VOLUME 12 NOMOR 2 DECEMBER 2025 ISSN 2548 – 611X

JURNAL
BIOTEKNOLOGI & BIOSAINS INDONESIA

Homepage Jurnal: http://ejournal.brin.go.id/JBBI/index

MORINGA OLEIFERA LEAF AS A POTENTIAL ANTITHROMBOTIC AGENT: AN IN VITRO EVALUATION

Evaluasi Potensi Daun Kelor (*Moringa oleifera*) sebagai Agen Antitrombosis *In Vitro*

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ABSTRACT

Cardiovascular disease (CVD) is a major cause of morbidity and mortality worldwide, one of which is triggered by an imbalance between fibrin formation and fibrinolysis processes, leading to fibrin accumulation that can lead to thrombosis. Commercial thrombolytic agents are currently widely used, but their use is known to cause serious side effects often and have limited effectiveness. This gap encourages initial screening of natural materials as an effort to explore the potential of new thrombolytic agents in the future. This study aims to evaluate the potential of *Moringa oleifera* leaf filtrate at concentrations of 25%, 50%, 75%, and 100% as an antithrombotic agent through qualitative identification of secondary metabolites and testing of thrombolytic activity and anticoagulant ability in vitro. The results showed that Moringa leaf filtrate at a concentration of 25% was able to lyse blood clots by 60%, compared to the positive control nattokinase (82%), with a relative effectiveness of 71.7%. In vitro anticoagulant activity testing showed an extension of blood clotting time from 10 minutes (control) to 35 minutes in the treatment. ANOVA analysis showed a significant difference between concentrations ($p < 0.05$). These findings support the initial potential of this natural product as a candidate antithrombotic agent and provide a scientific basis for further research.

Keywords: *Antithrombosis, Anticoagulant, Cardiovascular, Moringa oleifera, Clot lysis*

ABSTRAK

Penyakit kardiovaskular (Cardiovascular Disease, CVD) merupakan penyebab utama morbiditas dan mortalitas di dunia, salah satunya dipicu oleh ketidakseimbangan antara pembentukan fibrin dan proses fibrinolysis menyebabkan akumulasi fibrin yang dapat menimbulkan trombosis. Agen trombolitik komersial saat ini telah banyak digunakan, namun diketahui penggunaannya sering menimbulkan efek samping serius dan memilki keterbatasan efektivitas. Kesenjangan ini mendorong dilakukannya skrining awal terhadap bahan alam sebagai upaya eksplorasi potensi agen trombolitik baru di masa mendatang. Penelitian ini bertujuan untuk mengevaluasi potensi filtrat daun kelor (*Moringa oleifera*) pada konsentrasi 25%, 50%, 75%, dan 100% sebagai agen antitrombosis, melalui identifikasi kualitatif metabolit sekunder serta pengujian aktivitas trombolitik dan kemampuan antikoagulan secara in vitro. Hasil menunjukkan filtrat daun kelor konsentrasi 25% mampu melisiskan bekuan darah sebesar 60%, dibandingkan kontrol positif nattokinase (82%) dengan efektivitas relatif sebesar 71,7%. Uji aktivitas antikoagulan in vitro menunjukkan adanya perpanjangan waktu pembekuan darah dari 10 menit (kontrol) hingga 35 menit pada perlakuan. Analisis ANOVA menunjukkan perbedaan yang signifikan antar konsentrasi ($p< 0,05$). Temuan ini mendukung potensi awal bahan alam tersebut sebagai kandidat agen antitrombosis dan memberikan dasar ilmiah bagi penelitian lanjutan.

Kata kunci: *Antithrombosis, Antikoagulan, Kardiovaskular, Moringa oleifera, lisis bekuan*

Received*: 28 September 2025* ***Accepted****: 13 November 2025* ***Published****: 15 December 2025*

INTRODUCTION

Cardiovascular disease (CVD) is a pathological condition characterized by the formation of thrombi/blood clots in veins and arteries. It is a leading cause of death worldwide among degenerative diseases, and the WHO reports that CVD cases claim 17.9 million lives annually (World Health Organization, 2025). A factor influencing the etiology of CVD is an imbalance between fibrin formation and fibrinolysis. This can trigger the formation of intravascular thrombi (abnormal blood clots) that block blood vessels, impeding the flow of nutrients and oxygen to tissues and leading to tissue death (infarction). Disruptions in the fibrinolysis process can also stop thrombi from breaking down as they should (Altaf et al., 2021; Ayanti et al., 2022; Mackman, 2012).

Antithrombolytic agents such as antiplatelet agents, anticoagulants, and fibrinolytics are used to reduce blood clotting activity to prevent thrombus formation or destroy existing thrombi (Broderick et al., 2021; Lichota et al., 2020). Thrombus lysis, or thrombolysis, is crucial in cases of heart attack, myocardial infarction, and stroke. Various commercial antithrombotic agents are widely used today to reduce thrombus formation activity. However, many have been reported to cause numerous side effects, such as immunological (allergic) reactions, lysis of normal blood clots, high cost, low fibrin specificity, risk of gastrointestinal bleeding, and thermolability (Deng et al., 2018; Dubey et al., 2011; Ge et al., 2018; Nailufar et al., 2016). Therefore, preliminary exploration of bioactive compounds from plants is necessary as a natural resource that does not cause side effects and offers greater efficacy (Nuraini et al., 2021; Vos et al., 2016; Yu et al., 2018).

Moringa oleifera leaves, a tropical plant, have been widely reported to contain bioactive compounds such as antibacterial, antioxidant, cardioprotective, anticancer, antipyretic, and immunomodulatory properties (Barhoi et al., 2021; Kumolosasi et al., 2021; Palupi et al., 2021).

Research by (Phil et al., 2022), reported that Moringa flower extract exhibited in vitro thrombolytic activity with a blood clot lysis rate of up to 65% and contained alkaloids, flavonoids, tannins, and saponins. Meanwhile, (Kunwar et al., 2022) reported that Moringa leaf and flower extracts exhibited in vitro clot-dissolving activity of 35–43%, with streptokinase as a positive control (53%) and distilled water as a negative control. However, most of these studies used organic solvents or distilled water, which can affect the stability and observed results of thrombolytic activity. Plants with potential as thrombolytic agents generally contain bioactive compounds/secondary metabolites such as flavonoids, alkaloids, tannins, and saponins (Clements et al., 2020; Saputri et al., 2022). Based on the similarity of the bioactive compounds found in Moringa oleifera leaves to the active compounds in Moringa flowers and other plants known to possess thrombolytic activity.

This study aimed to identify the secondary metabolite content and evaluate the in vitro thrombolytic and anticoagulant activity of Moringa leaf filtrate. To date, no studies have specifically assessed this activity in Moringa leaf filtrate based on physiological solvents, although the leaf is known to be rich in bioactive compounds with thrombolytic potential. In this study, moringa leaf filtrate was prepared using PBS (Phosphate Buffered Saline), which is isotonic and does not cause spontaneous blood clot dissolution. This research is an initial step to explore the potential of moringa leaf filtrate as a natural thrombolytic and anticoagulant agent with potential for further development.

MATERIALS AND METHODS

Preparation of Moringa Leaf Filtrate

Fresh *Moringa oleifera* leaves were collected from Landasan Ulin Banjarbaru and determined at the Basic Laboratory of the Faculty of Mathematics and Natural Sciences, Lambung Mangkurat University. Fresh leaves were washed thoroughly with distilled water and then dried at room temperature for 25 minutes.

A total of 250 grams of fresh Moringa leaves were blended using phosphate buffer solution (PBS) with a ratio of 1:2 (w/v). The mixture was then filtered using a Buchner funnel with the help of a vacuum to obtain the filtrate. The filtrate was stored in a dark bottle in the refrigerator for 1x24 hours

before use. The filtrate obtained had a concentration of 100% (0.5 g/mL). For the purpose of testing the potential activity of thrombolytic agents, the Moringa leaf filtrate was diluted using PBS to obtain final concentrations of 25%, 50%, 75%, and 100% in a total volume of 20 mL each.

Phytochemical Screening

Qualitative phytochemical tests were conducted on the vacuum-filtrated moringa leaf filtrate to identify bioactive compounds. Flavonoids were tested using Shinoda test using magnesium powder and concentrated HCl, alkaloids using Wagner, Dragendorff, and Mayer reagents, saponins using the foam test, and tannins using the $FeCl_3$ reagent (Mondong, 2015; Zaman et al., 2015).

Evaluation of in vitro activity thrombolytic/clot lysis (%)

The in vitro thrombolytic activity was evaluated using the Gravimetric method in accordance with previous research (Akbor et al., 2023; Permatasari et al., 2024; Phil et al., 2022; Prasad et al., 2006). In this study, 500 µL of each moringa leaf filtrate concentration (25%, 50%, 75%, and 100%) was used as the thrombolytic agent. The positive control used was a commercial Nattokinase tablet dissolved in Phosphate Buffered Saline (PBS). Whole blood was drawn from 10 healthy female volunteers with no history of oral contraceptive use or anticoagulant therapy. Informed consent was obtained from all participants. The research protocol was approved by the Research Ethics Committee of STIKES Suaka Insan (Reference No. 208/KEPK-SI/VI/2025).

First, an empty microtube was weighed and its weight was recorded. 500 µL of blood was added to the microtube and incubated at 37°C for 45 minutes (for in vitro clot formation). After 45 minutes, the microtube was centrifuged at 3000 rpm for 5 minutes (to completely remove the serum), and the microtube was weighed again to determine the clot weight (clot weight = weight of the tube with clot - weight of the empty tube). 500 µL of each concentration of moringa leaf filtrate, 500 µL of sterile distilled water (negative control), and 500 µL of Nattokinase (positive control) were added to the microtubes containing the blood clots. All microtubes were incubated at 37°C for 90 minutes. Afterward, the fluid obtained after clot lysis was carefully removed from the tubes using a micropipette, and the tubes were reweighed to determine the weight of the clot after lysis (weight of the microtube with blood clot – weight of the microcentrifuge tube after clot lysis). The difference in clot weight after lysis was expressed as % clot lysis. All experiments were performed in triplicate (Ferdiani et al., 2023; Hidayati et al., 2021a, 2021b; Prasad et al., 2006).

Evaluation anticoagulant activity

In vitro anticoagulant activity was tested using a modified clotting time (CT) method to observe the blood clotting time. The test was conducted using plain glass Vacutainer tubes without additives to avoid disrupting the blood clotting process during the test. A total of 500 µL of Moringa leaf filtrate with concentrations of 25%, 50%, 75%, and 100% was added to each tube, then mixed with 1 mL of blood and homogenized using a roller mixer. A positive control (EDTA blood) and a negative control (blood without any treatment) were also prepared. A stopwatch was started to determine the time until clotting occurred. After 3 minutes, the tube was lifted and tilted to check for coagulation. The normal blood clotting time reference is between 3-18 minutes (Tangkery et al., 2013; Weliyani et al., 2015). All of these steps were then repeated as duplicates.

RESULTS AND DISCUSSIONS

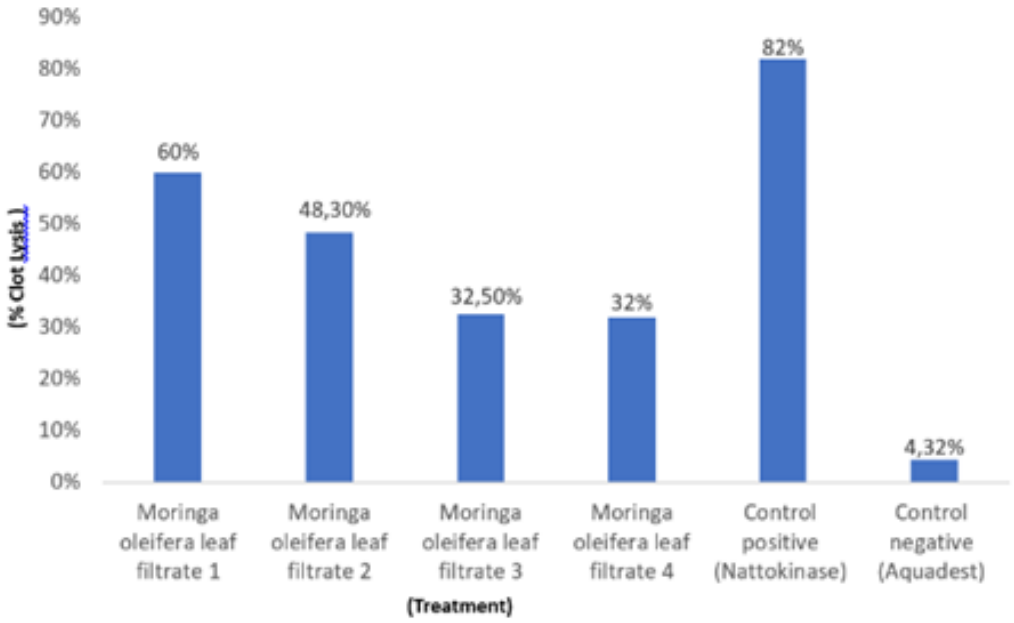
The initial qualitative phytochemical test results of the Moringa leaf filtrate showed that contains alkaloids, flavonoids, saponins, and tannins, as seen in Table 1.

Table 1. Phytochemical Test Results of Moringa *oleifera* Leaf Filtrate

No.	Phytochemical Test	Results
1	Alkaloid:	
	- Mayer's test	Positive
	- Dragendorff's test	Positive
	- Wagner's test	Positive
2	Flavonoid	Positive
3	Safonin	Positive
4	Tanin	Positive

Based Table 1, the Moringa leaf filtrate contains secondary metabolites such as alkaloids, flavonoids, tannins, and saponins. These findings are consistent with previous research identifying that moringa leaves are rich in flavonoids, tannins, saponins, and alkaloids (non-enzymatic compounds), each with various pharmacological activities (Iriani et al., 2023; Panova et al., 2025; Saputri et al., 2022).

A visual representation of the clot lysis results in the respondent's blood specimens treated with moringa leaf filtrate is shown in Figure 2. When 100 µL of distilled water was added to the negative control (K-) blood clot, the observed clot lysis showed that the distilled water did not affect in vitro thrombolysis and could be considered negligible. Thrombolytic agents function to increase blood flow by inhibiting platelet aggregation or preventing thrombus formation. The use of Nattokinase as a positive control serves to determine whether the thrombolytic activity of the studied moringa leaves can lyse blood clots in vitro, similar to a commercial thrombolytic agent. Nattokinase can break down blood clots by directly hydrolyzing fibrin and plasmin substrates, converting endogenous prourokinase to urokinase (uPA), degrading PAI-1 (plasminogen activator inhibitor-1), and increasing tissue plasminogen activator (t-PA), which supports fibrinolytic activity (Weng et al., 2017). The mean % clot lysis of moringa leaf filtrate (gravimetric) at concentrations of 25%, 50%, 75%, and 100%, as well as the positive and negative controls, are shown in Graphic 1.



Graphic 1. In vitro clot lysis activity of moringa leaf filtrate at concentrations of 25%, 50%, 75%, and 100%, Nattokinase, and Distilled Water

Based on Graphic 1, the mean results of the thrombolytic activity test show that the fresh moringa leaf filtrate at concentrations of 25%, 50%, 75%, and 100% positively demonstrated the ability to lyse blood clots. The highest mean % clot lysis was achieved by the 25% concentration of moringa leaf filtrate, at 60%. The data indicates that the 25% concentration exhibited the highest clot lysis activity, which subsequently decreased as the filtrate concentration increased. This finding suggests that moringa leaf filtrate has fibrin degradation capabilities, but its activity is still much lower compared to Nattokinase, which is a potent fibrinolytic agent.

The results of this in vitro study indicate that Moringa leaf filtrate has initial anticoagulant and thrombolytic activity, likely related to its secondary metabolites, namely flavonoids, alkaloids, tannins, and saponins. Although this research does not clarify the specific mechanisms, several previous studies have reported that these compounds can influence both coagulation and fibrinolytic pathways through various means. Flavonoids, for example, have been reported to inhibit platelet aggregation and reduce thrombin enzyme activity, as well as increase tissue plasminogen activator (tPA) activity, which plays a role in fibrin dissolution. They also inhibit thrombin activity and fibrin formation in vitro studies (Marchelak et al., 2023). Flavonoids may be useful as coadjuvants in the treatment of cardiovascular pathologies (Zaragozá et al., 2022). Alkaloids can inhibit the activation of coagulation factors such as factor X and thrombin, while tannins can chelate calcium ions necessary for fibrin formation. The pharmacological properties of single and specific saponins are reported with antithrombotic, antiplatelet aggregation, and anticoagulation effects, which can reduce Ca^{2+} in platelets and reduce platelet aggregation (Kim & Park, 2019; Mieres-Castro & Mora-Poblete, 2023; Olas et al., 2020).

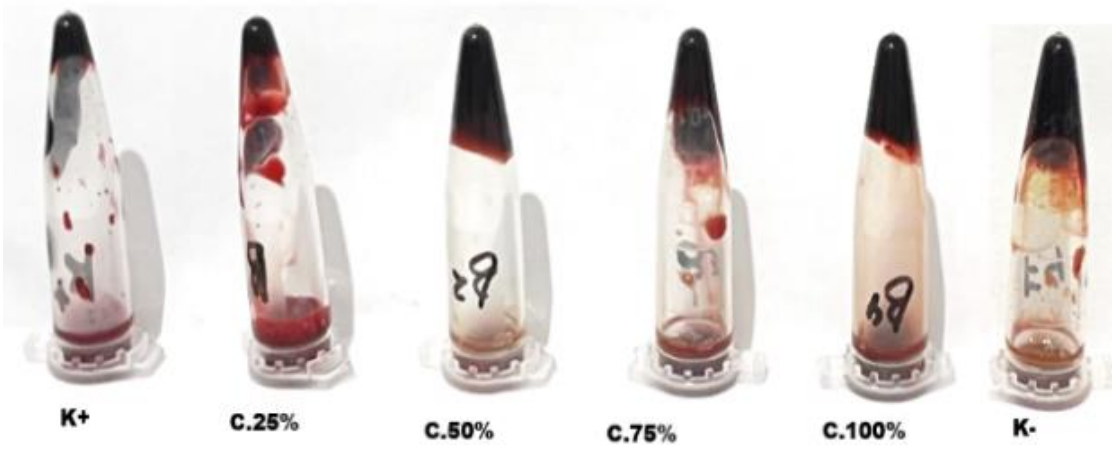


Figure 1. Blood Clot Lysis Test Results (Gravimetry) of *Moringa oleifera* Leaf Filtrate. The tubes were filled with blood clots with K+ (Positive Control), Concentration 25%, 50%, 75% and 100%, K- (Negative Control).

Statistical analysis using a one-way ANOVA test showed a significant difference between treatment groups ($F = 3.826$; $p = 0.018$), indicating that varying filtrate concentration significantly affected in vitro thrombolytic ability. These results indicated that the 25% concentration provided the highest thrombolytic activity compared to the other concentrations, although its effectiveness was still lower than that of the positive control. These preliminary findings suggest that Moringa leaf filtrate has potential in vitro as a natural thrombolytic agent, but its activity appears to decrease at higher concentrations, possibly due to the presence of inhibitory compounds or interactions between components that reduce thrombolytic effectiveness.

Anticoagulant Activity Test

As seen in Figure 2, all blood samples treated with Moringa leaf filtrate at various concentrations showed suboptimal anticoagulant activity, indicated by the formation of

coagulation (blood clots). For comparison, the positive control (K3EDTA) exhibited a longer clotting time (Table 2). These results qualitatively indicate that moringa leaf filtrate possesses anticoagulant activity.

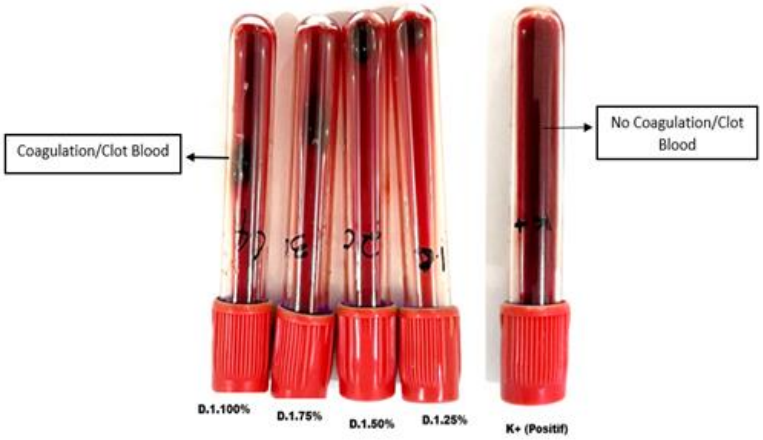


Figure 2. Visualization of Anticoagulant Activity Test on Blood Specimens after adding fresh *Moringa oliefera* leaf filtrate at concentration of 25%, 50%, 75%, and 100%.

However, differences were found in the clotting time (CT) values. The anticoagulant activity of moringa leaf filtrate is quantitatively demonstrated by its ability to prolong the CT value compared to the negative and positive controls. Table 3 shows that treatments involving the addition of various concentrations of moringa leaf filtrate to the test blood can prolong the CT by 10 to 35 minutes. Overall, Moringa leaf filtrate performed better in preventing blood clots. The best anticoagulant activity of all was demonstrated by blood with K3EDTA. These results serve as an initial exploratory reference to illustrate the anticoagulant's ability, indicating that Moringa leaf filtrate has initial potential as a natural anticoagulant agent. However, there is still a possibility that, through the process of purifying the active compounds or further optimizing the concentration, the Moringa leaf filtrate can have much better anticoagulation activity.

Table 2. Results of the Anticoagulant Activity Test of Moringa Leaf Filtrate Based on the Lee-White Method

Moringa Leaf Filtrate Concentration	Lee-White Anticoagulant Activity Time (mins) *
Positive Control/K3EDTA	NA
Negative control	NA
25%	10±0.33
50%	18±0.24
75%	20±0.37
100%	35±0.32

Note: *NA = Not applicable; all tests were repeated in 3x

CLINICAL IMPLICATION

The results of this study demonstrate the antithrombotic activity of *Moringa oleifera* leaf filtrate in vitro, namely the ability to lyse blood clots up to 60% at a concentration of 25% and the ability to act as an anticoagulant at various concentrations. However, these results are still preliminary and only obtained from simple tests using the blood of healthy volunteers in vitro under conditions that do not reflect pathological conditions in the human body. In vivo effectiveness may vary due to metabolic factors, bioavailability, and complex biological interactions that have not been tested. In addition, the safety and toxicity aspects of the extract have not been analyzed, so further studies

that include toxicity tests, in vivo models, and purification of bioactive compounds as candidate thrombolytic agents are needed to ensure the potential and safety of Moringa leaves as an antithrombotic agent.

LIMITATIONS

Limitations of this study include the use of thrombolytic and anticoagulant activity tests conducted only in vitro with the blood of healthy volunteers. These results do not necessarily reflect the effectiveness of the moringa leaf filtrate, where factors such as metabolism, bioavailability, distribution, and complex biological interactions can influence therapeutic response.

The use of whole moringa leaf filtrate as the test sample also presents limitations, as the filtrate is a mixture of various secondary metabolites such as flavonoids, alkaloids, saponins, tannins, enzymes, and minerals that have not been specifically standardized or separated. This makes it difficult to identify the dominant bioactive compounds responsible for the thrombolytic and anticoagulant activity. Furthermore, the possible presence of antagonist compounds in the mixture could influence the test results.

Further research recommends fractionation and purification of the active compounds to identify the primary constituents acting as thrombolytic agents. In vivo validation of efficacy and safety is also crucial, including evaluation of toxicity and bioavailability. Additionally, comparison with proven clinical antithrombotic controls will provide a more accurate picture of the therapeutic potential of moringa leaves as a treatment alternative.

CONCLUSIONS

This study provides preliminary evidence that moringa leaf filtrate has thrombolytic and anticoagulant activity in vitro, although it is not yet fully optimized. These results are preliminary due to the limitations of in vitro testing and therefore cannot be generalized to pathological conditions of thrombosis in humans. The possible influence of inhibitory compounds in the filtrate also needs to be considered. Further research should focus on purification of the active compounds and in vivo and clinical testing to confirm their effectiveness, safety, and therapeutic potential as natural antithrombotic agents.

CONFLICT OF INTEREST

The authors have no financial or commercial ties that could create a conflict of interest with this research.

AUTHOR CONTRIBUTIONS

Designing the test experiments, the initial manuscript draft, and manuscript review were completed by Bio Putri Ayanti. Nurbidayah designed the moringa leaf filtration and phytochemical experiments. Nurul Amalia and Syafina Azzahra conducted the respondent blood collection process and the in vitro clot lysis & anticoagulant experiments. Amalya Amini provided the necessary resources and contributed to data analysis and formatting.

ACKNOWLEDGMENTS

The authors would like to express their deepest gratitude to the Directorate General of Research and Development of the Ministry of Education, Science, and Technology of the Republic of Indonesia for the financial support through Penelitian Dosen Pemula (PDP) scheme for the year 2025.

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