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Pengusul: Dr. dr. Nugrahaningsih WH, M.Kes

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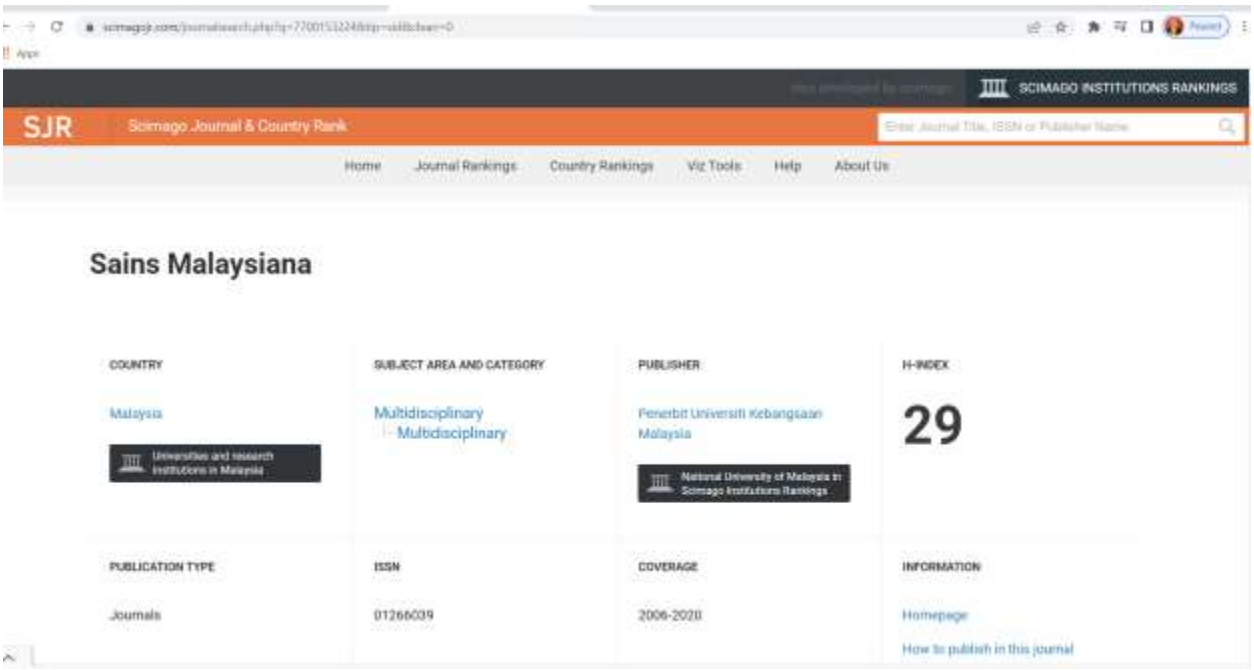

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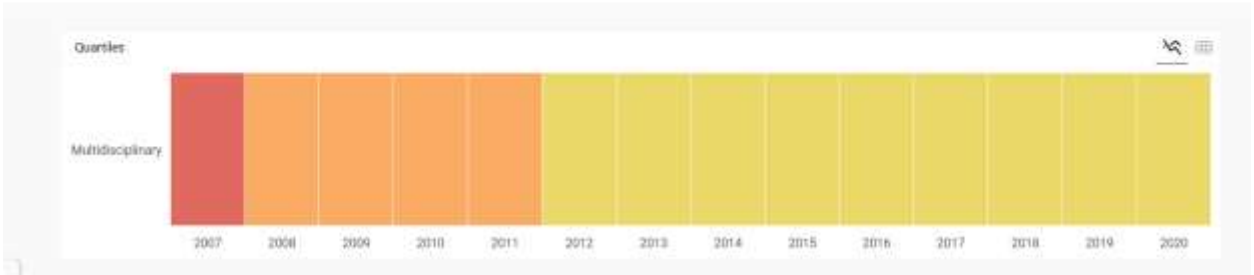

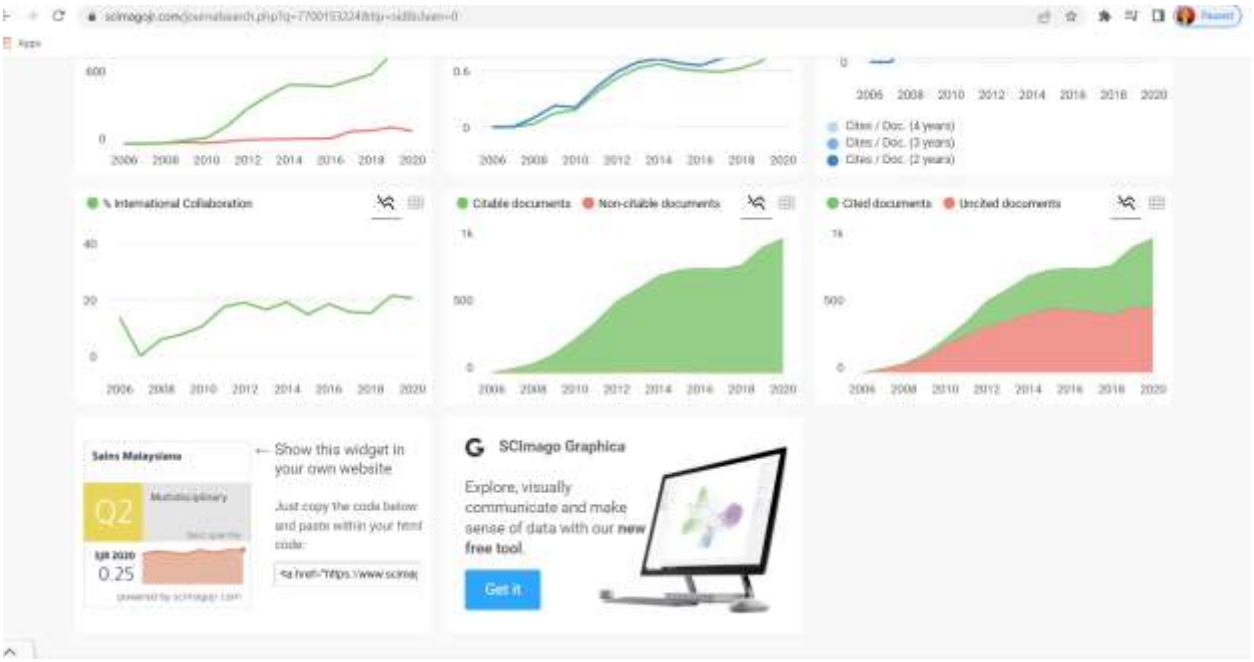
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PHARMACOKINETICS OF THE FLAVONOID AFTER ORAL ADMINISTRATION OF CASSAVA LEAVES EXTRACT

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Abstract

The leaves of cassava were used as a traditional medicine such as ringworm, tumor, abscess, conjunctivitis, sores, headaches, rheumatism, and fever diseases in several countries. Phytochemical investigation revealed leaves of cassava contained of flavonoids. The cassava leaves extract as herb medicines need to have several data that related with safety, effectiveness, toxicity and pharmacokinetic. The purpose of this research was to observe pharmacokinetic parameters of flavonoid in rat plasma after oral administration cassava leaves extract. Pharmacokinetics indicators were absorption ($C_{(0)}$, $t_{(0)}$, and $AUC_{(0-24)}$) and elimination (K_e and $t_{1/2}$). The 14 healthy male rats were divided into 7 groups (each group was 2 rats). The single dose (600 mg) of cassava leaves extract was given by oral. The blood samples were collected and separated at different time series (0; 0.5; 1; 2; 4; 6; 12; and 24 hr). The plasma flavonoid concentration was analyzed by HPLC-UV-VIS method. The plasma flavonoid concentration were 0 mg/mL (0 hr), 0.1515 mg/mL (0.5 hr), 0.176 mg/mL (1 hr), 0.18 mg/mL (2 hr), 0.184 mg/mL (4 hr), 0.163 mg/mL (6 hr), 0.15 mg/mL (12 hr) and 0.1225 mg/mL (24 hr) respectively. The main pharmacokinetic parameters were: $C_{(0)}$ 0.184 mg/mL

that was reach on 4 hr (t_{max}) after oral administration; AUC_{0-24} was 3.583 mg hr/mL and $t_{1/2}$ was 94.54 hr. The conclusion of the study was that flavonoid of cassava leaves extract reached maximum concentration in 4 hr after oral administration and were inside in the plasma more than 24

Keywords: Absorption, Cassava Leaves Extract, Flavonoid, Pharmacokinetics

Abstrak

Di beberapa negara daun singkong biasa digunakan untuk pengobatan tradisional seperti kecacingan, tumor, abses, radang selaput mata, luka, sakit kepala, rematik dan demam. Penelitian fitokimiawi mengungkapkan adanya kandungan flavonoid dalam daun singkong. Pengembangan daun singkong menjadi obat herbal memerlukan data tentang keamanan, keefektifan, toksisitas dan farmakokinetik. Penelitian ini bertujuan untuk mendapatkan data parameter farmakokinetik flavonoid dalam plasma tikus setelah pemberian ekstrak daun singkong secara oral. Indikator farmakokinetik meliputi absorbs (C_{max}, t_{max}, dan AUC_{0-24h}) dan eliminasi (Ke and $t_{1/2}$). Empat belas ekor tikus jantan sehat dibagi dalam 7 kelompok (masing-masing 2 ekor). Dosis tunggal (600 mg) ekstrak daun singkong diberikan secara oral. Sampel darah diambil secara serial pada ; 0.5; 1; 2; 4; 6; 12; dan 24 jam setelah pemberian ekstrak. Kadar flavonoid dalam plasma diukur dengan HPLC-UV-VIS. Kadar flavonoid plasma adalah 0 mg/mL (0 jam), 0.1515 mg/mL (0.5 jam, 0.176 mg/mL (1 jam), 0.18 mg/mL (2 jam), 0.184 mg/mL (4 jam), 0.163 mg/mL (6 jam), 0.15 mg/mL (12 jam) and 0.1225 mg/mL (24 jam). Parameter farmakokinetik adalah C_{max} 0.184 mg/mL yang dicapai pada 4 jam (t_{max}) setelah pemberian oral; AUC_{0-24} adalah 3.583 mg jam/mL dan $t_{1/2}$ was 94.54 jam. Dapat disimpulkan bahwa flavonoid dalam ekstrak daun singkong mencapai kadar maksimal dalam plasma 4 jam setelah pemberian per oral dan berada dalam plasma lebih dari 24 jam.

Kata kunci: **Absorbsi; Ekstrak daun singkong; flavonoid; farmakokinetik**

Introduction

Cassava was one of the shrubs that belong to the family Euphorbiaceae. This plant originated in South America and continues to spread to Asia including Indonesia. Cassava tubers become source of carbohydrates. Cassava leaves were widely consumed as a vegetable and potentially as a medicine. Cassava leaves were traditionally used to treat fever, rheumatism, headaches, and hemorrhoids. Nigeria utilizes cassava leaves to protect patient from ringworm, tumor, abscess, conjunctivitis, and sores (Miladiyah 2011).

Phytochemical compounds of the cassava leaves extract was flavonoids (Tao *et al.* 2015). Flavonoids were phenolic compounds and were found in cereals, vegetables, and fruits that vary in their type, content, and antioxidant activity (Redha 2010). Flavonoids consist of 15 carbon skeletons containing two benzene rings (A and B) connected by a heterolic ring (C).The flavonoids have several biological activities that beneficial for the body (Kumar and Abhay 2013). Chloroform extract of cassava leaves has activity against bacteria such as *V. cholera*, *Shigellaflexneri*, *S. thyphi*, *P. aeruginosa* (Zakaria 2006). Cassava leaves have been activity as anti-bacterial, anti-inflammatory, hepatoprotective, anti-cancer, and anti-viral agents (Kumar and Abhay 2013). Cassava leaves in the form of aqueous extract, methanol, and ethanol can inhibit LDL oxidation, chelate cupric ion, reducing ferric ions. These biological activities were attributed due to the presence of several phytochemical compounds in the cassava leaves extract such as anthocyanins, polyphenol compounds, and flavonoids (Wong *et al.* 2006; Suresh *et al.* 2011). Based on these activities, the cassava leaves extract were being sold as herb medicine.

The safety and effectiveness of flavonoid compounds in cassava leaves also need attention. Though a number of bioactivities reported on cassava leaves extract, but there was

no report available on pharmacokinetic studies of the cassava leaves extract. The studies were important to understand the bioavailability of the flavonoids of the cassava leaves extract in liquid biology, such as in the plasma (Nessa *et al.* 2013). Compounds or substances will experience the process of absorption, distribution, metabolism, and excretion (ADME) if were given by oral. Ingested compounds or substances such as flavonoids cassava leaves extracts undergo extensive intestinal metabolism. Metabolites of flavonoid were then transported to the liver via hepatic portal vein and undergo further metabolism. The liver metabolites can be transported to targeted cells and tissues through blood, excreted to bile and undergo enterohepatic re-circulation, or eliminated via urine or feces (Thilakarathna and Rupasinghe 2013). The metabolites of flavonoid bind with the plasma protein or free in plasma (Setyawati 2015).

The presence of a compound in a plasma, tissue, or organ will provide much information to determine the drug of choice, therapeutic management and residual analysis (Shargel *et al.* 2005). So, this result was important to supported the cassava leaves extract as herb medicine. In our previous work we have reported a high performance liquid chromatography (HPLC) method for analysis of these flavonoids of the cassava leaves extract and in the

Materials and Methods

Experimental Animal

Health Male Wistar rats (number of rats: 14) weighing between 150-200 g from Laboratory of Biology, Faculty of Mathematics and Natural Sciences UNNES. The rats were nourished with standard diet pellets and water *ad libitum* (Kanimozhi 2016). The total of rats were divided into 7 groups. Each group then was kept in cages and were allowed food and water *ad libitum* during acclimatization (5 days) (Nessa *et al.* 2013).

Experimental Study

Rats were let without food for 12 hours and received only water *ad libitum*. Each

animal was used only once. The rats were given an oral single dose (600 mg) of cassava leaves extract in water. Blood samples (1.5 ml) were taken at 0, 0.5, 1, 2, 4, 6, 12, and 24 hours was after oral administration. The Blood sample was taken from one group for time series. Blood samples taken from the orbital vein and were collected in EDTA tube. Blood samples were immediately centrifuged at 3000 rpm for 5 minutes. The level of flavonoid plasma was analysis by HPLC (Nessa *et al.* 2013; Kanimozhi 2016).

Determination of flavonoid in plasma

Flavonoid of cassava leaves extract was determined by a method based on that Kanimozhi (2016) with some modifications. Extraction procedure was carried out in measure glass tubes (10 ml). Plasma aliquot (0.1 ml) were shaken with 1.0 methanol for 2 min and filtered by membrane filter (45 µm). The methanol extract was transferred to dry tube. Finally, a 20 µl filtrate of each sample was injected into the chromatographic system.

Chromatographic conditions

The profile of flavonoids in rat plasma was analyzed by HPLC with a UV detector. Chromatographic separation was achieved by using a reverse phase C18 column (150 mm and 4.6 mm, 5 µm pore size). The mobile phase used consisted of eluent A acetonitrile (27%) and eluent B (methanol (8%): water (87%): acetic acid (5%)) (73%), pH adjusted to 3.64 with acetic acid with a motion phase flow of 0.5 ml / min, a column temperature of 25 ° C and a wavelength of 347 nm. The experiment was performed two times and the mean was used for the calculations (Kanimozhi 2016 with modification).

Calibration curves

The calibration curves as standard flavonoid curve. The calibration curves were prepared by spiking standard solution of flavonoids Rutin (Merck)) with methanol to give concentration 12.5, 25, 50, 100, and 200 ppm. The solution was injected into the HPLC system for analysis. From the curve can resulted a equation to determine flavonoid concentration of cassava leaves extract in the plasma. The calibration curve was shown in Figure 1.

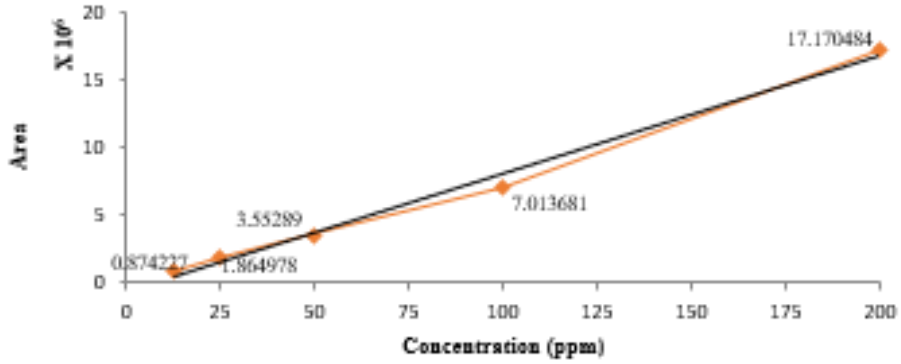

Figure 1. The Calibration curve of flavonoid

Data Analysis

The Microsoft Excel was used for analysis the equation of calibration curve. Flavonoids concentration in blood plasma was analyzed descriptively. The maximum plasma concentration C_{max} and the time to reach C_{max} (t_{max}) were determined directly from the data. The AUC_{0-24h} was calculated using the linear trapezoidal rule. The apparent terminal elimination half life ($t_{1/2}$) was determined using 0.693/Ke (Ke was the slope of the linear regression of the plasma metabolite concentration) (Mullen *et al.* 2009).

Results and Discussion

Results

The calibration curve of flavonoids was linear in the range concentration of 12.5, 25, 50, 100, and 200 ppm. Linear regression analysis was using the equation y = bx + a. The equation was determine by Microsoft excel. The equation was y = 86398 x – 600586. The values of x was flavonoid concentration and y was the area under the peak of flavonoid chromatogram. The equation curve was showed in Figure 1. The equation curve of flavonoid in Figure 1 was used to calculate of flavonoid concentrations in plasma that marked with Routin (Merck).

The flavonoids studied were easily absorbed and readily detected in rat plasma after

oral administration of the cassava leaves extract to the rat. The mean blood concentration versus time curve of the flavonoids were presented in fig. 2. Maximum plasma concentration (C_{max}) and the time to achieve the maximum concentration (T_{max}) were obtained from visual inspection of the plasma concentration versus time curve. The area under concentration curve (AUC) from 0 to 24 was determined by linear trapezoidal rule. Elimination half-life (t1/2) was calculated by 0.693/Ke. Means and S.D were determined for the pharmacokinetic parameters. The pharmacokinetic parameters were tabulated in **Table 1**. After administration of cassava leaves extract, the peak concentration (C_{max}) was reached (0.184 ± 0.022 mg/mL) and T_{max} (4 h). The value of AUC t_0-t_{24} was 3.583 ± 0.58 mg.h/mL and the $t_{1/2elimination}$ was 94.54 h after oral administration of cassava leaves extract.

Table 1. Pharmacokinetic parameters of flavonoids in plasma after 600 mg oral administration of cassava leaves extract

Pharmacokinetic parameters	**Values**	**Units**
C_{max}	0.184 ± 0.022	mg/mL
T_{max}	4	hr
AUC (*Area Under Curve*)	3.583 ± 0.58	mg hr/mL
$t_{1/2}$	94.54	hr

Discussion

Flavonoid was present in rat plasma only in conjugated/metabolites form. The metabolism of flavonoid involved two important organs: the liver, where biotransformation enzymes covert flavonoid or their metabolites into conjugated forms such as glucoronides or sulphates (Shargel and Yu 1992 in Richelle *et al.* 1999), and the colon, where microorganism degrade unabsorbed flavonoids (Rowland and Tozer 1995). The extraction procedure of flavonoids from rat plasma was simple and rapid. It demonstrated the isolation of flavonoid of cassava leaves extract from the plasma.

In the present study, the levels of Rutin in plasma were appeared the kinetic of flavonoid from 600 mg/mL cassava leaves extract, but not its metabolites. The analysis of the compound (flavonoid) in the plasma provides useful information in determining the dosage and the timing of administration of an appropriate drugs. Plasma concentration curve represent the net results of two opposite processes: absorption vs elimination (Richelle *et al.* 1999). This time-concentration curve signifies the potential for enterohepatic receptor flavonoids. Rutin was present in high amounts in cassava leaves extract and was therefore used as a marker of the absorption of cassava leaves extract.

During the post absorptive period, whilst absorption in the small intestine was declining (due to transit of digest and dilution of remaining digest by endogenous material), flavonol absorption took place in the large intestine (Kanimozhi 2016). After consumption of a single dose of cassava leaves extract, flavonoid was rapidly absorbed and reached their maximum plasma concentration (C_{max}) in 4 hr after oral administration. This suggest that flavonoid was quickly metabolized by the intestinal enzymes and strongly bound to albumin (Manach *et al.* 1999), which might delay their emigration and so as to preferentially excrete in bile (Jain *et al.* 2013). The C_{max} and t_{max} values suggested the circulation of metabolites/conjugated flavonoid. The extravascular administration was need to consider this parameters (C_{max} and T_{max}). The parameters (C_{max} and t_{max}) was important to develop of any new drug or formulation. Slow drug absorption was characterized by a reduction in C_{max} and increase of T_{max} (Rowe 2012).

The curve in Fig. 2 illustrated the decrease of levels after the t_{max} was reached, very slowly and not sharply. It means that the flavonoids of cassava leaves extract was still in the plasma with sufficient levels and has not yet eliminated from plasma. The value of Ke (elimination rate) obtained was smaller (0.00733 hr^{-1}) than the value of Ka (absorption rate) (0.01686 hr^{-1}). This value indicates that the process of elimination was slow and absorption

196 occurs more quickly. The value of Ka and Ke was a proportional supporting parameter. If
197 Ka's values was greater than Ke, then the absorption rate was faster than the absorption rate
198 and vice versa. Slow elimination implicated that no repetition was required in the application
199 of cassava leaves extract in one day.

200 The peak concentration value (0.184 mg/mL) has not reached a half-decline of up to
201 24 hours (0.125 mg/mL), so the value of $t_{1/2}$ over 24 hours was 94.54 hours. The total
202 absorption of flavonoid as determined from the area under the plasma concentration-time
203 curve (AUC). The value of AUC_{0-24h} was 3.583 mg.hr/mL. The AUC was a measureable of
204 the extent of drug bioavailability. The AUC reflects the total amount of active drug that
205 reaches the systemic circulation (Shargel and Yu 2012). The AUC values was affected by
206 C_{max} and $t_{1/2}$ concentration, where the higher concentration for each time, the higher value of
207 AUC (Paradina *et al.* 2015). The half-life indicates the time it takes for the drug to reach half
208 concentration of its original content (Setiya *et al.* 2009). The half-life describes the
209 elimination of compounds in the plasma before undergoing a process of distribution to a
210 liver-like tissue. This $t_{1/2}$ duration corresponds to the flavonoid concentrations curve in the
211 plasma against time which indicates a decrease point still relative to the axis point. So there
212 was still a need to add some times after 24 hours to see the concentrations flavonoids actually
213 halve or disappear from the plasma to the target tissue. The difference in half-life between
214 individuals or animals is caused by absorption, metabolism and excretion factors.

215 Flavonoids were conjugated and hydrolyzed in the small intestine, liver and colon. All
216 flavonoids were conjugated to O-glucuronides, sulphate ester, o-methyl esters and any
217 aglycones. The conjugated of flavonoids were present in the plasma (Landete 2012). After
218 oral administration, the flavonoids have cross the intestinal wall and undergo to further
219 catabolism. The first conjugation of flavonoids was occurs in the small intestine, resulted
220 metabolites were transported to the liver via hepatic portal vein. The metabolites were

transported to targeted cells and tissues, excreted to bile and undergo enterohepatic re-circulation, or eliminated via urine and/or feces (Thilakarathna and Rupasinghe 2013). The compounds that were not absorbed in the intestine will reach the colon and be subjected to structural modification by colon microfolia (Del Rio *et al.* 2010). Aglycones can further be catabolized to low molecular weight compounds that can readly be absorbed (Thilakarathna and Rupasinghe 2013).

Enterohepatic recirlculation of metabolites flavonoid may indicate that flavonoid was reabsorbed in the colon. These processes resulted the second rise of level, might be due the act of colonic bacteria on flavonoid glycosides bound to the food matrix such as dietary fiber. The released glycosides of flavonoid may be hydrolyzed in colon (Aherne and O'Brien 2002). In the colon, bacterial glucosides cleave the flavonoid ring, that resulting in ring fission products such hydroxyl phenylacetic acid (Aherne and O'Brien 2002; Mullen *et al.* 2008). The different absorption phase among subject or object may have been the result of carrier-mediated transport processes, physiological differences such as pH changes along the intestinal tract, and distinct transit time (Lee and Alyson 2012).

The structure of flavonoids also affects the absorption process. Flavonoid aglycone more easily absorbed by intestinal than flavonoids glycosides that must be converted into aglikon first (Hollman 2004). Flavonoids were found in blood plasma only in conjugate form (Graefe *et al.* 2001). The forms of conjugate metabolites found in plasma were glucuronide and glucuronide/sulphate (Piskula and Junji 1998). Absorption of flavonoids cassava leaves extract per oral relatively quickly compared with flavonoids that give in pure form. In the Kanimozhi study (2016) as much as 50 mg/kg of flavonoids given orally reached peak time after 6 hours. In routine oral and quarcetin administration, glucuronide and quarcetin sulfate appear in the plasma at 5 minutes after administration, indicating a very rapid absorption compared to cassava leaf extract (Yang et al 2005). Giving tea buckling peak concentrations

achieved at peak times which are almost equal to oral administration of cassava leaves extract is 4.3 ± 1.8 hr. Pure routine delivery achieved a longer peak time of 7.0 ± 2.9 hr (Graefe *et al.* 2001), but was more fast on metabolite flavonoid (4 hr) after oral administration cassava leaves extract.

The absorption in each experimental animal or between individuals varies depending on the given dosage form, the anatomy and the physiology of the absorption site. The flavonoid absorption process was influenced by several things such as physicochemical properties including molecular size, shape, lipophilicity, solubility and pKa (Kumar and Abhay 2013). Another factor that affects absorption was food. In this study the dietary factors are minimized or eliminated by letting rats for 12 hours without eating and only give drinking water. Flavonoids (such as quarcetin and routine) when administered with intravenous pathways cannot be detected particularly routine (Graefe*et al.* 2001). On oral administration there may be decreased bioavaibility and bioavailability due to imperfect absorption or drug interactions with other substances (Shargel and Yu 1988). The dosage form was given liquid, so it can be easily absorbed in the body.

Conclusion

The flavonoid of cassava leaves extract absorbed into small intestine and reach plasma less than 30 minute after oral administration. The value of flavonoid plasma stay high indicated the long acting of extract. The extract was slowly eliminated from plasma. In addition, in general variations in pharmacokinetic parameters can be caused by physiological factors, such as differences in body weight, body composition, and gastric motility, or molecular factors. Molecular factors include differences in activity or synthesis of differences in transporters or enzymes involved in biotranformation (Meibohm et al 2002).

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Quarcetin in Rats. *Journal of Food and Drug Analysis*, 13(3): 244-250.

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Kegiatan 2. Mendapat Jawaban dari Prof. Zarani Zakaria (Chief in Editor)

TGL 18 September 2018

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Nugrahaningsih WH <nugrahaningsihwh@mail.unnes.ac.id>

[Sains Malaysiana] Submission Acknowledgement - ID: 27819

1 message

Sarani Zakaria <jsm@ukm.edu.my> Tue, Sep 18, 2018 at 12:34 PM
To: Nugrahaningsih WH <nugrahaningsihwh@mail.unnes.ac.id>

Dear Nugrahaningsih WH:

Thank you for submitting the manuscript, "PHARMACOKINETICS OF THE FLAVONOID AFTER ORAL ADMINISTRATION OF CASSAVA LEAVES EXTRACT" to Sains Malaysiana. With the online journal management system that we are using, you will be able to track its progress through the editorial process by logging in to the journal web site:

Manuscript URL: http://ejournal.ukm.my/jsm/author/submission/27819
Username: nugrahaningsih_wh

Please note that with effect from 1st July 2016 onwards, all new submission will be subjected to 1500MYR publication fee once the paper is accepted for publication.

If you have any questions, please contact me. Thank you for considering this journal as a venue for your work.

Sincerely,

Sarani Zakaria
Sains Malaysiana
Editor-in-Chief
Sains Malaysiana
Faculty of Science and Technology
Universiti Kebangsaan Malaysia

Sains Malaysiana
http://ejournal.ukm.my/jsm

Kegiatan 3. Mendapat email dari Reviewer (Prof. Dr. Siti Balkis Budin), berisi uraian yang harus direvisi

TGL 25 JANUARI 2019

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Nugrahaningsih WH <nugrahaningsihwh@mail.unnes.ac.id>

[Sains Malaysiana] Editor Decision

2 messages

Prof DR Siti Balkis Budin <balkis@ukm.edu.my> Fri, Jan 25, 2019 at 2:19 PM
To: Nugrahaningsih WH <nugrahaningsihwh@mail.unnes.ac.id>

Dear Nugrahaningsih WH:

The referee has commented on your paper titled: "PHARMACOKINETICS OF THE FLAVONOID AFTER ORAL ADMINISTRATION OF CASSAVA LEAVES EXTRACT".

We would be glad to reconsider the paper if you are willing to amend the paper according to the recommendations by the referee. Please find the comments with this email. Please provide a List of Corrections made on the paper when resubmitting the revised paper. Re-submission should be made online within 4 weeks.

Thank you.

Sincerely,

Prof DR Siti Balkis Budin
balkis@ukm.edu.my

Reviewer A:

Comments on the manuscript for authors:
The authors aimed to observe pharmacokinetic parameters of flavonoid in rat plasma after oral administration cassava leaves extract.

The title is defective. Effect of flavonoid will not change after consumption. Please make it more easier e.g. effect of cassava extract on.....
OR
Effect of flavonoids in cassava extract on.....
OR even something better.

Please end the abstract with a strong implication. Do not end the abstract with the results.

Chemical structure of active compounds/ flavonoids present in cassava leaves need to be added in the text in the introduction section.

Please add the reference-Osman et al. The effect of cassava leave intake on thyroid hormone and urinary iodine. East Afr Med J. 1993 May;70(5):314-5.. This articles describes effect of cassava leaves on the thyroid hormones and it is important.

The introduction has not been written properly. First describe the herb, its uses, side effects if any, doses etc. and then proceed to the active compounds/flavonoids etc. present in the extract.

Please add the reference- Nik Hassan MK. The Effect of Apigenin, Berberine and Rutin on Cholesterol Metabolism in Hep G2 Cancer Cell (Kesan Apigenin, Berberin dan Rutin terhadap Metabolisme Kolesterol pada Sel Kanser Hep G2). Sains Malaysiana 43(4)(2014): 559–566 . This reference is with regard to rutin.

A conclusion cannot have any reference cited in it. Please delete it.

Highlight the limitations of the study.

The English language needs to be edited as there are many errors.

Sains Malaysiana
http://ejournal.ukm.my/jsm

Kegiatan 4. Memberi kesanggupan untuk melalukan revisi

TGL 25 Januari 2029

Nugrahaningsih WH <nugrahaningsihwh@mail.unnes.ac.id> Fri, Jan 25, 2019 at 5:18 PM
To: Prof DR Siti Balkis Budin <balkis@ukm.edu.my>

Dear Prof. DR. Siti Balkis Budin,
Thank you very much for your advise. As soon as I will send the revised article.

Sincerely,

Nugrahaningsih WH
[Quoted text hidden]

Kegiatan 5. Mengunggah manuskrip yang telah direvisi di sistem online

TGL 20 Pebruari 2019

Kegiatan 6. Menerima jawaban dari Reviewer untuk mengunggah list revisi dan menandai bagian yang direvisi

TGL 27 FEBRUARI 2019

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Nugrahaningsih WH <nugrahaningsihwh@mail.unnes.ac.id>

[Sains Malaysiana] Editor Decision

2 messages

Prof Dr Siti Balkis Budin <balkis@ukm.edu.my> Wed, Feb 27, 2019 at 6:17 PM
To: Nugrahaningsih WH <nugrahaningsihwh@mail.unnes.ac.id>

Dear Nugrahaningsih WH:

We have received your latest revision. However, please submit a List of Correction to highlight your response to each of reviewer's comment to aid us in evaluating your revised manuscript.

Thank you.

Sincerely,

Prof Dr Siti Balkis Budin
balkis@ukm.edu.my

Sains Malaysiana
http://ejournal.ukm.my/jsm

Kegiatan 7. Mengirim manuskrip yang telah direvisi beserta list revisi melalui sistem

Nugrahaningsih WH <nugrahaningsihwh@mail.unnes.ac.id> Thu, Feb 28, 2019 at 1:13 PM
To: Prof Dr Siti Balkis Budin <balkis@ukm.edu.my>

Thank you very much. Please check, I have revised my manuscript with list revision in below my article. and I send for you by system. Thank you very much for your consideration.

Warm regards
Nugrahaningsih

[Quoted text hidden]

List of revision

Part	Origin	Revised	Line
Tittle	Pharmacokinetics of the Flavonoid After Oral Administration of Cassava Leaves Extract	The Effect of Cassava Leaves Extract on Pharmacokinetics Profile of Rutin Plasma	1
Abstract	No recommendation	Add recommendation	28-29
Introduction	Add chemical compound of extract		36-38
	The introduction has not been written properly. First describe the herb, its uses, side effects if any, doses etc. and then proceed to the active compounds/flavonoids etc. present in the extract.	Have been edited	
	Add the reference-Osman et al. The effect of cassava leave intake on thyroid hormone and urinary iodine. East Afr Med J. 1993 May;70(5):314-5.	Add reference	51-53
	Please add the reference- Nik Hassan MK. The Effect of Apigenin, Berberine and Rutin on Cholesterol Metabolism in Hep G2 Cancer Cell (Kesan Apigenin, Berberin dan Rutin terhadap Metabolisme Kolesterol pada Sel Kanser Hep G2). Sains Malaysiana 43(4)(2014): 559–566	Add reference	49-50
Conclusion	any reference cited	no reference cited	242
limitations of the study.	No limitation of study	Add limitation of study	238-240
language	Many error	Edited	All

Kegiatan 8. Menerima jawaban dari Reviewer , Perlu sertifikat proofread dan abstrak dalam Bahasa Melayu

TGL 25 MARET 2019

11/9/21, 8:20 AM UNNES Mail - [Sains Malaysiana] Editor Decision

UNNES
UNIVERSITAS NEGERI SEMARANG

Nugrahaningsih WH <nugrahaningsihwh@mail.unnes.ac.id>

[Sains Malaysiana] Editor Decision
2 messages

Prof Dr Siti Balkis Budin <balkis@ukm.edu.my> Mon, Mar 25, 2019 at 3:58 PM
To: Nugrahaningsih WH <nugrahaningsihwh@mail.unnes.ac.id>

Dear Nugrahaningsih WH:

Regarding you submission entitled"PHARMACOKINETICS OF THE FLAVONOID AFTER ORAL ADMINISTRATION OF CASSAVA LEAVES EXTRACT".

We would be glad to reconsider the paper if you are willing to send your manuscript for English edit service and provide us with the certificate of proof. Also, please provide a translation of your abstract in Bahasa Melayu as required in Sains Malaysiana's guidelines.

Re-submission should be made online within 4 weeks.

Thank you.

Sincerely,

Prof Dr Siti Balkis Budin
balkis@ukm.edu.my

Sains Malaysiana
http://ejournal.ukm.my/jsm

List of revision

Title: The Effect of Cassava Leaves Extract on Pharmacokinetics Profile of Rutin Plasma

Author Nugrahaningsih WH, et.al

Part	Origin	Revised	Line
Abstract	No abstract in Malaysian language	Add abstract in Malaysian language	35-58
Proofread	No certificate of proof reader	certificate of proof reader in attach file	

Kegiatan 9. Mengirim sertifikat proofread dan revisi manuskrip

Tanggal 9 April 2019

Nugrahaningsih WH <nugrahaningsihwh@mail.unnes.ac.id> Wed, Apr 10, 2019 at 7:20 AM
To: Prof Dr Siti Balkis Budin <balkis@ukm.edu.my>

Dear Prof. Siti Balkin Budin

I apologize for the delay in replying to your email. I hereby inform you that I have sent a revised article and completed it with abstracts in Malay. I send the proofread certificate in an attachment file. thank you for the review and advice

Best regards

Nugrahaningsih WH
[Quoted text hidden]

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Certificate of Proofreading

Manuscript Title

The Effect of Cassava Leaves on Pharmacokinetics Profile of Rutin Plasma

Authors

Nugrahaningsih WH, Fatimatuz Zahroh, Lisdiana, Ari Yuniastuti and Ely Rudyatmi

Date Issued

March 25, 2019

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This document certifies that the manuscript listed above was edited for proper English language, grammar, punctuation, spelling, and overall style by one or more of the highly qualified native English speaking editors at Native Proofreading Service (NPS)

Kegiatan 10. Mendapat email dari Chief Editor, untuk proof read sebelum publish

TGL 17 SEPTEMBER 2019

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Nugrahaningsih WH <nugrahaningsihwh@mail.unnes.ac.id>

Proof August 2019 (Paper 16)

2 messages

Siti Nur Aliaa Abu Talib <sitinuraliaa@ukm.edu.my> Tue, Sep 17, 2019 at 8:25 AM
To: nugrahaningsihwh@mail.unnes.ac.id
Cc: Azean Baharuddin <azean.baharuddin@ukm.edu.my>

Dear author,

Attached please find the proof for checking. Appreciate if you could return it to us before/on 19 September 2019 for our further action.

Please take note of the followings:-

1. No addition or removal of co-authors is allowed at proof stage as the paper was reviewed with the existing authors.
2. Abstract/Abstrak was written in italic, therefore, any italic words like the scientific name was written using normal font to show the difference.
3. Keywords/Kata kunci was arrange alphabetically according to the language it was written.

Thank you.

Aliaa
c/o Chief Editor
Sains Malaysiana

--
Siti Nur Aliaa Binti Abu Talib,
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Universiti Kebangsaan Malaysia.

16 Nugrahaningsih WH.pdf
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Kegiatan 11. Memberikan persetujuan proofread melalui email

Nugrahaningsih WH <nugrahaningsihwh@mail.unnes.ac.id> Tue, Sep 17, 2019 at 3:23 PM
To: Siti Nur Aliaa Abu Talib <sitinuraliaa@ukm.edu.my>

Dear editor,
I have read the last manuscript sent and I decide the manuscript as the final version of my research paper. I have checked the note and sure that there is no change/revision for the final paper. Thank you.

Regards,
Nugrahaningsih WH
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#27819 REVIEW

SUMMARY REVIEW EDITING

SUBMISSION

Authors	Nugrahaningsih WH, Fatmatuz Zahroh, Lisdiana Lisdiana, Ari Yuniastuti, Ely Rudyatmi
Title	PHARMACOKINETICS OF THE FLAVONOID AFTER ORAL ADMINISTRATION OF CASSAVA LEAVES EXTRACT
Section	Chemistry
Editor	Siti Balkis Budin

PEER REVIEW

ROUND 1

Review Version	[illegible] DOCX 2018-09-28
Initiated	2019-01-16
Last modified	2019-01-17
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EDITOR DECISION

Decision	Accept Submission 2019-05-24
Notify Editor	Editor/Author Email Record 2019-03-21
Editor Version	[illegible] ED.DOCX 2019-05-24
Author Version	[illegible] ED.DOCX 2019-02-28 DELETE [illegible] ED.DOCX 2019-02-28 DELETE [illegible] ED.DOCX 2019-04-09 DELETE [illegible] ED.DOCX 2019-04-09 DELETE [illegible] ED.PDF 2019-04-09 DELETE
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Kegiatan 12. Pemberitahuan bahwa artikel telah terbit.

TGL 7 OKT 2019

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Nugrahaningsih WH <nugrahaningsihwh@mail.unnes.ac.id>

Sains Malaysiana Web Updated - Volume 48 Number 8 August, 2019

1 message

Jurnal Sains Malaysiana PPFG UKM <jsm@ukm.edu.my> Mon, Oct 7, 2019 at 7:49 AM
To: wufzchina@163.com, rodzi@usm.my, karthigeyan-1994@graduate.utm.my, dzarifah@upm.edu.my, pshariff@gmail.com, anchittha.satjarak@gmail.com, caixiao.dong@163.com, hiisl@ucts.edu.my, zengqingmei-1@163.com, aiman.bobaker@uob.edu.ly, leetienping@rsciucd.edu.my, mohdheikalyunus@yahoo.com, drnorma@usm.my, LEE SOO LENG STUDENT <leng527@siswa.um.edu.my>, nugrahaningsihwh@mail.unnes.ac.id, zambrimakhbul@gmail.com, wannurazreena@um.edu.my, drnorsyahida@ukm.edu.my, irahmad@kku.edu.sa, nooraniza@umt.edu.my, aini_zainuddin@utp.edu.my, habshahmidi@gmail.com, ESRA YIGIT <eyigit@gazi.edu.tr>, "Professor Dr. Muhammad Hisyam Lee" <mhl@utm.my>
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Dear Authors,

We wish to inform you that SAINS MALAYSIANA website has been updated with your article for Volume 48, No. 8 (August 2019) and is now available for download. The pdf file of articles for this issue can be downloaded for free and available until at least when the next issue is published. Please click the link below for the English version:

http://www.ukm.my/jsm/english_journals/vol48num8_2019/contentsVol48num8_2019.html

You can also download the article by clicking the CONTENT below.

Please cite these articles in your manuscripts in the future. Thank you for your contributions to Sains Malaysiana.

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