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Research Article

Pharmacokinetic Interaction Between Bay Leaves (*Syzygium polyanthum*) Infusion and Captopril in Rats

Interaksi Farmakokinetik Antara Infusa Daun Salam (Syzygium polyanthum) dan Captopril pada Tikus

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ABSTRACT

Captopril, an ACE inhibitor, is commonly prescribed as first-line therapy for hypertension. In practice, patients often combine synthetic drugs with herbal remedies such as bay leaves (*Syzygium polyanthum*), raising concerns about potential interactions. This study investigated the effect of bay leaves infusion on the pharmacokinetic profile of captopril in white rats (Rattus norvegicus). Ten rats were divided into two groups: group 1 received 25 mg of captopril, while group 2 received the same dose in combination with bay leaves infusion. Blood samples were collected via the tail vein at 0; 0.5; 1; 2; 4; 6; 12 and 24 hours, and analyzed using a UV-VIS spectrophotometer (205 nm). Pharmacokinetic parameters assessed included absorption rate constant (K_a), elimination rate constant (K_e), half-life ($t½$), peak time (tmax), maximum concentration (Cpmax), and area under the curve (AUC). Results showed that bay leaves infusion increased Cpmax (2.646 → 3.105 µg/ml), prolonged $t½$ (3.347 → 16.116 h), and elevated AUC (23.382 → 56.479 µg.h/ml). These findings indicate that bay leaves infusion significantly alters the pharmacokinetic profile of captopril.

Keywords: Captopril, Infution, Bay Leaves, *Syzygium polyanthum*, Pharmacokinetics

ABSTRAK

Captopril merupakan golongan ACE inhibitor yang sering digunakan sebagai terapi lini pertama untuk hipertensi. Masyarakat kerap memadukan obat sintetik dengan herbal, termasuk daun salam (Syzygium polyanthum), meskipun kombinasi tersebut berpotensi menimbulkan interaksi. Penelitian ini bertujuan mengetahui pengaruh infusa daun salam terhadap profil farmakokinetik captopril pada tikus putih (Rattus norvegicus). Sebanyak 10

ekor tikus dibagi menjadi dua kelompok: kelompok 1 diberi captopril 25 mg, sedangkan kelompok 2 kombinasi captopril 25 mg dan infusa daun salam. Sampel darah diambil melalui vena ekor pada waktu 0; 0,5; 1; 2; 4; 6; 12; dan 24 jam, kemudian dianalisis menggunakan spektrofotometer UV-VIS pada panjang gelombang 205 nm. Parameter farmakokinetik yang diukur meliputi konstanta laju absorbsi (K_a), konstanta laju eliminasi (K_e), waktu paruh ($t½$), waktu puncak (tmax), kadar maksimum (Cpmax), serta area under curve (AUC). Hasil penelitian menunjukkan bahwa pemberian infusa daun salam meningkatkan Cpmax dari 2,646 menjadi 3,105 µg/ml, memperpanjang t½ dari 3,347 menjadi 16,116 jam, dan meningkatkan AUC dari 23,382 menjadi 56,479 µg.jam/ml. Berdasarkan hal tersebut maka dapat disimpulkan bahwa infusa daun salam terbukti mempengaruhi profil farmakokinetik captopril.

Kata Kunci: Captopril, Infusa, Daun Salam, Syzygium polyanthum, Farmakokinetik

I. INTRODUCTION

Hypertension is one of the most prevalent health problems worldwide, and its incidence continues to rise each year. This condition can lead to severe complications and, in some cases, even death. According to the World Health Organization (2020), an estimated 1.56 billion people globally suffer from high blood pressure, and this figure is projected to increase by 30% by 2025 (Anggriani, 2016).

In Indonesia, the prevalence of hypertension among individuals aged 18 years and above reached 25.8%. Specifically, in North Maluku Province, the prevalence rate was reported at 5.71% (Ministry of Health of the Republic of Indonesia, 2018). In Ternate City, the population in 2022 was recorded at 206,715, with 1,724 reported cases of hypertension. By 2023, although the population slightly declined to 202,871, the number of hypertension cases rose sharply to 7,141. This sharp increase, despite the population decrease, highlights a concerning trend and underscores the urgent need to strengthen awareness campaigns and implement effective public health interventions in the region (BPSI, 2023).

Captopril, an angiotensin-converting enzyme (ACE) inhibitor, is one of the most widely prescribed antihypertensive drugs and is often considered a first-line therapy for hypertension (Harrison et al., 2021; Unger et al., 2020). Its popularity is attributed not only to its effectiveness in reducing blood pressure but also to its wide availability and affordability (Mayasari, 2020). A study reported that ACE inhibitors, particularly captopril, accounted for the highest proportion of antihypertensive use at 31%, followed by calcium channel blockers (CCBs) such as Amlodipine (25%), and diuretics including Hydrochlorothiazide (7%) and Furosemide (7%) (Harrison et al.,

2021; Mandasari et al., 2022; Unger et al., 2020). Similarly, another study confirmed that ACE inhibitors remain the most frequently used antihypertensive class, with captopril showing a utilization rate of 23.5% (Chen et al., 2021; Lutfiyati et al., 2017; Momoniat et al., 2019).

Herbal medicines are frequently consumed as adjunct therapies alongside synthetic drugs to enhance therapeutic outcomes. Over the past decade, the use of herbal remedies in hypertension management has grown significantly, largely driven by the perception that they cause fewer side effects. A study by Suryaningsih & Septiari (2023) reported that many patients believe combining conventional antihypertensive therapy with complementary herbal medicines can improve clinical outcomes. However, despite their perceived safety, the concurrent use of herbal and synthetic drugs carries the potential risk of drug–herb interactions (Saputri et al., 2022).

One commonly used herbal ingredient is bay leaves (*Syzygium polyanthum*), which are widely utilized as a culinary spice in both fresh and dried forms (Dafriani, 2016). Bay leaves contain bioactive compounds such as flavonoids, which have demonstrated antihypertensive effects (Rhamadan et al., 2022). Flavonoids exert these effects primarily through their antioxidant activity, preventing oxidative stress and cellular damage. Since elevated oxidative stress is a key contributor to degenerative diseases, including hypertension, the antioxidant properties of flavonoids may play a protective role in cardiovascular health (Aulya & Dahlan, 2024).

The combination of herbal and synthetic medicines can significantly influence pharmacokinetic profiles. Interactions may arise not only between drugs themselves but also with herbs, alcohol, or tobacco smoke, potentially leading to adverse effects or, in some cases, therapeutic benefits (Cicih et al., 2022). Pharmacokinetic interactions occur during the ADME processes—absorption, distribution, metabolism, and excretion—when one substance alters the pharmacokinetics of another, thereby increasing or decreasing the availability of the drug to exert its therapeutic effect (Ramadhan, 2021). In this context, the present study was designed to analyze the pharmacokinetic profile of *S. polyanthum* leaves infusion in combination with captopril in white rats (*Rattus norvegicus*).

II. METHOD

A. Preparation of Animals

The experimental animals used in this study were ten male Wistar strain white rats (*Rattus norvegicus)* aged 2–3 months, weighing 180–250 grams. which were

maintained under standard laboratory conditions. Prior to the experiment, the animals were acclimatized for two weeks in a controlled environment with a temperature range of 22–25 °C, relative humidity of 50–60%, and a 12-hour light/dark cycle. During acclimatization, the rats were provided with standard pellet feed and water ad libitum. Before treatment, the animals were fasted for 12 hours while still given free access to water to reduce variations in absorption. A total of 10 healthy adult rats were used and randomly assigned into two groups, with each group consisting of five rats. The method used in this study received ethical approval from the Research Ethics Committee, Faculty of Medicine and Health Sciences, Khairun University (Approval Number: 049/UN44/C.9/KEP/2024).

B. Preparation of Bay Leaves (*Syzygium polyanthum*) Infusion

Ten fresh and young bay leaves were used as the sample, equivalent to 13 g of leaves. The extraction was carried out using the infusion method by soaking the leaves in 180 mL of warm water (75°C) for 20 minutes with continuous stirring. The bay leaf infusion was then filtered and transferred into a glass container for oral administration to the experimental animals (Istichomah et al., 2024).

The final volume of the infusion was 180 mL. This volume was subsequently converted for administration to rats, resulting in a dose of 3.24 mL per 200 g of body weight.

C. Preparation of Captopril

The 25 mg dose of captopril was converted for use in rats, resulting in a dose of 2.25 mg/kg body weight for the experimental animals. Captopril tablets were crushed into a fine powder, dissolved in distilled water (aqua dest), and administered orally to the rats.

D. Preparation of Phosphate Buffer (pH 6.8)

The phosphate buffer (pH 6.8) was prepared by first making separate 0.2 M solutions of KH_2PO_4 and NaOH. The KH_2PO_4 solution was prepared by dissolving 6.8 g of potassium dihydrogen phosphate in 250 mL of carbon dioxide–free water. In a separate container, 2 g of sodium hydroxide was dissolved in 250 mL of carbon dioxide–free water to obtain a 0.2 M NaOH solution. Next, 125 mL of the NaOH solution was added gradually to the KH_2PO_4 solution while continuously monitoring the pH. If the pH had not yet reached 6.8, additional small amounts of NaOH solution were added carefully until the desired pH was achieved. Finally, the solution was diluted with carbon dioxide–

free distilled water to obtain a final volume of 1,000 mL (Wahyuni et al., 2022).

E. Determination of the Maximum Wavelength of Captopril

An accurately weighed amount of captopril IPRS (Indonesian Pharmacopoeia Reference Standard) equivalent to 50 mg was transferred into a 50 mL volumetric flask and dissolved with phosphate buffer solution (pH 6.8) to obtain a final volume of 50 mL. From this solution, 2.2 mL was pipetted into a 100 mL volumetric flask and diluted to volume with phosphate buffer (pH 6.8). The absorbance of the resulting solution was scanned using a UV spectrophotometer within the wavelength range of 200–400 nm to identify the maximum absorption wavelength (λmax) of captopril (Rasyad et al., 2011).

F. Development of the Captopril Standard Curve

The absorbance of captopril standard solutions was measured using a UV spectrophotometer at the predetermined maximum wavelength. Standard solutions with concentrations of 4 ppm, 6 ppm, 8 ppm, 10 ppm, and 12 ppm were prepared, and their absorbance values were recorded. A calibration curve was then constructed by plotting absorbance against concentration. From this curve, the linear regression equation was derived to describe the relationship between absorbance and concentration, which served as the basis for determining sample concentrations (Wahyuni et al., 2022).

G. Treatment Administration to Experimental Animals

The experimental animals were divided into two groups. Group 1 (K1) received captopril 2.25mg/kg body weight orally. Group 2 (K2) received a combination treatment: captopril was administered first at a dose of 2.25 mg/kg body weight, followed immediately by oral administration of bay leaves infusion (3.24ml/200g Body Weight) without any time interval between treatments. Following drug administration, approximately 1 mL of blood was collected from the tail vein at predetermined time points of 0, 0.5, 1, 2, 4, 6, 12, and 24 hours. Each blood sample was transferred into vials containing 10% Na-EDTA solution as an anticoagulant and then centrifuged at 3,000 rpm for 5 minutes to obtain plasma through protein precipitation (Nugrahaningsih & Afanin, 2022).

H. Data Analysis

Plasma samples were analyzed using a UV-VIS spectrophotometer within the wavelength range of 200–400 nm (Saputri et al., 2022). The absorbance values obtained were then converted into captopril concentrations based on the previously established standard calibration curve (Umar & Fajriansyah, 2015).

Data on captopril and bay leaves infusion levels in plasma were first described descriptively before being subjected to quantitative analysis. Plasma concentrations of captopril at each specified time point were used to construct concentration–time profiles. From these profiles, pharmacokinetic parameters were determined, including the maximum plasma concentration (Cmax) and the time to reach maximum concentration (Tmax), obtained directly from the concentration–time curve. The area under the concentration–time curve (AUC) was calculated to assess overall drug exposure, while the elimination half-life (t1/2) was determined using the equation $t1/2 = 0.693/K_e$, where K_e represents the elimination rate constant.

III. RESULTS AND DISCUSSION

Bay leaves used in this study were obtained from plantations in Toboleu Village, North Ternate District, North Maluku, Indonesia. Flavonoids contained in bay leaves act as natural ACE (angiotensin-converting enzyme) inhibitors that can lower blood pressure by inhibiting the conversion of angiotensin I to angiotensin II (Noer et al., 2023; Rhamadan et al., 2022).

Extraction was carried out using the infusion method, chosen for its simplicity and cost-effectiveness. A total of 13 g of bay leaves powder was steeped in 180 mL of hot water at 75°C for 20 minutes with occasional stirring, then filtered. The extraction temperature of 75°C was selected to optimize the recovery of thermolabile bioactive compounds while minimizing their degradation (Bitwell et al., 2023).

Although flavonoids were previously mentioned as the major contributors to activity, several specific chemical constituents present in *S. polyanthum* leaves are known to play a role in antihypertensive effects (Nazri et al., 2025).

Among the identified flavonoids, quercetin and kaempferol are considered key active compounds. Quercetin has been widely reported to exert antihypertensive activity through multiple mechanisms, including inhibition of angiotensin-converting enzyme (ACE), enhancement of endothelial nitric oxide (NO) production, and reduction of oxidative stress within vascular tissues (Jan et al., 2022). These

effects contribute to vasodilation and decreased peripheral vascular resistance. Similarly, kaempferol has been shown to improve endothelial function and modulate vascular smooth muscle contraction through antioxidant and anti-inflammatory pathways. (Istichomah et al., 2024; Rachmawati & Suriawati, 2019).

In addition to flavonoids, bay leaves contain phenolic compounds such as eugenol, which exhibits vasorelaxant activity by influencing calcium channel modulation and improving endothelial-dependent relaxation (Nazri et al., 2025). Tannins and other polyphenolic constituents may also contribute indirectly through their antioxidant properties, reducing reactive oxygen species that impair nitric oxide bioavailability in hypertensive conditions.

After completing the infusion preparation, the maximum wavelength of captopril was determined using spectrophotometric analysis. The results (Table I) showed that captopril 25 mg IPRS had an average λmax of 205.4 nm. This value is consistent with the reference in the Indonesian Pharmacopoeia, Edition VI, which states a maximum wavelength of 205 nm (Ministry of Health of the Republic of Indonesia, 2020). The close agreement with the literature confirms the reliability of the measurement and supports the validity of the spectrophotometric method used in this study.

Table I. Wavelength determination of captopril 25 mg

Sample	Wavelength (nm)			
	R1	R2	R3	Average
Captopril IPRS	205.9	205.8	204.6	205.4

Notes: R is replication

Table II. Determination of the standard curve for captopril 25 mg

concentration (ppm)	Absorbance (nm)			
	R1	R2	R3	Average ± SD
4	0.296	0.280	0.212	0.263 ± 0.045
6	0.430	0.367	0.335	0.377 ± 0.048
8	0.583	0.555	0.362	0.500 ± 0.120
10	0.650	0.614	0.477	0.580 ± 0.091
12	0.814	0.837	0.583	0.745 ± 0.140

Notes: R is replication

In the standard curve measurement of captopril 25 mg (Table II), absorbance was recorded at various concentrations of 4 ppm, 6 ppm, 8 ppm, 10 ppm, and 12 ppm. The resulting calibration curve (Figure 1) demonstrated a linear relationship between captopril concentration and absorbance values. This linearity confirms the reliability of the spectrophotometric method and validates its suitability for accurately determining captopril concentrations in the samples under investigation.

In the absorbance measurement of the single captopril 25 mg group (K1) (Table III), observations were conducted over a 24-hour period in five rats. At baseline (0 hours), the average absorbance was 0.064. The value increased markedly at 0.5 hours to 0.115 and reached its peak at 1 hour with an average absorbance of 0.175.

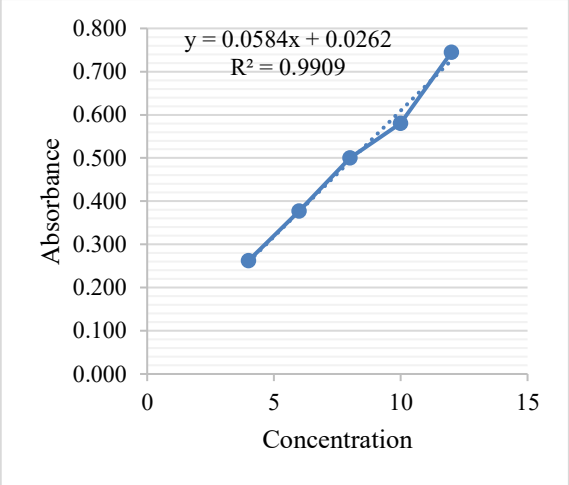

Figure 1. Captopril standard curve graph

Following this peak, the absorbance decreased to 0.083 at 2 hours, indicating a decline in the concentration of light-absorbing compounds. Interestingly, a secondary rise was observed at 4 hours (0.129) and continued at 6 hours (0.155). However, after 12 hours the absorbance dropped to 0.062, and by 24 hours it further declined to 0.036, reflecting a substantial reduction in captopril concentration.

Table III. Absorbance data of single captopril 25mg with a combination of captopril 25mg and *S. polyanthum* leaves

Time (Hours)	Absorbance (mean ± SD)	
	Captopril 25 mg	Captopril 25 mg + Bay Leaves Infusion 3.24ml/200gBW
0	0.064 ± 0.047	0.114 ± 0.105
1/2	0.115 ± 0.097	0.057 ± 0.022
1	0.175 ± 0.135	0.154 ± 0.090
2	0.083 ± 0.039	0.130 ± 0.101
4	0.129 ± 0.038	0.143 ± 0.087
6	0.155 ± 0.087	0.256 ± 0.184
12	0.062 ± 0.033	0.164 ± 0.118
24	0.036 ± 0.004	0.125 ± 0.116

Table IV. Pharmacokinetic parameter data of captopril literature, captopril 25 mg single and combination of captopril 25 mg with *S. polyanthum* leaves infusion

Pharmaco-kinetic Parameter	Captopril 25 mg	Captopril 25 mg + Bay Leaves Infusion 3.24ml/200 gBW
K_a (h^{-1})	1.352	0.333
K_e (h^{-1})	0.207	0.043
$t_{1/2}$ (h)	3.347	16.116
t_{maks} (h)	1.634	7.041
Cp_{maks} ($\mu g.ml^{-1}$)	2.646	3.105
AUC_{Total} ($\mu g.h.ml^{-1}$)	23.382	56.479

In the combination group of captopril 25 mg and *S. polyanthum* leaves infusion (Table III), absorbance was measured over a 24-hour period in five rats. At baseline (0 hours), the mean absorbance was 0.114. This value decreased at 0.5 hours to 0.057, followed by a sharp increase at 1 hour, reaching 0.154. A slight decline was observed at 2 hours (0.130), after which the absorbance rose again to 0.143 at 4 hours. At 6 hours, the mean absorbance reached its peak value of 0.256. Subsequently, the absorbance declined to 0.164 at 12 hours and further decreased to 0.125 at 24 hours, indicating a gradual reduction in concentration over time.

The pharmacokinetic parameter results are presented in Table IV. The first parameter, the absorption rate constant (Ka), describes the rate at which a drug enters systemic circulation (Ramadhan, 2021). In the single captopril 25 mg group (K1), the Ka value was 1.352$hour^{-1}$, whereas in the combination group of Captopril with *S. polyanthum* leaves infusion, the K_a value was markedly lower at 0.333 $hour^{-1}$. This finding indicates that the presence of bay leaves infusion slows the absorption of captopril in the gastrointestinal tract. Such an effect may be attributed to interactions between the active compounds in bay leaves and captopril, which interfere with the absorption process (Salman et al., 2024). Consequently, the reduced K_a suggests that captopril enters the systemic circulation more slowly, potentially delaying its onset of action and thereby slowing the blood pressure–lowering effect when co-administered with bay leaves infusion.

Furthermore, the elimination rate constant (K_e) represents the fraction of a drug eliminated per unit time (Ramadhan, 2021). In the single captopril group (K1), the K_e value was 0.207 $hour^{-1}$, which is consistent with the findings of Siska et al. (2018), who reported a K_e value of 0.217 $hour^{-1}$ for captopril. In contrast, the combination group of captopril with *S. polyanthum* leaves infusion (K2) showed a much lower K_e value of 0.043 $hour^{-1}$. This result suggests that co-administration with bay leaves infusion slows the elimination of captopril, thereby extending its presence in the body. The CYP2D6 enzyme, a member

of the cytochrome P450 (CYP450) family, plays a crucial role in hepatic drug metabolism (Gayatri et al., 2023). Bay leaves infusion may inhibit captopril-metabolizing enzymes, such as CYP450, thereby prolonging the drug's systemic retention. While this interaction could extend the antihypertensive effect of captopril, it also raises the potential risk of drug accumulation with long-term use.

The half-life (t½) parameter represents the time required for the plasma concentration of a drug to decrease by 50% of its initial level (Ramadhan, 2021). In the single captopril group, the half-life was 3.347 hours, which is consistent with the findings of Siska et al. (2018), who reported a t½ of 3.62 hours. In contrast, the combination group of captopril with *S. polyanthum* leaves infusion (K2) exhibited a markedly prolonged half-life of 16.116 hours. This significant increase indicates that captopril remains in the body for a longer duration, thereby potentially extending its pharmacological effects. The prolonged half-life is attributable to slower drug elimination, as reflected by the decreased K_e value. Since half-life is inversely related to K_e, reduced elimination leads directly to an increase in t½ (Salman et al., 2024). Consequently, while a longer half-life may allow for less frequent dosing, it also raises the risk of drug accumulation and adverse effects such as prolonged hypotension if not carefully managed.

Peak time (tmax) is the time for a drug to reach its maximum plasma concentration (Cpmax) (Ramadhan, 2021). In the single captopril group (K1), tmax was 1.634 hours, while in the combination with *S. polyanthum* leaves infusion, it increased to 7.041 hours. This delay indicates slower absorption due to interactions with bay leaves compounds, resulting in a later onset of captopril's therapeutic effect (Salman et al., 2024).

The maximum concentration (Cpmax) is the highest drug level in plasma, occurring at the same time as peak time (tmax). In the single captopril group (K1), Cpmax was 2.646 $\mu g.ml^{-1}$, while in the combination group with bay leaves infusion (K2), it increased to 3.105 $\mu g.ml^{-1}$. This suggests that bay leaves infusion enhances captopril's bioavailability. Although absorption is slower, the higher Cpmax may strengthen its antihypertensive effect but also increase the risk of adverse effects such as hypotension.

The Area Under the Curve (AUC) represents total drug exposure in plasma over time (Ramadhan, 2021). In the single captopril group (K1), AUC was 23.382 $\mu g.h.ml^{-1}$, while in the combination with *S. polyanthum* leaves infusion (K2), it increased to 56.479 $\mu g.h.ml^{-1}$. This indicates enhanced and prolonged captopril

exposure, which may strengthen its therapeutic effect but also increase the risk of side effects such as dizziness or hypotension.

Overall, these results indicate that *S. polyanthum* leaves infusion affects the pharmacokinetic profile of captopril by slowing absorption, prolonging half-life (t½), increasing AUC, and reducing elimination. The combination of captopril with bay leaves infusion enhances bioavailability, resulting in a longer antihypertensive effect. However, the slower absorption rate (K_a) and extended peak time (tmax) delay the onset of action, while the prolonged half-life (t½) and reduced elimination rate (K_e) may increase the risk of drug accumulation and side effects, such as prolonged hypotension.

To maintain therapeutic effectiveness and minimize potential interactions, bay leaves infusion should be taken 2–3 hours after captopril. Saputri et al. (2022) reported that administering herbal medicines two hours post-captopril reduces significant alterations in its pharmacokinetic parameters compared to simultaneous use. This timing strategy helps preserve the benefits of both treatments without affecting drug absorption or elimination. Nevertheless, this combination should be used under medical supervision, and further research is needed to fully assess its therapeutic effects and potential side effects.

IV. CONCLUSION

The study on the effect of bay leaves (*Syzygium polyanthum*) infusion on captopril pharmacokinetics in white rats (*Rattus norvegicus*) showed that co-administration increased Cpmax (2.646 → 3.105 $\mu g.ml^{-1}$), half-life (t½) (3.347 → 16.116 hours), and AUC (23.382 → 56.479 $\mu g.h.ml^{-1}$). Bay leaves infusion also altered other key pharmacokinetic parameters of captopril, including K_a, K_e, and tmax.

CONFLICT OF INTEREST

All authors declare that there is no conflict of interest in this research.

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