

EFEK EKSTRAK DAUN KELOR (Moringa oleifera) TERHADAP KADAR GLUKOSA DARAH TIKUS DIABETES INDUKSI ALOKSAN

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Absorption of Flavonoid Rutin after oral Treatment of Carica papaya Leaf Extract

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Abstract. Carica papaya leaves have many benefits, such as cancer treatment, lactation, digestive problem, and dengue fever. Papaya leaves contain various bioactive components such as alkaloids, flavonoids, tannins, saponins, carbohydrates, proteins, fats and steroids. Rutin is a flavonoid contained in Carica papaya leaf. Utilization of Carica papaya leaves as a herbal remedy requires data safety, effectiveness, bioavailability and stability of bioactive compounds of herbal medicine in the body. This study aimed to explore Carica papaya leaf extract's absorption by measuring the serial flavonoids in the plasma. The flavonoid profile of plasma was analogue by Rutin concentration profile. Time-series designs were conducted on fourteen rats were divided into seven groups. The single dose of papaya leaf extract (900 mg dissolved in 2 mL of aquadest) was given orally. Blood samples were collected about 1.5 mL at 0.5, 1, 2, 4, 6, 12 and 24 hours after oral administration. HPLC measured plasma Rutin flavonoid level. The maximum concentration (C_{max}) was 0.026 mg/mL that reach 4 hours after oral administration (T_{max}). The half-time (t_{1/2}) was 94.683 hours, and the area under the curve (AUC₀₋₄) was 0.362 mg. h/mL. Carica papaya leaf extract was slowly absorbed and stayed in the plasma for a long time. The implication of the data of flavonoid profile can be used to manage the dose and frequency of extract oral treatment.

Key words: carica papaya, flavonoid, HPLC, pharmacokinetic

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INTRODUCTION

Papaya leaves have many benefits, such as cancer treatment, lactation, digestive problem, dengue fever (Otsuki et al., 2010) and malaria (Ihwan & Koda, 2017). Herbal juice of papaya leaves increases the platelets in the patients with dengue (Kala, 2012). Dengue and leaf juice also affected in hematology of anemic mice (Hamidah et al., 2017). More than its fruit and seeds, the highest antioxidant found in papaya leaves, thus shown its potential that promises to be utilized as a secondary antioxidant (Maisarah et al., 2013) and anti-inflammatory (Vaishali, 2014). Utilization of papaya leaves as a herbal remedy requires data security, effectiveness, bioavailability and stability of bioactive compounds of herbal medicine in the body through the plasma or serum. Papaya leaf extract as a model in drug discovery must fulfil the requirements of pre-clinic tests to strengthen data and information in the framework of industrial development medicinal herbs.

Carica papaya leaves contain various bioactive components such as alkaloids, flavonoids, tannins, saponins, carbohydrates, proteins, fats and steroids (Somayaji et al., 2016). The extract by phytochemical screening results was found alkaloids, poly-phenolates, tannins, flavonoids,

monoterpene and sesquiterpene compounds. Flavonoids from the extract were the main substance from a primary bioactive compound of whole papaya leaves. The presence of flavonoids in papaya leaf extract reached 0.23% from the isolated flavonoids result of papaya leaves (Musa, 2015). According to (Zunjar et al., 2014), the levels of total flavonoids in papaya leaves occupied a middle position between the highest (seeds and papaya fruit) and the lowest (root and stem of papaya plant), i.e. 9.09 µg Qtn/mg.

Flavonoids that orally enter the body will run into the absorption, distribution, metabolism, and excretion (ADME) process. Bioactive components of flavonoids in plants can be absorbed and reach the systemic circulation. Then with or without the biotransformation process, flavonoids were excreted out from the body. The entire process is known as the pharmacokinetics process and passes off simultaneously. The pharmacokinetics of a substance is used for conceiving the correlation between its physiochemical physically and its pharmacology or clinical effects (Shargel L & Yu AC, 2016). Pharmacokinetic, utilizing its parameters, discuss the correlation substance levels in plasma over time in the body, which may explain the presence

of several substances in the body at any given time. Pharmacokinetic parameters describe the effectivity of substances which can be used to declare how long are the period of effective substances in the body.

Humans must consume the safety and effectiveness data of substances. Pharmacokinetics studies must be learned, including its blood level profile, distribution pattern and excretion after administering papaya leaf extract in rats. Kinetic data of substance in the body are very important to determine the correlation between substance levels in the body and the rate of absorption. The absorption data of substances in plasma can be used as the profile of substance level development in the body. Based on the background, furthermore study about the pharmacokinetic profile of flavonoid Rutin level of *Carica papaya* leaf extract were needed, especially in the development and utilization of papaya leaf extract as herbal medicine.

METHODS

Experiment Animal

This study used male Wistar rats between 2-3 months old with an average weight of 215.36 g. Fourteen rats were divided into seven groups to take blood samples on each time series with twice repetition (Duplo). Rats were obtained from Biology Laboratory, FMIPA UNNES. Each rat was only used once per time series they were acclimatized (for 5 days) and were fasted for 12 hours with free access to water (ad libitum) (Ouyang et al., 2013). The research using experimental animals has received a permission letter from the Ethics Committee of the State University of Semarang by the ethical clearance number 049/KEPK/EC/2018.

Plasma Collecting

A single dose of *Carica papaya* leaf extract (900 mg dissolved in 2 mL of aquadest) was given orally. Blood samples were collected about 1.5 mL at 0.5, 1, 2, 4, 6, 12 and 24 h after an oral administration of *Carica papaya* leaf extract. Blood samples were occupied in heparinized microtubes. Then immediately centrifuged at 3000 rpm for 5 min (40°C). Plasma samples were taken and stored in a -20°C freezer until analysis (Kanimozhi, 2016.).

Flavonoid Rutin concentration analysis in papaya leaf extract and plasma

Flavonoid containing extract was analyzed using the HPLC-UV VIS C-18 column. The mobile phase consisted of 73 % methanol and water (99.5:0.5) (solvent A) and 27 % acetonitrile (solvent B), pH adjusted to 3.64 with glacial acetic acid. The separation was performed under an isocratic condition with a constant flow rate of 1.5ml/min, column temperature 25°C and the detector wavelength 347 nm.

The first step of HPLC measurement was to determine the standard curve. The standard curve was made by dissolved 1.04 g of Rutin in the 1000 mL methanol as Rutin standard solution (Lu et al., 2013). It used five different concentrations of Rutin that are 200, 100, 50, 25, and 12.5 ppm. The equation of the standard curve was arranged from the result of five doses of Rutin.

Analysis of flavonoid concentration in papaya leaf extract was done by dissolved 0.5 g papaya leaf extract in 50 ml methanol. Then, a solution of papaya leaf extract was injected into the HPLC column. The result of this stage was that the total of 900 mg extract contained 33.903 mg of flavonoid.

Analysis of concentration flavonoids in plasma was done by adding 1.0 mL methanol into 0.1 mL plasma then shaking until homogenous. The flavonoid plasma was filtrated into a sterile tube reaction using a 0.45 µm filter membrane (RC-membrane). The filtrate was injected into the HPLC column. The result was analyzed using linear regression of the Rutin standard curve and plasma. The measurement of flavonoid content in plasma on each time series was done. The result obtained was analyzed using Microsoft Excel for obtaining standard curve equations.

Data analysis

Pharmacokinetic parameters consist of Area Under Curve (AUC), maximum substance concentration in the plasma (C_{max}), time for peak plasma level (T_{max}) and half-life time ($t_{1/2}$). Pharmacokinetic parameters were analyzed descriptively. The data were analyzed by comparing the flavonoid level in plasma rate based on time series.

RESULTS AND DISCUSSION

Plasma Levels of Flavonoid Rutin

Calculation of plasma levels of flavonoids based on the area square data of samples were obtained by chromatogram of HPLC. The area

square data of five concentrations of standard solutions were obtained from the standard curve equation of flavonoids $y = 53243x - 143400$. Calculation results of plasma levels of flavonoids are shown in Figure 1. Figure 1 demonstrated the absorption and elimination process rate during 0-24 hours in the body after administration of papaya leaf extract. During the absorption phase in the plasma levels of flavonoids time curve, the absorption rate was higher than the elimination rate. The absorption phase predominated in plasma levels of flavonoids curve rather than the elimination phase. Figure 1 described plasma levels of flavonoids time series were calculated about its value of the pharmacokinetic parameters

AUC was an area under the plasma concentration-time curve, and $t_{1/2}$ was a half-life of absorption.

Plasma levels of flavonoids time curve obtained pharmacokinetic parameters. The $t_{1/2}$ value was measured by the formula $t_{1/2} = 0.693/K$. The AUC_{0-t} value was measured by accumulating each area between two times spaces serially on plasma levels of flavonoids time series curve using the trapezoidal rule. T_{max} and C_{max} values were obtained by observation of Figure 1. All of the data in Table 1 expressed about values of the pharmacokinetic profile of flavonoids in plasma after papaya leaf extract administration

Pharmacokinetic parameters explained the effectivity of substance that might be used to

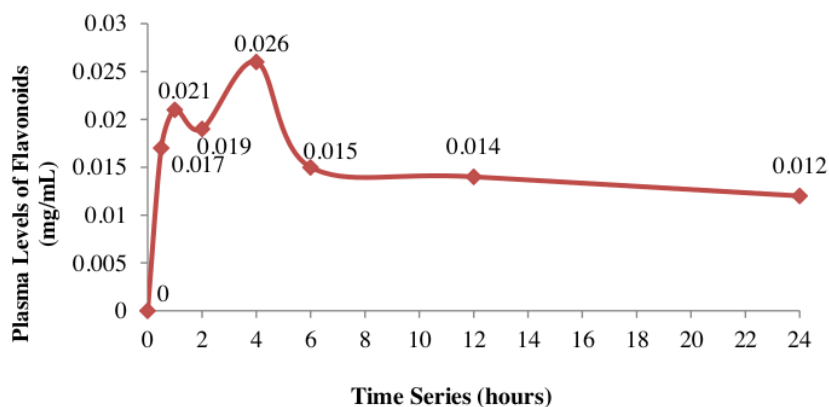


Figure 1. The curve of plasma levels flavonoid after an oral administration of 900 mg of papaya leaf extract

AUC_{0-t} , K_a , and $t_{1/2}$. Data of C_{max} and T_{max} were obtained from Figure 1.

The Pharmacokinetic Parameters of Papaya Leaf Extract Flavonoids in Plasma

Pharmacokinetic data were demonstrated by T_{max} , C_{max} , AUC_{0-t} and $t_{1/2}$ values. The parameters expressed in the absorption and distribution are in Table 1. T_{max} was a corresponding time for obtained maximum levels in plasma. C_{max} was a maximum plasma level.

declare how long the period of substance effective in the body was—pharmacokinetics data of flavonoids plasma as an implication for determining drug administration frequency in the further experimental subject. Furthermore, studies about the pharmacokinetic profile of flavonoids levels of papaya leaf extract were needed. It would be necessary for drug development, especially for using papaya leaf extract as a medicinal herb.

The whole extract of papaya leaf contains a bioactive compound that biotransformation

Table 1. Pharmacokinetics data of Rutin plasma after giving of Carica papaya leaf Extract orally

Pharmacokinetic Parameter	Value ± SD	
T_{max}	4	h
C_{max}	0.026 ± 0.005	mg/mL
$t_{1/2}$	94.683	h
AUC_{0-t}	0.362 ± 0.05	mg h/mL
K_a	0.017	mg/h
K	0.0073	mg/h

process performed slowly in the liver. Study that some components in papaya leaf extract were potential as antioxidants such as tocopherol, lycopene, quercetin glycosides, and benzylthiocyanates. Qualitatively, phytochemical screening for papaya leaf extract contains alkaloids, flavonoids, glycosides, tannins, and saponin (Begum, 2014). Flavonoids contain in papaya leaf extract belong to flavonols group such as Rutin. Rutin had performed Pre-treatment analysis as a standard solution. Rutin as standard included to flavonols group. Flavonoids that were detected in a sample of papaya leaf extract was Rutin. Rutin was a glycosides form of quercetin (glycosides quercetin)(Kelly GS, 2011).

C_{max} value of papaya leaf extract had reached at 4 h (T_{max}), i.e. 0.026 mg/mL. If it was compared by the result of Yang et al. (Ou-Yang et al., 2013) study after 4 g/kg mulberry leaf extract, the T_{max} result, i.e. 1 h, indicating that the rate of absorption of papaya leaf extract more slowly to appeared into pharmacological effect in the body. Observation by K_a result of flavonoids of mulberry leaf extracts, i.e. 0.358 mg/h, whereas flavonoids of papaya leaf extract, i.e. 0.017 mg/h. In another study, *Artemisia frigida* extract at 0.5 g/kg BW dose only needed 2 hours to reach C_{max} . T_{max} value which was lower than others, noticed that just a few times as needed to reach C_{max} and the rate of absorption was rapid.

The previous study needed at the same time, i.e. 4 h, to reach peak concentration of pure Rutin at dose 500 mg/kg BW per oral (Boyle et al., 2000). It means the time reached to appear effective in the body and the absorption rate were both the same. T_{max} at some studies were compared to each the rate of flavonoids absorption from herbal extract or flavonoids in the pure form. Flavonoids levels had not occurred a descent yet at 24 h. The same thing occurs with C_{max} ,

The AUC value appeared the bioavailability of *Carica papaya* leaf extract, which observes the plasma concentration over a given time. Bioavailability depends on the form of remedies, and the mode of administration, by the intravenous way as the gold standard. The bioavailability of flavonoids increased when loaded in nanocarrier (Bilia et al., 2014). AUC was on the same line with the dose. Another study asserted that AUC at 200 mg pure Rutin dose was obtained 8.3 mg h/mL, whereas at 100 mg pure Rutin dose only 3.3 mg h/mL (Williamson & Manach, 2005). The AUC is also on the same line with plasma levels and time. More increase the AUC value, the plasma levels increase too, and it will take a long more time to

pass off the elimination.

Some factors that influenced absorption include solubility and lipophilicity pH of the compound, absorption site, routes of administration, physiology status of the animal test, and physicochemical feature. Many factors influence the absorption process. One of them is solubility. The dissolved compound in fats and unloaded (non-ion) was rapidly absorbed than the loaded (ion) compound with high water solubility. Solubility of papaya leaf extract in solution form (liquid), given orally, is easily absorbed in the small intestine. Flavonoids with high lipophilicity can be easily absorbed, depending on their absorption rate (K_a) is higher than its elimination rate (K).

The rate of absorption is influenced by the molecular weight (physico-chemically). The rats fed by food contains flavonols (Rutin and Quercetin), quercetin was faster absorbed than Rutin (Kanimozhi, 2016). The maximum concentration (C_{max}) of quercetin in plasma was 20 times higher and reached (T_{max}) over 10 times after glycosides than rutinoides administration (Hollman, 2004). The T_{max} does not depend on its dose but depends on its rate of absorption (K_a) and elimination (K) (Shargel & Yu, 2016). The molecular weight of quercetin causes these, i.e. 302.236 g/mol is less than Rutin, i.e. 610.52 g/mol.

The half-life of elimination ($t_{1/2}$) after papaya leaf extract administration has resulted in 94.683 h. This half-life means that was needed 94.683 h for flavonoids of papaya leaf extract got to pass off through the blood, since the initial concentration until reach the clearance. This case indicates that flavonoids of papaya leaf extract were slowly distributed and metabolized, even it was needed more than 24 hours to reach lower or same as the line at time zero of plasma levels of flavonoids. A long half-life time indicates that flavonoids concentration of papaya leaf extract still arises in plasma at 24 h.

The K_a value asserted that systemic absorption includes several reaction rate processes. The dissolving of a compound and its transport through the cell membrane of the small intestine wall. Generally, the absorption of a compound occurs faster than the elimination. The K value was detected at 0.0073 mg/h and the K_a at 0.017 mg/h. The elimination rate was slowly represented by the K value, which was less than the K_a value. The half-life value contributes that the rate of elimination was passed off slowly. Based on the half-life value was needed a long time to reach the

moiety of the initial concentration in the body. The rate of elimination occurs against the rate of absorption. When the rate of elimination went slowly, the absorption rate went rapidly. The rate of absorption and elimination on the peak of the curve was equal. The absorption rate was consistent until the flavonoids in the small intestine were passed off.

The plasma levels of flavonoids decrease at 2 h. From 0.021 mg/ml at 1 h into 0.019 mg/ml. Two possibilities explained the phenomenon of the enterohepatic circulation and the bodyweight effect. Flavonoids may be accumulated in the liver or other organs. It caused the plasma levels of flavonoids to be low at 2 hr. The curve with two peaks at 1 h and 4 h was showed that the enterohepatic circulation occurs. It was relevant to the previous study (Gabrielsson et al., 2016). Flavonoids that had been excreted into the colon were then reabsorbed until they reached the maximum concentration of the plasma levels of flavonoids at 4 h.

The result of the plasma levels of flavonoids curves overtime at 0 h until 4 h showed absorption phase. After T_{max} , the data points explained that the absorption still occurred, although after the time of flavonoid absorption reached the peak of the curve. The other side of this curve represented post-absorption with a slow absorption rate. The distribution and elimination occur from 0 until 24 h simultaneously. The plasma levels of flavonoids obtained at 24 h were lower than 0.5 h. These data showed that the plasma levels decreased of flavonoids occur in the body, which started to eliminate.

Papaya leaf extract needs to dissolve to be absorbed in the gastrointestinal duct. During the absorption time, the elimination process occurs simultaneously. Papaya leaf extract that goes into the gastrointestinal duct runs into dissolution or dissolving of smaller particles that is flavonoids and the other bioactive compound into the gastrointestinal fluid to be absorbed. Flavonoids of papaya leaf extract overall have already accumulated in the small intestine. Flavonoids towards the liver and distributed in the systemic circulation of rats after the absorption process. Metabolites secreted into bile eventually will be excreted into the duodenum through the bile. Metabolites can be excreted in feces or reabsorbed and re-enter the systemic.

0.4 mg/L of flavonoids has begun to be absorbed in the small intestine starting at 10 minutes (Ou-Yang et al., 2013). A study of 0.0025 mg/mL plasma levels of flavonoids was detected

10 minutes after oral treatment. Measurement of plasma levels of flavonoids in papaya leaf extract, especially in this study, starts at 0.5 hr. At that time, results have been obtained that there are flavonoids in the plasma. It was not precisely known what time of absorption in the body before 0.5 h was started. Required time to decrease the plasma levels of flavonoids in rats was taken a long time to reach clearance which is twice the half-life. The length of the half-life showed that flavonoids levels of papaya leaf extract in plasma was still high within 24 hr. This case indicated that flavonoids of papaya leaf extract need more than 24 h to reach a plasma level of flavonoids that are lower or equal to the level at 0 hours. Extension of more than 24 h is needed to obtain clearance.

This research resulted in new data completed the previous study. No pharmacokinetic data of extract Carica papaya leaf was published before. The implication of the pharmacokinetic data of flavonoids can be used to manage the therapeutic dose, maintenance dose and frequency of oral treatment of Carica papaya leaf extract, including determining how many times the extract is consumed daily.

CONCLUSION

The digestive tract absorbed the Carica papaya leaf extract and reached the plasma begun 0.5 h after oral treatment. The peak concentration (C_{max}) was 0.026 mg/mL, reach at 4 h (T_{max}). Bioavailability (AUC) of extract 0.362 mg. h/mL, and needed 94.683 h for papaya leaf extract to reach the clearance from the blood. The pharmacokinetic profile of research of flavonoids concluded that Carica papaya leaf extract was slowly absorbed and stayed in the plasma for a long time. Carica papaya leaf extract contains flavonoids, and other bioactive compounds need more than 24 h to reach clearance. Further research is needed before being applied to human subjects.

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