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Research

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Anticoagulant effects of combined extracts of *Curcuma xanthorrhiza* Roxb., *Mimusops elengi* Linn., and *Averrhoa carambola* in mice

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Abstract

Background *Curcuma xanthorrhiza* Roxb. rhizome, the *Mimusops elengi* Linn. leaves, and *Averrhoa carambola* leaves contain bioactive compounds such as alkaloids and flavonoids. Flavonoids influence calcium ion levels, which play critical roles in cardiovascular functions, including heart function and blood coagulation. However, the effects of these plant extracts on blood clotting remain unclear.

Objective This study aimed to evaluate the anticoagulant effects of a combination of these plant extracts in mice.

Methods Twenty-five mice were divided into five treatment groups, receiving either distilled water (0.5 mL/25 g BW), aspirin (0.2 mg/20 g BW), *Curcuma xanthorrhiza* extract (0.1344 mg/20 g BW), or a combination of the three extracts at two doses (0.63 mg/20 g BW and 2.52 mg/20 g BW). Extracts were administered orally, bleeding and coagulation times were measured at 3-, 6-, and 9-hours post-administration.

Results The combined extract significantly prolonged bleeding and coagulation times compared to a single *Curcuma xanthorrhiza* extract. The most pronounced effect was observed at a dose of 2.52 mg/20 g BW, with the peak effect occurring at the 3rd hour.

Conclusion The combination of *Curcuma xanthorrhiza*, *Mimusops elengi*, and *Averrhoa carambola* extracts demonstrated significant anticoagulant activity, with the highest potency observed at a dose of 2.52 mg/20 g BW, surpassing the effects of aspirin. The synergistic interaction between these extracts is suggested to enhance their anticoagulant properties.

Keywords: anticoagulant effect | *Averrhoa carambola* | blood clotting | *Curcuma xanthorrhiza* Roxb. | *Mimusops elengi* Linn.

Introduction

Anticoagulant is a drug used to prevent and treat blood clots in the blood vessels and the heart in reducing the risk of stroke. Anticoagulants are also widely used to control and treat venous thromboembolism, including deep vein thrombosis and pulmonary embolism, as well as in patients with acute coronary syndrome (van den Heuvel *et al.*, 2018; Martinez & Campos, 2023). Anticoagulants prevent blood clotting by inhibiting the function of several blood clotting factors (Lu *et al.* 2016), such as calcium.

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Studies have shown that several plants, including *Curcuma xanthorrhiza* Roxb. rhizomes, Tanjung (*Mimusops elengi* Linn.) leaves, and sweet star fruit leaves (*Averrhoa carambola*), have exhibited anticoagulant effects (Daud *et al.*, 2013). Tanjung leaf extract contains quercetin or flavonoid compounds, sterols, sugar derivatives, and tannins (Gami *et al.*, 2012; Roqaiya, 2015; Rahminiwati *et al.*, 2019). Sweet star fruit leaf extract contains alkaloids, flavonoids, saponins, and tannins (Fitriyati *et al.*, 2023), while ethanol extract of *Curcuma xanthorriza* rhizomes contain flavonoids, alkaloids, and triterpenoids (Megawati & Yuliana, 2019). Flavonoids such as quercetin, luteolin, and kaempferol have potential anticoagulant effects by prolonging the activated partial thromboplastin time (APTT) (Pouyfung & Sukati, 2021). Furthermore, alkaloids can suppress cytosolic calcium mobilization and inhibit platelet aggregation (Ain *et al.*, 2016; Zainudin,2021).

Rahminiwati *et al.* (2019) have examined the effect of combining extracts of these plants on heart function in cats. Combining these extracts at a dose of 21 mg/2 kg BW and 82 mg/2 kg BW affects heart performance. This effect was suggested to correspond to the potential of flavonoids as inhibitors of calcium influx (Gao *et al.*, 2016; Puzserova & Bernatova, 2016) and a down regulator of intracellular calcium ions (Liu *et al.*, 2014). Calcium plays a significant role in the blood clotting process. However, the effect of the combination of these extracts as an anticoagulant has never been reported. This study aimed to determine the anticoagulant effect of a combination of *Curcuma xanthorrhiza* rhizomes, Tanjung leaf, and sweet star fruit leaf extract based on its impact on bleeding and coagulation time.

Methods

Extracts preparation

Curcuma xanthorrhiza (CZ) rhizomes, Tanjung (ME) leaves, and sweet starfruit (SF) leaves were obtained from the Bogor area, West Java, Indonesia. CZ, ME, and SF simplicial powders, 50 g each, were put into an Erlenmeyer tube containing 600 mL of distilled water and then heated over a water bath (Memmert, Germany) for 3 hours starting from the water temperature of 90°C. Stirring of infusion was carried out occasionally. The infusion was filtered using a flannel cloth while the temperature was hot. The filtrate obtained was concentrated using a rotary evaporator (Yamamoto, Japan) at a temperature of 70°C until a thick extract was obtained (Rahminiwati *et al.*, 2019). The combined extract preparation was made with the composition of CZ 22.43%, ME 18.69%, and SF 18.69%.

Experimental animals

Twenty-five male mice, aged 2–2.5 months weighing 25–30 g, were purchased from el-Rosa Laboratory, iRATco Group, Bogor, Indonesia. Mice were kept in plastic cages with the size of 40 cm×30 cm×18 cm with a wire cover and a husk bottom, five mice/cage. The plastic cage was placed in a room at a temperature of 27–28ºC. The lighting cycle was set at 12 hours of light and 12 hours of darkness using natural light or fluorescent lamps with a light intensity of 40 lux. Feed and drinking water were provided *ad libitum* (Mutiarahmi *et al.*, 2020; Putri, 2018).

The experimental mice that had been prepared were divided into five treatment groups. Group 1 consisted of 5 experimental mice given distilled water at a dose of 0.5 ml/25 g BW as a negative control (control (-)). Group 2 consisted of 5 experimental mice given aspirin (Bayer, Germany) at a dose of 0.2 mg/20g BW as a positive control (control (+)). Group 3 consisted of 5 expeimental mice given the extract of CZ at a dose of 0.1344 mg/20 g BW. Group 4 consisted of 5 experimental mice given a combination of (CZ+ME+SF) at a dose of 0.63 mg/20 g BW. Group 5 consisted of 5 experimental mice given a combination of (CZ+ME+SF) at a dose of 2.52 mg/20 g BW (Rahminiwati *et al.*, 2019). The tested regiment was administered orally with a gastric probe before treatment. Bleeding and coagulation times were measured at the 3rd hour, 6th hour, and 9th hour post treatment.

Bleeding time observation

This research procedure has received approval from the Animal Ethics Commission (KEH) SKHB IPB with Number 151/KEH/SKE/XII/2023. The experimental mice were put into the restrainer. The tip of the mouse's tail was cleaned using 70% alcohol, and then the mouse's tail was punctured using pen lancets to a maximum depth of 2 mm and a distance of 2 cm from the tip of the tail. Every time an observation was conducted, the puncture point during the next test was raised 2 cm from the first puncture. The dripping blood is absorbed with filter paper (blood-absorbing paper). Bleeding time is determined by calculating the time interval from the first blood drip until the blood stops dripping on the filter paper (Fadilla *et al.*, 2023; Musdalifah *et al.*, 2022; Indriani *et al.*, 2021).

Coagulation time testing

Coagulation time measurements were carried out at the 3rd hour, 6th hour, and 9th hour after administration of the tested regimen. Blood from the tip of the tail was absorbed using a 10 cm capillary tube (Marienfeld, Germany) with a mark every 1 cm. The capillary tube was broken every 15 seconds. The formation of fibrin threads in the broken part of the capillary tube determines the coagulation time. The time required for fibrin threads to be formed was then recorded (Fadilla *et al.*, 2023; Musdalifah *et al.*, 2022; Indriani *et al.*, 2021).

Statistical analysis

The data obtained were analyzed statistically with SPSS 23 using two-way ANOVA and Duncan's post hoc test. The Leven test was used to determine data homogeneity, while the Kolmogorov-Smirnov Shapiro-Wilk test assessed the normality of data. A p-value<0.05 was considered statistically significant.

Results

Effect of formula on bleeding time

Bleeding time is the period from the first drop of blood until the blood stops dripping. The average results of bleeding time measurements in this study are presented in **Figure 1**. The longest bleeding time occurred at the 3rd hour of measurement, followed by a decrease of the bleeding time at the 6th hour, and approached the control group (-) level at the 9th hour. The treatment group with the shortest average bleeding time was the control group (-), followed by the bleeding time for CZ, CZ+ME+SF 0.63 mg/20 g BW, the control group (+), and the longest was CZ+ME+SF 2.52 mg/20 g BW.

The results of statistical analysis using Two-way ANOVA for a completely randomized experimental design (CRD), followed by Duncan's post hoc test, showed that the bleeding time for CZ, CZ+ME+SF at doses of 0.63 and 2.52 mg/20 g BW, as well as a positive control, was remarkably more extended than the bleeding time for the negative control group. Bleeding time for CZ+ME+SF at a dose of 2.52 mg/20 g BW was also significantly higher than that of the control group (+). The effect of measurement time on the length of bleeding time showed that the best average bleeding time occurred in the 3rd hour after administration of the extract.

Effect of combining extract on blood coagulation time of mice

Coagulation time is the time required for blood clotting to occur or when blood begins to be drawn until clotting occurs. The longest coagulation time is at the 3rd hour of measurement; the coagulation time gets shorter as the measurement time increases. The short coagulation time was found in the control group (-), followed by the average coagulation time for CZ, CZ+ME+SF 0.63 mg/20 g BW, control group (+), and the longest was CZ+ME+SF 2.52 mg/20 g BW (**Figure 2**).

The results of statistical analysis using ANOVA followed by Duncan showed an effect of the treatment group on coagulation time ($p<0.05$). The average coagulation time for all treatments except for dose CZ was significantly different from the control group (-); on the other hand, the coagulation time for CZ+ME+SF 2.52 mg/20 g BW was also considerably longer than the coagulation time for the control group (+). The longest coagulation time was found at the first 3rd hour of treatment.

Discussion

Coagulation time is the degree of the intrinsic power of blood to convert fibrinogen to fibrin, while bleeding time relates to how quickly small blood vessels in the skin stop bleeding (Oktavia *et al.*, 2015). The bleeding time test was carried out to assess the platelets' functioning in the initial clot formation phase, followed by the blood coagulation phase. In response to exposed collagen, platelets will be activated and migrate to the injury site, inducing blood vessel constriction and promoting fibrin formation (Fadilla *et al.*, 2023).

The single extract of CZ significantly prolongs the bleeding time (**Figure 1**). However, it did not considerably influence coagulation time (**Figure 2**). The effect of CZ rhizomes on coagulation time was strengthened when CZ extract was given in combination with ME+SF. The extent of the impact depends on the dose of usage. At the highest dose, namely 2.52 mg/20 g BW., the influence of the combined extract on bleeding time was significantly higher than that of the control (-) and the CZ single

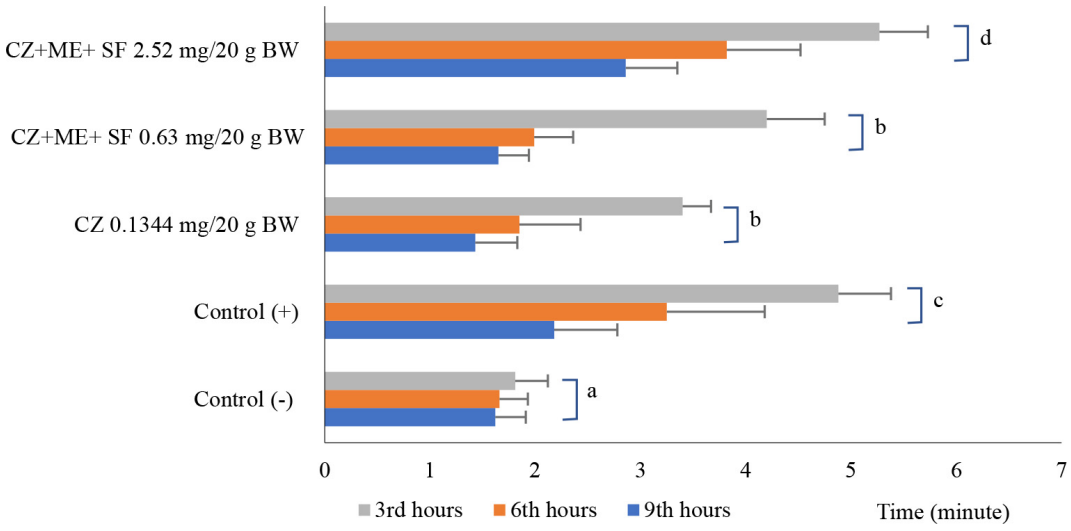

Figure 1 Effect of combination *Curcuma xanthorrizha* Roxb. rhizomes, *Mimusops elengi* Linn. leaves, and star fruit (*Averrhoa carambola*) leaves on bleeding time of mice. A combination of CZ+ME+SF significantly extended the bleeding time, with the best effect found at a dose of 2.52 mg/20 g BW. Its effect is also better than the positive control. Different superscript letters indicate statistically significant at the $p<0.05$ (ANOVA, Duncan), n = 5/group; mean ± SD; control (-): negative control that was given distilled water; control (+): positive control that was given aspirin; CZ: *Curcuma xanthorrhiza* rhizomes; ME: *Mimusops elengi* leaves, SF: star fruit (*Averrhoa carambola*) leaves.

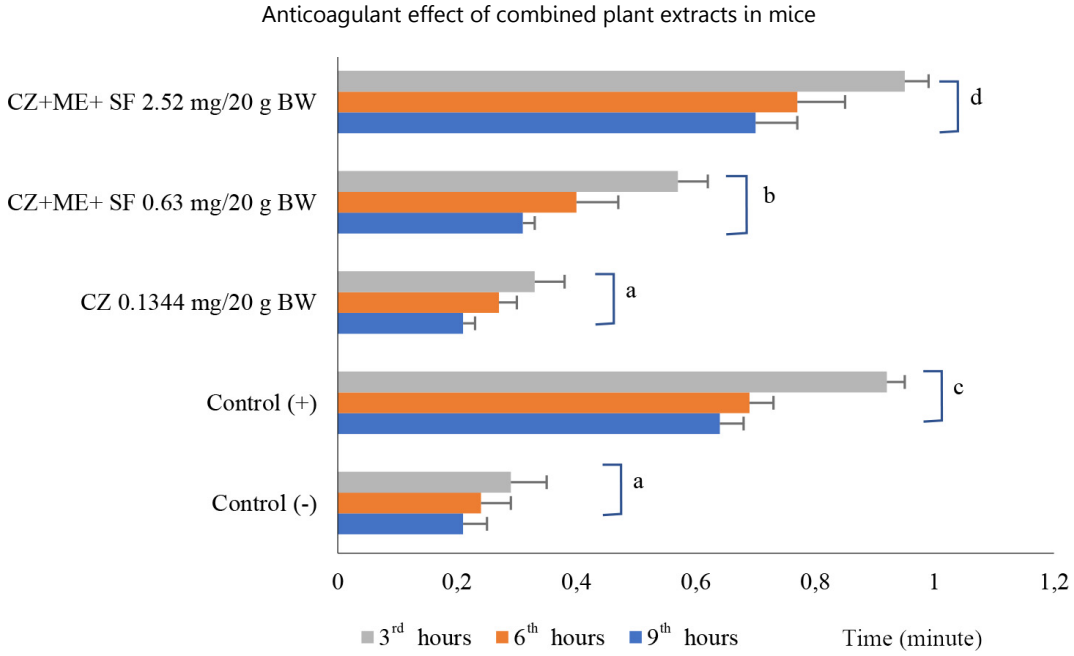

Figure 2 Effect of combination of *Curcuma xanthorrizha* Roxb. rhizomes, *Mimusops elengi* Linn. leaves, and star fruit (*Averrhoa carambola*) leaves on coagulation time of mice. A combination of CZ+ME+SF significantly extended the bleeding time, with the best effect found at a dose of 2.52 mg/ 20 g BW. Its effect is also better than the positive control. Different superscript letters indicate significant differences at the $p < 0.05$ (ANOVA, Duncan), SD: standard deviation, n = 5/group; mean ± SD; Control (-): negative control that was given distilled water; Control (+): positive control that was given aspirin; CZ: *Curcuma xanthorrhiza* rhizomes; ME: *Mimusops elengi* leaves, SF: star fruit (*Averrhoa carambola*) leaves.

extract. However, at a low dose of 0.63 mg/20 g BW, the combined CZ+ME+SF significantly affected the blood coagulation but not the bleeding time.

The effect of the combined extract on bleeding time is dose-dependent. It was characterized by changes in potency resulting from variations in the dose of the combined ME+SF+CZ extract. The dose increased from 0.63 mg/20 g BW to 2.52 mg/20 g BW administered to mice showed the longest bleeding and coagulation times. The increase in bleeding time and coagulation time from a dose of 0.63 mg/20 g BW in mice was 53.53% and 72%, respectively, compared to the negative control, whereas at a dose of 2.52 mg/20 g BW in mice, an increase in bleeding time and coagulation time, respectively, by 134.12% and 224% higher than the negative control group.

The anticoagulant effect of the single composition of CZ that significantly prolonged bleeding time compared to coagulation time (**Figure 1** and **Figure 2**) suggested that the flavonoid and alkaloid compounds in CZ rhizomes influence the primary hemostatic process more than secondary hemostatic (Indriani *et al.*, 2021). Primary hemostatic is related to bleeding time, while secondary hemostatic is related to coagulation time. In addition, the strengthened CZ rhizomes effect on the length of coagulation when given in combined form with ME leaves and SF leaves at a dose of 2.52 mg/20 g BW displayed a synergistic interaction between CZ, ME, and SF on coagulation time. According to Ngan Kee *et al.* (2014), combination preparations are synergistic when they provide more significant effects than preparations with a single composition. The synergistic effect of the extract combination is suggested to occur through multitarget synergism in which the active ingredients of the extract combination work on several blood clotting factors.

The prolongation of bleeding time and coagulation time is caused by vasodilation of blood vessels due to suppression of the cyclooxygenase enzyme, leading to the decrease of thromboxane A2 level and blood clotting activity (Indriani *et al.*, 2021). This effect may have resulted from the action of flavonoid and alkaloid compounds. These two compounds are reported to be found in CZ rhizomes, ME leaves, and SF leaves (Megawati & Yuliana, 2019; Kurdiansyah *et al.*, 2022; Utami *et al.*, 2023). The flavonoid compounds in ME leaf extract were reported to show an anticoagulant effect by inhibiting the formation of factor Xa in the coagulation process; therefore, blood clotting does not occur (Choi *et al.*, 2016; Putri *et al.*, 2021). Furthermore, flavonoids have anticoagulant activity, prolonging bleeding time (Afifi *et al.*, 2018) and inhibiting the release of calcium ions, which play a role in activating intracellular factors from platelet cells so that platelet aggregation is inhibited (Sinaga *et al.*, 2024). Meanwhile, alkaloids inhibit collagen, and ADP induces platelet aggregation, thus prolonging coagulation time (Ain *et al.*, 2016).

The multi-target action of the combined extract is suggested to contribute to the strength of its effect as an anticoagulant, which is reflected in the impact of a dose of 2.52 mg/20 g BW in mice. The combined extract is better than the control (+) aspirin during bleeding and coagulation times. It is characterized by the increased bleeding time and coagulation time by 15.69% and 8%, respectively, better than aspirin. Aspirin is an anticoagulant that prolongs bleeding time by inhibiting thromboxane and the formation of prostacyclin (Santos-Galleo & Badimon, 2021). In addition, aspirin acts as

an antiplatelet blocker of adenosine diphosphate (ADP) receptors, which causes platelet inactivation and blood clotting, which can cause bleeding (Ain *et al.*, 2016).

The 3rd hour is the best time for the combined extracts to provide an anticoagulant effect. The prolongation of bleeding time and coagulation time at 3 hours is suggested to be caused by the high levels of flavonoids and alkaloids in the plasma after being absorbed in the gastrointestinal tract as time increases. The drug will be excreted slowly by the kidneys (Krisnayanti *et al.*, 2019). The same results were also obtained in research conducted by Fadilla *et al.* (2023) regarding the measurement of bleeding and coagulation time of melon juice, which provides a high anticoagulant effect in the 3rd hour after administration of melon juice.

Conclusion

The combination of *Curcuma xanthorrhiza* rhizomes, Tanjung leaves, and sweet star fruit leaves interact to result in the anticoagulant effect. The best combination dose that elicits anticoagulant effect is 2.52 mg/20 g BW, with the potential to be an anticoagulant is better than the positive control aspirin at the dose tested. This result highlighted the possibility of a multitargeted action of combination extract in the coagulation process.

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Author contribution: MR: conceptualization, methodology, resources, validation, writing original draft, writing – review & editing; RU: conceptualization, formal analysis, investigation, methodology, resources, writing original draft; RH: supervision.

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