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The Potency of *Ipomoea pes-caprae* Leaf Extract From North Lombok on Antiplatelet Activity in Balb/C Mice Strain

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ABSTRAK

Agen antiplatelet banyak digunakan untuk pencegahan sekunder gangguan serebrovaskular untuk mengurangi risiko stroke, tetapi penggunaannya dikaitkan dengan efek samping seperti perdarahan dan resistensi obat. Oleh karena itu, pengembangan agen antiplatelet baru, termasuk yang berasal dari produk alami, diperlukan. Ekstrak daun *I. pes-caprae* telah menunjukkan aktivitas antiplatelet yang lebih kuat daripada batang secara in vitro, dengan konsentrasi penghambatan 727,78 µg/mL. Penelitian ini bertujuan untuk mengevaluasi efek agregasi antiplatelet ekstrak daun *I. pes-caprae* dengan menilai waktu perdarahan dan pembekuan. Sebuah studi eksperimental dilakukan dengan menggunakan tikus Balb/C yang dibagi menjadi kelompok kontrol positif (aspirin 80 mg), kelompok kontrol negatif, dan kelompok perlakuan yang menerima ekstrak daun *I. pes-caprae* dengan dosis 20, 40, 80, 100, dan 120 mg/kg berat badan. Waktu perdarahan dan pembekuan diukur sebelum pengobatan (D0) dan sembilan hari setelah pemberian ekstrak (D9). Hasilnya tidak menunjukkan perbedaan yang signifikan secara statistik dalam waktu perdarahan antara kelompok kontrol positif dan yang diobati dengan ekstrak pada dosis apa pun. Namun, waktu perdarahan meningkat secara signifikan pada tikus yang menerima dosis ekstrak 40, 80, dan 100 mg/kg berat badan dibandingkan dengan kontrol negatif ($p < 0,05$). Perpanjangan waktu pembekuan yang signifikan diamati pada dosis 100 mg/kg berat badan dibandingkan dengan kontrol negatif ($p < 0,05$). Kesimpulannya, ekstrak daun *I. pes-caprae* meningkatkan waktu perdarahan dan pembekuan, dengan efek yang paling menonjol pada berat badan 100 mg/kg, menunjukkan potensinya sebagai agen antiplatelet alami.

Kata kunci: Antiplatelet, Waktu pendarahan, Waktu pembekuan, I. pes-caprae, *In Vitro*

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ABSTRACT

Antiplatelet agents are widely used for the secondary prevention of cerebrovascular disorders to reduce stroke risk, but their use is associated with adverse effects such as bleeding and drug resistance. Therefore, the development of novel antiplatelet agents, including those derived from natural products, is necessary. I. pes-caprae leaf extract has demonstrated stronger antiplatelet activity than the stem in vitro, with an inhibition concentration of 727.78 µg/mL. This study aimed to evaluate the antiplatelet aggregation effect of I. pes-caprae leaf extract by assessing bleeding and clotting time. An experimental study was conducted using Balb/C mice divided into a positive control group (aspirin 80 mg), a negative control group, and treatment groups receiving I. pes-caprae leaf extract at doses of 20, 40, 80, 100, and 120 mg/kg body weight. Bleeding and clotting times were measured before treatment (D0) and nine days after extract administration (D9). The results showed no statistically significant difference in bleeding time between the positive control and extract-treated groups at any dose. However, bleeding time was significantly increased in mice receiving extract doses of 40, 80, and 100 mg/kg body weight compared to the negative control ($p < 0.05$). A significant prolongation of clotting time was observed at a dose of 100 mg/kg body weight compared to the negative control ($p < 0.05$). In conclusion, I. pes-caprae leaf extract increases bleeding and clotting times, with the most pronounced effect at 100 mg/kg body weight, indicating its potential as a natural antiplatelet agent.

Keywords: *Antiplatelet, Bleeding time, Clotting time, I. pes-caprae, In Vitro*

INTRODUCTION

Stroke is a leading cause of death and long-term disabilities (Krishnamurthi et al., 2017). According to the Basic Health Research (Riskesdas), the prevalence of stroke in Indonesia has increased from 7 to 10.9 per 1,000 population (Fadhilah et al., 2020). Antiplatelet therapy can reduce the risk of recurrent stroke attacks by 13-22%. However, antiplatelet therapy has the side effect of bleeding. Studies in Central Asia have shown that bleeding due to the use of antiplatelet aspirin and clopidogrel occurs in 16.6% of cases, with 82.1% of them experiencing intracranial bleeding (Awada et al., 2019).

The high risk of bleeding due to antiplatelet therapy has led to the development of antiplatelet agents from natural ingredients. Researchers have widely studied and tested natural ingredients from various regions and countries as potential antiplatelet agents. The natural product Rhus verniciflua contains urushiol, isomaltol, and pentagalloyl, which inhibit arachidonic acid, adenosine diphosphate (ADP), and collagen, which induce platelet aggregation and platelet receptors (Kim & Park, 2019).

Indonesia has a wealth of natural

ingredients, especially in coastal areas of West Nusa Tenggara (NTB), which have medicinal plants such as *katang-katang* or morning glory (*I. pes-caprae* L.). Empirically, residents and tourists have widely used this plant to treat jellyfish or sea urchin stings (Andayani & Hardiyanti, 2018). A preliminary study conducted by Hunaifi et al. (2025) reported that *I. pes-caprae* leaves showed antiplatelet activity in vitro by inhibiting adenosine diphosphate (ADP) (Hunaifi et al., 2025). Therefore, in vivo studies on the antiplatelet activity of *I. pes-caprae* leaves are urgently needed. This study aimed to evaluate the extract's antiplatelet aggregation effectiveness using bleeding and blood clotting time as parameters.

RESEARCH METHODS

a. Materials:

Laboratory experimental research with a pre- and post-test control group design. The research sample used was Balb/c strain mice with inclusion criteria of male sex, weight 20-30 grams, age 3-4 months, and body and tail in good health, while exclusion criteria included mice that died during the study, diarrhea, tail wounds, or lesions. *I. pes-caprae* leaf from Pemenang Beach, North Lombok Regency, was taxonomically identified as *I. pes-caprae* at the Advanced Biology Laboratory, Faculty of Mathematics and Natural Sciences, University of Mataram. The Medical Faculty and Health Sciences University of Mataram Ethics Committee approved this study (No. 096/UN18.F8/ETIK/2025).

b. *I. pes-caprae* Leaf Extract Procedure:

I prepared the I. pes-caprae leaf extract by weighing the simplicia powder and extracting it using the maceration method with 96% ethanol at a 1:7.5 ratio. I left the extraction for 24 hours with two replications. The extraction filtrate is evaporated using a rotary evaporator at 45 °C until a thick extract is obtained (Hunaifi et al., 2025).

c. Sample Grouping and Treatment:

The research sample of 35 mice strain Balb/c was divided into 7 groups: positive control (K+) with aspilet 80 mg, negative control (K-) with CMC-Na, and five treatment groups with *I. pes-caprae* leaf extract doses of 20 (D1), 40 (D2), 80 (D3), 100 (D4), and 120 (D5) mg/kgBW. Treatment was administered for 9 days by oral gavage. Figure 1 shows the experimental design.

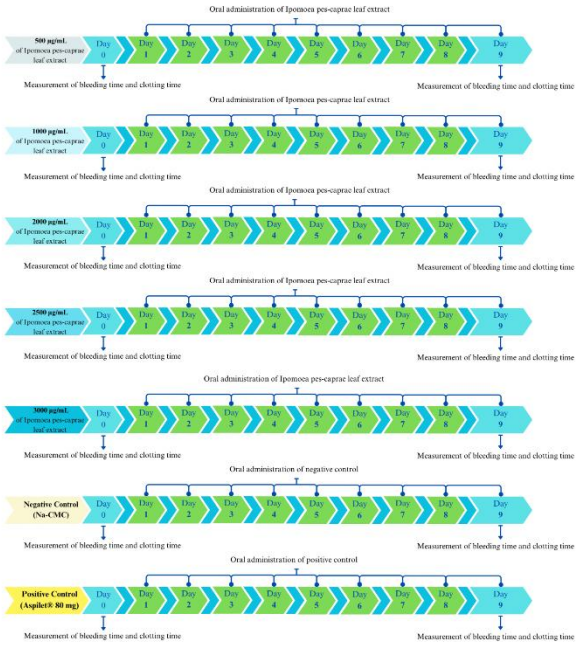


Figure 1. The Experimental Design and Study Timeline

Bleeding and clotting time were measured on days 0 and 9 by drawing blood from the tip of the mice's tails. Blood was taken by cleaning the tail with alcohol and injuring the base end of the tail by 2 mm. When the blood comes out, the stopwatch and the filter paper are placed on the blood droplets. When the bleeding stops, the bleeding time is recorded (Putri et al., 2014). Meanwhile, blood clotting time is measured by placing blood on a prepared glass. The blood is then examined by touching it and slowly pulling it with a needle until fibrin threads appear, indicating clotting. When the blood clots, the time is stopped, and the blood clotting time is recorded (Bain & Briggs, 2017).

d. Phytochemical Test Using LC-HRMS:

The compounds in *I. pes-caprae* leaf extract were analyzed using LC-Q-TOF-MS on the Waters Acquity SDS. The column type was ACQUITY UPLC BEH C18 (1.7µM) with serial number 04633408725164, and column temperatures were 15.2ºC and 40ºC, respectively. Table 1 shows the gradient system for the mobile phases.

Table 1. The Gradient System of Mobile Phases

Time	Mobile phase	
	A (%)	B (%)
Initial	95.0	5.0
10.00	10.0	90.0
13.00	10.0	90.0
13.10	95.0	5.0
16.00	95.0	5.0

Keterangan :
(A). Formic acid 0.1% in H_2O
(B). Acetonitrile

The Q-TOP-MS system was operated in ESI positive mode [H+1] ionization. The Q-TOP-MS was set to a source temperature of 140 °C, a gas flow of 50.0 L per hour, a capillary voltage of 0.50 kV, and a mass range of 50.0–1200.0 m/z.

e. Data Analysis:

All data were analyzed using GraphPad Prism version 9. The normality of the data distribution was assessed using the Shapiro–Wilk test. Data are presented as mean ± standard deviation (SD). The antiplatelet potential activity of *I. pes-caprae* was analyzed using *one-way*

ANOVA, *Friedman Test,* and *Post Hoc Test*. Results were statistically significant if $p < 0.05$.

RESULTS AND DISCUSSION

Bleeding time is a clinical laboratory test that evaluates platelet function by measuring how long it takes the body to stop bleeding after trauma in the laboratory. This involves making a standard incision and measuring the time until bleeding stops. This test measures hemostasis (Ismail et al., 2024; Russeau et al., 2023). Bleeding time measures the interaction between platelets and vascular walls during coagulation (Putri et al., 2014). Long bleeding times indicate reduced platelet aggregation due to cyclooxygenase inhibition, which lowers thromboxane A2 levels. Reduction of thromboxane A2 leads to vasodilation, prolonged bleeding, and a higher risk of bleeding (Rucker & Dhamoon, 2022). Clotting time is defined as the duration from the onset of clot formation to the point at which fibrin polymers are first produced, typically measured until the clotting curve amplitude reaches 2 mm above baseline (Burton & Jandrey, 2020). Clotting time measures how long it takes to form a clot.

a. Bleeding time

Bleeding time reflects platelet adhesion and aggregation in vivo. Prolongation of bleeding time reflects inhibition of platelet hemostasis due to platelet activation pathways (Amirou et al., 2023). Based on Figure 1, baseline measurements (day 0) showed no significant differences between the experimental groups, indicating similar initial hemostatic conditions before treatment. After 9 days of repeated administration of *I. pes-caprae* leaf extract, there was a significant increase in bleeding time ($p<0.0156$) between groups. These findings support an antiplatelet-dependent effect, as indicated by prolonged bleeding time, suggesting antiplatelet potential through inhibition of platelet aggregation in primary hemostasis (Chen et al., 2014). This effect suggests that bioactive components in plant extracts provide sustained systemic exposure, allowing effective modulation of platelet function by inhibiting platelet aggregation (Lamponi et al., 2021).

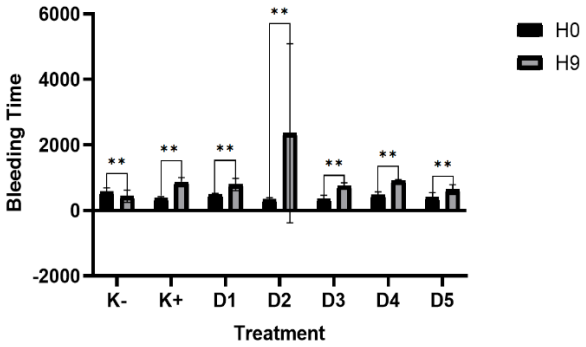


Figure 1. Effect of *I. pes-caprae* leaf extract on bleeding time in mice measured before treatment (H0) and after 9 days

Figure 2 shows the comparison of bleeding times between groups. Bleeding time on day 9 showed significant differences between the treatment groups, as indicated by one-way ANOVA results (p

< 0.0056), indicating that *I. pes-caprae* leaf extract significantly extended bleeding time at doses of 40 (D2), 80 (D3), and 100 (D4) mg/kg BW compared to the negative control group. Meanwhile, the highest dose differed significantly from the positive control, aspirin (p<0.0222), which decreased bleeding time.

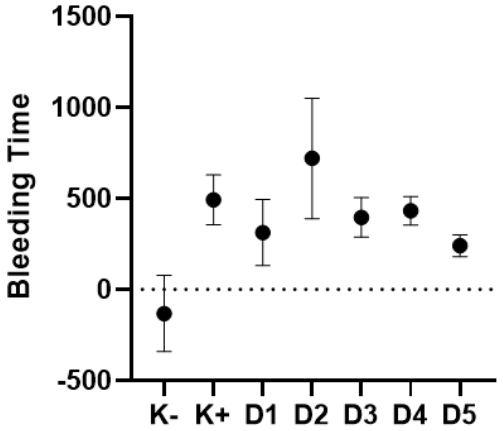


Figure 2. Effect of *I. pes-caprae* leaf extract on bleeding time after 9 days of treatment

b. Clotting Time

Results showed comparable clotting time among all experimental groups at baseline (Day 0). However, after 9 days of administration, the blood clotting time was much longer in mice given *I. pes-caprae* leaf extract than in the negative control group. The bidirectional ANOVA showed a significant effect (p < 0.0001) on Day 9 compared to Day 0, confirming an increase in the time-dependent anticoagulant effect.

The clotting time reflects the efficiency of the intrinsic and extrinsic coagulation pathways. Extended clotting time after administration of *I. pes-caprae* leaf extract indicates disturbances in coagulation factor activation or thrombin formation, which may synergise with the antiplatelet effects observed in the bleeding time test (Lamponi et al., 2021). This may occur due to the effect of *I. pes-caprae* leaf extract at several doses, as shown in Figure 3.

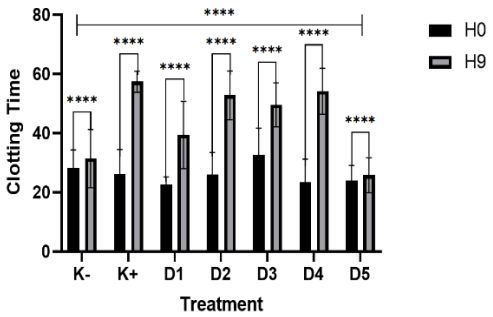


Figure 3. Effect of *I. pes-caprae* leaf extract on bleeding time in mice measured before treatment (H0) and after 9 days (H9).

Results on day 9 for coagulation time, illustrated in Figure 4, showed a significant difference between treatment groups (p<0.05), with I. pes-caprae extract extending clotting time at a dose of 100 (D4) mg/kg BW compared with the negative control group and comparable to the aspirin-given group. More details can be seen in Tabel S1.

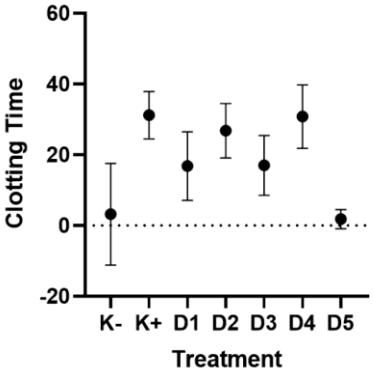


Figure 4. Effect of *I. pes-caprae* leaf extract on clotting time after 9 days of treatment

The increased clotting time with I. pes-caprae extract at 100 mg/kg BW indicates that this dose is more effective at modulating the coagulation pathway. A similar phenomenon was observed in the clotting time of the methanol extract (raw), as well as the hexane and ethyl acetate fractions of C. crepidioides, which were significantly longer ($p<0.05$) at 10 mg/mL than at 20 mg/mL (Ayodele et al., 2019).

c. Analysis of active compounds

The result of LC-Q-TOF-MS showed 84 compounds detected in *I. pes-caprae* leaf extract (Figure 5), but only 45 compounds could be identified in the extract (Table S1). The compounds could not be identified because their mass spectra did not match any reference spectra available in the MS database. Several compound groups were identified, including phenolics, flavonoids, alkaloids, terpenoids, steroids, unsaturated fatty acids, and saturated fatty acids. Stearidonic acid, classified as an unsaturated fatty acid, was the most abundant compound in *I. pes-caprae* extract (Figure 6). Stearidonic acid has been reported to exhibit antiplatelet activity by inhibiting thrombin, collagen, and AA-induced platelet aggregation. Stearidonic acid was also shown to affect endogenous arachidonate oxygenation triggered by low-dose thrombin stimulation (Kockmann et al., 1989). Many alkaloids, steroids, and terpenoid compounds were also found in the *I. pes-caprae* leaf extract, but their antiplatelet activity has not yet been investigated.

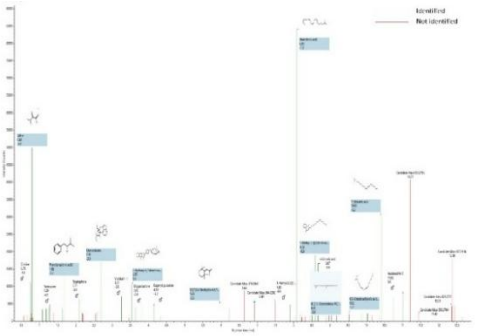


Figure 5. Total Ion Chromatograph (TIC) of *I. pes-caprae* leaf extract

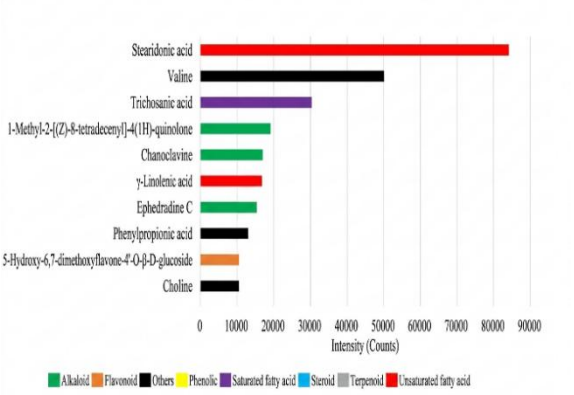


Figure 6. The top ten compounds in *I. pes-caprae* leaf extract

Flavonoids can impede platelet aggregation by blocking the release of arachidonic acid mediators from cell

membranes, thereby inhibiting the cyclooxygenase metabolic pathway (Putri et al., 2014). Flavonoids demonstrate considerable fibrinolytic activity, the mechanism of dissolving blood clots. Flavonoids can influence fibrinogen, altering its activity or concentration. Research indicates that flavonoids such as epicatechin and epigallocatechin gallate can interact with fibrinogen, affecting its activity and possibly its involvement in clot formation and dissolution. Additionally, flavonoids derived from several plant sources have exhibited thrombolytic action in vitro. For example, extracts from plants such as Madras Nelli (*Phyllanthus maderaspatensis*) and Homalomena aromatica have exhibited substantial clot-lysing effects, comparable to or surpassing those of conventional thrombolytic agents like streptokinase (Amin et al., 2025). The 5-Hydroxy-6,7-dimethoxyflavone-4'-O-β-D-glucoside was the highest flavonoid compound detected in *I. pes-caprae* leaf extract. The aglycon of this compound was reported to have antiplatelet aggregation activity in vitro (Chen et al., 2007).

Aspirin is a non-steroidal anti-inflammatory drug that has antiplatelet activity. This drug is used to treat cardiovascular diseases. Aspirin irreversibly acetylates the enzyme cyclooxygenase-1 (COX-1) in platelets, inhibiting the synthesis of thromboxane A2, an aggregation agent (Undas et al., 2007; Doutremepuich et al., 2012). Aspirin consistently prolongs bleeding time (Mielke, 1982). Even at low doses, aspirin increases the risk of bleeding. The incidence rate of this bleeding varies with the individual's underlying bleeding risk (Whitlock et al., 2016). In the Dominica study, aspirin significantly reduced platelet aggregation ($p < 0.05$) in male Balb/c mice (Dominica, 2007). Another study by Nasirotuzahroh & Susanti showed that aspirin increased bleeding time compared with a control group that did not receive aspirin (Nasirotuzahroh & Susanti, 2023).

The findings of this study indicate that the ethanol extract of *I. pes-caprae* leaves exhibits in vivo antiplatelet activity, as evidenced by significant increases in both bleeding time and clotting time in male Balb/c mice following a 9-day administration period. This observation reinforces previous in vitro results demonstrating the extract's capability to inhibit platelet aggregation via the ADP pathway. This potential suggests that I. pes-caprae could emerge as a viable candidate for a natural antiplatelet agent, which may help prevent cardiovascular diseases linked to thrombus formation. However, because it prolongs bleeding time, this extract must be

used with caution, with careful attention to safety and optimal therapeutic dosage. Further investigations are needed to identify the active compounds, elucidate the molecular mechanisms in detail, and evaluate its safety and efficacy through toxicological assessments and clinical trials before it can be considered for medical use.

CONCLUSION

I. pes-caprae leaf extract has potential antiplatelet activity by affecting bleeding time and clotting time in Balb/C Mice Strain with dose of 100 mg/kg BW. The antiplatelet effect of *I. pes-caprae* leaf extract was attributed to the presence of flavonoid bioactive compounds identified in the extract, such as chlorogenic acid, stearidonic acid, γ-linoleic acid, and derivatives of kaempferol and quercetin

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