Clinical and Pharmaceutical Sciences Journal

Research article

Pharmacokinetic Evaluation of Paracetamol Co-administered with *Moringa oleifera* and *Caesalpinia sappan* Extracts Individually in *Sprague Dawley* Rats

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Received: 13 December 2025 | Revision: 19 December 2025 | Accepted: 31 January 2026

Abstract

Paracetamol is widely used as an analgesic and antipyretic agent. However, concomitant use with herbal products may alter its pharmacokinetics and lead to potential drug–herb interactions. *Moringa oleifera* leaves and *Caesalpinia sappan* heartwood are commonly used in herbal foods and beverages in Indonesia, rich in flavonoids and phenolic compounds that may influence drug metabolism. This study aimed to evaluate the pharmacokinetic profile of paracetamol when co-administered with *Moringa oleifera* leaf extract or *Caesalpinia sappan* heartwood extract in male *Sprague-Dawley* rats. Rats were randomly assigned to a control group receiving oral paracetamol (9 mg/200 g body weight) or treatment groups receiving paracetamol co-administered with *Moringa oleifera* leaf extract or *Caesalpinia sappan* heartwood extract. Blood samples were collected from the lateral tail vein at 30, 60, 120, 180, and 240 minutes post-administration. Plasma paracetamol concentrations were determined using a validated ultraviolet-visible (UV–Vis) spectrophotometric method at 244 nm, and pharmacokinetic parameters were calculated using non-compartmental analysis. Co-administration of *Caesalpinia sappan* extract resulted in a significant increase in the apparent volume of distribution of paracetamol (453.10%, $p<0.05$), whereas *Moringa oleifera* extract did not produce statistically significant changes in paracetamol pharmacokinetic parameters ($p>0.05$). These findings suggest that *Caesalpinia sappan* may alter the distribution characteristics of paracetamol, indicating a potential drug–herb interaction, highlighting the need for caution in concurrent use of herbal preparations with conventional drugs. Meanwhile, *Moringa oleifera* showed minimal pharmacokinetic impact under the study conditions. Further studies are required to elucidate the underlying mechanisms and assess clinical relevance.

Keywords: *Caesalpinia sappan*, moringa leaf extract, paracetamol, pharmacokinetic parameters, UV-Vis spectrophotometer

Introduction

Indonesia's rich ethnobotanical landscape is characterised by numerous therapeutic species, with Moringa oleifera and Caesalpinia sappan being particularly significant [1,2,3,4]. Moringa has benefits in all plant parts, including leaves, bark, flowers, fruits, and roots [5,6]. Moringa plants are commonly used as nutritious vegetables to complement meals [7]. Generally, people consume Moringa as a simple addition to their daily meals, often by boiling or stir-frying it as a vegetable [8]. The use of Moringa as a natural herbal remedy, claimed by many cultures, is gradually being confirmed through research [5]. Moringa leaves, extracted through maceration using 96% ethanol as a solvent, contain alkaloids, flavonoids, phenolics, triterpenoids/steroids, tannins, and saponins [9,10,11]. Based on previous research, Moringa leaves have been found to have various benefits, including immunomodulatory, antidiabetic, antipyretic, and antimicrobial properties, and can be used to treat skin diseases and promote

cardiovascular health [12,13]. In addition, Moringa possesses antioxidant, anti-hyperuricaemia, anticancer, anti-hyperglycaemic, anti-inflammatory, and anti-hyperlipidaemic effects [14,15]. Caesalpinia sappan L. (Leguminosae), commonly referred to as Sappanwood or "Secang" in Indonesia, is a medicinal plant of significant economic and therapeutic value [3]. In traditional Indonesian practice, the heartwood is extensively consumed in the form of functional beverages such as "Wedang Uwuh" in the Yogyakarta region and "Bir Pletok" in the Jakarta region, which are believed to enhance vitality and treat internal disorders [16,17]. In Indonesian ethnomedicine, the heartwood of C. sappan is frequently consumed to improve blood circulation, detoxify the body, and reduce inflammation [18].

The therapeutic efficacy of C. sappan is attributed to its complex phytochemical composition. The heartwood contains a variety of structural classes, primarily homoisoflavonoids (such as Brazilin and Brazilein), protosappanins, xanthones, coumarins, and gallic acid [19]. Pharmacological screening has revealed that these extracts possess a wide spectrum of biological activities, including significant antioxidant capacity, anti-inflammatory effects, and hepatoprotective potential [18]. Consequently, the widespread consumption of C. sappan in traditional beverages necessitates a deeper understanding of its pharmacokinetic profiles and potential interactions with synthetic drugs.

In the past four weeks, 24.4% of individuals utilised the services of a traditional practitioner and/or engaged in the use of traditional medicine, while 32.9% employed complementary medicine [16,20]. Many people combine traditional herbal remedies with conventional medicines, based on their own experiences or those of those around them, to aid in their treatment [21,22]. Traditional herbal remedies and conventional medicines can interact with each other. Drug interactions occur when the presence of another drug, herbal remedy, food, beverage, or other chemicals in the environment alters the effect of a drug. Drug interactions are considered clinically significant if they increase toxicity or reduce effectiveness, especially when the drug has a narrow therapeutic index [23,24,25,26].

The ethanol extract of sappan wood exhibited analgesic activity against acetic acid-induced pain in mice. The activity of the ethanol extract of sappan heartwood is similar to that of mefenamic acid, an NSAID that inhibits prostaglandin synthesis by binding and blocking prostaglandin receptors in cells. An ethanol extract of sappan heartwood at a dose of 8.4 mg/20 g body weight in Webster strain mice showed analgesic activity similar to that of mefenamic acid [27]. Sappan wood contains flavonoids and phenols [28,29], which can negatively affect the metabolism, efficacy, and toxicity of drugs, including paracetamol.

Paracetamol is a widely used analgesic and antipyretic drug worldwide [30]. This drug has a spectrum of action similar to that of NSAIDs and resembles COX-2 selective inhibitors. Although its analgesic effects are weaker than those of NSAIDs or COX-2 selective inhibitors, paracetamol is preferred because of its better tolerance. The main mechanism of action of paracetamol is the inhibition of cyclooxygenase-3 (COX-3) in the central nervous system and the selective inhibition of COX-2 [31,32,33,34]. Paracetamol does not work on immune cells with high peroxide levels, making it ineffective as an anti-inflammatory. Inhibition of COX enzymes in the brain can reduce headaches and lower fever [35,36,37].

Paracetamol is a commonly used over-the-counter conventional medicine for self-medication. Paracetamol is used to relieve mild-to-moderate pain and reduce mild fever [38,39]. Paracetamol is a substrate of the cytochrome P450 (CYP) enzymes CYP2E1, CYP1A2, and CYP3A4, and it is an intermediate substrate of P-glycoprotein (P-gp). Quercetin and chrysin, which are flavonoids, act as P-glycoprotein modulators and inhibitors of CYP2E1 and CYP1A2. Paracetamol and flavonoids in Moringa leaf extract can interact by inhibiting and inducing P-glycoprotein and CYP enzymes [40]. The use of herbal medicines together with synthetic drugs without medical advice has been practiced by millions of people. This can lead to various drug interactions or unintended side effects. The main cause is the lack of information or knowledge among the general public about traditional medicine and the belief that herbal medicine can reduce the side effects of drugs and enhance the effectiveness of treatment. However, many herbal medicines have been found to interact with synthetic drugs, resulting in dangerous side effects, reducing drug effectiveness, and herbal medicines that have effects similar to synthetic drugs can enhance the effects of these synthetic drugs [41,42,43]. Therefore, this study aimed to investigate whether the administration of Moringa leaf and Caesalpinia sappan extract influences the pharmacokinetic profile of paracetamol.

Materials and Methods

Materials

Fresh Moringa oleifera L. leaves were obtained from the Moringa Organik Indonesia farm in Blora, Central Java. Caesalpinia sappan L heartwood was obtained from the Center for Research and Development of Medicinal Plants and Traditional Medicines and has been determined by B2P2TOOT. In addition, test materials such as paracetamol (solarbio), 96% ethanol (PRIME GRADE), 99% sodium nitrite (MERCK), 99% trichloroacetic acid (MERCK), 98% sodium hydroxide (MERCK), plasma and serum obtained from blood collected with and without anticoagulants from Sprague-Dawley rats, aquadest (PURE WATER), and heparin (Golden VacTM) were also used.

The equipment used in this study included Blender (Miyako), vacuum pump (Rocker), Buchner funnel (W. Haldenwangger), glassware (Pyrex), filter paper (Hawach), porcelain crucible (Pyrex), stoppered flask (Pyrex), oven (Binder), rotary evaporator (B-ONE), analytical balance (ADAM Nimbus 250g), water bath (Memmert), UV-Vis spectrophotometer (K-Lab), cuvette (K-Lab), gastric probe, syringe (Terumo), pipette, vortex mixer (Corning), centrifuge (Oregon), conical reaction tube (Pyrex), beaker glass (Pyrex), stirring rod (Pyrex).

Male Sprague Dawley rats (300-350 g, 3-4 months) were used in this study. Animals were acclimatised for one week under standard laboratory conditions (temperature 22–25°C, 12 h light/dark cycle) with free access to standard chow and water. Before drug administration, rats were fasted overnight with free access to water. All experimental procedures were approved by the Ethics Committee of Universitas Pembangunan Nasional Veteran Jakarta (No. 46/III/2023/KEPK).

Methods

This study was a true experimental study with a post-test-only control group design using a one-way, completely randomised design in vivo. The test animals were divided into three groups: group I (positive control; paracetamol), group II (paracetamol + sappan heartwood extract), and group III (paracetamol + M. oleifera leaf extract). Each group consisted of six white male rats.

Preparation of Moringa leaf and Caesalpinia sappan extract

Moringa leaves and sappan bark are sorted while still wet, cleaned, and washed. The cleaned moringa leaves and sappan bark were then dried at room temperature. After the Moringa leaves and sappan bark were dried, they underwent dry sorting and were ground into powder using a blender. The Moringa leaf and sappan bark powders were extracted using the maceration method with 96% ethanol in a 1:1 (w/v) ratio for 3 × 24 h. After filtering the Moringa leaves and sappan bark, the filtrate was processed using a rotary evaporator under vacuum conditions to remove the solvent and obtain a concentrated extract. The resulting extract was weighed, and the yield was calculated [44]. In this study, 3 kg of Moringa leaves and sappan bark were extracted using the maceration method. The concentrated Moringa leaf extract weighed 1.30384 kg. The yield percentage of the Moringa leaf extract from 3 kg of leaves was 43.46%.

Preparation of moringa leaf and sappan bark extract suspension

Moringa leaf and sappan bark extracts are slightly soluble in distilled water, and their use in the form of a suspension, compared to a solution, is very efficient because suspensions can reduce the decomposition of active substances that are unstable in water. The suspending agent used is CMC Na; CMC Na has the advantage of being a suspending agent, which can increase the viscosity and stability of the resulting suspension. The dosage of Moringa leaf extract used in this study was 300 mg/kg BW rats, which is significant for anti-inflammatory and analgesic effects [45]. The dose was converted to 60 mg/200 g BW of rats. Moringa leaf and sappan bark extracts were weighed as much as 60 mg/200 g BW rats and added to 1% CMC Na slowly while stirring until homogeneous. Distilled water was added dropwise to 100 ml and stirred until homogeneous. The rats were administered sappan heartwood extract at a dose of 294 mg/kg BW.

Preparation of paracetamol suspension

Paracetamol 500 mg was converted into 9mg/200gBB rats, then weighed and added to CMC Na 1% while stirring until homogeneous; aqua dest was added little to 100 ml and stirred until homogeneous. The paracetamol dose set for the test subjects was 500 mg/kg, with a conversion factor of 0.018 g/kg.

Preparation of the raw solution and determination of the maximum wavelength of paracetamol

Paracetamol weighed 10 mg, was put in a 10 ml measuring flask, and dissolved with aqua dest, obtaining a standard parent solution of 1 mg/ml. From the parent standard solution, raw working solutions with concentrations of 20, 50, 100, 150, 200, 250, and 300 mg/l were prepared [46]. Paracetamol absorption occurs in the UV region. Therefore, the maximum wavelength was determined to be between 200 and 400 nm [46] [47].

Paracetamol standard curve

The standard working solution was taken as much as 0.5 ml, inserted into the test tube, and 3% TCA (5 ml) was added, followed by homogenisation with a vortex for 30 s. The mixture was centrifuged for 10 min at 3000 rpm, and 2 ml of the supernatant was transferred to another test tube using a micropipette. Then, 0.5 ml of 0.07 M sodium nitrite was added and homogenised with a vortex for 5 s. The samples were incubated for 10 min in a water bath at 37°C ± 1, 100 µl of 8 M NaOH was added, and the samples were homogenised using a vortex for 30 s. Its absorbance was observed at the maximum λ.

Pharmacokinetic test treatment

This research protocol was approved by the Ethics Committee of the Universitas Pembangunan Nasional Veteran (National Development University "Veteran) Jakarta (KEP UPN Veteran Jakarta) (No. 46/III/2023/KEPK). Blood sampling was performed through the lateral veins of the rat tails using lidocaine cream as a local anaesthetic. Blood collection was performed using a syringe of as much as 0.5 ml in each blood sampling, accommodated in a tube containing heparin. Blood sampling was performed at 30, 60, 120, 180, and 240 min. The study was divided into two groups, namely the control and treatment groups, as seen in Table 1.

Table 1. Test Group

Group	Test treatment
Control group	Paracetamol 9mg/200g BW rats orally
Treatment groups	a) Paracetamol 9mg/200gBW rats, Moringa leaf extract 60mg/200gBW rats orally b) Paracetamol 9mg/200gBW rats, sappan heartwood extract at 294mg/kg BW rats orally

Redetermination of paracetamol levels added to the blood (recovery)

The principle of this method is based on the reaction of paracetamol (n-acetyl-p-aminophenol), which results from the deproteinisation of a sample with sodium nitrite to form 2,4-nitro-4-acetaminophenol, which turns yellow in an alkaline medium [46]. Blood samples (0.5 ml) from the test subjects were placed in a test tube, and a secondary raw solution (0.5 ml) was added. Then, 5 ml of 3% TCA was added and homogenised with a vortex for 30 s. The mixture was centrifuged for 10 min at 3000 rpm, and 2 ml of the supernatant was transferred to another test tube using a micropipette. Then, 0.5 ml of 0.07 M sodium nitrite was added, and the mixture was vortexed for 5 s. The samples were incubated for 10 min in a water bath at 37°C ± 1, 100 µl of 8 M NaOH was added, and the samples were homogenised using a vortex for 30 s. The absorbance was measured at the maximum λ [46].

Determination of paracetamol levels in the blood by the UV-Vis spectrophotometer method

Blood (0.5 ml) was collected from the treated test subjects and placed in a test tube for analysis. Then, 3% TCA (5 ml) was added, and the mixture was homogenised with a vortex for 30 s. The mixture was centrifuged for 10 min at 3000 rpm, and 2 ml of the supernatant was transferred to another test tube using a micropipette. Then, 0.5 ml of 0.07 M sodium nitrite was added and homogenised with a vortex for 5 s. The samples were incubated for 10 min in a water bath at 37°C ± 1, 100 µl of 8 M NaOH was added, and the samples were homogenised using a vortex for 30 s. The absorbance was then observed at the maximum λ [46].

Determination of Paracetamol Pharmacokinetic Profiles

Paracetamol pharmacokinetic profiles were determined using plasma concentration–time data obtained from both control and treatment groups. Pharmacokinetic parameters were calculated manually based on a one-compartment open model with first-order absorption and elimination.

Data analysis

The pharmacokinetic parameters were Ka, Cpmax, tmax, Vd, Ke, AUC, t½, and Cl. In the data analysis process using the assumption of the first-order extravascular compartment, one model with linear regression and residual methods was calculated using Microsoft Excel 2019. Residual methods help adjust curves to experimental drug data when the drugs do not follow a single-compartment model. The results were analysed using the Kolmogorov-Smirnov test as a test of distribution normality, followed by an unpaired t-test to determine the difference between two samples with a 95% confidence level in IBM SPSS Statistics 25 software.

Results and Discussion

In this study, UV-Vis spectrophotometry was used to determine the paracetamol levels. UV-Vis spectrophotometry is an easy-to-use, inexpensive, sensitive, and precise method for the quantitative analysis of compounds with chromophore and autochrome groups, such as paracetamol [48,49]. The maximum wavelength was determined because the wavelength of a compound can differ when determined under different conditions and using different tools. The maximum wavelength is the wavelength at which electronic excitation occurs, resulting in maximum absorbance. The purpose of measuring at the maximum wavelength is that the change in absorbance for each concentration unit is the greatest at the maximum wavelength, so that the maximum analytical sensitivity will be obtained [50]. In this study, the maximum wavelength of paracetamol was 244 nm. The maximum wavelength

indicates that paracetamol absorption is in the UV region because it is in the wavelength range of 200-400 nm. Theoretically, the maximum uptake of paracetamol is 244 nm [51,52]. Paracetamol standard curve methods were adapted from Barros [46].

Method linearity was evaluated by constructing a calibration curve using paracetamol standard solutions over a concentration range of 20–300 mg/L. Absorbance measurements were performed at the optimum wavelength of paracetamol (244 nm), and corrected absorbance values were calculated by subtracting the blank absorbance from the sample absorbance. Linear regression analysis demonstrated a proportional relationship between paracetamol concentration (x) and corrected absorbance (y), yielding the regression equation: $y = 0.0091x + 1.2779$, with a correlation coefficient ($r = 0.9956$). The calibration data for standard paracetamol solutions and the corresponding calibration curve are presented in Table 2 and Figure 1, respectively.

The correlation coefficient exceeded the commonly accepted threshold for analytical linearity ($r \geq 0.99$), indicating that the method exhibits acceptable linearity within the tested concentration range. The non-zero intercept is consistent with baseline absorbance and potential matrix-related effects inherent to UV–Vis spectrophotometric analysis of biological samples. Nevertheless, the calibration curve satisfied linearity requirements for quantitative determination of paracetamol concentrations in rat plasma for pharmacokinetic evaluation.

Table 2. Calibration Data for Paracetamol Standard Solutions

Working Blank Concentration (mg/L)	Standard Paracetamol Absorbance		
	Blanko	Sample	Corrected Absorbance
20	0,03371	1,42869	1,39498
50	0,03371	1,76886	1,73515
100	0,03371	2,25273	2,21902
150	0,03371	2,70441	2,6707
200	0,03371	3,19313	3,15942
250	0,03371	3,6539	3,62019
300	0,03371	3,94317	3,90946

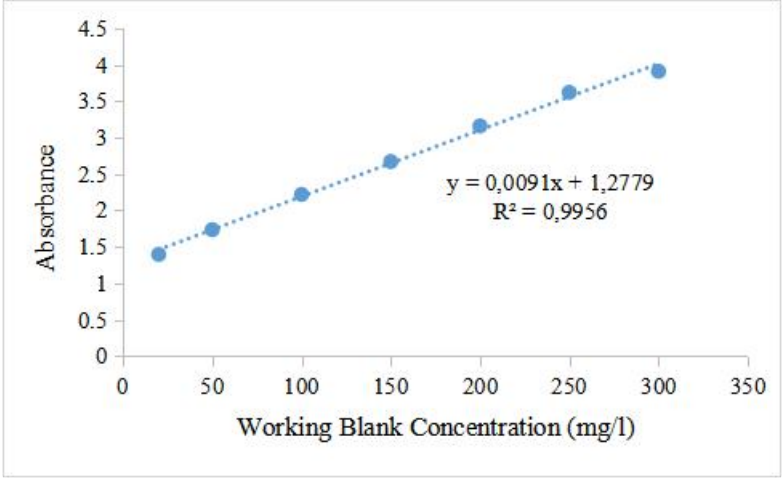

Figure 1. Calibration Curve of Standard Paracetamol

Accuracy was assessed using a recovery study by spiking known concentrations of paracetamol (20, 50, 100, 150, 200, 250, and 300 mg/L) into rat blood samples. Accuracy was expressed as percentage recovery (%), calculated as the ratio of measured concentration to nominal concentration. Linear regression analysis demonstrated a proportional relationship between paracetamol concentration (x) and corrected absorbance (y), yielding the regression equation: $y = 0.0084x + 1.386$, with a correlation coefficient ($r = 0.9956$). The recovery curve of paracetamol in rat blood under in vitro conditions and the accuracy parameters of the analytical method are presented in Figure 2 and Table 3, respectively.

A standard curve of a paracetamol standard solution was prepared to determine the relationship between absorbance and concentration; the higher the concentration of the standard solution, the greater the absorbance

obtained. At higher concentrations, paracetamol also increased. In addition, the Lambert-Beer law shows that changes in the concentration of a particular sample will change the absorbance at each wavelength by a constant factor [53]. A standard curve of paracetamol raw solution was prepared at concentrations of 20, 50, 100, 150, 200, 250, and 300 mg/L, measured by absorption at the maximum wavelength of paracetamol (244 nm), which gives the equation line Y = 0.0091x + 1.2779 with a correlation coefficient (r) value of 0.9956.

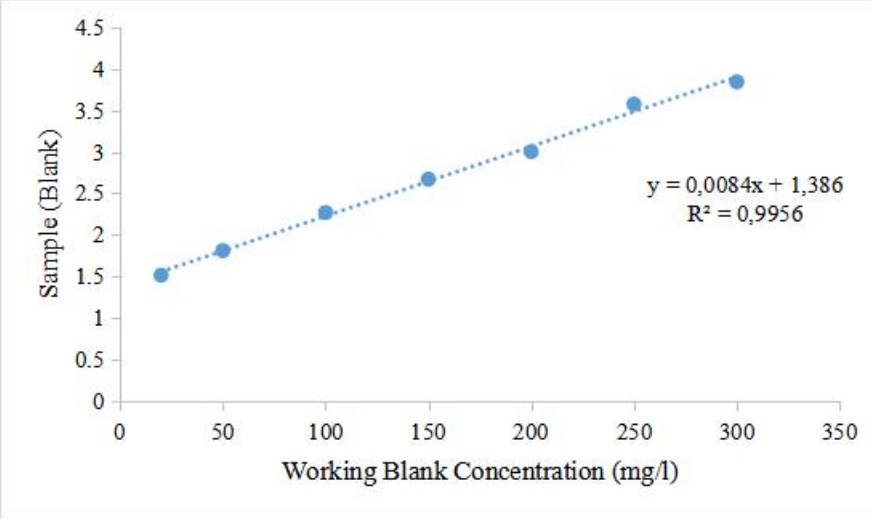

Figure 2. Recovery Curve in Rat Blood (in vitro)

Table 3. Accuracy Parameters

Working Blank Concentration (mg/L)	Standard Absorbance			Recovered Concentrations (mg/L)	Recovery (%)
	Blank	Sample	Sample (Blank)		
20	0,03371	1,54607	1,51236	25,765	128,824
50	0,03371	1,84293	1,80922	58,387	116,774
100	0,03371	2,30177	2,26806	108,809	108,809
150	0,03371	2,70441	2,6707	153,055	102,037
200	0,03371	3,03656	3,00285	189,555	94,778
250	0,03371	3,60933	3,57562	252,497	100,999
300	0,03371	3,87827	3,84456	282,051	94,017
% recovery means					106,605

The value of the correlation coefficient obtained was close to 1; therefore, it can be said that absorbance and concentration have a robust correlation and meet the acceptance criteria, namely the value of the correlation coefficient of $0.99 \leq r \leq 1$ [54,55,56]. The linear range value obtained shows that the standard curve applies the Lambert-Beer law, so that the line equation can be used to validate the paracetamol content determination methods using a UV-Vis spectrophotometer [53].

One of the validations of the method for determining paracetamol levels is an accuracy test; accuracy is a measure that shows the degree of proximity of the analysis results to the actual levels. Accuracy can also be determined by conducting a recovery test, and the accuracy test results can be expressed as a percentage of recovery (%recovery). The percentage recovery was calculated to determine the accuracy of the levels obtained. A good range of cent recovery values is 80–110% [57]. The average recovery value in this study was 106.6052%, which was a good value. The ideal recovery percentage is 100%; an increase in recovery indicates the addition of solvent-derived analytes during preparation [58].

Pharmacokinetic parameters are mathematically derived from the measurement of drugs or active metabolites in the blood or urine. Pharmacokinetic parameters are generally classified into primary, secondary, and derivative parameters. Primary parameters are pharmacokinetic parameters whose prices are directly influenced by the biological variables. Examples of primary parameters include Ka, Cl, and Vd. Secondary parameters are pharmacokinetic

parameters whose prices depend on the primary parameters. Examples of secondary parameters include t½ and Ke. In comparison, derived parameters depend on primary parameters and other quantities, for example, tmax, Cpmax, and AUC [59,60]. The pharmacokinetic parameters established in this study included the absorption, distribution, and elimination phases.

Table 4 shows the results of the unpaired t-test between the control and treatment groups. Statistical analysis indicated that administering sappan heartwood extract suspension at a dose of 294 mg/kg body weight to rats, along with paracetamol at a dose of 45 mg/kg body weight, resulted in a significant difference in the Vd parameter ($p < 0.05$). The Vd value was higher in the treatment group than in the control group. The parameters Cl, absorption half-life (t1/2 absorption), elimination half-life (t 1/2 elimination), AUC0-120, AUC0-inf, total AUC, ka, ke, Cpmax, and tmax did not show any significant differences or were similar between the control and treatment groups.

During the initial stage, extravascularly administered drugs are absorbed into the systemic circulation. The physicochemical properties of the drug, its dosage form, and the anatomy and physiology of the absorption site influence this process. Factors such as the surface area of the gastrointestinal tract, gastric emptying time, gastrointestinal motility, and blood flow to the absorption site affect the rate and extent of drug absorption for orally administered drugs [61] [62] [63]. Proper absorption is crucial for achieving the desired pharmacological effect, as delayed or incomplete absorption can lead to variable drug responses and therapeutic failure. Pharmacokinetic parameters involved in the absorption phase include Ka, Tmax, Cmax, and AUC [64], [65].

Drugs administered extravascularly undergo absorption to reach the systemic circulation. The physicochemical properties of a drug influence its absorption into the systemic circulation, the dosage form of the drug, and the anatomy and physiology of the site of absorption. In orally administered drugs, factors such as the surface area of the gastrointestinal tract and blood flow to the absorption site affect the drug absorption rate [66] [67]. The pharmacokinetic parameters in the absorption phase are Ka, tmax, Cpmax, and AUC.

Table 4. The values of pharmacokinetic parameters and the unpaired t-test for paracetamol in the control and treatment groups of Moringa leaf extract

Parameter	Parameter values (mean ± SD)		% Difference	p-value
	Control Group	Treatment Group		
Vd (mL)	141,30 ± 9,55	142,35 ± 31,16	0,73	0,96
Cl (mL/min)	0,14 ± 0,08	0,237415 ± 0,14	37,11	0,40
T½ elimination (min)	816,38 ± 503,04	583,85 ± 495,65	-39,83	0,60
AUC_{0-240} (mcg. min/mL)	17790,96 ± 926,16	20857,04 ± 3019,64	14,70	0,22
AUC_{0-inf} (mcg. min/mL)	100421,10 ± 62518,72	70751,19 ± 61276,14	-41,94	0,59
AUC TOTAL (mcg. min/mL)	118212,10 ± 61970,18	91608,23 ± 58799,20	-29,04	0,62
Ka (/min)	0,02 ± 0,01	0,03 ± 0,01	14,54	0,74
Ke (/min)	0,001 ± 0,0005	0,001 ± 0,001	39,62	0,38
Cp_{max} (mcg/mL)	0,68 ± 0,26	0,62 ± 0,24	-10,29	0,77
T_{max} (min)	199,58 ± 82,66	144,43 ± 38,04	-38,18	0,38

Note:
Control group (oral administration of paracetamol 9mg/200g BW rats)
Treatment group (oral administration of paracetamol 9mg/200g BW rats and Moringa leaf extract 60mg/200gBW rats)

The rate of absorption states that systemic absorption of a drug includes several reaction rate processes, including the process of dissolving the drug and transporting the drug across the cell membrane of the small intestinal wall. The results of the study showed that giving Moringa leaf extract together with paracetamol can increase the Ka value by 14.54%; this indicates that the rate of absorption speed of paracetamol given together with Moringa leaf extract is greater absorbed by the body than that given paracetamol alone [68]. The increase in the absorption rate occurs because Moringa leaves contain flavonoids in the form of quercetin 3-O-glucoside. Quercetin 3-O-glucoside is more easily absorbed than quercetin, rutin, and quercetin 3-O-rhamnoside because, in the small intestine, there is SGLT1, which acts as a membrane transport, so that it is absorbed more quickly by the body [69,68]. Moringa leaf extract and paracetamol affected the increase in absorption speed, but the results were not statistically significant ($p>0.05$).

The time taken by the drug to reach its maximum level in the blood is the maximum time required to reach its highest level. The tmax parameter is influenced by other parameters, namely, absorption speed and elimination. The

higher the absorption speed of the drug, the faster the time required to reach the maximum level or directly proportional; if the time required to reach the maximum level is fast, the elimination speed of the drug is faster or directly proportional. The sooner the drug reaches the max value, the faster the drug provides pharmacological effects [70] [71]. Based on the results of the research obtained showed that giving Moringa leaf extract together with paracetamol can reduce the tmax value by 38.1832%. The decrease in tmax showed that the drugs in the treatment group reached maximum levels and provided pharmacological effects faster than the controls. Moringa leaf extract and paracetamol administration affected the decrease in tmax value, but was not statistically significant ($p > 0.05$).

Cpmax is the maximum concentration of the drug in plasma after oral administration. The concentration of drugs in plasma can affect the pharmacological effects of a drug. Cpmax can indicate that the drug is absorbed systemically enough for a therapeutic response. In addition, Cpmax can also provide clues to the possible presence of toxic levels of the drug [72] [73]. Cpmax is inversely proportional to the Kel value; the lower the Ke resulting in higher Cpmax [74]. In this study, the value of Ke in the treatment group was higher than that in the control group, resulting in a lower Cpmax (maximum plasma concentration) in the treatment group than that in the control group. The results showed that administering Moringa leaf extract along with paracetamol reduced the Cpmax value by 10.2933%. The decrease in Cpmax values showed that the drugs in the treatment group could provide pharmacological effects faster than those in the control group. Moringa leaf extract and paracetamol affected the decrease in Cpmax value, but the effect was not statistically significant ($p > 0.05$).

Table 5: The values of pharmacokinetic parameters and unpaired t-test for paracetamol in the control and treatment groups of Caesalpinia sappan.

Pharmacokinetic Parameters	Parameter values (mean ± SD)		% Difference	p-value
	Control	Treatment		
Vd (mL)	141.30±9.56	781.59±41.81	453.11	$1.05x10^{-8}$*
Cl (mL/minute)	0.15±0.08	0.58±0.92	286.74	0.28
T1/2 absorption (minute)	56.00±45.42	35.13±17.86	-37.27	0.09
T1/2elimination (minute)	816,38±503.04	8457.17±8514.54	935.94	0.19
AUC0-120 (mcg.menit/mL)	17791±926.16	24645.73±521.74	38.53	0.39
AUC infinity (mcg. minute /mL)	100421±62518.72	1400791±1357095	1294.92	0.34
AUC TOTAL (mcg. minute /mL)	61970.20±61970.18	1425437±1356688	2200.20	0.34
Ka	0.02±0.01	0.03±0.02	43.55	0.11
Ke	0.00±0.00	0.0007±0.001	28.91	0.14
Cpmax	0.26±0.26	0.82±0.25	214.86	0.07
Tmax	199.58±82.66	219.81±123.99	10.13	0.24

Note:
Control group (oral administration of paracetamol 9 mg/200g BW)
Treatment group (oral administration of paracetamol 9 mg/200gBW rats, sappan heartwood extract 294 mg/kg BW)

The AUC parameter reflects the total number of active drugs that reach the systemic cycle. The value of the AUC parameter is closely related to the Vd parameter; the more significant the Vd price of a drug, the smaller the AUC price of the drug [75]. The AUC value is affected by Cpmax and t½. The AUC is directly proportional to the rate in the plasma and time. The AUC value of a compound corresponds to the Cpmax value. The greater the AUC value obtained, the greater the Cpmax value, resulting in a longer time to eliminate and vice versa [76]. AUC0-t is used when drug concentration measurements are available only until a specific time or when the concentration decreases significantly after the last measurement. AUC0-inf is used when the drug concentration is measured for a long enough period, and the drug concentration can still be measured accurately after the last measurement [77,78]. The results of the study obtained showed that giving Moringa leaf extract together with paracetamol could increase the AUC0-240 value by 14.70%, while the results on AUC0-inf obtained showed that giving Moringa leaf extract together with paracetamol decreased the AUC0-inf value by 41.95%. AUC0-t and AUC0-inf are not always directly proportional to each other.

Several factors can affect the relationship between AUC0-t and AUC0-inf, including the rate of absorption and elimination of the drugs. Suppose that drug absorption occurs rapidly and drug elimination is relatively slow. In this case, AUC0-t accounts for most of the drug exposure, and AUC0-inf makes a negligible contribution to the total drug exposure. Increased Cl values indicate that the drug is rapidly metabolised and eliminated from the body. An increased

Cl value resulted in an increased AUC0-t because most of the drug was eliminated or metabolised. However, because the drug is rapidly eliminated, AUC0-inf, reflecting total drug exposure over an infinite period, will decrease [77,78]. In this study, the total AUC decreased by 29.0409%. The AUC is a measure of the bioavailability of a drug. A decrease in AUC indicates that the number of drugs available in the body is decreasing. A decrease in AUC indicates that paracetamol administered along with Moringa leaf extract is not absorbed properly, which causes the active substances that successfully move from the gastrointestinal tract to the systemic circulation less that bioavailability is low [79]. Moringa leaf extract and paracetamol administration increased AUC0-240, decreased AUC0-inf, and decreased total AUC; however, the differences were not statistically significant ($p>0.05$).

After a drug is absorbed into the plasma, the drug molecules are distributed throughout the body via the systemic circulation. Blood carries drug molecules to receptors to provide drug action, and some are carried to tissues where adverse reactions may occur. Drug distribution generally occurs rapidly, and most small drug molecules easily penetrate the capillary membranes. The speed of blood flow affects how fast and how much of the drug reaches the receptor side [80,81] . The distribution of drugs is influenced by weight and body composition, including body fluids, muscle mass, and function. Vd represents the blood circulation in various organs. Vd is the pharmacokinetic parameterised with the distribution phase [82].

The concentration of drugs in plasma or tissues is determined by the total amount of drug absorbed systemically and the volume of distribution. The volume of distribution is used to approximate the extent of drug distribution throughout the body [80,83,84]. Drug distribution is influenced by body weight and composition, including body fluids, muscle mass, function, and blood circulation in various organs [82,85,86]. The results showed that the administration of Moringa leaf extracts together with paracetamol increased the Vd value by 0.7349%. The increased Vd of paracetamol was probably due to competition between the binding of the drug and plasma proteins. The volume of distribution is related to the pharmacological response of the drug. The greater the volume of distribution of a drug, the greater the amount of free drug that reaches the receptors; therefore, the resulting pharmacological response is more pronounced [87,88,89]. The increase in Vd occurred because the flavonoids in the moringa leaf extract have lipophilic properties [90]. Drugs with lipophilic properties have a large Vd because they can be distributed to the adipose tissue and intracellularly [91]. The administration of Moringa leaf extract and paracetamol affected the increase in Vd; however, the difference was not statistically significant ($p> 0.05$).

Drugs are excreted from the body through various elimination processes. Drugs are eliminated from the body through various routes. Metabolism is divided into two main components: metabolism (biotransformation) and excretion. Metabolism converts drug molecules into other chemical forms, called metabolites, which are usually mediated by enzymatic reactions. Elimination is the clearance of drugs from the body via the kidneys and bile ducts. The liver and kidneys are the main organs responsible for elimination from the body. The kidneys are the primary excretory organs responsible for removing metabolic waste products and play a crucial role in maintaining the body fluid volume and electrolyte composition [80.92]. The pharmacokinetic parameters that describe the elimination phase include Cl, Ke, and t½.

Cl is the primary parameter that explains the elimination kinetics of paracetamol. The Cl parameter significantly influences the elimination kinetics of a drug; the higher the Cl value, the faster the drug is eliminated from the body. The process of drug elimination from the body is influenced by the metabolic process of the drug; the faster the metabolic process of a drug, the faster the drug is eliminated from the body. The results showed that the administration of Moringa leaf extract and paracetamol increased the Cl value by 37.1143%. The treatment group had a better Cl value, indicating that the paracetamol metabolic process was fast, causing paracetamol to be excreted from the body more quickly [93] [80,94]. The increase in metabolic rate in the treatment group could be caused by paracetamol and flavonoids contained in Moringa leaf extract, which resulted in interactions that induced CYP enzymes [40]. CYP enzymes in mice and humans are generally similar, and the similarity is higher in Sprague-Dawley rats than in other rat strains [95]. The induced cytochrome p450 enzyme is a paracetamol metabolising enzyme, causing paracetamol metabolism to proceed quickly [96]. The administration of moringa leaf extract and paracetamol affected the increase in clearance, but the difference was not statistically significant ($p> 0.05$).

Ke indicates the speed at which the body eliminates; Ke is slower than Ka. The relationship between Ke and Ka is inversely proportional [68]. The Cl parameter greatly influences the values of Ke and t½ parameters, where the higher the Cl, the higher the Ke value, and the drug is quickly eliminated from the body (low t½) [96]. The control group had the lowest Cl and Ke values; therefore, it had the highest t½ value. Furthermore, the treatment group had a high Cl and Ke value; therefore, it had the lowest t½ value. The results showed that the administration of Moringa leaf extract and paracetamol increased the Ke value by 39.6152%. The administration of Moringa leaf extract and paracetamol affected the increase in Ke, but the difference was not statistically significant ($p> 0.05$).

T½ is the time required for the drug to reach half of its initial plasma concentration. T½ is a constant number, regardless of dose size, administration interval, plasma level, and route of administration. The half-life (t½) is related to the absorption and elimination rates. The longer the t½, the longer it takes for the compound to decrease from its

initial level and the longer the elimination process from the plasma. Conversely, if t½ is obtained quickly or shows a small value, the levels of these compounds decrease quickly from the initial levels and are eliminated from the plasma in a short period [97,98]. Based on the research results obtained, administering moringa leaf extract together with paracetamol reduced the t½ value by 39.8271%. The administration of moringa leaf extract and paracetamol affected the decrease in t½, but the effect was not statistically significant ($p>0.05$).

The findings indicate that co-administration of sappan heartwood extract with paracetamol delayed the Tmax of paracetamol by 10.133%. This delayed Tmax aligns with previous studies on the impact of phenolic compounds on paracetamol absorption [99]. Furthermore, the study revealed a 37.268% reduction in absorption half-life (t½). While a slower Tmax is typically caused by a decrease in the absorption rate (Ka), this study observed an increase in the absorption rate (Ka). Therefore, the increased absorption rate may only affect the decrease in the absorption half-life, whereas the increase in Tmax is likely influenced by other unidentified factors.

An increase or delay in Tmax implies that the drugs in the treatment group require more time to reach their maximum concentration, resulting in a longer time to achieve pharmacological effects compared to those in the control group [80,100]. However, the increase in Tmax was not statistically significant between the control and treatment groups ($p>0.05$). This indicates that the administration of sappan heartwood extract at a dose of 294 mg/kgBW in rats, along with paracetamol at a dose of 45 mg/kgBW, affects the Tmax of paracetamol, but the effect is not statistically significant. These findings differ from those of previous studies, in which flavonoid content significantly affected the Tmax of paracetamol when administered concurrently [101]. This discrepancy may be attributed to the presence of other compounds in the sappan heartwood extract or differences in the concentrations of the studied flavonoids.

The peak plasma concentration (Cpmax) is a secondary pharmacokinetic parameter that reflects the observed maximum drug concentration in plasma after oral administration, typically coinciding with Tmax. Cpmax, like Tmax, is influenced by absorption and elimination rates [98]. It serves as an indicator of the pharmacological response to a drug, as the response depends on the drug concentration in the body. Higher plasma drug concentrations within the therapeutic range generally lead to better pharmacological responses [80,102].

Based on Table 5, the study findings demonstrated a significant 214.860% increase in Cpmax when sappan heartwood extract was administered concurrently with paracetamol. This increase in Cpmax may be attributed to the enterohepatic cycle of paracetamol within the body. Paracetamol that undergoes enterohepatic circulation is more effectively absorbed, resulting in higher plasma concentrations. Oral administration of drugs involves the enterohepatic cycle during absorption, and paracetamol can undergo this cycle via its glucuronidation metabolic pathway, in which the conjugated form of paracetamol participates in the enterohepatic cycle [96]. The observed increase in Cpmax is consistent with previous studies on the influence of phenolic compounds on paracetamol [99]. However, this increase was not statistically significant between the control and treatment groups ($p>0.05$). This suggests that the administration of sappan heartwood extract at a dose of 294 mg/kgBW in rats, along with paracetamol at a dose of 45 mg/kgBW, affects the Cpmax of paracetamol, but not significantly. These findings are consistent with those of previous studies in which the flavonoid content did not yield a statistically significant difference in the Cpmax of paracetamol when administered concurrently [101].

The area under the curve (AUC) is a pharmacokinetic parameter influenced by dose, drug administration rate, and primary parameters. It measures the total amount of intact drugs that reach the systemic circulation. The AUC depends on the fraction of the drug absorbed, the absorption rate, and the volume of distribution. For oral administration, the absorbed drug fraction ranged from 0–1. The AUC is independent of the drug administration route and elimination process. Some drugs exhibit a proportional relationship between the AUC and dose, whereas others show dose-dependent kinetics. The intensity of a drug's action correlates with its AUC, which represents the total drug amount at the receptor site [80,103].

This study revealed a 38.529% increase in AUC0-120 when HE-SW was administered concurrently with para. However, this increase was not statistically significant between the control and treatment groups ($p>0.05$). Thus, the administration of 294 mg/kgBW of sappan heartwood extract alongside 45 mg/kgBW of paracetamol in rats affected the paracetamol AUC, albeit without a statistically significant difference. These results differ from those of previous studies, which showed a significant influence of flavonoid content on the AUC of paracetamol when administered concurrently [101]. Possible reasons for this discrepancy include the presence of other substances in the sappan heartwood extract or variations in the flavonoid concentrations examined.

Drugs are systemically distributed throughout the body upon absorption into the bloodstream. They are transported by blood to target receptors to exert their pharmacological effects, whereas some may reach tissues where adverse reactions occur. Drug distribution generally occurs rapidly, with small drug molecules easily crossing the capillary membranes. The rate of blood flow determines the speed and amount of drug that reaches the receptor site [80,104].

The volume of distribution (Vd) is a primary pharmacokinetic parameter that characterizes drug distribution and represents the theoretical volume in which the drug is uniformly dissolved [96]. Vd is used to estimate the extent of drug distribution in the body [105]. It is influenced by the physicochemical properties of the drug, characteristics of the capillary membranes, and the balance between free drugs and drugs bound to plasma proteins [106,107]. Lipid-soluble drugs generally traverse capillary membranes more easily than water-soluble drugs, and smaller drug molecules diffuse more rapidly than larger drug molecules. The binding of a drug to plasma proteins increases its effective size [80]. A higher fraction of free drugs leads to an increased Vd, whereas a greater proportion of protein-bound drugs results in a reduced Vd [87,108]. Paracetamol exhibits low plasma protein binding (10-30%) [109]. Vd is associated with the pharmacological response of the drug. A larger Vd allows more free drugs to reach the receptors, resulting in a more pronounced pharmacological effect [87,110,111].

The present study revealed that the concurrent administration of sappan heartwood extract with paracetamol caused a significant 453.108% increase in the volume of distribution of paracetamol. The elevated Vd of paracetamol may be attributed to competition for drug binding to plasma proteins [80,112]. The observed difference in Vd between the control and treatment groups was significant ($p<0.05$). These findings indicate that the co-administration of sappan heartwood extract at a dose of 294 mg/kgBW with paracetamol at a dose of 45 mg/kgBW in rats significantly affects the volume of distribution of paracetamol. These results align with those of previous studies, demonstrating the significant impact of flavonoid content on the Vd of paracetamol when administered concurrently [101].

Drug elimination involves irreversible processes through various routes in the body. It consists of metabolism and excretion, with the liver and kidneys playing major roles [80,92]. Metabolism involves the enzymatic conversion of drugs into metabolites, whereas excretion removes drugs from the kidneys or bile. The primary pharmacokinetic parameters for elimination are clearance (Cl), elimination rate constant (k), and elimination half-life (t½) [113,114].

Clearance represents the rate at which a drug is eliminated and is determined by the volume of drug cleared per unit time [113,115]. Total clearance encompasses all elimination processes in the body, including renal, pulmonary, and hepatic clearance. It depends on the constants k and Vd, which are influenced by the blood flow rates. Clearance is influenced by organ function and blood flow [80,116].

Sappan heartwood contains flavonoid glycosides that are metabolised in the liver via phase I and II reactions. Phase I involves CYP450 enzymes, which are also involved in the metabolism of paracetamol. Phase II includes methylation, sulfation, and glucuronidation. Metabolites are excreted in bile and urine and potentially undergo enterohepatic circulation. After distribution, conjugates bind to plasma proteins, such as albumin, and paracetamol also binds to albumin [68].

The study showed a 286.743% increase in paracetamol clearance when it was administered with sappan heartwood extract. However, the difference in clearance between the control and treatment groups was not statistically significant ($p>0.05$). Thus, the concurrent administration of 294 mg/kgBW sappan heartwood extract and 45 mg/kgBW paracetamol in rats influences paracetamol clearance but lacks statistical significance.

The elimination rate constant (Ke) is a secondary pharmacokinetic parameter that represents the elimination of a drug from the body. Ke is influenced by total clearance (Cl) and volume of distribution (Vd). In this study, the concurrent administration of sappan heartwood extract (294 mg/kgBW) with paracetamol (45 mg/kgBW) in rats increased the paracetamol elimination rate by 28.913%. However, the increase in Ke was not statistically significant compared with that in the control group ($p>0.05$). This suggests that the combined treatment affects the Ke of paracetamol, but the effect is not statistically significant.

The elimination half-life (t1/2) is a pharmacokinetic parameter that represents the time required for the concentration of a drug in the body to decrease by half. It is influenced by factors such as total clearance (Cl) and drug elimination rate (Ke) [117]. A longer t1/2 indicates a prolonged presence of the drug in the body, leading to a longer pharmacological effect of the drug. Total clearance and elimination rate are inversely related to t½, meaning that higher clearance and elimination rates result in shorter t1/2 values, indicating faster drug elimination [80]. Previous research has suggested that the co-administration of paracetamol with phenolic compounds can increase its elimination half-life [99].

The study found that The simultaneous administration of sappan heartwood extract and paracetamol resulted in a significant 935.941% increase in the elimination half-life of paracetamol. The treatment group exhibited a longer t½ than the control group. This prolongation of t½ can be attributed to the increased volume of distribution (Vd) of paracetamol due to the administration of sappan heartwood extract. Other factors that may contribute to t1/2 variation include genetic differences in hepatic enzyme activity, enzyme induction or inhibition, age, nutrition, and pathological conditions [118]. The extended t½ leads to a longer duration of paracetamol action in the body, resulting in a prolonged pharmacological response. t½ is often used to guide the dosing frequency of drugs to prevent their accumulation and potential toxicity. A higher t½ value indicates a less frequent dosing schedule[119,120]. However, the increase in t½ observed in this study was not statistically significant between the control and treatment groups

($p>0.05$). This suggests that the concurrent administration of 294 mg/kgBW sappan heartwood extract with 45 mg/kgBW paracetamol in rats affects the t½ of paracetamol, but the effect is not statistically significant.

Concurrent administration of sappan heartwood extract at a dose of 294 mg/kgBW in rats along with paracetamol at a dose of 45 mg/kgBW led to changes in the pharmacokinetic profile of paracetamol during the absorption and distribution phases. However, these changes were not statistically significant for any of the absorption phase parameters ($p>0.05$). An increase in the absorption rate constant (Ka) results in a shorter time to reach the maximum concentration (Tmax); however, it does not necessarily lead to an increase in the maximum concentration (Cmax) [121]. The increase in Ka affects the area under the curve (AUC), indicating a longer duration of drug action in the body [80]. Concurrent administration did not cause significant pharmacokinetic interactions during the absorption phase of paracetamol.

In the distribution phase, the administration of sappan heartwood extract with paracetamol significantly increased the volume of distribution (Vd) of paracetamol ($p<0.05$). The Vd parameter, which is related to the AUC, theoretically suggests that a larger Vd value leads to a smaller AUC value [96]. However, the observed increase in Vd may be attributed to data variation among the limited number of participants. The volume of distribution is inversely related to the concentration of the drug in plasma (Cp). When a drug is extensively bound to plasma proteins or is present in the bloodstream, the plasma drug concentration increases, resulting in a reduced Vd [80]. The increase in Vd may be due to factors such as decreased drug-protein binding, competition for protein binding, and fluid accumulation in the body [122]. Flavonoid glycosides in sappan heartwood extract may bind to albumin and reduce paracetamol binding to proteins [68]. This could potentially increase the free drug concentration, enhance drug distribution to other organs and tissues, and ultimately increase toxicity [122].

Overall, the concurrent administration of sappan heartwood extract at a dose of 294 mg/kgBW in rats along with paracetamol at a dose of 45 mg/kgBW significantly increased Vd in the distribution phase, indicating a potential pharmacokinetic interaction between the two drugs. Therefore, careful monitoring and avoidance of the combination of sappan heartwood extract and paracetamol are recommended.

The administration of sappan heartwood extract at a dose of 294 mg/kgBW in rats along with paracetamol at a dose of 45 mg/kgBW affected the pharmacokinetic parameters of paracetamol in the elimination phase; however, these changes were not statistically significant ($p>0.05$). Clearance influences the elimination rate constant (Ke) and elimination half-life (T1/2). Higher clearance values result in higher Ke values and faster drug elimination [96]. The research findings showed that the third treatment group had the highest Ke and Cl values, with the lowest T1/2. The fourth treatment group had the lowest Ke and Cl values and the longest half-life (T1/2).

Conclusion

The results of the study showed that the effect of administering moringa leaf extract at a dose of 60 mg/200 g BW to rats along with paracetamol at a dose of 9 mg/200 g BW to rats orally affected the parameters of paracetamol, but not significantly ($p> 0.05$). The effect of Moringa leaf extract on the primary parameters of paracetamol pharmacokinetics, namely, Ka, Cl, and Vd, increased by 14.5397 %, 37.1143%, and 0.73496 %, respectively. The effect of Moringa leaf extract on the secondary parameters of paracetamol pharmacokinetics, namely t½ elimination, decreased by 39.82706%, and Ke increased by 39.61517%. The effect of Moringa leaf extract administration on tertiary paracetamol pharmacokinetic parameters, namely Cpmax decreased by 10.29327%, tmax decreased by 38.18321%, AUC0-240 increased by 14.70046%, AUC0-inf decreased by 41.93556%, and total AUC decreased 29.0409%. The pharmacokinetic profile of paracetamol shows that the co-administration of sappan extract at a dose of 294 mg/kgBW in rats along with a dose of 45 mg/kgBW of paracetamol significantly affects the Vd of paracetamol, which is a primary pharmacokinetic parameter. The Vd value increased by 453.108% ($p<0.05$). Other parameters also showed an increase, but they were not statistically significant ($p>0.05$), such as Ka (43.551 %), Cl (286.743 %), Cmax (214.860 %), Tmax (10.133 %), Ke (28.913 %), T1/2 (935.941 %), and AUC (38.529 %).

Acknowledgment

This research was supported by the Research and Community Service Fund of LPPM UPN Veteran Jakarta under Grant, whose financial support and institutional guidance were instrumental in conducting this study. We thank the LPPM UPN Veteran Jakarta review panel for their valuable feedback and the laboratory staff for their assistance with data collection and compliance with the project.

Declarations

Author contribution	:	Dhigna Luthfiyani Citra Pradana contributed to the conceptualization and study design, data interpretation, and manuscript writing. Syifa Nur was responsible for data collection, data curation, and formal analysis. Annisa Ayu Nur Hakim contributed to laboratory work, assisted with statistical analysis, and participated in manuscript editing. Eldiza Puji Rahmi contributed to methodology development, data acquisition, and validation of the results. Annisa Farida Muti provided supervision and was responsible for project administration.
Funding statement	:	This research was supported by the Research and Community Service Fund of LPPM UPN Veteran Jakarta under Grant, whose financial support and institutional guidance were instrumental in the execution of this study.
Conflict of interest	:	The authors declare no nflicts of interest related to this study. If any potential conflicts arise during the final manuscript preparation, please disclose them here with a brief description of the nature of the interest and its relevance to the work.
Ethics Declaration	:	This study was conducted in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval was obtained from the relevant ethics committee of UPN Veteran Jakarta (approval number: 46/III/2023/KEPK). All procedures involving animals were approved by the UPN Veteran Jakarta Ethics Committee (permit number 46/III/2023/KEPK) and followed the national guidelines for the care and use of laboratory animals. Data collection, handling, and reporting complied with applicable ethical guidelines and privacy protection.
Additional information	:	There is not any more information available for this paper.

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