.

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Even though traditional medicine is medicine that comes from nature, the assumption that traditional medicine is safe to use and avoids harmful effects is wrong. The use of traditional medicine must be able to consider various things such as the correct dose, the exact time and method of use, as well as the accuracy of information review, because the inappropriate use of traditional medicine can potentially increase various unwanted symptoms. Not only synthetic drugs, traditional medicines also have a considerable risk of causing organ damage.[26] To find out the benefits of a plant as a medicine, it is necessary to do toxicity testing. Toxicity is the harmful effect of a chemical compound on target organs in living organisms.[27] Toxicity test is a preliminary test that is attempted to determine the toxic effects and thresholds for the use of a plant as medicine.[28] Toxicity test aims to observe the pharmacological activity of a compound that occurs in a short time after exposure or administration in certain doses. Toxicity testing has the principle that bioactive components are always toxic when given in high doses and becomes a drug if given at low doses or measured doses.[29]

Based on the duration of the test, toxicity testing is divided into three groups, namely acute, subchronic, and chronic toxicity testing. Acute toxicity testing aims to find toxic effects in a short time, this test is useful for initial assessment of toxicity, determining target organs, obtaining hazard information after acute exposure to a substance, and sensitivity of test animals.[30] Subchronic toxicity test is a test to detect toxic effects that appear after administration of the test preparation with repeated doses, the test preparation is given to the test animals for 10% of the entire age of the animals. The principle of the subchronic toxicity test is that the test group of animals is given the test preparation every day at several dose levels for 90 days.[31] Meanwhile, chronic toxicity is a test conducted to determine the ability of a compound to cause adverse health effects as a result of long-term drug exposure.[32] Of the three toxicity tests, the acute toxicity test is a test that needs to be carried out before carrying out other toxicity tests,[33] through the toxicity test is expected to be able to provide an overview of the initial data that can be used as a basis in determining a safe dose to avoid the occurrence of toxic effects.[4] The toxic effect in question can be in the form of a burning book,[34] decreased movement activity,[4] and the death of the test animals.[35]

Given the potential possessed by ciplukan roots and stems and their extensive use as medicine, it is necessary to test the acute toxicity of ciplukan roots and stems. It is hoped that the results of this study can provide information and enrich knowledge about the safety of the ciplukan roots and stems themselves.

MATERIALS AND METHODS

Extraction process

The extraction of ciplukan roots and stems refers to the Harborne[36] method. A total of 460.98 g of ciplukan roots and stems were cleaned, then cut into small pieces, and dried to produce a dry weight of 70 g. After that, the dried samples were macerated at room temperature using 96% ethanol solvent. The maceration process was carried out three times by adding new ethanol for each repetition. Then, the filtrate from the roots and stems of ciplukan was concentrated using a vacuum evaporator and a yield of 10.3 g was obtained.

Preparation of test animals

The test animals used were male white mice (*Mus musculus*), weighing 20 g-30 g, healthy condition, with an age range of 6-8 weeks. Prior to the experiment, all test animals were acclimatized for 7 days by providing standard food and drink ad libitum. The testing procedure has received a statement letter from the Health Research Ethics Commission, Faculty of Health Sciences, Respati University, Yogyakarta No. 019.3/FIKES/PL/I/2021.

Determination of toxicity and observation of accompanying toxic symptoms

The implementation of the toxicity test refers to Weil.[37] A total of 8 mice as test animals were divided into 4 groups, each group consisting of 2 mice. Each test animal was given ethanol extract of ciplukan roots and stems, the test preparations were given orally. Each test group was given a different test dose with a 10-fold dose interval, namely a dose of 0.56 mg/20 g body weight (marked on the head); dose 5.6 mg/20 g body weight (with dorsal marking); dose of 56 mg/20 g body weight (with markings on the tail); and a dose of 560 mg/20 g body weight (no signs). To distinguish individuals at each dose, a yellow mark is given on the body of the test animal, while to distinguish individuals in each dose group, a dot is given on the tail of the test animal. The test was carried out by counting the number of test animals that died within the first 24 hours after administration of the test preparation. This acute toxicity test was modified by adding observations on individuals who did not experience death for 3 days, namely at 24 to 96 hours.

RESULTS

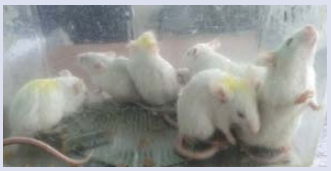
The abundance of biodiversity in Indonesia is utilized by the community, one of which is as traditional medicine. Utilization of biodiversity in the form of traditional medicine is an alternative that is considered more economical,[38] and generally have lower side effects than synthetic drugs.[11] Traditional medicine will be safe and useful if it is used properly, be it the dosage, the duration of administration, the method of use, the selection of ingredients, and adjustments to certain indications.[39,40] However, in the development of traditional medicines, inaccuracies in their use are often encountered and this occurs because of misinformation and erroneous assumptions about traditional medicines and how to use them. One of them is that synthetic drugs cannot be consumed in arbitrary quantities, traditional medicines also have dosages that must be adhered to.[26] Therefore, many studies have been conducted to seek and collect scientific evidence about the safety and efficacy of traditional medicines. With scientific evidence, people can use traditional medicine safely and usefully.[41] To test the safety of a traditional medicine, a toxicity test is carried out. The purpose of the toxicity test is to be able to assess various clinical symptoms and toxic effects caused by consuming plants used as traditional medicines[28,42] and ciplukan is one of the plants that has been traditionally used by the people of Indonesia, especially the people of West Kalimantan to treat jaundice and ciplukan is one of the plants that has been traditionally used by the people of Indonesia, especially the people of West Kalimantan to treat jaundice.[3]

A compound contained in traditional medicine will be toxic if given at high doses and becomes a drug if given at low doses or measured doses.[29] this means that a drug at a certain dose has the potential to be toxic in the body.[42] Acute toxicity test is a toxicity test to look for the toxic effects of a chemical compound. The acute toxicity test is carried out by giving the test preparation once or several times within 24 hours.[42] The acute toxicity test is a preclinical test designed to determine the lethal dose of a test preparation.[5] Through the acute toxicity test it is expected to be able to provide an overview of damage to an organ as a result of the compounds contained in the test preparation,[4,43] the emergence of unwanted effects is influenced by many factors, including the type of substance involved, the size of the dose given, and the length of exposure to the substance in the body.[43] Therefore, this study was conducted to evaluate the acute toxicity of ethanol extract of ciplukan roots and stems. The results of the acute toxicity test with graded doses for 24 hours are presented in table 1. An overview of the condition of the test animals during the administration of the test extract for 24 hours is presented in table 2. An overview of the conditions during the administration of the test extract from the 24th to the 96th hour is presented in table 3.

Table 1: The number of deaths of test animals due to administration of ethanol extract of ciplukan roots and stems. Observation of death was carried out for 24 hours after administration of the test preparation with graded doses.

No	Treatment Group	Number of tests animals (heads)	Number of dead animals (tails)
1	Dosage 0.56 mg/20 g body weight	2	0
2	Dosage 5.6 mg/20 g body weight	2	2
3	Dosage 56 mg/20 g body weight	2	2
4	Dosage 560 mg/20 g body weight	2	2

Table 2: Description of the condition of the test animals after administration of ethanol extract of ciplukan roots and stems in observations made for 24 hours.

No	Date	Information	Picture
1	March 01 2022 6.45 AM	Administration of ciplukan root and stem extracts to the test animals.	
2	March 01 2022 08.02 AM	All test animals treated at a dose of 0.56 mg/20 g body weight and a dose of 5.6 mg/20 g body weight were agile and active. One animal tested at a dose of 56 mg/20 g body weight and one animal at a dose of 560 mg/20 g body weight was agile and active, while one other animal at that dose died.	
3	March 01 2022 08.53 AM	All test animals treated at a dose of 0.56 mg/20 g body weight tended to be silent. All test animals treated at a dose of 5.6 mg/20 g body weight were agile and actively moving. Each test animal was treated with doses of 56 mg/20 g body weight and 560 mg/20 g body weight, agile and moving a lot.	-
4	March 01 2022 09.15 AM	All test animals that are still alive are slightly mobile.	-
5	March 01 2022 09.35 AM	All test animals were treated with a dose of 0.56 mg/20 g body weight. One test animal treated with 5.6 mg/20 g body weight tended to sleep and the hair covering its body looked bristling and erect, while the other test animal treated with a dose of 5.6 mg/20 g body weight was agile, moved a lot, and the hair covered the body was clean. One animal tested at a dose of 56 mg/20 g body weight, and one animal tested at a dose of 560 mg/20 g body weight was agile, moved a lot, and the hair covering its body was clean.	
6	March 01 2022 09.48 AM	All test animals were treated with a dose of 0.56 mg/20 g body weight. One test animal treated with 5.6 mg/20 g body weight tended to sleep and the hair covering its body looked bristling and erect, while the other test animal treated with a dose of 5.6 mg/20 g body weight was agile, moved a lot, and the hair covered the body was clean. One animal tested at a dose of 56 mg/20 g body weight, and one animal tested at a dose of 560 mg/20 g body weight was agile, moved a lot, and the hair covering its body was clean.	-
7	March 01 2022 10.03 AM	All test animals sleep, no activity.	
8	March 01 2022 10.12 AM	All test animals sleep, no activity.	-
9	March 01 2022 10.27 AM	All test animals treated at a dose of 0.56 mg/20 g body weight tended to be quiet and sleep. One animal tested at a dose of 5.6 mg/20 g body weight tended to be still and sleepy, while one animal tested at a dose of 5.6 mg/20 g body weight moved slightly. One animal tested at a dose of 56 mg/20 g body weight, and one animal tested at a dose of 560 mg/20 g body weight tended to sleep and had no activity.	-
10	March 01 2022 10.37 AM	All test animals sleep, no activity	-
11	March 01 2022 11.06 AM	One animal tested at a dose of 0.56 mg/20 g body weight moved and was agile, while the other animal tended to be quiet and sleep. All animals tested at a dose of 5.6 mg/20 g, one animal treated at a dose of 56 mg/20 g body weight, and one animal tested at a dose of 560 mg/20 g body weight tended to be quiet and sleep, no activity.	

		One animal tested at a dose of 0.56 mg/20 g body weight moved and was agile, while the other animal tended to be quiet and sleep.	
12	March 01 2022 11.20 AM	All animals tested at a dose of 5.6 mg/20 g, one animal treated at a dose of 56 mg/20 g body weight, and one animal tested at a dose of 560 mg/20 g body weight tended to be quiet and sleep, no activity.	-
13	March 01 2022 11.30 AM	All animals tested at a dose of 0.56 mg/20 g body weight, one animal tested at a dose of 5.6 mg/20 body weight, and one animal tested at a dose of 560 mg/20 g body weight tended to be quiet and sleep, no activity. Whereas one animal tested at a dose of 5.6 mg/20 g body weight and 56 mg/20 g body weight made little movement	-
14	March 01 2022 11.40 AM	All animals tested at a dose of 0.56 mg/20 g body weight, one animal tested at a dose of 5.6 mg/20 body weight, and animals tested at a dose of 560 mg/20 g body weight tended to be quiet and sleep, no activity. Whereas one other test animal with a dose of 5.6 mg/20 body weight and 56 mg/20 g body weight tended to move a lot.	-
15	March 01 2022 11.50 AM	All test animals that are still alive tend to be quiet and sleep, there is no activity.	-
16	March 01 2022 12.00 PM	All test animals that are still alive tend to be quiet and sleep, there is no activity.	-
17	March 01 2022 12.10 PM	All test animals that are still alive tend to move swiftly.	-
18	March 01 2022 12.20 PM	All test animals that are still alive tend to be quiet and sleep, there is no activity.	
19	March 01 2022 14.30 PM	All test animals treated at a dose of 0.56 mg/20 g body weight tended to move slightly and had hair that covered their bodies clean and not bristling. All animals were treated with a dose of 5.6 mg/20 g body weight, one animal was treated with 56 mg/20 g body weight, and one animal was treated with 560 mg/20 g body weight.	
20	March 01 2022 15.00 PM	All animals tested at a dose of 0.56 mg/20 g of body weight slept, no activity.	
21	March 01 2022 15.10 PM	All animals tested at a dose of 0.56 mg/20 g of body weight slept, no activity.	-
22	March 01 2022 15.20 PM	All animals tested at a dose of 0.56 mg/20 g of body weight slept, no activity.	-
23	March 01 2022 15.30 PM	All animals tested at a dose of 0.56 mg/20 g of body weight slept, no activity.	-
24	March 01 2022 15.45 PM	All animals tested at a dose of 0.56 mg/20 g of body weight slept, no activity.	-
25	March 01 2022 16.00 PM	All animals tested at a dose of 0.56 mg/20 g of body weight slept, no activity.	
26	March 01 2022 16.15 PM	All animals tested at a dose of 0.56 mg/20 g of body weight slept, no activity.	-
27	March 01 2022 16.30 PM	One animal tested at a dose of 0.56 mg/20 g body weight tended to sleep and had no activity, while the other animal tended to move a lot.	-
28	March 01 2022 16.49 PM	All test animals treated at a dose of 0.56 mg/20 g body weight tended to move slightly.	-

29	March 01 2022 17.07 PM	All test animals treated at a dose of 0.56 mg/20 g body weight moved a lot and ate a lot.	
30	March 01 2022 17.17 PM	All test animals treated at a dose of 0.56 mg/20 g body weight moved a lot and ate a lot.	-
31	March 01 2022 17.26 PM	All test animals treated at a dose of 0.56 mg/20 g body weight moved a lot and ate a lot.	-
32	March 01 2022 17.43 PM	All test animals treated at a dose of 0.56 mg/20 g body weight moved agile and ate.	-
33	March 01 2022 05.50 AM	All test animals treated at a dose of 0.56 mg/20 g body weight moved a lot and the hair that covered their bodies looked clean.	-
34	March 02 2022 06.03 AM	All animals tested at a dose of 0.56 mg/20 g body weight moved a lot.	
35	March 02 2022 06.15 AM	All animals tested at a dose of 0.56 mg/20 g body weight moved a lot.	
36	March 02 2022 06.25 AM	All test animals treated at a dose of 0.56 mg/20 g body weight moved a lot and ate a lot.	
37	March 02 2022 07.00 AM	All animals tested at a dose of 0.56 mg/20 g of body weight slept, no activity.	

DISCUSSSION

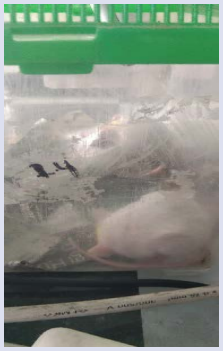
Each test animal was given ethanol extract of ciplukan roots and stems orally and in each test group a different dose was given at a 10-fold interval, namely a dose of 0.56 mg/20 g body weight (marked on the head); 5.6 mg/20 g body weight (with dorsal marking); 56 mg/20 g body weight (with markings on tail); and 560 mg/20 g body weight (no sign). The test was carried out by counting the number of deaths of the test animals during the first 24 hours after being given the test preparation, then followed by observations for 3 consecutive days on the test animals that were still alive. From the observations made it was known that at 06.45 in the morning the researchers gave ethanol extract of ciplukan roots and stems to the test animals and it was found at 08.02 in the morning there was death in 1 test animal treated with a dose of 56 mg/20 g body weight and 1 test animal treated with a dose of 560 mg /20 g of body weight, then at 14.30 noon there were also deaths in all test animals treated with a dose of 5.6 mg/20 g body weight, and additional deaths in 1 tested animal treated with 56 mg/20 g body weight, and 1 animal tested treated with a dose 560 mg/20 g body weight.

Table 3: Description of the condition of the test animals after administration of ethanol extract of ciplukan roots and stems. Observations were made from the 24th to the 96th hour.

No	Date	Information	Picture
1	March 02 2022 07.00 AM	All animals tested at a dose of 0.56 mg/20 g body weight tended to sleep, no activity.	
2	March 02 2022 08.28 AM	All animals tested at a dose of 0.56 mg/20 g body weight moved a lot.	
3	March 02 2022 09.00 AM	All animals tested at a dose of 0.56 mg/20 g body weight moved a lot.	
4	March 02 2022 13.12 PM	All animals tested at a dose of 0.56 mg/20 g body weight moved a lot.	
5	March 02 2022 14.00 PM	All animals tested at a dose of 0.56 mg/20 g body weight moved a lot.	
6	March 02 2022 14.30 PM	All animals tested at a dose of 0.56 mg/20 g body weight moved a lot.	
7	March 02 2022 15.00 PM	One animal tested at a dose of 0.56 mg/20 g body weight slept, had no activity and one animal tested at a dose of 0.56 mg/20 g body weight moved a lot.	
8	March 02 2022 15.30 PM	All animals tested at a dose of 0.56 mg/20 g body weight moved a lot.	

9	March 02 2022 16.00 PM	All animals tested at a dose of 0.56 mg/20 g of body weight slept, no activity.	
10	March 03 2022 06.38 AM	All test animals treated at a dose of 0.56 mg/20 g body weight moved a lot, ate, and had clean fur.	
11	March 03 2022 07.30 AM	All animals tested at a dose of 0.56 mg/20 g body weight moved a lot.	
12	March 03 2022 08.00 AM	All animals tested at a dose of 0.56 mg/20 g of body weight slept, no activity.	
13	March 03 2022 08.30 AM	All test animals treated at a dose of 0.56 mg/20 g body weight tended to move slightly.	
14	March 03 2022 09.00 AM	All animals tested at a dose of 0.56 mg/20 g of body weight slept, no activity.	
15	March 03 2022 13.28 PM	All animals tested at a dose of 0.56 mg/20 g body weight moved a lot.	
16	March 03 2022 16.09 PM	All animals tested at a dose of 0.56 mg/20 g of body weight slept, no activity.	

17	March 03 2022 16.30 PM	All animals tested at a dose of 0.56 mg/20 g body weight moved a lot.	
18	March 04 2022 06.43 AM	All animals tested at a dose of 0.56 mg/20 g body weight moved a lot.	
19	March 04 2022 08.00 AM	One animal tested at a dose of 0.56 mg/20 g body weight moved a lot and had red spots on its fur and one animal tested at a dose of 0.56 mg/20 g body weight moved a lot.	
20	March 04 2022 08.47 AM	All animals tested at a dose of 0.56 mg/20 g of body weight slept, no activity.	
21	March 04 2022 13.03 PM	All animals tested at a dose of 0.56 mg/20 g body weight moved a lot.	
22	March 04 2022 13.31 PM	One animal tested at a dose of 0.56 mg/20 g body weight moved a lot. One test animal was treated with a dose of 0.56 mg/20 g of body weight sleeping, no activity.	
23	March 04 2022 14.30 PM	All animals tested at a dose of 0.56 mg/20 g of body weight slept, no activity.	

24	March 04 2022 16.00 PM	All animals tested at a dose of 0.56 mg/20 g of body weight slept, no activity.	
25	March 05 2022 07.00 AM	All animals tested at a dose of 0.56 mg/20 g body weight moved a lot.	

Traditional medicine has a considerable risk of causing organ damage, the use of traditional medicine must consider the correct dosage, timeliness and method of use, as well as the accuracy of information review to prevent various unwanted symptoms.[26] The death of mice showed that the increase in the dose given to the test animals and the length of observation time resulted in an increase in the percentage of deaths in the test animals,[44] Emilia *et al*.[45] stated that the high doses applied to the test animals would result in the test animals being exposed to the most of the tested extracts, and the length of time of observation of the test animals would give an illustration that initially the test animals were able to adapt to the doses given then gradually weakened because of the test extracts. inside his body begins to react and accumulate which will cause toxic symptoms. Toxic symptoms observed before the test animals died were individuals who were agile, moved a lot, with sparse fur, slept, moved little, and died. Clinical effects of adverse toxicity tests are effects that may produce functional impairment of organs and biochemical lesions that may alter the function of the organism in general or of specific organs.[46] Furthermore, Fithria *et al*.[34] states that clinical symptoms from toxicity testing can include changes in behavior, changes in skin and coat color, hair loss, gastrointestinal (constipation and diarrhea), vasodilatation, and movement (violent, tremor, convulsions, paralysis, and passivity), and death.

According to Aufia *et al*.[47] toxicity tests are used to observe the pharmacological activity of a compound that has bioactive components that are toxic when given at high doses. The existence of a toxicity test can provide an overview of initial data in determining a safe dose and to avoid toxic effects.[48] Furthermore, the acute toxicity test will provide information about the lethal dose, therapeutic index, and degree of safety of the tested agent.[46] Information on the lethal dose of a test compound can be seen from the number of mice that died and mice that were still alive in the test group,[48] this corresponds to Chinedu *et al*.[46] stated that the main parameter for measuring acute toxicity is to assess the dose that can kill 50% of the test animal population. In this study, the death of the test animals was related to the effects that appeared after administering graded doses of the compounds contained in ciplukan root and stem extracts. In ciplukan roots there are alkaloid group compounds,[10] phenolics,[49] alkaloid, phenolics, flavonoid, anthraquinone, and terpenoid.[50] These studies show that ciplukan roots contain alkaloid compounds,[10,50] phenolics,[49,50] flavonoid, anthraquinone, and terpenoid.[50] The ciplukan stems are reported to contain steroid group compounds, alkaloid, saponin, and flavonoid,[9] phenolics and flavonoid,[49] alkaloid, steroid, flavonoid, anthraquinone, and terpenoid.[50] From these studies it can be seen that ciplukan stems contain alkaloid compounds, flavonoids,[9,49,50] steroid,[9,50] saponin,[9] phenolics,[49] and anthraquinone.[50]

Even though these compounds are useful in the body, in reality the use of chemical compounds must be within the specified limit because if it exceeds the limit it will cause toxic effects on the body. Alkaloid compounds that have a harmful impact on the body are caffeine which causes dependence,[51,52] abnormal hearbeat,[51] tremors,[51,53] anxiety,[54] headaches, insomnia, stomach and digestive disorders, anxiety, and memory loss.[51] Compounds of the saponin group have negative effects on livestock, which can irritate the lining of the mouth and digestive tract, affect nutrient absorption, fail to form zygotes, fail implantation, and abortion, and reduce iron absorption.[55] Steroid compounds also have harmful effects on the body, namely female masculinization, testicular atrophy, gynecomastia in males, stretch marks, tissue damage, nerve injuries, paralysis, behavioral and personality disorders, and even death.[56] Meanwhile, according to Widyasari,[57] compounds belonging to the flavonoid group can cause poisoning effects on the body and the resulting effects are allergies. Anthraquinone compounds can cause digestive discomfort, stomach cramps, dermatitis, nausea, vomiting, dizziness, and bloody diarrhea.[58] The phenolic compounds have the effect of inactivating enzymes and denaturing proteins which causes disruption of the transport of organic ions into cells, thereby inhibiting cell growth or even causing cell death.[59]

Toxic symptoms appeared in the treatment group at doses of 5.6 mg/20 g body weight, 56 mg/20 g body weight, and 560 mg/20 g body weight. Before the test animals died, the test animals tended to be less mobile, and bristling/sparse fur was found in the test animals treated at a dose of 5.6 mg/g body weight. The decrease in movement activity in test animals is closely related to depression of the central nervous system and muscle relaxation,[4] whereas bristling hair is a general sign of toxicity which affects the integrity of the coat, in this case the active compounds present in the test material cause hair loss so that the hair on the test animal looks sparse.[34] According to Yusuf[35] the death of

the test animals is related to the response of individual sensitivity to the given test dose. Observations on test animals treated at a dose of 0.56 mg/20 g body weight were carried out until the third day, from observations made on test animals treated at a dose of 0.56 mg/20 g body weight, test animals were agile and actively moving, sleeping, moving a little, having an appetite which is good, and has good fur, and one of the test animals has red spots on its back.

CONCLUSION

Administration of ethanol extract of ciplukan roots and stems at a dose of less than or equal to 0.56 mg/20 g body weight in the acute toxicity test was relatively safe for the test animals.

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