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1	18 September 2018	Submit manuskrip pada jurnal melalui online. Mendapat ID: 27819
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Demikian, agar dapat menjadi periksa.

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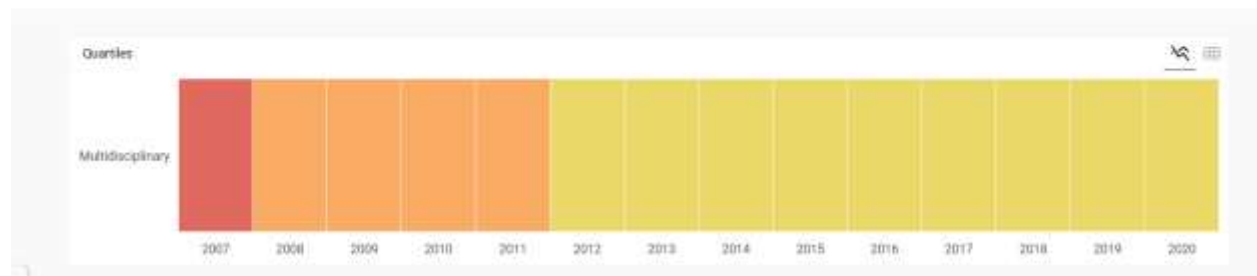
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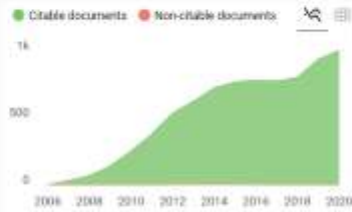
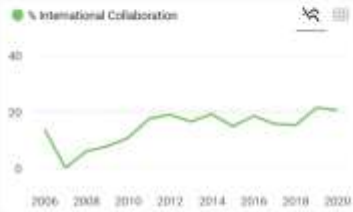
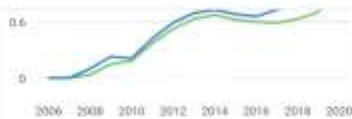
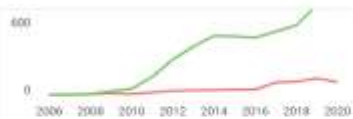
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1 | PHARMACOKINETICS OF THE FLAVONOID AFTER ORAL ADMINISTRATION OF
2 | CASSAVA LEAVES EXTRACT

3 |
4 | Nugrahaningsih WH^{1*}, Fatimatuz Zahroh², Lisdiana¹, Ari Yuniastuti¹ and Ely Rudyatmi¹

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10 |
11 | **Abstract**

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

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

30 Keywords: Absorption, Cassava Leaves Extract, Flavonoid, Pharmacokinetics

31

32

Abstrak

33 Di beberapa negara daun singkong biasa digunakan untuk pengobatan tradisional seperti
34 kecacangan, tumor, abses, radang selaput mata, luka, sakit kepala, rematik dan demam.
35 Penelitian fitokimisi mengungkakan adanya kandungan flavonoid dalam daun singkong.
36 Pengembangan daun singkong menjadi obat herbal memerlukan data tentang keamanan,
37 keefektifan, toksisitas dan farmakokinetik. Penelitian ini bertujuan untuk mendapatkan data
38 parameter farmakokinetik flavonoid dalam plasma tikus setelah pemberian ekstrak daun
39 singkong secara oral. Indikator farmakokinetik meliputi absorbs (C_{max} , t_{max} , dan AUC_{0-24h})
40 dan eliminasi (K_e and $t_{1/2}$). Empat belas ekor tikus jantan sehat dibagi dalam 7 kelompok
41 (masing-masing 2 ekor). Dosis tunggal (600 mg) ekstrak daun singkong diberikan secara oral.
42 Sampel darah diambil secara serial pada ; 0.5; 1; 2; 4; 6; 12; dan 24 jam setelah pemberian
43 ekstrak. Kadar flavonoid dalam plasma diukur dengan HPLC-UV-VIS. Kadar flavonoid
44 plasma adalah 0 mg/mL (0 jam), 0.1515 mg/mL (0.5 jam), 0.176 mg/mL (1 jam), 0.18 mg/mL
45 (2 jam), 0.184 mg/mL (4 jam), 0.163 mg/mL (6 jam), 0.15 mg/mL (12 jam) and 0.1225
46 mg/mL (24 jam). Parameter farmakokinetik adalah C_{max} 0.184 mg/mL yang dicapai pada 4
47 jam (t_{max}) setelah pemberian oral; AUC_{0-24} adalah 3.583 mg jam/mL dan $t_{1/2}$ was 94.54 jam.
48 Dapat disimpulkan bahwa flavonoid dalam ekstrak daun singkong mencapai kadar maksimal
49 dalam plasma 4 jam setelah pemberian per oral dan berada dalam plasma lebih dari 24 jam.

50

51 Kata kunci: ~~Absorpsi; Ekstrak daun singkong; flavonoid; farmakokinetik;~~

52

53

Introduction

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

60 Phytochemical compounds of the cassava leaves extract was flavonoids (Tao *et al.*
61 2015). Flavonoids were phenolic compounds and were found in cereals, vegetables, and fruits
62 that vary in their type, content, and antioxidant activity (Redha 2010). Flavonoids consist of
63 15 carbon skeletons containing two benzene rings (A and B) connected by a ~~heteropic~~ ring
64 (C). The flavonoids have several biological activities that beneficial for the body (Kumar and
65 Abhay 2013). Chloroform extract of cassava leaves has activity against bacteria such as *V.*
66 *cholera*, ~~*Shigella flexneri*, *S. thymphi*, *P. aeruginosa*~~ (Zakaria 2006). Cassava leaves have been
67 activity as anti-bacterial, anti-inflammatory, hepatoprotective, anti-cancer, and anti-viral
68 agents (Kumar and Abhay 2013). Cassava leaves in the form of aqueous extract, methanol,
69 and ethanol can inhibit LDL oxidation, chelate cupric ion, reducing ferric ions. These
70 biological activities were attributed due to the presence of several phytochemical compounds
71 in the cassava leaves extract such as anthocyanins, polyphenol compounds, and flavonoids
72 (Wong *et al.* 2006; Suresh *et al.* 2011). Based on these activities, the cassava leaves extract
73 were being sold as herb medicine.

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

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

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

93

94 **Materials and Methods**

95 **Experimental Animal**

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

101 **Experimental Study**

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

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

109 **Determination of flavonoid in plasma**

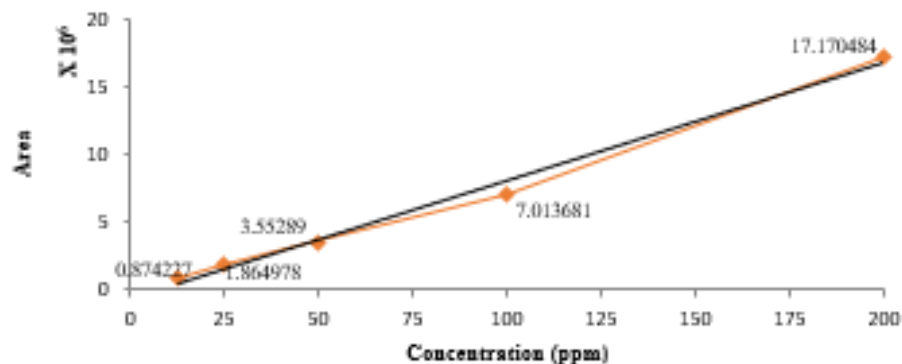
110 Flavonoid of cassava leaves extract was determined by a method based on that
111 Kanimozhi (2016) with some modifications. Extraction procedure was carried out in measure
112 glass tubes (10 ml). Plasma aliquot (0.1 ml) were shaken with 1.0 methanol for 2 min and
113 filtered by membrane filter (45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

115 **Chromatographic conditions**

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

123 **Calibration curves**

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



130

131

Figure 1. The Calibration curve of flavonoid

132 **Data Analysis**

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

139

140 **Results and Discussion**

141 **Results**

142 The calibration curve of flavonoids was linear in the range concentration of 12.5, 25,
 143 50, 100, and 200 ppm. Linear regression analysis was using the equation $y = bx + a$. The
 144 equation was determine by Microsoft excel. The equation was $y = 86398 x - 600586$. The
 145 values of x was flavonoid concentration and y was the area under the peak of flavonoid
 146 chromatogram. The equation curve was showed in Figure 1. The equation curve of flavonoid
 147 in Figure 1 was used to calculate of flavonoid concentrations in plasma that marked with
 148 Rutin (Merck).

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

150 oral administration of the cassava leaves extract to the rat. The mean blood concentration
 151 versus time curve of the flavonoids were presented in fig. 2. Maximum plasma concentration
 152 (C_{max}) and the time to achieve the maximum concentration (T_{max}) were obtained from visual
 153 inspection of the plasma concentration versus time curve. The area under concentration curve
 154 (AUC) from 0 to 24 was determined by linear trapezoidal rule. Elimination half-life ($t_{1/2}$)
 155 was calculated by $0.693/K_e$. Means and S.D were determined for the pharmacokinetic
 156 parameters. The pharmacokinetic parameters were tabulated in **Table 1**. After administration
 157 of cassava leaves extract, the peak concentration (C_{max}) was reached (0.184 ± 0.022 mg/mL)
 158 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
 159 94.54 h after oral administration of cassava leaves extract.

160 **Table 1.** Pharmacokinetic parameters of flavonoids in plasma after 600 mg oral
 161 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

162

163 Discussion

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

171 In the present study, the levels of Rutin in plasma were appeared the kinetic of
172 flavonoid from 600 mg/mL cassava leaves extract, but not its metabolites. The analysis of the
173 compound (flavonoid) in the plasma provides useful information in determining the dosage
174 and the timing of administration of an appropriate drugs. Plasma concentration curve
175 represent the net results of two opposite processes: absorption vs elimination (Richelle *et al.*
176 1999). This time-concentration curve signifies the potential for enterohepatic receptor
177 flavonoids. Rutin was present in high amounts in cassava leaves extract and was therefore
178 used as a marker of the absorption of cassava leaves extract.

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

191 The curve in Fig. 2 illustrated the decrease of levels after the t_{max} was reached, very
192 slowly and not sharply. It means that the flavonoids of cassava leaves extract was still in the
193 plasma with sufficient levels and has not yet eliminated from plasma. The value of K_e
194 (elimination rate) obtained was smaller (0.00733 hr^{-1}) than the value of K_a (absorption rate)
195 (0.01686 hr^{-1}). This value indicates that the process of elimination was slow and absorption

196 occurs more quickly. The value of K_a and K_e was a proportional supporting parameter. If
197 K_a 's values was greater than K_e , 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 (Landeta 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

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

227 Enterohepatic ~~recirculation~~ of metabolites flavonoid may indicate that flavonoid was
228 reabsorbed in the colon. These processes resulted the second rise of level, might be due the
229 act of colonic bacteria on flavonoid glycosides bound to the food matrix such as dietary fiber.
230 The released glycosides of flavonoid may be hydrolyzed in colon (~~Abeme~~ and O'Brien
231 2002). In the colon, bacterial glucosidases cleave the flavonoid ring, that resulting in ring
232 fission products such hydroxyl phenylacetic acid (~~Abeme~~ and O'Brien 2002; Mullen *et al.*
233 2008). The different absorption phase among subject or object may have been the result of
234 carrier-mediated transport processes, physiological differences such as pH changes along the
235 intestinal tract, and distinct transit time (Lee and Alyson 2012).

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

246 achieved at peak times which are almost equal to oral administration of cassava leaves extract
247 is 4.3 ± 1.8 hr. Pure routine delivery achieved a longer peak time of 7.0 ± 2.9 hr (Graefe *et al.*
248 2001), but was more fast on metabolite flavonoid (4 hr) after oral administration cassava
249 leaves extract.

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

261 Conclusion

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

269

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272 Biosciences and Medical Engineering (FBME), ~~Universiti Teknologi~~ Malaysia.

273

274

References

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- 350

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

TGL 18 September 2018

11/9/21, 8:15 AM

UNNES Mail - [Sains Malaysiana] Submission Acknowledgement - ID: 27819



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

11/9/21, 8:17 AM

UNNES Mail - [Sains Malaysiana] Editor Decision



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

[Sains Malaysiana] Editor Decision

2 messages

Prof DR Siti Balkis Budin <balkis@ukm.edu.my>
To: Nugrahaningsih WH <nugrahaningsihwh@mail.unnes.ac.id>

Fri, Jan 25, 2019 at 2:19 PM

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.

11/9/21, 8:17 AM

UNNES Mail - [Sains Malaysiana] Editor Decision

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 melakukan revisi

TGL 25 Januari 2029

Nugrahaningsih WH <nugrahaningsihwh@mail.unnes.ac.id>
To: Prof DR Siti Balkis Budin <balkis@ukm.edu.my>

Fri, Jan 25, 2019 at 5:18 PM

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

The screenshot shows the journal submission system interface for Sains Malaysiana. The page is titled "#27819 REVIEW" and displays the submission details, peer review history, and editor decision.

Submission Details:

Author:	Yusufhanipah W.H, Fatmahanik Edrith, Lidiana Lidiana, An Yuzanita, Ely Kholifah
Title:	PHARMACOKINETICS OF THE PLANT FOOD AFTER ORAL ADMINISTRATION OF CAMBALEAVES EXTRACT
Category:	Chemistry
Editor:	Siti Salsila Rada

Peer Review History:

Round	Review Version	Accepted	Last Modified	Uploaded By
ROUND 1	2781944604-1-AD.DOCX	2018-04-18	2018-01-16	None

Editor Decision:

Version	Accepted	Deleted
Editor Version	2781944604-1-AD.DOCX	2018-01-21
Author Version	2781944604-1-AD.DOCX	2018-01-21
Editor Version	2781944604-1-AD.DOCX	2018-02-26
Author Version	2781944604-1-AD.DOCX	2018-04-08
Editor Version	2781944604-1-AD.DOCX	2018-04-08
Author Version	2781944604-1-AD.DOCX	2018-04-08
Editor Version	2781944604-1-AD.DOCX	2018-04-08

Upload Author Version:

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

TGL 27 FEBRUARI 2019

11/9/21, 8:19 AM

UNNES Mail - [Sains Malaysiana] Editor Decision



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

[Sains Malaysiana] Editor Decision

2 messages

Prof Dr Siti Balkis Budin <balkis@ukm.edu.my>
To: Nugrahaningsih WH <nugrahaningsihwh@mail.unnes.ac.id>

Wed, Feb 27, 2019 at 6:17 PM

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>
To: Prof Dr Siti Balkis Budin <balkis@ukm.edu.my>

Thu, Feb 28, 2019 at 1:13 PM

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
Title	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



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

[Sains Malaysiana] Editor Decision

2 messages

Prof Dr Siti Balkis Budin <balkis@ukm.edu.my>
To: Nugrahaningsih WH <nugrahaningsihwh@mail.unnes.ac.id>

Mon, Mar 25, 2019 at 3:58 PM

Dear Nugrahaningsih WH:

Regarding your 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~~ 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>
To: Prof Dr Siti Balkis Budin <balkis@ukm.edu.my>

Wed, Apr 10, 2019 at 7:20 AM

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]

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

TGL 17 SEPTEMBER 2019

11/9/21, 8:21 AM

UNNES Mail - Proof August 2019 (Paper 16)



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

Proof August 2019 (Paper 16)

2 messages

Siti Nur Aliaa Abu Talib <sitinuraliaa@ukm.edu.my>
To: nugrahaningsihwh@mail.unnes.ac.id
Cc: Azean Baharuddin <azean.baharuddin@ukm.edu.my>

Tue, Sep 17, 2019 at 8:25 AM

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,
Pembantu Penyelidik,
Sains Malaysiana,
Universiti Kebangsaan Malaysia.

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Kegiatan 11. Memberikan persetujuan proofread melalui email

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11/9/21, 8:21 AM

UNNES Mail - Proof August 2019 (Paper 16)


Nugrahaningsih WH <nugrahaningsihwh@mail.unnes.ac.id>
To: Siti Nur Aliaa Abu Talib <sitinuraliaa@ukm.edu.my>

Tue, Sep 17, 2019 at 3:23 PM

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
[Quoted text hidden]

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#27819 REVIEW

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SUBMISSION

Author Nopriatnengah W.H, Fatmahanik Zahroh, Lidiana Lidiana, Ari Yuzawan, Dik Nohyatin
Title PHARMACOKINETICS OF THE PLAVIXIN[®] AFTER ORAL ADMINISTRATION OF CAMAWALEWES EXTRACT
Section Chemistry
Editor Siti Sukris Indira

PEER REVIEW

ROUND 1

Review Version 2781944861.1.ED.DOCX 2018-09-18
Issued 2018-01-18
Last modified 2018-01-17
Uploaded file None

EDITOR DECISION

Decision Accept Submission 2018-01-24
Finaly Editor [Edit](#) [Edit](#) [Author Email Contact](#) 2018-01-21
Editor Version 2781944861.1.ED.DOCX 2018-01-24
Author Version 2781944861.1.ED.DOCX 2018-01-20 [DELETE](#)
2781944861.1.ED.DOCX 2018-01-20 [DELETE](#)
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Kegiatan 12. Pemberitahuan bahwa artikel telah terbit.

TGL 7 OKT 2019

11/9/21, 8:22 AM

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



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

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

1 message

Jurnal Sains Malaysiana PPFK 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, hiisi@ucts.edu.my, zengqingmei-1@163.com, aiman.bobaker@uob.edu.ly, leetienping@rsciucd.edu.my, mohdheikalayunus@yahoo.com, dmnorma@usm.my, LEE SOO LENG STUDENT <leng527@siswa.um.edu.my>, nugrahaningsihwh@mail.unnes.ac.id, zambrimakhbul@gmail.com, wannurazreena@um.edu.my, dmorsyahida@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>

Cc: "Sahrim Hj. Ahmad" <sahrim@ukm.edu.my>, Sarani Zakaria <szakaria@ukm.edu.my>, Roslan Abd Shukur <ras@ukm.edu.my>, Wan Aida Mustapha <wanaidawm@gmail.com>, Choong Chee Yen <cychoong@ukm.edu.my>, Mohd Talib Latif <talib@ukm.edu.my>, Endom Ismail <eismail@ukm.edu.my>, Chia Chin Hua <chia@ukm.edu.my>, Goh Thian Lai <gohthianlai@ukm.edu.my>, Norbert Simon <norbsn@ukm.edu.my>, ccyap@ukm.edu.my, slwee@ukm.edu.my, Rusli Daik <rusli.daik@ukm.edu.my>, Anuar Mohd Ishak <anuar_mi@ukm.edu.my>, Noriszura Ismail <ni@ukm.edu.my>, mhmarlia@ukm.edu.my, roohaida@ukm.edu.my, Siti Balkis Budin <balkis@ukm.edu.my>, m.firdaus@ukm.edu.my, Nur Azlina Mohd Fahami <nurazlinamf@ukm.edu.my>, nhaslizla@ukm.edu.my, inspeceipa@theiet.org

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

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