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Preliminary In Vitro Antiplatelet Potential of *Ipomoea pes-caprae* from North Lombok with Adenosine Diphosphate-Induced Platelet Aggregation

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Abstract

***Background**: Cardiovascular diseases, particularly ischemic stroke, remain a global health burden, necessitating potential candidate for further antiplatelet with fewer side effects. **Objectives**: This study aimed to evaluate the antiplatelet potential of ethanolic extracts from the leaves and stems of Ipomoea pes-caprae (Katang-katang) from North Lombok, Indonesia, through ADP-induced platelet aggregation. Phytochemical screening, total tannin quantification, and in vitro antiplatelet assays were conducted. **Methods**: The leaves and stems were macerated with 96% ethanol, followed by qualitative phytochemical tests, Folin-Ciocalteu-based tannin analysis, and platelet aggregation inhibition assays using human platelet-rich plasma. **Results**: The extracts contained alkaloids, flavonoids, and tannins, with higher tannin levels in leaves (4.02 ± 0.02 mgEAT/g) than stems (3.67 ± 0.17 mgEAT/g). Concentration-dependent antiplatelet activity was observed, with leaf extracts showing inhibition (85.9% at 2000 µg/mL) compared to stems (79.5%) and aspirin (77.3%). IC_{50} values were 727.78 µg/mL (leaves) and 349.95 µg/mL (stems). Statistical analysis confirmed significant differences across concentrations ($p < 0.05$). **Conclusion**: These findings demonstrate that Ipomoea pes-caprae exhibits potent antiplatelet activity, attributed to its tannin and phytochemical content, with leaves being more effective. Although these findings suggest preliminary antiplatelet potential, further analysis is required to validate the method using aspirin IC_{50}, and subsequent in vivo and pharmacological investigations are necessary before therapeutic application can be claimed.*

***Keywords:** adenosine diphosphate, antiplatelet, Ipomoea pes-caprae, phytochemical, tannin*

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INTRODUCTION

Platelets, or thrombocyte fragments, are non-nucleated cytoplasmic fragments of megakaryocytes formed in the bone marrow. In their mature form, they measure 2–4 µm and exhibit a biconvex disc shape. Platelets play a critical role when blood vessels are damaged or the skin is injured, leading to leakage that causes blood to exit the vessels, resulting in bleeding (Lobang, 2021). Platelets can contribute to thrombosis through activation, leading to adhesion and aggregation, ultimately forming a clot. These clots form when platelet levels in the blood exceed normal levels. Thrombosis can result in cardiovascular diseases, particularly ischemic stroke, when clots form in the brain's blood vessels (Ashorobi et al., 2024).

Globally, approximately 15 million people suffer from stroke annually. Of these, 5 million die and another 5 million are left permanently disabled, placing a heavy burden on families and communities. Stroke is rare in individuals under 40; when it does occur, hypertension is the primary cause. However, stroke also affects approximately 8% of children with sickle cell disease **(**WHO, 2025). In Indonesia, the prevalence of stroke increased by 3.9 per 1,000 population between 2013 and 2018 (Kemenkes RI, 2018). As the predominant form of stroke, ischemic stroke highlights the urgent need for effective prevention, especially through antiplatelet therapy (Hackam et al., 2019).

Antiplatelet agents commonly used in the treatment of non-cardioembolic ischemic stroke and transient ischemic attacks include aspirin, aspirin-dipyridamole, clopidogrel, and ticagrelor (Hackam et al., 2019). Aspirin inhibits platelet aggregation by blocking thromboxane A2 synthesis in platelets (Arif & Aggarwal, 2023). Dipyridamole inhibits phosphodiesterase and adenosine deaminase, preventing the conversion of cAMP and cGMP to their inactive forms. This increases intracellular cAMP and cGMP levels, thereby reducing platelet aggregation and thrombosis (Kerndt & Nagalli, 2023). While dipyridamole has relatively weak antiplatelet activity alone, its combination with aspirin is effective for secondary stroke prevention (Phillips & Gibson, 2021). Clopidogrel irreversibly inhibits the platelet P2Y12 adenosine diphosphate (ADP) receptor, preventing activation of the glycoprotein IIb/IIIa receptor complex and reducing aggregation (Beavers et al., 2025). Ticagrelor acts by reversibly binding to the P2Y12 ADP receptor to inhibit platelet activation and aggregation (Fuller & Chavez, 2012).

Despite their effectiveness, antiplatelet agents also have adverse effects. Aspirin, clopidogrel, and ticagrelor can cause bleeding, while dipyridamole may lead to dizziness, chest tightness, and abdominal pain (Wei et al., 2024; Whitlock et al.,2016; Lee et al., 2016). Therefore, alternative treatments derived from natural sources are needed. Natural compounds are considered due to their abundance in Indonesia (Indriani & Ardiana, 2023), their generally milder side effects compared to synthetic drugs (Sumayyah & Salsabila, 2017), and their substantial potential for therapeutic development (Novianti, 2017).

One plant with demonstrated antiplatelet properties is katang-katang (*Ipomoea pes-caprae*). According to research by Rogers et al. (2000), *I. pes-caprae* significantly inhibits ADP-induced platelet aggregation. This plant contains secondary metabolites such as alkaloids, flavonoids, tannins, and terpenoids (Akinniyi et al., 2022), all of which contribute to its antiplatelet effects. Alkaloids inhibit platelet aggregation by blocking thromboxane A2 synthesis induced by ADP, arachidonic acid, and collagen (Ain et al., 2016). Flavonoids interfere with arachidonic acid metabolism, thus disrupting platelet function (Zaragoza et al., 2022). Tannins exert antiplatelet effects through their antioxidant properties and inhibition of reactive oxygen species (ROS) production in platelets. They also increase antioxidant enzyme levels and prevent protein modification due to oxidative stress (Marcinczyk et al., 2022). The tannin content in plant extracts has been positively correlated with antiplatelet activity (Wiyono et al., 2018), indicating that higher tannin concentrations result in stronger antiplatelet effects. Therefore, quantification of tannin levels in katang-katang extracts is essential.

Additionally, the unique and relatively unexplored coastal environment of North Lombok presents an opportunity to investigate variations in the bioactive compound content of katang-katang. One method commonly used to determine antiplatelet activity in natural products is the ADP-induced platelet aggregation assay. This study aims to identify the qualitative presence of secondary metabolite compounds, quantify total tannin content, and evaluate the antiplatelet activity of the katang-katang plant using ADP induction methods.

MATERIALS AND METHODS

Materials

The materials used in this study include $AlCl_3$ p.a (Merck), amyl alcohol p.a (Merck), anhydrous acetic

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acid p.a (Merck), aspilet tablet, chloroform p.a (Merck), concentrated H_2SO_4 p.a (Merck), concentrated HCl p.a (Merck), Dragendorff reagent, ethanol 96%, $FeCl_3$ 5%, Folin-Ciocalteu reagent, tannic acid standard, gelatin 5%, HCl 2 Nildu, Katang-katang (*Ipomoea pes-caprae*) leaf and stem dry powder, Mayer Reagent, Mg powder, Na_2CO_3, Platelet Poor Plasma (PPP), Platelet Rich Plasma (PRP) sodium acetate 1 M, sodium citrate 3.2%, syringe 22, Wagner Reagent, Whole Blood sample (Inclusion criteria included healthy adult volunteers aged 18–40 years with normal blood pressure, glucose, and lipid levels, non-smokers, and not currently on any medication. Volunteers were selected regardless of gender, but with moderate and stable physical activity levels (no recent intense exercise or physical stress).

Tools

The tools used in this study include 1000 uL micropipette (Dragonlab), analytical balance (Ohauss), dehydrator, hot plate (Labnet), UV-Vis spectrophotometry, vacuum rotary evaporator (Heidolph).

Method

***Ipomoea pes-caprae* determination**

The katang-katang plant (*Ipomoea pes-caprae*) collected from Pemenang Beach, North Lombok Regency, was taxonomically identified as *Ipomoea pes-caprae* at the Advanced Biology Laboratory, Faculty of Mathematics and Natural Sciences, University of Mataram.

Extraction of *Ipomoea pes-caprae*

The leaves and stems of *Ipomoea pes-caprae* were extracted using the maceration method with a sample-to-solvent ratio of 1:10, utilizing 96% ethanol as the solvent. The maceration process was conducted for 24 hours with two replications, accompanied by occasional stirring. After 24 hours, the extract was filtered using mori cloth and subsequently evaporated using a vacuum rotary evaporator at 45 °C. The remaining liquid macerate was further dried using a hotplate at 40 °C to obtain a thick extract. This extract was then analyzed both qualitatively and quantitatively, and evaluated for secondary metabolite activity.

Phytochemical screening

Alkaloid test

Qualitative test of alkaloids used three reagents consisting of Dragendorff, Mayer, and Wagner reagents. A 0.1 g of thick extract was dissolved into 10 mL of 96% ethanol. The extract solution was heated on a hotplate for 2 minutes. Then, the extract solution was made and put into three different test tubes (Ananta et al., 2024). Each tube was filled with 3 mL of extract solution and added with 1 mL of 2 N HCl. Tube I was added 2-3 drops of Mayer reagent with positive results of white precipitate formation. Tube II added 2-3 drops of Wagner's reagent with positive results of orange-to-brown precipitate formation. Tube III added 2-3 drops of Dragendorff reagent with positive results of orange precipitate formation (Harahap, 2023). Qualitative positive results of alkaloids were indicated by positive results in two of the three experiments (Meigaria et al., 2016).

Flavonoid test

0.1 g of thick extract and 10 mL of 96% ethanol were combined in a beaker. In addition, 1 mL of concentrated HCl, 1 mL of amyl alcohol, and magnesium powder were added. The extract solution was thoroughly shaken (Ananta et al., 2024). The appearance of red, yellow, or orange color in the amyl alcohol layer indicates that this extract containds flavonoids (Zahra et al., 2021).

Tannin test

Qualitative tannin test used 5% FeCl3 reagent and 10% gelatin. A 0.1 g of thick extract was dissolved with 10 mL of 96% ethanol. The extract solution was divided into 2 test tubes. In tube I were given 5 drops of 5% FeCl3 reagent and positive results were marked by a color change to dark blue or greenish black (Puspitasari et al., 2013). Tube II was given drops of 10% gelatin and positive results were characterized by forming a white precipitate (Astarina et al., 2013).

Saponin test

A 0.1 g of concentrated extract was mixed with 10 mL of ethanol and boiled with water at 100°C for five minutes. The filtrate was collected and used as the test solution. In a closed test tube, the filtrate was agitated for ten seconds and left for ten minutes. A 1 mL of 2 M HCl developed the foam after shaking. When a steady foam forms for 30 seconds and has a 1-3 cm height, it indicates that the extract contains saponins (Padmasari et al., 2013; Marami et al., 2021)

Total tannin test

Preparation of saturated sodium carbonate

A total of 37 g of sodium carbonate was dissolved in distilled water. A 100 mL volumetric flask was filled with the solution and then distilled water was added to finish the capacity. Several minutes were spent vortexing the solution.

Preparation of standard solution and concentration series

A 100 mL of distilled water was mixed with 10 milligrams of tannic acid to achieve a 100 µg/mL concentration (Ryanata et al., 2015). The stock solution

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was diluted into 5 series of 20, 40, 60, 80, and 100 µg/mL.

Determination of maximum wavelength

One mL of a standard solution containing 20 µg/mL was combined with 7.5 mL of distilled water and 0.5 mL of Folin-Ciocalteu reagent (Kurniawati et al., 2024). One milliliter of saturated sodium carbonate was added after the solution had stood for three minutes (Pratama et al., 2019) and then incubated for 15 minutes. The absorbance was measured in the 400-800 nm range (Pratama et al., 2019). The maximum lambda was determined at the highest absorbance.

Preparation of standard curve

Each concentration series was taken up to 1 mL and combined with 7.5 mL of distilled water and 0.5 mL of Folin- Ciocalteu reagent. After standing for 3 minutes, 1 mL of saturated sodium carbonate was added and incubated for fifteen minutes. The absorbance was determined using the highest wavelength. The linear regression equation and standard curve were created by plotting the concentration and absorbance data onto a curve.

Determination of sample tannin content

A 0.5 g of the extract was weighed and then dissolved in 10 mL of distilled water. One milliliter of the solution was extracted and combined with 0.5 milliliters of Folin-Ciocalteu reagent and 7.5 milliliters of distilled water. After letting the solution stand for three minutes, one milliliter of saturated sodium carbonate was added. After that, it was incubated once again for fifteen minutes. The highest wavelength attained was used to measure the absorbance. Three replications of the measurement were made. The regression equation was used to compute the levels.

Antiplatelet activity

Preparation of whole blood, platelet rich plasma (PRP), and platelet poor plasma (PPP)

The samples used were Whole Blood, Platelet Rich Plasma (PRP), and Platelet Poor Plasma obtained from volunteers with inclusion criteria are normal blood pressure, glucose levels, and blood cholesterol. PRP was prepared by taking blood samples from the veins of the arms of healthy volunteers. A total of 20 mL of blood was transferred into a centrifuge tube containing 3 mL of 3.2% sodium citrate. The blood was centrifuged for 15 min at 1000 rpm. The upper plasma layer was carefully separated. The plasma layer is PRP (Platelet Rich Plasma). The remaining blood in the centrifuge tube was again centrifuged for 15 minutes at 3500 rpm. The upper plasma layer was carefully separated. The plasma layer is PPP (Platelet Poor Plasma). PPP was used as a blank (Lubis, 2015).

Preparation of aspirin stock solution

A mortar and pestle were used to grind the 80 mg aspilet (aspirin tablet). Up to 25 milligrams of powdered aspirin pill was weighed. After that, a 25 mL volumetric flask was filled with it. After adding distilled water to the maximum, the mixture was homogenized for ten minutes using a sonicator set at 35°C (Wijayanti et al., 2022).

Preparation of ADP (adenosine diphospate) 5 uM

In a 5 mL volumetric flask, 0.125 mL of ADP (Adenosine Diphospate) was dissolved with 5 mL of pure water, and then homogenized using a vortex mixer. Prior to usage, the solution was kept in the refrigerator (Wijayanti et al., 2022).

Preparation of katang-katang (*Ipomoea pes-caprae*) extract solution

Four concentration series—250, 500, 1000, and 2000 µg/mL —were created from the extract solution. 50 mg of the thick extract was weighed and then dissolved with a small amount of distilled water until the limit was reached in a 25 mL volumetric flask. A vortex mixer was used to homogenize the mixture. A 2000 µg/mL of the extract solution was diluted to 1000, 500, and 250 µg/mL. In a 5 mL volumetric flask, each dilution was pipetted in accordance with the calculation and mixed with distilled water until the limit was reached.

Antiplatelet activity test

PPP, as much as 3 mL was used as a blank, aspirin 0.4 mL: PRP 1.8 mL was positive control, distilled water 0.4 mL: PRP 1.8 mL was negative control, while each series contained 0.4 mL of test solution: PRP 1.8 mL were the test solutions. All of them were homogenized using a vortex for 3 minutes and measured using UV-VIS spectrophotometry at 600 nm. This absorbance result was the absorbance before ADP administration. Then positive control, negative control, and concentration series solution were each added 0.08 mL of ADP and incubated for 10 minutes in an incubator at 37°C. All of them were measured absorbance using UV-Vis spectrophotometry at 600 nm. The result of the absorbance was the absorbance after ADP administration (Lubis, 2015).

Data analysis

Data were obtained by measuring absorbance values before and after the addition of ADP to calculate the percentage of platelet aggregation. The percentage of platelet aggregation inhibition was determined by comparing the negative control group with the treatment

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groups, which included the positive control (aspirin) and the Katang-katang stem and leaf extracts. Statistical analysis was conducted using SPSS, which included the Shapiro–Wilk test for normality, Levene's test for homogeneity of variance, one-way ANOVA, and Tukey's HSD post hoc test. The IC_{50} value was determined through linear regression analysis between the logarithm of extract concentrations and the mean percentage of platelet aggregation inhibition. The formulas used to calculate the percentage of platelet aggregation and its inhibition are presented below:

$$\%\ platelet\ aggregation = 1 - \frac{B}{A} x\ 100\% \quad \ldots\ldots\ldots\ldots\ldots 1)$$

Notes:

A = Absorbance before the addition of ADP

B = Absorbance after the addition of ADP

$$\%\ platelet\ aggregation\ inhibition = \frac{A-B}{A} x\ 100\% \ldots\ldots (2)$$

Notes

A = Persentase agregasi platelet pada kontrol negatif (%)

B = Persentase agregasi platelet pada kelompok perlakuan (%)

IC_{50} calculation

The IC_{50} values were calculated using linear regression analysis between the logarithm of concentration and the percentage of platelet aggregation in the stem and leaf extracts of *Ipomoea pes-caprae*. The log concentrations were obtained by applying a logarithmic transformation to the concentration data. These two variables were then plotted to produce a linear graph. From the linear regression analysis, the R^2 value and the regression equation were obtained. This equation was subsequently used to determine the IC_{50} values by setting y to 50, from which the corresponding x value representing the IC_{50} of each extract was derived.

RESULTS AND DISCUSSION

Results

Extracts yield

Based on the data in Table 1, the 96% ethanol extract of *Ipomoea pes-caprae* leaves yields 20,63%, while the stem extract only reaches 10,09%.This yield is calculated from the ratio of the weight of the extract to the weight of the initial dry plant.The leaf extract is produced from 300 g of dry plant into 61.91 g of extract, while the stem with an initial weight of 213 g of dry plant yields 21.491 g of extract.

Tabel 1. Ethanolic extracts of leaf and stem *Ipomoea pes-caprae* yields

No.	Extract Name	Dry plant weight (g)	Extract Weight (g)	Yield (%)
1	Ethanol extract of katang-katang leaves (*Ipomoea pes-caprae*)	300	61.9	20,63%
2	Ethanol extract of katang-katang stems (*Ipomoea pes-caprae*)	213	21.5	10,09%

Table 2. Phytochemical screening results for the 96% ethanol extract of *Ipomoea pes-caprae*

Testing		Leaf extract			Stem extract		
		Results	Interpretation	Result Image	Results	Interpretation	Result Image
Alkaloid	Dragendorff	Orange-colored sediment	(+)		Orange-colored sediment	(+)	
	Mayer	white precipitate	(+)		white precipitate	(+)	
	Wagner	Brownish-red sediment	(+)		Brownish-red sediment	(+)	
Tannin	FeCl 5%	Dark greenish color	(+)		Dark greenish color	(+)	
	Gelatin 10%	white precipitate	(+)		white precipitate	(+)	

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Flavonoid	Brick red color	(+)		Brick red color	(+)	
Saponin	A stable foam not form for 15-20 minutes.	(-)		A stable foam not form for 15-20 minutes	(-)	

Information:
(+) = positive contains compounds
(-) = negative contains compounds

Phytochemical screening

The results of the phytochemical screening of 96% ethanol extracts of the leaves and stems of *Ipomoea pes-caprae* in Table 2 show that both types of extracts contain various bioactive compounds.The alkaloid test using Dragendorff, Mayer, and Wagner reagents showed positive results, indicated by the formation of orange precipitates, white precipitates, and reddish-brown precipitates, both in the leaf and stem extracts.Tannin content was also detected in both extracts, indicated by a color change to dark green when tested with 5% $FeCl_3$ solution and the formation of a white precipitate with 10% gelatin. The flavonoid test showed positive results with the formation of a brick-red color, while the saponin test not produced stable foam for 15–20 minutes, which was also confirmed negative in both leaf and stem extracts.

Tannic acid standard curve

The standard curve data of tannic acid from 20 to 100 µg/mL shows a positive relationship between concentration and absorbance value, in accordance with the Beer-Lambert Law principle. At a concentration of 20 µg/mL, the absorbance recorded was 0.177, then gradually increased to 0.443 at 100 µg/mL. This increase indicates that the higher the concentration of tannic acid, the more light is absorbed by the solution.

Table 3. Tannic acid standard curve 20 to 100 µg/mL

Concentration (µg/mL)	Absorbance
20	0.177
40	0.250
60	0.318
80	0.407
100	0.443

The results of the linear regression from the standard curve of tannic acid show a very strong relationship between the concentration of tannic acid (20–100 µg/mL) and the absorbance value.The obtained regression equation is y = 0.0034x + 0.1128, with a coefficient of determination (R^2 = 0.9881).The R^2 value close to 1 (98.81%) indicates that 98.81% of the variation in absorbance can be explained by changes in tannic acid concentration, while the remaining 1.19% may be due to experimental factors such as measurement errors or minor variations in sample preparation.

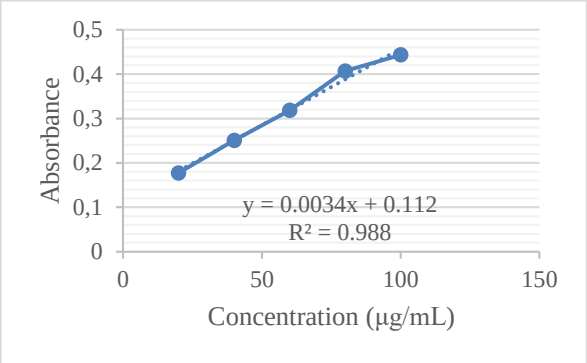

Figure 1. Tannic acid standard curve graph

Determination of total tannin content

The data on tannin content in the leaf and stem extracts of *Ipomoea pes-caprae* show a significant difference between the two parts of the plant.Based on three replications, the leaf extract has an average tannin content of 4.02 ± 0.02 mgEAT/g, while the stem extract has an average tannin content of 3.673 ± 0.168 mgEAT/g.The absorbance values of the leaf samples in the three replicates were very consistent (0.799; 0.797; 0.794), resulting in stable tannin levels (4.04; 4.02; 4.00 mgEAT/g).The low standard deviation (±0.02) indicates high precision in the measurements.There is greater variation in the absorbance of the stem samples across the three replicates (0.755; 0.754; 0.705), especially in the third replicate which is lower.This causes the tannin content to vary (3.78; 3.76; 3.48 mgEAT/g) with a relatively high standard deviation (±0.17), indicating instability or external factors affecting the results.The tannin content in the leaves (4.02 mgEAT/g) is 9.4% higher than in the stems (3.67 mgEAT/g).

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Platelet aggregation data

The results of the platelet aggregation test in Table 5 show that the positive control (aspirin 1000 µg/mL) had the lowest aggregation value, at 2.15% ± 1.15, while the negative control (aquadest) showed a high aggregation value of 9.34% ± 2.03. In the stem extract of *Ipomoea pes-caprae*, aggregation decreased with increasing concentration, from 5.08% ± 1.80 at 250 µg/mL to 1.98% ± 0.91 at 2000 µg/mL. A similar pattern was observed in the leaf extract, where aggregation decreased from 6.17% ± 0.73 at 250 µg/mL to 1.21% ± 0.50 at 2000 µg/mL. Overall, both leaf and stem extracts exhibited concentration-dependent inhibition of platelet aggregation, with leaf extracts showing greater inhibition than stem extracts at the same concentration.

Platelet aggregation inhibiton data

The results of the platelet aggregation inhibition test in Table 6 showed that the positive control (aspirin 1000 µg/mL) produced an inhibition of 77.26% ± 12, while the negative control (aquadest) showed no inhibition activity (0%). In the stem extract of *Ipomoea pes-caprae*, the percentage of inhibition increased with the concentration, from 46.07% ± 15.34 at 250 µg/mL to 79.51% ± 5.50 at 2000 µg/mL. Similarly, in the leaf extract, the inhibition of aggregation increased from 32.80% ± 8.90 at 250 µg/mL to 85.90% ± 7.78 at 2000 µg/mL. Overall, the leaf extract showed a higher percentage of inhibition compared to the stem extract at concentrations of 1000 µg/mL and 2000 µg/mL, indicating a stronger potential for antiplatelet activity in the leaf extract.

Table 4. Tannic content in leaves and stems extract of *Ipomoea pes-caprae*

Sample	Replication	Absorbance	Tannin Concentration (µg/mL)	Tannin Content (mgEAT/g)	Mean Tannin Content (mgEAT/g) ± SD
Leaves	1	0.799	202.03	4.04	4.02 ± 0.02
	2	0.797	201.5	4.02	
	3	0.794	200.44	4	
Stems	1	0.755	189.09	3.78	3.67 ± 0.17
	2	0.754	188.88	3.76	
	3	0.705	174.29	3.48	

Table 5. Platelet aggregation data for the 96% ethanol leaf and stem extract of *Ipomoea pes-caprae*

Groups	Concentration (µg/mL)	Mean Platelet Agregation (%) ± SD
Positive Control	1000	2.15 ± 1.15
Negative Control	-	9.34 ± 2.03
Stem	250	5.08 ± 1.78
	500	4.28 ± 1.24
	1000	3.16 ± 1.28
	2000	1.98 ± 0.91
Leaf	250	6.17 ± 0.73
	500	3.13 ± 0.36
	1000	1.83 ± 0.63
	2000	1.21 ± 0.50

Table 6. Platelet aggregation inhibition data for the 96% ethanol leaf and stem extract of *Ipomoea pes-caprae*

Groups	Concentration (µg/mL)	Mean Platelet Agregation Inhibition (%) ± SD
Positive Control	1000	77.26 ± 12
Negative Control	-	0
Stem	250	46.07 ± 15.34
	500	53.66 ± 13.51
	1000	66.79 ± 10.21
	2000	79.51 ± 5.5
Leaf	250	32.8 ± 8.9
	500	65.69 ± 6.23
	1000	79.31 ± 8.94
	2000	85.9 ± 7.78

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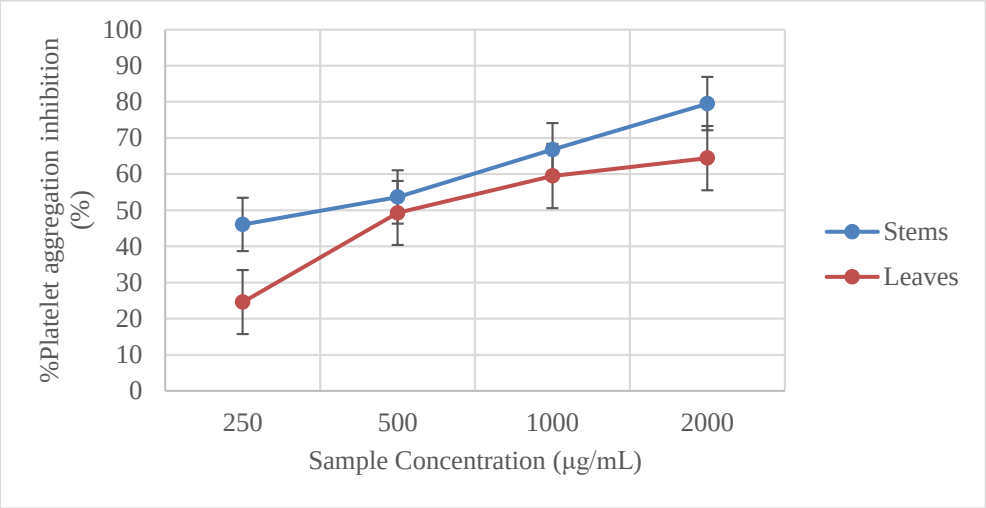

Figure 2. Graph of sample concentration vs % platelet aggregation inhibition from leaf and stem extracts of katang-katang (*Ipomoea pes-caprae*)

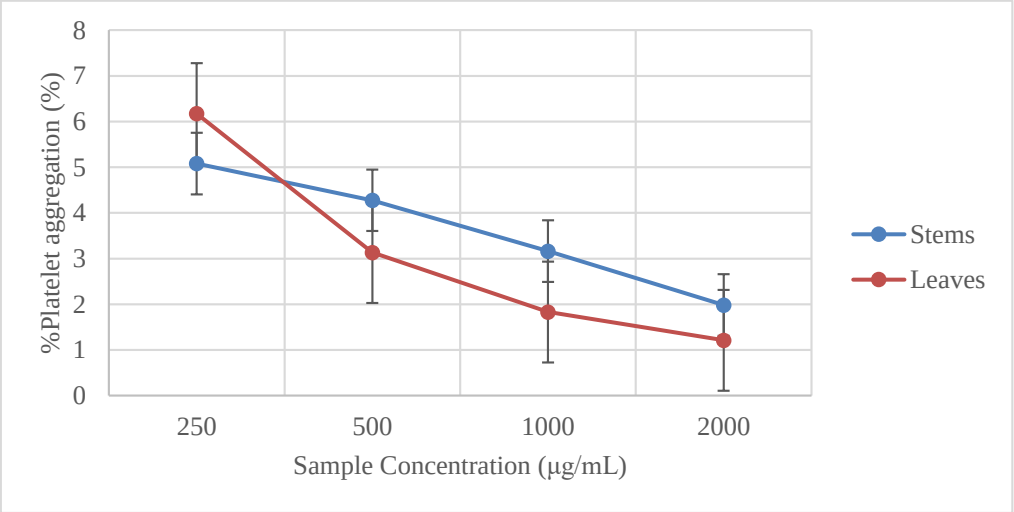

Figure 3. Graph of sample concentration vs % platelet aggregation from leaf and stem extracts of katang-katang (*Ipomoea pes-caprae*)

Graph of concentration vs response

The graph of the relationship between the concentration of leaf and stem extracts of *Ipomoea pes-caprae* and the percentage of platelet aggregation inhibition shows an interesting pattern. At a concentration of 250 µg/mL, the stem extract provided an inhibition of 46.07%, while the leaf extract only showed 24.60%, indicating that the stem is more effective at lower doses. However, this trend changes with increasing concentration. At 500 µg/mL, the inhibition of the stem extract increased to 53.66%, while the leaf extract reached 49.26%, indicating a narrowing difference. A significant increase was observed at a concentration of 1000 µg/mL, where the leaf extract showed the highest inhibition at 79.51%, far surpassing the stem extract which was only 66.79%. This confirms that the leaf extract has greater potential as an anti-platelet aggregation agent at the optimal dose. However, at the highest concentration (2000 µg/mL), the inhibition of the leaf extract decreased to 64.43%, while the stem extract remained stable at 64.43%. This decrease in the leaf extract may be due to the toxic effects of active compounds or receptor saturation at excessively high concentrations.

The graph of the relationship between the concentration of leaf and stem extract samples of *Ipomoea pes-caprae* and the percentage of platelet aggregation shows a trend of decreasing aggregation with increasing concentration, indicating a stronger inhibitory effect. At a concentration of 250 µg/mL, the stem extract resulted in platelet aggregation of 6.17%, while the leaf extract was more effective with an

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aggregation of 5.08%. Increasing the concentration to 500 µg/mL enhances this effect: stem aggregation decreases to 4.28%, and leaf aggregation reaches 3.16%. At a concentration of 1000 µg/mL, both extracts showed a significant decrease in aggregation. The stem extract reached 3.13%, while the leaf extract was superior with an aggregation of 1.98%. This trend continues at the highest concentration (2000 µg/mL), where the stem extract recorded an aggregation of 1.83%, while the leaf extract showed the lowest value, which is 1.21%.

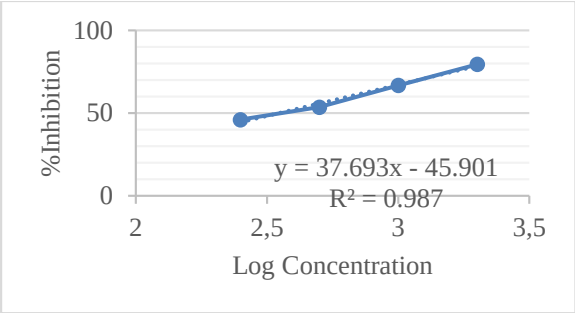

Figure 3. Linear regression curve of log concentration vs %inhibition of platelet aggregation of the stem sample of katang-katang (*Ipomoea pes-caprae*)

The results of the linear regression in Figure 3, which analyzes the relationship between the log concentration of *Ipomoea pes-caprae* stem extract and the percentage of platelet aggregation inhibition, show a very strong relationship. The obtained regression equation is $y = 37.693x - 45.901$, with a coefficient of determination ($R^2 = 0.987$). The R^2 value approaching 1 (98.7%) indicates that 98.7% of the variation in % inhibition can be explained by changes in log concentration, while the remaining 1.3% may be influenced by other factors or experimental error. The slope (37.693) indicates that for every increase of 1 unit in log concentration, the percentage of platelet aggregation inhibition increases by 37.693%. Meanwhile, the intercept (–45.901) represents the theoretical inhibition value when the log concentration is 0 (concentration of 1 µg/mL), although this value is not practically relevant because it falls outside the range of the tested data.

The linear regression analysis in Figure 4, which examines the relationship between the log concentration of *Ipomoea pes-caprae* leaf extract and the percentage of platelet aggregation inhibition, yields the equation $y = 43.087x - 73.333$ with a coefficient of determination ($R^2 = 0.8923$). This R^2 value indicates that 89.23% of the variation in % inhibition can be explained by changes in log concentration, while the remaining 10.77% may be influenced by other factors such as biological variation or measurement error. The positive slope (43.087) shows that for every 1-unit increase in log concentration, platelet aggregation inhibition increases by 43.087%. However, the negative intercept (–73.333) has no practical significance because it falls outside the tested concentration range (250–2000 µg/mL).

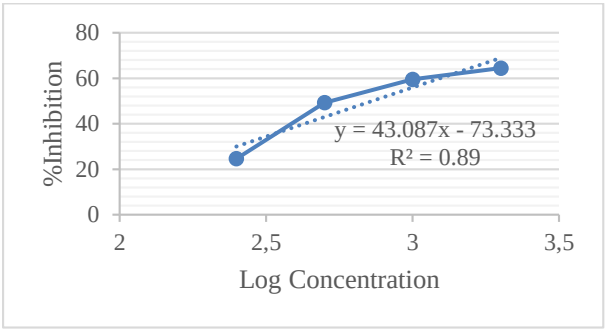

Figure 4. Linear regression curve of log concentration vs %inhibition of platelet aggregation of the leaf sample of katang-katang (*Ipomoea pes-caprae*)

Statistical analysis

The results of the Shapiro-Wilk normality test on the stem and leaf samples of *Ipomoea pes-caprae* indicate that all data groups do not significantly deviate from a normal distribution, with p-value (Sig.) values above 0.05. In the stem samples, the p-value ranged from 0.173 (500 µg/mL) to 0.772 (250 µg/mL), while in the leaf samples, the p-value was more homogeneous, ranging from 0.385 (250 µg/mL) to 0.556 (2000 µg/mL). The control group (+) also meets the normality assumption with a p-value of 0.689.

The results of the Levene's homogeneity test show that the data on the percentage of platelet aggregation inhibition in the stem extract (Sig. = 0.56) and leaves (Sig. = 0.78) have homogeneous variances (p-value > 0.05). This meets the basic assumption for One-Way ANOVA analysis, so the ANOVA results can be considered valid. In the stem extract, the One-Way ANOVA results yielded Sig. = 0,23 (< 0.05), indicating a significant difference in the effects of platelet aggregation inhibition among the concentrations (250, 500, 1000, 2000 µg/mL). In other words, the increase in the concentration of the stem extract statistically significantly affects the percentage of inhibition. On the other hand, in the leaf extract, the One-Way ANOVA results showed Sig. = 0.00 (< 0,05), which means there is a significant difference in the inhibition effect of platelet aggregation between concentrations. Statistically, the leaf samples can affect platelet antiaggregation activity.

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Table 11. Tukey HSD post hoc test for the stem extract sample of katang-katang (*Ipomoea pes-caprae*)

Test Groups	p-value	Interpretation
C (+) vs B1	0.054	Not significantly different
C (+) vs B2	0.179	
C (+) vs B3	0.809	
C (+) vs B4	0.999	
B1 vs B2	0.928	
B1 vs B3	0.272	
B1 vs B4	0.038	Significantly different
B2 vs B3	0.662	Not significantly different
B2 vs B4	0.127	
B3 vs B4	0.686	

Table 12. Tukey HSD post hoc test for the leaf extract sample of katang-katang (*Ipomoea pes-caprae*)

Test Groups	p-value	Interpretation
C (+) vs D1	0.001	Significantly different
C (+) vs D2	0.540	Not significantly different
C (+) vs D3	0.998	
C (+) vs D4	0.763	
D1 vs D2	0.008	Significantly different
D1 vs D3	0.001	
D1 vs D4	<0.001	
D2 vs D3	0.395	Not significantly different
D2 vs D4	0.113	
D3 vs D4	0.891	

Discussion

Phytochemical screening

This study used dry powder derived from the leaves and stems of Katang-katang (*Ipomoea pes-caprae*), obtained from fresh samples collected at Pemenang Beach, North Lombok Regency. After the extraction process, the yield of the leaf and stem extracts was determined by comparing the weight of the extract obtained to the weight of the dry plant used. Extract yield refers to the ratio of the dry weight of the extract to the amount of raw material utilized. A higher yield indicates a greater concentration of compounds extracted from the raw material (Senduk et al., 2020). As shown in Table 1, the extract yields from the leaves and stems of Katang-katang were 20.63% and 10.09%, respectively. According to Farmakope Herbal Indonesia (Kemenkes RI, 2017), a good extract should have a yield greater than 10%. Thus, both extracts meet the quality standard for yield.

However, the difference in yield between the two extracts may be attributed to anatomical differences between the samples. Leaves, as the main photosynthetic organ, are rich in secondary metabolites, comprising approximately 83–88% of their content (Destailleur et al., 2021). The parenchyma tissue in the leaves stores these metabolites and facilitates their extraction by ethanol, which can penetrate and disrupt cell walls, thereby enhancing the release of secondary compounds (Yulianti et al., 2020). Moreover, ethanol's polarity allows it to extract both polar and non-polar compounds (Karepu et al., 2020). In contrast, the stem contains more structural tissue dominated by lignin and cellulose. Although most lignin can dissolve in pure ethanol, the presence of water in the solvent—such as in 96% ethanol, which contains 4% water—reduces the amount of lignin that can be dissolved (Tindall et al., 2020).

Phytochemical screening was performed on both extracts to detect the presence of alkaloids, tannins, steroids/triterpenoids, flavonoids, and saponins, as summarized in Table 2. The results showed that both extracts contain secondary metabolites such as alkaloids, tannins, and flavonoids, while saponins were not detected.

Alkaloids in both extracts were identified using Dragendorff's, Mayer's, and Wagner's reagents. Dragendorff's reagent forms a precipitate through the coordination of potassium ions (K^+) with alkaloids, resulting in potassium-alkaloid complexes (Sangkal et al., 2020). Mayer's reagent similarly produces a

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precipitate by forming a potassium-alkaloid complex via the interaction between K^+ ions and nitrogen atoms within the alkaloid structure (Wardhani & Supartono, 2015). Wagner's reagent also forms a potassium-alkaloid complex through coordination bonds between K^+ ions and alkaloid nitrogen atoms (Adhariani et al., 2018).

Tannins were detected through the addition of 5% $FeCl_3$ and 5% gelatin. The phenolic groups in tannins react with $FeCl_3$ to form a dark-colored triscianoferric (III) complex (Desinta, 2015; Ananta et al., 2024). Meanwhile, gelatin reacts with tannins to form stable, water-insoluble copolymers, leading to the crystallization of proteins and the formation of a white precipitate (Lestari et al., 2024).

Flavonoids were identified using the Shinoda test, which involves the addition of magnesium powder and concentrated HCl. Concentrated HCl hydrolyzes O-glycosides by replacing the glycosidic group with protons due to its electrophilic nature, while magnesium reduces the flavonoid carbonyl group, allowing it to form complexes. The addition of amyl alcohol facilitates the development of a colored complex or precipitate, confirming the presence of flavonoids (Ananta et al., 2024).

Total tanin test

The determination of total tannin content in the leaf and stem extracts of *Ipomoea pes-caprae* (katang-katang) was conducted using an in vitro method. Tannic acid was used as the standard, as it represents a hydrolyzable form of tannin and is commonly found in most aerial parts of plants (Safitri et al., 2023; Maharani et al., 2022). Tannic acid is a natural polyphenolic compound that contains phenolic hydroxyl and carboxyl groups, and shares structural similarities with tannins found in plants (Basri et al., 2023).

The standard tannic acid solution and the sample extracts were reacted with the Folin–Ciocalteu reagent, which forms a blue-colored complex due to the interaction between phenolic compounds and the molybdenum-tungsten components of the reagent. Since the formation of this blue complex requires an alkaline environment, sodium carbonate was added to the reaction mixture (Riyanti et al., 2023). Once the reaction was complete, the absorbance of the colored solution was measured using a UV-Vis spectrophotometer.

To determine the maximum wavelength, the absorbance of the sample was scanned in the range of 400–800 nm. The maximum absorbance for tannic acid was found at 650 nm. A standard curve was generated using five concentration series (20, 40, 60, 80, and 100 µg/mL) prepared by diluting a stock solution of 1000 µg/mL. Each concentration was reacted with the reagents and its absorbance was measured at 650 nm. From the absorbance versus concentration data, the linear regression equation obtained was $y = 0.0034x + 0.1128$, with a correlation coefficient (r) of 0.994, indicating strong linearity (Karim et al., 2021). To determine whether the obtained correlation coefficient (R) from the regression is statistically significant, the degrees of freedom (df) were calculated as $n - 2$, where n represents the number of data points. In this study, five concentration levels of tannic acid were used (20, 40, 60, 80, and 100 µg/mL), resulting in $n = 5$, and thus $df = 3$. Referring to the Pearson correlation significance table, the critical value of r at df = 3 for a two-tailed test at the 0.05 significance level is 0.8783. The calculated correlation coefficient $r = 0.994$ exceeds the critical value, indicating a statistically significant linear relationship between tannic acid concentration and absorbance. This confirms that the standard curve exhibits a valid and reliable linearity for further quantification analysis.

For the sample measurements, 500 mg of each extract (leaf and stem) was dissolved in 10 mL of distilled water. The resulting solution was reacted with the Folin–Ciocalteu reagent and incubated for 15 minutes to allow the reaction to stabilize (Riyanti et al., 2023). Each sample was analyzed in triplicate. The absorbance values obtained from the samples were then plotted into the standard regression equation to calculate the total tannin content in the extracts.

In Table 3, five concentration levels of tannic acid (20, 40, 60, 80, and 100 µg/mL) were used to construct the standard curve. The selection of these concentrations was intended to minimize potential errors that could affect the accuracy of the regression line. As the concentration of tannic acid increases, the absorbance also increases, due to the compound's ability to absorb ultraviolet light measured by the spectrophotometer (Kriechbaum & Bergstrom, 2020).

As shown in Figure 1, the standard curve of tannic acid exhibits a linear relationship with an R^2 value of 0.9881, and a linear regression equation of $y = 0.0034x + 0.1128$. The R^2 value indicates a strong linear correlation, as a good correlation coefficient generally ranges from 0.7 to 0.99 (Gupta et al., 2024). The closer the R^2 value is to 1, the more accurate the linearity of the regression model becomes. This linear regression equation was then used to determine the total tannin content in the sample extracts.

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The calculation of total tannin content is based on the tannin concentration derived from the regression equation, the volume of the solution, the dilution factor, and the weight of the extract. The results are expressed in mg EAT/g (milligrams of tannic acid equivalent per gram), indicating the amount of tannin in the sample equivalent to a certain amount of pure tannic acid.

Based on Table 4, the average tannin content in the leaf extract was 4.02 mg EAT/g, while the stem extract contained 3.673 mg EAT/g. This difference reflects the variation in tannin compound distribution between the plant organs. Although tannins are generally present in various plant parts, including leaves, fruits, bark, and stems (Suhaenah et al., 2024), the higher lignin content in stems compared to leaves can inhibit the extraction efficiency. Since the solvent used is less effective at dissolving lignin, less tannin is extracted from the stems than from the leaves.

Antiplatelet activity in vitro

The antiplatelet activity of the leaf and stem extracts of Katang-katang (*Ipomoea pes-caprae*) was evaluated using the in vitro ADP-induced platelet aggregation method with UV-Vis spectrophotometry (Wijayanti et al., 2022). ADP (adenosine diphosphate) is a platelet agonist that induces changes in platelet shape and promotes aggregation, playing a key role in the formation of thromboxane A2 (Jin et al., 2002). ADP contributes to primary platelet aggregation by interacting with specific surface receptors, leading to platelet activation, morphological changes, aggregation, thromboxane A2 formation, and granule release (Puri & Colman, 1997; Daniel et al., 1998). The in vitro antiplatelet testing method with ADP induction serves as an initial approach to determine the antiplatelet activity of katang-katang extract (*Ipomoea pes-caprae*), thus providing a foundation for future katang-katang antiplatelet research.

Fresh blood samples (20 mL) were collected from human volunteers who met the inclusion criteria. The positive control used was aspilet (1 mg/mL), containing aspirin, a COX-1 inhibitor that suppresses thromboxane A2 synthesis, thereby inhibiting platelet aggregation. Distilled water served as the negative control.

Sodium citrate was added to the blood samples as an anticoagulant. It functions by chelating calcium ions, thereby preventing the formation of thrombin, which is necessary for converting fibrinogen to fibrin during the coagulation process. Sodium citrate also stabilizes erythrocytes and maintains blood integrity for up to 4 hours post-collection. From the blood samples, PRP (Platelet-Rich Plasma) and PPP (Platelet-Poor Plasma) were prepared. PRP contains a high concentration of platelets, while PPP contains relatively few. The platelet aggregation response was measured using a UV-Vis spectrophotometer. ADP serves to induce platelet activation and aggregation (Wijeyeratne & Heptinstall, 2011). The leaf and stem extracts of *Ipomoea pes-caprae* are expected to exhibit inhibitory effects on platelet aggregation in response to ADP stimulation.

The parameters assessed in this study were the percentage of platelet aggregation and the percentage of platelet aggregation inhibition. Platelet aggregation refers to the adhesion and clumping of platelets, which play a crucial role in hemostasis during vascular injury. Aggregation is typically induced by agonists such as adenosine diphosphate (ADP) and collagen, which are present at the injury site (Rumbaut et al., 2010).

The percentage of platelet aggregation was calculated using Formula 1, based on the change in turbidity of the blood sample during the aggregation process. Prior to aggregation, platelets are uniformLy suspended in the plasma, causing the sample to appear turbid and resulting in high absorbance due to limited light transmission. As aggregation occurs, the platelets clump together, reducing turbidity and increasing light transmission, which leads to lower absorbance readings. ADP functions as an aggregation inducer by promoting platelet adhesion and aggregate formation.

The percentage of platelet aggregation inhibition was calculated using Formula 2, which quantifies the reduction in aggregation in treated samples compared to the negative control. As shown in Table 4, platelet aggregation increased with increasing extract concentrations, suggesting that the leaf and stem extracts exert inhibitory effects on platelet aggregation in a concentration-dependent manner.

The positive control, aspirin at a concentration of 1 mg/mL, exhibited a significantly lower platelet aggregation value compared to the negative control. This outcome is consistent with the known antiplatelet properties of aspirin, which functions by inhibiting the cyclooxygenase-1 (COX-1) enzyme, thereby reducing the synthesis of thromboxane A_2, a key mediator of platelet aggregation. Aspirin exerts its antiplatelet effect primarily through the irreversible inhibition of cyclooxygenase-1 (COX-1) by acetylating the serine residue at its active site. This modification leads to a substantial reduction in prostaglandin biosynthesis. In platelets, COX-1 is not rapidly regenerated due to the lack of a nucleus, and thus, its enzymatic activity can only be restored through the formation of new platelets. As a result, aspirin significantly impairs the synthesis of

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thromboxane A_2, prostaglandin E_2, and prostacyclin (PGI_2), all of which play critical roles in platelet aggregation and vasoconstriction. This inhibition ultimately disrupts normal hemostatic function by diminishing the capacity for platelet-driven coagulation (Ornelas et al., 2017). The platelet aggregation value obtained for the positive control was 2.1506%, substantially lower than that of the negative control. Correspondingly, the percentage inhibition of platelet aggregation reached 77.261%. This high inhibition value reflects the potent mechanism of aspirin in suppressing platelet activity, validating its role as an effective antiplatelet agent in this in vitro model.

The negative control group exhibited the highest platelet aggregation among all groups, as it only received distilled water, which lacks antiplatelet properties. Conversely, Table 5 demonstrates that the percentage of platelet aggregation inhibition increased with concentration in both the leaf and stem extract groups. Notably, the 2000 µg/mL concentrations of both extracts exhibited higher inhibition percentages than the positive control (aspirin), suggesting that *Ipomoea pes-caprae* leaf and stem extracts may have potential as potential candidate for further antiplatelet.

Based on Figure 2, the inhibition of platelet aggregation by the stem extract was greater than that of the leaf extract. This may be due to the higher baseline aggregation observed in the stem extract group, resulting in greater inhibition values, as illustrated in Figure 3.

The half-maximal inhibitory concentration (IC_{50}) is a widely used and informative measure of a drug's efficacy, representing the concentration required to inhibit a biological process by 50%. It serves as an important indicator of the potency of an antagonist drug in pharmacological research (Aykul & Martinez-Hackert, 2016). In this study, IC_{50} values were determined using the logarithm of extract concentrations and their corresponding percentages of platelet aggregation inhibition. Transforming concentration data into logarithmic form facilitates comparison of dose-response curves and provides a more manageable scale at low concentrations, where responses change rapidly (Yartsev, 2015).

The regression equation for the stem extract was $y = 37.693x + 45.901$ with an R^2 value of 0.982, while the leaf extract yielded $y = 43.087x – 73.333$ with an R^2 of 0.8923. Based on these models, the IC_{50} values calculated from Tables 8 and 10 were 349.945 µg/mL for the stem extract and 772.779 µg/mL for the leaf extract. According to these results, the stem extract exhibits moderate inhibitory potency, whereas the leaf extract shows lower potency.

The observed differences in antiplatelet activity between the stem and leaf extracts are likely influenced by the varying composition of secondary metabolite compounds present in each plant part. Although the total tannin content was found to be higher in the leaves (4.02 ± 0.02 mgEAT/g) compared to the stems (3.673 ± 0.16773 mgEAT/g), this does not necessarily correlate directly with greater biological activity. It is possible that the stems contain other bioactive compounds with more potent antiplatelet effects than tannins. This suggests that while tannins are present in higher amounts in the leaves, the primary contributors to platelet aggregation inhibition may be other secondary metabolites that are more abundant or more active in the stems. Compounds such as alkaloids and flavonoids have been previously reported to exhibit antiplatelet activity and may play a significant role in this effect (Ain et al., 2016; Zaragoza et al., 2022). When compared to aspirin, which has an IC_{50} of 4.45 µg/mL (24.7 µM), both katang-katang extracts demonstrate significantly lower antiplatelet activity, indicating lower efficacy relative to this standard drug.

Statistical analysis

Statistical analysis was conducted using SPSS software to evaluate the platelet aggregation inhibition activity of *Ipomoea pes-caprae* leaf and stem extracts, alongside a positive control (aspirin). Normality and homogeneity tests confirmed that all data sets were normally distributed and had equal variances ($p \geq 0.05$; Tables 11 and 12).

One-Way ANOVA revealed a significant difference in platelet aggregation inhibition between the stem and leaf extracts ($p \leq 0.05$; Table 12). Subsequent Post Hoc Tukey HSD tests for the stem extract (Table 13) indicated no significant differences between most concentration groups ($p > 0.05$), except for a significant increase in inhibition at 2000 µg/mL (B4) compared to 250 µg/mL (B1) ($p = 0.038$). The mean difference of -33.45% demonstrates a statistically higher inhibition of platelet aggregation at 2000 µg/mL relative to the lowest tested concentration.

In contrast, the leaf extract showed more distinct differences among concentration groups (Table 12). The positive control (C (+)) significantly inhibited platelet aggregation more than the 250 µg/mL group (D1) ($p = 0.001$), with a mean difference of 44.47%. No statistically significant difference was observed between the positive control and the higher concentrations of 500

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μg/mL (D2), 1000 μg/mL (D3), and 2000 μg/mL (D4) ($p > 0.05$).

Within the leaf extract concentrations, 250 μg/mL (D1) was significantly less effective than 500 μg/mL (D2), 1000 μg/mL (D3), and 2000 μg/mL (D4) ($p < 0.05$). The largest inhibition increase was observed between 250 μg/mL and 2000 μg/mL (-53.10%), indicating a dose-dependent enhancement of platelet aggregation inhibition. However, no significant differences were detected among the higher concentration groups (D2 vs D3, D2 vs D4, D3 vs D4), suggesting a saturation effect where inhibition plateaus beyond 500 μg/mL.

These findings indicate that both stem and leaf extracts of *Ipomoea pes-caprae* exhibit significant antiplatelet activity in a concentration-dependent manner, with maximal inhibitory effects reached at higher concentrations. The stem extract showed a more gradual dose-response, while the leaf extract achieved near-maximal inhibition at concentrations above 500 μg/mL.

Study limitations

The antiplatelet activity test was conducted as a preliminary in vitro screening using ADP-induced platelet aggregation, observed through turbidity changes via UV-Vis spectrophotometry. This method is adapted from Lubis (2015) and Wijayanti et al. (2022), and while it offers a simplified model, it does not replace the precision of aggregometry-based assessments. Further validation using standard aggregometry is required to confirm the findings. This study provides early-stage insights into the potential antiplatelet activity of *Ipomoea pes-caprae* extracts. However, future studies using aggregometry, in vivo models, and different agonists are necessary for more accurate and conclusive results.

CONCLUSION

The study demonstrated that ethanol extracts from the leaf and stems of *Ipomoea pes-caprae* (Katang-katang) from North Lombok contain bioactive compounds, including alkaloids, flavonoids, and tannins. The leaf exhibited higher tannin content (4.02 mgEAT/g) than the stems (3.67 mgEAT/g). Both extracts showed antiplatelet activity with IC_{50} value 349.95 μg/mL for stem extract and 727.78 μg/mL for leaf extract of katang-katang (*Ipomoea pes-caprae*), indicating moderate inhibitory potency. These results suggest preliminary potential of *I. pes-caprae* as a natural antiplatelet agent; however, comparison with aspirin IC_{50} and further pharmacological evaluations are needed to validate its therapeutic relevance.

Further studies are required to determine the IC_{50} value of the positive control (aspirin) to validate the method, followed by in vivo antiplatelet activity tests using animal models. Comprehensive safety assessments including acute and subchronic toxicity, as well as pharmacokinetic and pharmacodynamic profiling in appropriate dosage forms, are essential prior to therapeutic exploration.

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AUTHOR CONTRIBUTIONS

Conceptualization, I.H.; Methodology, M.N.F.A., L.H.H., M.I.F.; Software, I.H.; Validation, L.H.H.; Formal Analysis, M.N.F.A., I.H.; Investigation, M.I.F.; Resources, L.H.H.; Data Curation, M.N.F.A.; Writing - Original Draft, M.N.F.A.; Writing - Review & Editing, N.I.H., R.H., D.S.; Visualization, M.I.F.; Supervision, I.H.; Project Administration, I.H.; Funding Acquisition, I.H.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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