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Research Article

PHARMACOKINETICS OF SALICYLIC ACID IN AN INTERACTION STUDY OF AQUEOUS EXTRACT OF *HIBISCUS SABDARIFFA* L WITH ASPIRIN IN RAT PLASMA

Zahriah [1], Fadlina Chany Saputri [2]*, Yahdiana Harahap [3]
[1]Graduate Program, Faculty of Pharmacy, Universitas Indonesia, Kampus UI Depok, 16424, Indonesia
[2]Laboratory of Pharmacology, Faculty of Pharmacy, Universitas Indonesia, Kampus UI Depok, 16424, Indonesia
[3]Laboratory of Bioavailability and Bioequivalence, Faculty of Pharmacy, Universitas Indonesia, Kampus UI Depok, 16424, Indonesia
*Corresponding Author Email: fadlina.chany@farmasi.ui.ac.id

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ABSTRACT

This study intends to find out whether co-administration of aqueous extract of *Hibiscus sabdariffa* L and aspirin would affect the pharmacokinetics profile of aspirin's metabolite, namely salicylic acid. Four groups of Sprague Dawley rats (n=6/group) received aspirin alone (10 mg/kg orally), aqueous extract of *Hibiscus sabdariffa* L 62.5 mg/kg with Aspirin 10 mg/kg, orally, aqueous extract of *Hibiscus sabdariffa* L 125 mg/kg with Aspirin 10 mg/kg, orally, and aqueous extract of *Hibiscus sabdariffa* L 250 mg/kg with Aspirin 10 mg/kg, orally. Aqueous extract of *Hibiscus sabdariffa* L was given once daily for seven days. On the 7th day, 30 minutes after administration of aqueous extract of *Hibiscus sabdariffa* L followed by administration of aspirin, then the plasma sample was taken at a different point. HPLC-UV method was used to identify the pharmacokinetics profile of salicylic acid contained in rat plasma. Co-administration of aqueous extract of *Hibiscus sabdariffa* L and aspirin showed an increase in AUC, Cmax, and t1/2 of salicylic acid, but the increase was not significant ($p>0.05$). In conclusion, aqueous extract of *Hibiscus sabdariffa* L does not affect the pharmacokinetics profile of salicylic acid

Keywords: *Hibiscus sabdariffa* L; aspirin; salicylic acid; pharmacokinetics profile

INTRODUCTION

The use of herbs as a key element in traditional medicine has been going on for a long time. In addition, the use of herbs also continues to increase, although the data related to their efficacy and safety are still inadequate. Literature shows that herbs are used by around 25% of adult societies in developed countries and more than 80% of people in most developing countries[1].

The high use of herbs cannot be separated from the growing belief in society, that herbs are a safe treatment option because everything contained in herbs is natural. This belief is certainly not fully justified and even tends to be dangerous, because, in the end, the community is not careful in using herbs.

The use of herbs that are increasingly massive raises various studies related to important aspects of herbs. Many herbs side effects have also been reported and reviewed, including side effects caused by interactions between herbs and drugs. A lot of active components contained in herbs causes the potential for interactions between herbs and drugs to be higher compared to drug-to-drug interactions because conventional or synthetic drugs usually only contain a single chemical entity[2]. Some cases due to herbs-drug interactions that have been reported to be interfered with are ginkgo-thiazide diuretic interactions causing an increase in blood pressure, ginkgo-trazodone interactions cause coma, interactions between ginseng-phenelzine induce a mania condition, and ginkgo–aspirin interactions cause hyphema[1]. Based on data shown by Tsai et al[3] aspirin is one of the drugs that are often used together with herbs. The literature study shows that the frequency of interactions between herbs-aspirin is 36 incidents.

Low-dose aspirin has antiplatelet activity. Aspirin is a relatively selective inhibitor of the constitutive isoforms of cyclooxygenase-1 (COX-1). The mechanism of action of aspirin in inhibiting platelet function is through acetylation of cyclooxygenase platelets which is in its essential amino acid, serine529. This reaction prevents the access of the substrate (arachidonic acid) to the catalytic site of the enzyme in tyrosine 385. This causes irreversible inhibition of thromboxane formation[4]. In the body, aspirin is metabolized into salicylic acid by the esterase enzyme found in the small intestine, liver, and erythrocytes. The metabolic rate of aspirin to salicylic acid varies depending on age, sex and accompanying disease[5].

Aspirin is the gold standard of antiplatelet. Aspirin has been shown to be effective as a preventive therapy in patients at risk for cardiovascular disease (primary prevention) and for patients who have had one or more cardiovascular diseases (secondary prevention)[6].

According to Liperoti et al[7], in the management of cardiovascular disease, the use of herbs is more prominent than the treatment of using conventional medicines. One of herbs that is believed to have efficacy in maintaining cardiovascular function is *Hibiscus sabdariffa* L. *Hibiscus sabdariffa* L has antioxidant activity[8,9], antihypertensive[10] and anticoagulant and antiplatelet activity[11].

The use of *Hibiscus sabdariffa* L in the community has been going on for years and is used in various preparations such as tea, flavored drinks and also food coloring. The variety of uses of *Hibiscus sabdariffa* L allows the use of *Hibiscus sabdariffa* L and drugs together may be high.

Hibiscus sabdariffa L contains a lot of active components. Therefore, due to interactions that may arise because the use of drugs together varies. One of the active components contained in *Hibiscus sabdariffa* L is chlorogenic acid. In the body chlorogenic acid is metabolized by the esterase enzyme into caffeic acid and quinic acid[12], besides that chlorogenic acid is mentioned can also increase the activity of enzyme esterase[13]

The presence of herbs-drug interactions can cause severity with varying levels, from conditions that can still be tolerated to conditions that can cause death. Therefore, the researcher intends to investigate whether co-administration *Hibiscus sabdariffa* L and aspirin would affect the pharmacokinetics profile of aspirin's metabolite, namely salicylic acid.

MATERIALS & METHODS

Materials and Animals

Salicylic acid (BPFI, Indonesia), furosemide (Ipca, India), acetonitrile and methanol (HPLC grade, Merck, Germany), perchloric acid (Merck, Germany), potassium dihydrogen phosphate (Merck, Germany), ethyl acetate (Merck, Germany), aqua bidest (Ikapharma, Indonesia), aqueous extract of *Hibiscus sabdariffa* L (Balittro, Indonesia), carboxymethyl cellulose (Daichii, Japan), aspirin (Sigma-Aldrich, China).

Male Sprague Dawley rats with body weight (100-200 grams) are purchased from the Bogor Agricultural Institute. The use of animals in this study has passed the ethical approval of the ethics committee of the medical faculty, Universitas Indonesia with the approval number 0643/UN2.F1/ETIK/2018.

HPLC Instruments

High performance liquid chromatography devices (Shimadzu, LC-20AD) consisting of pumps, degassers (Shimadzu, DGU-20A5), column C18 (Waters, Reliant ™ 5µm; 250 x 4.6 mm); UV-Vis detectors (Shimadzu, SPD-20A), oven columns (Shimadzu, CTO 10AS), autosampler (Shimadzu, SIL-20A), data processing software (Lab Solutions); computer (DELL); UV spectrophotometer (Jasco).

Chromatography Conditions

The analytical method used is high-performance liquid chromatography (HPLC) UV-Vis detector at the wavelength (λ) 230 nm. The column used is C18 column measuring 250 mm x 4.6 mm with a particle size of 5 µm (Waters, Reliant TM 5µm; 250 x 4.6 mm). The condition of the analysis uses a mobile phase of acetonitrile with 20 mM phosphate buffer (35:65) at pH 2.5; flow rate of 1.0 mL/minute; column temperature 35˚C.

Plasma Extraction Procedure

A total of 250 µL of plasma was put into a sample cup, then 20 µL of furosemide was added as internal standard (10 µg/mL), 20 µL of 15% perchloric acid, then the mixture was shaken with vortex for 10 seconds. Then added 500 µL of ethyl acetate and vortex for 3 minutes then centrifuged at 12000 rpm for 3 minutes. The organic layer was separated and evaporated to dryness at 50°C for 20 minutes. Then the evaporated aliquots were reconstituted with 35 µL of acetonitrile and 65 µL of phosphate buffer and then shake with vortex for 15 seconds. The final solution was transferred to the vial insert, and as much as 20 µL was injected into HPLC.

Method Validation

In this study, the validation of the method used is partial validation which is carried out with a minimum parameter of linearity, accuracy and precision The stock solution is obtained by mixing salicylic acid (10 mg) into 10 mL acetonitrile to get a concentration of 1000 µg/mL (1000 ppm). Whereas for internal standard, furosemide (10 mg) is dissolved into 10 mL of methanol to get 1000 µg/mL (1000 ppm). All standard solutions are stored at 4°C. A calibration curve solution was made by diluting stock solution salicylic acid 1000 µg/mL with plasma. Dilution was carried out to produce salicylic acid's concentration 0.2; 0.8; 2; 5; 10; 15; and 50 µg/mL. This sample is prepared by adding internal standard solution 10 µL and then processed as plasma extraction procedures. 20 µL aliquots were injected into the HPLC-UV. Peak area ratio salicylic acid to furosemide (internal standard) was calculated and plotted. Parameter analysis of calibration curve is linearity and accuracy. The linearity of the calibration curve is strengthened when the coefficient of determination (r^2) is greater than 0.995 and % accuracy does not exceed ± 15%, except the LLOQ concentration does not exceed ± 20%.

Accuracy and precision tests were carried out using LLOQ concentration (0.2 µg/mL) and tree quality control (QC) samples concentration namely QCL (0.6 µg/mL), QCM (23.75 µg/mL) , and QCH (37.5 µg/mL) for once analysis (intra-batch). For QC samples, accuracy and precision values within the ±15% were considered acceptable in the experimental concentration range and LLOQ with accuracy and precision less than ± 20%.

Pharmacokinetic Study

Based on previous research, LD_{50} of aqueous extract of *Hibiscus sabdariffa* L in rats is 2500 mg /kg and 1/10 of the LD_{50} is assumed to be a safe dose of aqueous extract of *Hibiscus sabdariffa* L which is 250 mg/kg. Furthermore, aqueous extract of *Hibiscus sabdariffa* L was carried out with a dose 250 mg/kg against the time of rat bleeding and the results showed a significant increase in bleeding time with an average time of 14 minutes. Then, this dose is determined as dose 3 of aqueous extract of *Hibiscus sabdariffa* L for testing the pharmacokinetic interactions of aqueous extract of *Hibiscus sabdariffa* L and aspirin, then followed by a dose 2 (125 mg/kg) and dose 1 (62.5 mg/kg). The dose variation was used to investigate whether the effect to be caused was influenced by the dose of aqueous extract of *Hibiscus sabdariffa* L.

This study used four groups of treatment with each group consisting of six rats. Group 1 (Aspirin 10 mg/kg, orally), Group 2 (aqueous extract of *Hibiscus sabdariffa* L 62.5 mg/kg + Aspirin 10 mg/kg, orally), Group 3 (aqueous extract of *Hibiscus sabdariffa* L 125 mg/kg + Aspirin 10 mg/kg, orally) Group 4 (aqueous extract of *Hibiscus sabdariffa* L 250 mg/kg + Aspirin 10 mg/kg. In group 1, 0.5% CMC was given for six days, and on the seventh day, aspirin was given orally 10 mg/kg. Then 0.5 mL of rat blood was taken through orbital sinus at 0, 0.08, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after administration of aspirin and the blood is inserted in a centrifuge tube containing EDTA. In groups 2, 3 and 4 were given aqueous extract of *Hibiscus sabdariffa* L for seven days. On the seventh day, after 30 minutes of administration aqueous extract of *Hibiscus sabdariffa* L, aspirin was given orally 10 mg/kg. Then, rat blood was taken as

in group 1. During the blood collection process, rats were given drinking water ad libitum and 0.9% NaCl orally every three hours. For each treatment, blood samples were centrifuged for 15 minutes with 5000 rpm and 250 µL of supernatant was transferred into a sample cup and stored at -20^{0}C for later analysis.

Pharmacokinetic Analysis

The area under the plasma concentration-time curve (AUC) was calculated using the linear trapezoidal rule. The half-life ($t_{1/2}$) is the time needed for a number of drugs or the concentration of the drug to be reduced to half, which is formulated to be $t_{1/2}$ = 0.693/kel. The volume of distribution is considered as the volume at which the drug is dissolved and calculated as the dose/C_0; C_0 is the concentration measured immediately after administration. Plasma clearance (CL) is expressed as a measure of drug elimination from the body and calculated as the dose/AUC. Analysis of pharmacokinetic parameters using PK solver software integrated in Microsoft Excel.

RESULT

Linearity

From the results of the calibration curve analysis obtained a linear regression equation for salicylic acid y = 0.008 + 0.266x (r = 0.9998).

Intrabatch Accuracy and Precision

The lower limit of quantitation (LLOQ) salicylic acid in plasma is within acceptable criteria, accuracy and precision are within ± 20%. Intra-batch precision and accuracy in plasma are presented in Table 1. Accuracy and precision values for QC samples are within ± 15% covering the actual range and experimental concentration considered acceptable. These results indicate that this method is reliable and valid for the analysis of salicylic acid in plasma for pharmacokinetic studies.

Pharmacokinetic Analysis

The validated method was successfully applied to salicylic acid pharmacokinetic studies in rat plasma after oral aspirin alone (10 mg/kg) and co-administration of aspirin (10 mg/kg) with aqueous extract of *Hibiscus sabdariffa* L 62.5 mg/kg, 125 mg/kg 250 mg/kg. The time curve of plasma concentration is shown in Figure. 1, and pharmacokinetic profiles are presented in Table 2. Pharmacokinetic analysis of salicylic acid in this study using PK Solver software. The results of pharmacokinetic profile analysis related to salicylic acid in rat plasma in three co-administration groups showed an increase in AUC, Cmax, and t1/2 of salicylic acid compared to aspirin's group, but the increase was not significant (p>0.05).

Table 1. Intra-batch Accuracy and Precision Salicylic Acid in Rat Plasma

Nominal concentration (µg/mL)	Peak area(µV/s)		PAR (Peak area ratio)	Observed Concentration(µg/mL)				
	Salicylic acid	Furosemide		**Observed concentration (µg/mL)**	**Mean**	**SD**	**Precision (% CV)**	**Accuracy (% *diff*)**
0.20	16543	273477	0.060	0.197	0.192	0.007	3.737	-1.332
	15650	275753	0.056	0.183				-8.357
	16550	275070	0.060	0.196				-1.942
	15860	275650	0.057	0.186				-6.88
	16880	276654	0.061	0.199				-0.348
0.60	32887	223147	0.147	0.524	0.518	0.012	2.375	-12.670
	31870	220666	0.144	0.512				-14.519
	32055	223450	0.143	0.509				-15.128
	31450	220053	0.142	0.507				-15.463
	31560	209329	0.150	0.536				-10.546
23.75	1720506	271004	6.348	23.830	23.345	0.869	3.724	0.366
	1440650	224650	6.412	24.078				1.382
	1324400	218600	6.058	22.746				-4.225
	1435650	225060	6.379	23.951				0.846
	1240220	210564	5.890	22.112				-6.893
37.50	2199650	227876	9.652	36.258	37.147	0.703	1.892	-3.309
	2658780	270727	9.820	36.890				-1.625
	2299540	226104	10.170	38.204				1.877
	2760878	278941	9.897	37.179				-0.855
	2870760	289862	9.903	37.202				-0.793

Table 2. Pharmacokinetic profile of salicylic acid in rat plasma

Profile	Group 1	Group 2	Group 3	Group 4
AUCo-t(µg/mL*h)	85,72±52,12	95,02±68,66	159,83±108,51	125,48±82,09
AUCo-oo(µg/mL*h)	86,70±51,76	97,63±67,05	165,09±110,80	128,21±82,32
Tmax(h)	3,17±1,72	3,16±1,83	2,50±0,83	2,17±1,16
Cmax(µg/mL)	16,20±9,1	16,84±12,25	30,51±17,24	19,49±13,14
t1/2(h)	3,11±1,82	5,99±4,63	5,32±2,85	4,39±0,87

Note : The data above shows the average with a standard deviation. p>0.05. n (6). AUC (area under the curve); Tmax (the time take to reach Cmax); Cmax (the maximum plasma concentration); t ½ (elimination half-life).Group 1 (Aspirin 10 mg/kg); Group 2 (aqueous extract of *Hibiscus sabdariffa* L 62.5 mg/kg + Aspirin 10 mg/kg); Group 3 (aqueous extract of *Hibiscus sabdariffa* L 125 mg/kg + Aspirin 10 mg/kg); Group 4 (aqueous extract of *Hibiscus sabdariffa* L 250 mg/kg + Aspirin 10 mg/kg).

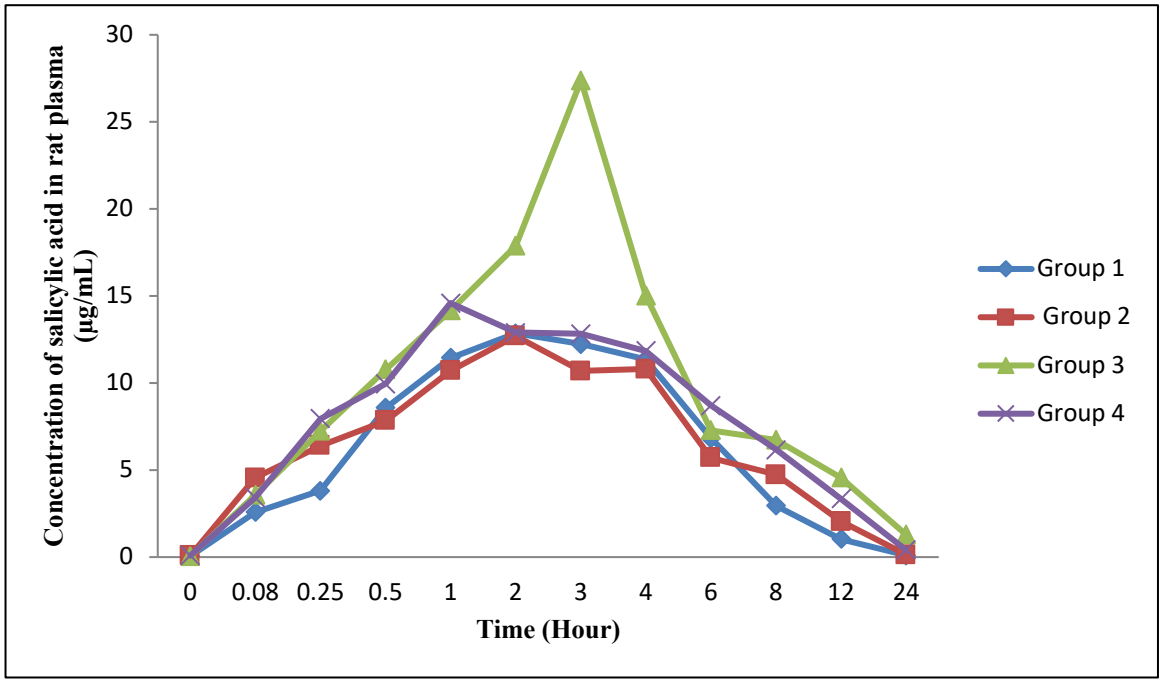

Figure 1. Mean plasma concentration-time profiles of salicylic acid in rats after oral administration of aspirin alone and co-administration aqueous extract of *Hibiscus sabdariffa* L and aspirin.

Note: Group 1 (Aspirin 10 mg/kg); Group 2 (aqueous extract of *Hibiscus sabdariffa* L 62.5 mg/kg + Aspirin 10 mg/kg); Group 3 (aqueous extract of *Hibiscus sabdariffa* L 125 mg/kg + Aspirin 10 mg/kg); Group 4 (aqueous extract of *Hibiscus sabdariffa* L 250 mg/kg + Aspirin 10 mg/kg).

DISCUSSION

Co-administration of herbs and conventional medicines is increasing and becomes a serious problem related to the impact of interactions that occur due to the use of these combinations. Drugs that have antiplatelet properties are often involved in herbal-drug interactions. Aspirin is a gold standard as an antiplatelet which is effective in inhibiting platelet aggregation. In low doses, aspirin is used as an antithrombotic agent to prevent platelet aggregation through inhibition of the cyclooxygenase enzyme. Aspirin has been shown to be effective as preventive therapy for patients at risk of cardiovascular disease (primary prevention) and for patients who have suffered from one or more cardiovascular diseases (secondary prevention).

In the body, aspirin is rapidly hydrolyzed into salicylic acid by the esterase enzyme that found in the intestine. In this metabolic process, differences in species have a significant effect related to the activity and specificity of the esterase enzyme. Based on previous research, esterase found in rat intestinal showed specificity three times stronger in metabolizing aspirin compared to esterase present in the human intestine[14]. Data from table 2 informs that the co-administration aqueous extract of *Hibiscus sabdariffa* L with aspirin showed a tendency to influence all pharmacokinetic profiles of salicylic acid when compared to the aspirin group. However, all effects on the pharmacokinetic profile were not statistically significant. In the AUC parameter, the AUC value of the single aspirin group was smaller than AUC in the three co-administration groups of aqueous extract of *Hibiscus sabdariffa* L and aspirin. The AUC value is associated with the number of systemically absorbed drugs. From this research data information, the presence of *Hibiscus sabdariffa* shows a tendency to increase the amount of absorbed salicylic acid. Salicylic acid which is absorbed is the result of aspirin metabolism by the esterase enzyme in the intestine. Theoretically, aspirin and *Hibiscus sabdariffa* L (chlorogenic acid) is the substrate of the esterase enzyme[15] besides that chlorogenic acid contained in aqueous extract of *Hibiscus sabdariffa* L also cause an increase in esterase activity[13]. Therefore, at the same time, chlorogenic acid will be metabolized by esterase and increasing the activity of the enzyme so that by increasing the activity of the esterase enzyme, the metabolism of aspirin into salicylic acid also increases. The results showed that the values of AUC and Cmax of salicylic acid were greater in the three co-administration groups of rosella water extract and aspirin than in the single aspirin group. Previous studies investigating the interaction between aspirin and *Panax notoginseng* showed an increase in AUC of salicylic acid when given in combination, but this increase was not statistically significant[16]. Based on the value of elimination half-life (t ½) salicylic acid in the co-administration group has increased compared to the single aspirin group, this means that the presence of an aqueous extract of *Hibiscus sabdariffa* L results in slower elimination of salicylic acid, but this increase is not statistically significant.

CONCLUSION

Co- administration of aqueous extract of *Hibiscus sabdariffa* L with aspirin in rat did not have a significant influence on the pharmacokinetics profile of salicylic acid, but further research is needed to determine the effect of interaction of aqueous extract of *Hibiscus sabdariffa* L with aspirin in human.

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REFERENCES

1. Chen XW, Serag ES, Sneed KB, Liang J, Chew H, Pan SY et al. Clinical Herbal Interactions with Conventional Drugs: From Molecules to Maladies. Current Medicinal Chemistry 2011;18:4836–4850. doi:10.2174/092986711797535317

2. Izzo AA. Interactions between herbs and conventional drugs: Overview of the clinical data. Medical Principles and Practice 2012; 21(5):404–428. doi:10.1159/000334488
3. Tsai HH, Lin HW, Simon PA, Tsai HY, Mahady GB. Evaluation of documented drug interactions and contraindications associated with herbs and dietary supplements: A systematic literature review. International Journal of Clinical Practice 2012;66(11):1056–1078. doi:10.1111/j.1742-1241.2012.03008
4. Schrör K. Aspirin and platelets: The antiplatelet action of aspirin and its role in thrombosis treatment and prophylaxis. Seminars in Thrombosis and Hemostasis 1997;23(4):349–356.
5. IARC. Aspirin. Handbooks of Cancer Prevention, 43–102 [Cited 2018 Apr 17]. Available from : http://publications.iarc.fr/_publications/media/download/3836/e94573116cf65a0552bd54ce79542a388879d9ed.pdf
6. Baigent C, Blackwell L, Collins R, Emberson J, Godwin J. Aspirin in the Primary and Secondary Prevention of Vascular Disease: Collaborative MetaAanalysis of Individual Participant Data from Randomised Trials. The Lancet 2009; 373(9678):1849-1860.
7. Liperoti R, Vetrano DL, Bernabei R, Onder G. Herbal Medications in Cardiovascular Medicine 2017; 69(9). doi:10.1016/j.jacc.2016.11.078
8. Usoh IF, Akpan E J, Etim EO, Farombi EO. Antioxidant Actions of Dried Flower Extracts of *Hibiscus sabdariffa* L. on Sodium Arsenite – Induced Oxidative Stress in Rats. Pakistan Journal of Nutrition 2005; 4(3): 135–141
9. Mossalam HH, Aty OAAE, Morgan EN, Youssaf SMS, Mackawy AMH. Biochemical and Ultra Structure Studies of the Antioxidant Effect of Aqueous Extract of Hibiscus sabdariffa on the Nephrotoxicity Induced by Organophosphorous Pesticide (Malathion) on the Adult Albino Rats. Life Science Journal 2011; 8(5):561–574.
10. Ojeda D, Jimenez FE, Zamilpa A, Herrera AA, Tortoriello J, Alvarez L. Inhibition of Angiotensin Converting Enzyme (ACE) Activity by the Anthocyanins Delphinidin- and Cyanidin-3-O-Sambubiosides from Hibiscus sabdariffa. Journal of Ethnopharmacology 2010; 127(1): 7–10
11. Rao TP, Htay HH, Yasuda NK, Sugino H, Ohkubo, Hayashi T, OTSK. Antioxidant and Anti-Thrombotic Properties of Selected Plant Extracts of Asia. Austin Journal of Nutrition & Metabolism 2015; 1(1): 6.
12. Da-Costa-Rocha I, Bonnlaender B, Sievers H, Pischel I, Heinrich M. Hibiscus sabdariffa L. A Phytochemical and Pharmacological Review. Food Chemistry 2014;165:424–443. doi:10.1016/j.foodchem.2014.05.002
13. Crepin VF, Faulds CB, Connerton IF. Functional Classification of the Microbial Feruloyl Esterases. Applied Microbiology and Biotechnology 2004; 63:647-652.
14. Michiko I, Masako M, Minoru T, Mamoru S. Species Difference and Characterization of Intestinal Esterase on the Hydrolyzing Activity of Ester-Type Drug. Japan J Pharmacol 1978;29:9-16.
15. Geoff WP, Maria TGC, Paul AK, Mike R, Saxon R, Gary W. Metabolism of Chlorogenic Acid by Human Plasma, Liver, Intestine and Gut Microflora. Journal of the Science of Food and Agriculture 1999; 79 (3).
16. Tian Z, Pang H, Du S, Lu Y, Zhang L, Wu H, Zhang Q. Effect of Panax notoginseng Saponins on the Pharmacokinetics of Aspirin in Rats. Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences 2017; 1040:136–143. doi:10.1016/j.jchromb.2016.12.007

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