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Toxicity Effect Test of leaf and stem bark Fraction of *Pometia pinnata* as Raw Material for Anticancer Drug

(*Uji Efek Toksisitas Fraksi Daun dan Kulit Batang Pometia pinnata Sebagai Bahan Baku Obat Antikanker*)

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ABSTRACT

Background: Cancer is a major cause of high morbidity and mortality, especially in developing countries such as Indonesian. Medical treatments such as chemotherapy, surgery, and radiation require are costtly with significant side effects. Therefore, there is a need for chemopreventive agents derived from nature such as plants. One plant that has the potential to be a chemopreventive agent is the leaves and stem bark of Matoa (*Pometia pinnata*). **Objective:** To test the toxicity effect of the *Pometia pinnata* leaf and stem bark fraction on *Artemia* salina Leach shrimp larvae. **Methods:** the extraction method used was multistage maceration using solvents based on increasing polarity, starting with n-heksane, choloroform. Ethyl acetate, and methanol. Phytochemical screening with color test, and toxicity test using brine shrimp lethality test method. **Result:** The results showed that all leaf and stem bark fractions of Pometia pinnata were toxic with LC_{50} values for leaf fractions:n-hexane (394.8 µg/mL), chloroform (244.3 µg/mL), ethyl acetat (180.6 µg/mL), and methanol (303.2 µg/mL), respectively. The stem bark fraction showed LC_{50} values in the order of n-hexane (203.9 µg/mL), chloroform (244.3 µg/mL), ethyl acetat (144.8 µg/mL), and methanol (58.3 µg/mL). **Conclusion:** Alla fraction fall into the toxic category and have potential as raw materials for anticancer drug.

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INTRODUCTION

Cancer is a significant cause of high morbidity and mortality rates, especially in developing countries like Indonesia. Basic Health Research (Kemenkes RI, 2019) data shows that the prevalence of cancer in Indonesia has increased from 1.4 per 1,000 population in 2013 to 1.79 per 1,000 population in 2018. The Global Burden of Cancer Study (Globocan) data from the WHO also reported a total of 396,914 cancer cases and 234,511 deaths in Indonesia in 2020.

Medical treatments for cancer, such as chemotherapy, surgery, and radiation, incur very high costs (Hidayanti, 2023). Cancer treatments still heavily relies on chemotherapy. Chemoterapy with anticancer drug is hindered by side effects, such as inhibiting the growth of normal cells in the human body, leading to issues like hair loss. Additionally, it can cause nausea, vomiting, dizziness, and drug resistance. Therefore, there is a need for the development of efficient and affordable chemopreventive agents to the public (Hidayanti, 2023; Wijayanti, 2023).

Matoa (*Pometia pinnata*) is one of the plants from the Sapindaceae family that has the potential as a chemopreventive agent. This plant is often used to produce raw materials for traditional medicine. Empirically, the bark of the matoa tree is utilized to treat suppurating wounds or burns, alleviate fever, stomachaches, diarrhoea, constipation, chickenpox, dysentery, cough, bone diseases, joint and muscle pain, headaches, diabetes, flu, and boils (BPTP Papua Annual Report, 2021).

The Literatur rereview indicates that the bark extract of the matoa tree contains the steroid stigmasterolwithan LC50 value of 41,334 µg/mL against shrimp larvae (Rohmawati et al., 2018). Various chemical compounds have been success fully isolated from the *Pometia pinnata* plant, such as the triterpenoid taraxerone from the bark of the *Pometia pinnata* tree (Trimedonaetal., 2015). A compound named Hederagenin Saponin (HGS) found in this plant exhibits anti obesity activity (Suzuki etal., 2021). Flavonoids like kaempferol-3-O-rhamnoside and quercetin-3-O-rhamnoside have also been identified and show inhibitory activity against the enzyme α-glucosidase (Utari etal., 2019). Several studies indicate that the matoa tree contains alkaloids, flavonoids, saponins, phenols, steroids, terpenoids, and tannins (Rahmawati et al., 2021). In a study comparing the total phenolic content in the peel, flesh fruit, and seed of matoa, the results show that the average total phenolic contentis highest in the fruit peel at 262.22 mg GAE/g, followed by the flesh fruitat 167.75 mg GAE/g, and the seed at 139.39 mg GAE/g (Irawan etal., 2017).

Research on the antioxidant activity of *Pometia pinn*ata indicates that ethanol extract from matoa leaves has an IC50 value, whichis the concentrationat which antioxidant activity reaches 50%, with variations across studies. Martiningsih etal. (2016) recorded an IC_{50} value of 45.78 µg/mL, while Islami etal. (2021) obtained a lowervalue, namely 1.403 µg/mL. Sauriasarietal. (2017) found that the ethanol extract of

matoa leaves also inhibited the activity of the tyrosinase enzyme in vitro, indicating the potential in volvement of this plant in protecting the skin from melanogenesis. Kuspradinietal. (2016) high lighted that the methanol extract from matoa leaves has a significant ability to scavenge DPPH free radicals, reaching a value of 90%. These findings indicate that matoa leaves have the potential as a source of antioxidant compounds that can help combat oxidative stress and provide health benefits, including potential skin protection.

Pometia pinnata has the potential to be developed as an anticancer drug due to its potent antioxidant properties. Cancer is generally caused by free radicals that cause oxidative stress in the human body. Antioxidant are compound that can reduce oxidative stress (Mulia, et, al., 2015; Garcia, 2019). Based on this concept, the *Pometia pinnata* plant is considered suitable to be developed as an anticancer drug. One method for initial screening of anticancer drug testing is toxicity test on *Artemia salina* Leach shrimp larvae. Based on this, research has been conducted on the toxicity effect test of *Pometia Pinnata* leaf and stem bark fraction as raw materials for anticancer drug using the *Brine Shrimp Lethality Tes*t (*BSLT)* method. The result of this research will be an important reference for the development of *Pometia pinnata* plants as potential raw materials in the production of anticancer drug.

MATERIAL AND METHODS

Materials

The samples of leaves and bark from Pometia pinnata were obtained from Mobagu City, North Sulawesi, in January 2023.The plant was taxonomically confirmed by Abdullah Walangadi S.Farm, Department of Pharmacy, Faculty of Sport and Health, Gorontalo State University with No. B/127/UN47.B7.LABFARM/TA.00.03/2023.The solvents used included technical-grade methanol, n-hexane, chloroform, and ethyl acetate that had been redistilled before use. The analysis method involved using thin-layer chromatography (TLC) with TLC plates and UV 254 and 366 as detectors. Reagents such as Libermann Bouchardat, Dragendorff, magnesium powder, concentrated HCl, $FeCl_3$, *Artemia salina* L. shrimp larvae, Dimethyl sulfoxide (DMSO), and seawater were also employed in the process of analysis and toxicity testing.

Extraction method

The extraction method used in this study is a multistage maceration, where solvents are selected based on increasing polarity, namely n-hexane, chloroform, ethyl acetat, and methanol. A totalof 500 grams of matoa leaf powder and matoa bark powder were separately ectracted with n-hexane for 72 hours, then filtered, and the filtrate was concentrated using an evaporator. Meanwhile, the residu was air-dried, weighed, and subjected to another extraction with chloroform for 72 hours. Subsequently, the process was repeated for yhe ethyl acetat and methanol extract, following the same procedures as the n-hexan

extract. All resulting fractions were weighed to calculate their yields, underwent phytochemical screening, and tested for toxicity using the BSLT method.

Phytochemical Screening Test

The crude extract is screened to determine the presence of flavonoids, alkaloids, terpenoids, tannins, steroids, and saponins. These compounds are screened in the laboratory using standard methods with slight modifications. The method is described in references such as Parbuntari et al. (2018); Pant et al. (2017) and Martiningsih et al. (2016). 2 grams of extract dissolved in chloroform then added ammonia-chloroform 0.05 N, filtered. The filtrate was added 2N sulfuric acid then shaken vigorously, allowed to stand until two layers were formed. the top layer was sulfuric acid and the bottom layer was chloroform. Alkaloid test, H_2SO_4 layer added a few drops of dregendorf reogen, orange or yellow color indicates a positive result of alkaloids. Steroids/triterpenoids test, the chloroform layer is added to the liberman bouchardat regent. if the color caused by the reddish orange color is positive for terpenoids and if the bluish green color shows positive steroids. Flavonoids test, Flavonoid test is carried out by Shinoda test method, namely 0.5 grams of extract dissolved in methanol and then heated for 5 minutes, a few drops of concentrated HCl and a certain amount of magnesium powder are added. red or pink color indicates positive flavonoid content. Saponins test, the sample is dried first, then boiled in water 2-3 minutes. the formation of stable foam indicates positive. Tannin test, 0.5 extract added $FeCl_3$ 10%. yellow color indicates positive for tannin.

Preparation of Extracts/fractions of Pometia pinnata leaves and bark

All extracts/fractions from matoa leaves and bark, including n-hexane extract, chloroform extract, ethyl acetate extract, and methanol extract, were each prepared as stock solutions at a concentration of 1000 ppm. These stock solutions were created by weighing 100 mg of crude extract and dissolving it in 100 mL of dimethyl sulfoxide (DMSO). Subsequently, concentration variations were made at 10, 20, 40, 80,160, 320, and 500 µg/mL.

Determination of the toxicity

This study employs the BSLT method to assess the toxicity of *Pometia pinnata*leaf and stem bark fractions, referring to references (Hasan, 2023; Cahya, 2023). The method involves using a double-insulated box, where one side is covered with aluminum foil containing seawater and eggs of Artemia salina shrimp. The box is placed under a UV lamp for 48 hours, leading to the hatching of the eggs into larvae. Leaf fractions are mixed with seawater at dilution concentrations of 500, 320, 160, 80, 40, 20, and 10 µg/mL. This study involves creating stem bark fractions at concentrations of 100, 10, and 1 µg/mL, each replicated three times. A vial bottle is used as a control without adding a test solution. The main solution is prepared by weighing 20 mg of the test extract dissolved in 2 mL of seawater or a few

drops Dimethylsulfoxide (DMSO) if the sample is difficult to dissolved. After being left for 24 hours, the count of live and dead shrimp larvae is recorded. BSLT data is then analyzed to understand the response of shrimp larvae to various concentrations of stem bark fractions, providing information about the level of toxicity and potential effects on shrimp larvae. The death rate or percentage of mortality was obtained by comparing the number of dead larvae divided by the total number of larvae and then analyzing it using probit values. The LC_{50} value is obtained based on the linear regression value. Fraksi is declared active if the LC_{50} value is smaller than 1000 µg/mL (Mayer, 1988).

RESULTS AND DISCUSSION

This study used samples of leaves and bark from Pometia pinnata. The extraction method employed is a multistep maceration. This means that the maceration process involves solvents based on increasing polarity, starting from n-hexane as a non-polar solvent, chloroform as another non-polar solvent, ethyl acetate as a semi-polar solvent, and methanol as a polar solvent. Each solvent will dissolve chemical components with similar properties (like dissolves). Polar compounds will dissolve in polar solvents, semi-polar compounds will dissolve in semi-polar solvents, and non-polar compounds will dissolve in non-polar solvents. All leaves and bark fractions were calculated as percent yield and their chemical components were identified using the color test method. The results of the percent yield calculation are shown in Table 1. The screening results can be seen in Table 2 and Table 3. In Table 2, the phytochemical screening results indicate that the n-hexane fraction from *Pometia pinnata* leaves contains alkaloids, the chloroform fraction contains flavonoids, alkaloids, and steroids, and the ethyl acetate fraction contains flavonoids and steroids. In contrast, the methanol fraction contains flavonoids, alkaloids, terpenoids, and tannins. The phytochemical screening results for the bark fraction of Pometia pinnata show that the n-hexane fraction contains terpenoids, the chloroform fraction contains flavonoids, tannins, and terpenoids, the ethyl acetate fraction contains flavonoids, terpenoids, and tannins, and the methanol fraction contains flavonoids, alkaloids, terpenoids, and tannins. The chemical content of the bark and leaves of *Pometia pinnata* is closely related to the biological activities of the plant extracts.

Table 1. Percent yield of Matoa Leaves and Bark

Matoa Plants	Solvents	Initial Sample Weight (g)	Weight of Extract (g)	Percent Yield (%)
Stem Bark	-n-Hexane -Chloroform -Ethyl acetat -Methanol	500 442 407 385	47 32 39 41	9.4 7.2 9.5 10.64
Matoa Leaves	-n-Hexane -Chloroform -Ethyl acetat -Methanol	500 448 392 363	54 38.2 35.8 41.4	10.8 8.5 9.1 11.4

Table 1 shows the percent yield in the Matoa stem bark and leaf fractions. The amount of percent yield indicates the amount of secondary metabolites or chemical components that are extracted into the solvent.

Table 2. Phytochemical Screening Results of *Pometia pinnata* Leaf Fraction

Phytochemical Test	Reagents	Extract/Fraction			
		N-hexane	Chloroform	Ethyl acetate	Methanol
Flavonoids	HCl + Mg Powder	-	+	+	+
Alkaloids	Dragendorf	+	+	-	+
Terpenoids	Liebermann Bouchardat	-	-	-	+
Steroids	Lieberman Bouchardat	-	+	+	-
Tannin	$FeCl_3$	-	-	-	+

Note: (-) = Negative, (+) = Positive

Toxicity testing of leaf and bark fractions of Pometia pinnata is presented in Table 3 and 4. The parameter used to indicate the toxicity of a substance is the LC_{50} value. Lethal Concentration (LC_{50}) is the concentration of a chemical compound that can cause 50% mortality in a population of test animals or specific living organisms. The smaller the LC_{50} value, the more toxic a substance is. An extract/fraction is considered toxic if the LC_{50} value is < 1000 µg/mL (Meyer, 1982). Toxicity testing in this study used the BSLT method, as it is not only easy and cost-effective but also serves as an initial pharmacological test for cancer screening. This method is a well-established test with a 95% confidence level to observe the toxicity of a compound in crude extracts. The Brine Shrimp Lethality Test for toxicity assessment utilizes *Artemia salina* larvae and is often analogized with the anticancer effects of a medicinal substance.

Table 3. Toxicity Testing Results (LC_{50}) of *Pomatia pinnata* Leaf Fraction

Fraction	CC(µg/mL)	Dead	Live	DA	LA	D/T	% Mortality
N-hexane	500	13	17	29	17	29/46	63.04
	250	7	23	16	40	16/56	28.57
	100	6	24	9	64	9/73	12.32
	50	2	28	3	92	3/95	3.15
	25	1	29	1	121	1/122	0.81
Chloroform	500	10	20	28	20	28/48	58.33
	250	8	22	18	42	18/60	30
	100	5	25	10	67	10/77	12.98
	50	3	27	5	94	5/99	5.05

	25	2	28	2	122	2/124	1.61
Etylacetat	500	23	7	52	7	52/59	88.13
	250	13	17	29	24	29/53	54.71
	100	7	23	16	47	16/63	25.39
	50	6	24	9	71	9/80	11.25
	25	3	27	3	98	3/101	2.97
Methanol	500	13	17	34	17	34/51	66.66
	250	10	20	21	37	21/48	43.75
	100	6	24	11	61	11/72	15.27
	50	4	26	5	87	5/92	5.43
	25	1	29	1	116	1/117	0.85

C: Concentration, DA: Dead Acumulation, LA: Live Acumulation, D/T:Dead/Total Dead + Live

The toxicity testing results on leaf fractions of *Pometia pinnata* at various concentrations were conducted in three replications and after 24 hours of incubation, as shown in Table 3. Table 3 indicates an increase in the percentage of mortality directly proportional to the concentration increase. This can be observed in the n-hexane extract, for example, with concentrations of 25, 50, 100, 250, and 500 µg/mL, resulting in mortality percentages of 0.81%, 3.51%, 12.32%, 28.57%, and 63.54%, respectively. Similarly, chloroform, ethyl acetate, and methanol fractions produced larval mortality proportional to the concentration increase.

The toxicity (LC_{50}) was determined by calculating the mortality percentage and determining the probit value, which was then plotted against the log concentration to obtain a linear regression equation and derive the LC_{50}value. Based on Table 3, the LC_{50} values for each fraction were, in order, n-hexane fraction (394.8 µg/mL), chloroform fraction (244.3 µg/mL), ethyl acetate fraction (180.6 µg/mL), and methanol fraction (303.2 µg/mL). An extract/fraction is considered acute toxicity if the LC_{50}value is less than 1000 µg/mL. All LC_{50}values fall into the toxic category as they are less than 1000 µg/mL (Meyer, 1982).

The toxic effect is related to the chemical compounds present in each fraction. Flavonoids act as antifeedants, inhibiting larval feeding, reducing digestive enzyme activity, and acting as stomach poison, leading to larval mortality (Yunita, 2009). Alkaloids generally act on the nervous system, causing digestive disturbances and acting as a poison when ingested by the larva (Khasanah, 2020).

Table 4. Toxicity Testing Results (LC_{50}) of *Pometia pinnata* Bark Stem Fraction

Fraction	CC(µg/mL)	Dead	Live	DA	LA	D/T	% mortality
n-hexane	100	26	4	33	4	33/37	89
	10	5	25	7	29	7/36	19.4
	1	2	18	2	47	2/49	4.08
Choloform	100	26	4	32	4	32/36	88.8
	10	4	26	6	30	6/36	16.6
	1	2	18	2	48	2/50	4
Ethyl acetat	100	28	2	39	2	39/41	75
	10	7	23	11	25	11/36	30.55
	1	4	26	4	51	4/55	7.27
Methanol	100	30	0	37	0	37/37	100
	10	6	24	7	24	7/31	22.5
	1	1	29	1	53	1/54	1.85

CC: Concentration, DA: Dead Acumulation, LA: Live Acumulation, D/T:Dead/Total Dead + Live

Toxicity testing (LC_{50}) on leaf fractions using the same method as for stem bark fractions of Pometia pinnata. The concentrations used in this test were 1, 10, and 100 µg/mL. The LC_{50}values for each fraction, in sequence, were n-hexane 203.9 µg/mL, chloroform 244.3 µg/mL, ethyl acetate 144.8 µg/mL, and methanol 58.3 µg/mL. These values fall into the toxic category as they are less than 1000 µg/mL (Meyer, 1982).

The comparison of LC50 values for leaf and bark fractions of *Pometia pinnata* is shown in Figure 1. The diagram in this figure indicates that the bark fraction of *Pometia pinnata* is more toxic than the leaf fraction for all fractions (n-hexane, chloroform, ethyl acetate, and methanol). Among all fractions, the methanol fraction exhibits the highest toxicity. As known, methanol is a universal solvent that can extract both polar and non-polar chemical components. The LC50 values for the n-hexane and chloroform fractions also show toxic effects, suggesting that non-polar compounds present in the plant are also toxic. Toxicity testing using *Artemia salina* Leach shrimp larvae is one of the screening methods for anticancer compounds. Fractions of *Pometia pinnata* have the potential to be used as raw materials for anticancer drugs. This is in line with the research of Sarvananda et al, 2018 on the immunomodulatory effects of the species *Cardiospermun halicacabun* L, from the family Sapindaceae and genus Pometia which concluded that this plant has anticancer activity and strong antioxidant activity.

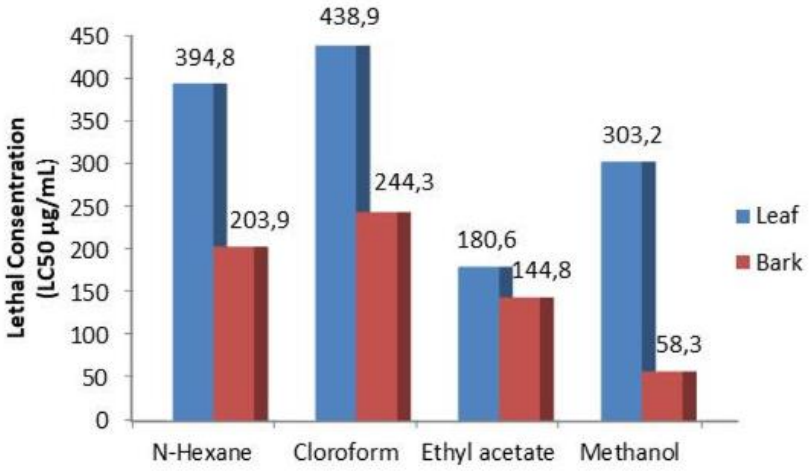

Figure 1. Comparison of LC_{50} Values of Leaf and Stem Bark Fraction of *Pometia pinnata*

CONCLUSION

Based on the research results, the toxicity effect with the parameter LC_{50} values of all bark stem fractions and leaf fractions of *Pometia pinnata i*s categorized as toxic because it is < 1000 µg/mL. Therefore, these plant fractions have the potential as raw materials for anticancer substances.

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All authors declare no conflict of interest.

CONFLICT OF INTEREST

Authors declare no conflict of interest

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