Antipyretic Effects of *(phaleria macrocarpa (scheff) boerl.)* Infusa In Mice Galur Wistar As Animal Model

Noval[1*]
[1] Sari Mulia School of Health Science
* novalhalim10@gmail.com

Ali Rakhman Hakim[1]
[1] Sari Mulia School of Health Science
alirakhmanhakim@gmail.com

Ahmad Irawan[2]
[2] Faculty of Mathematics and Natural Sciences, Garut University
baros.pratama@gmail.com

ABSTRACT

Objective: This study was conducted to prove the antipyretic effect of the *(Phaleria Macrocarpa (Scheff) Boerl.)* and the effect strength, because the scientific evidence and its benefits were still limited, although empirically its leaf has been widely used by society as antipyretics.
Methods: Measurements were performed prior to condensation solution until after the solvent solution was performed at minute 0, 30, 60, 90, 120, and 180. The presence of antipyretic effect was indicated by a statistically significant different down temperature between the test groups and the positive control group. Statistical analysis using ANOVA (Analysis of Variance) and LSD (Least Significant Different) Test.
Results: Results at concentrations of 3% showed a decrease in body temperature actively different against positive controls at 60, 120 and 180 ($p < 0.05$), at a concentration of 6% showing a decrease in body temperature to positive controls at 120 and 180 minutes ($P < 0.05$), whereas at a concentration of 12% showed a decrease in body temperature was actively different against positive controls at 30, 60, 120 and 180 ($p < 0.05$).
Conclusion: A 12% concentration showed the best antipyretic activity with the faster onset of action and the longest duration of action.

Keywords: Antipyretic Effects, Mice Galur Wistar, Phaleria Macrocarpa (Scheff) Boerl.

I. INTRODUCTION

Traditional medicine and medicinal plants are widely used people had down. This happens as people believe in drugs derived from natural or traditional medicines whose effects are smaller and relatively safer to use. Most of the plant compounds that have been found to be medicinally useful and interesting tend to be secondary metabolites including alkaloids, phenolics, acetogenins and terpenoids. Secondary metabolites represent features that can be expressed in terms of ecological, taxonomic and biochemical differentiation and diversity. The wide chemical diversity of secondary metabolites throughout the plant kingdom represents an extremely rich biogenic resource for the discovery of novel drugs and for developing innovative remedies [1,2].

Phaleria macrocarpa, commonly known as God's crown, Mahkota dewa or Pau is an Indonesian plant of family Thymelaceae

that grows in tropical areas of Papua island. It is a complete tree, including stem, leaves, flowers and fruits. Its height ranges from 1 m to 18 m with 1 m long straight root exuding sap, brownish green bark and white wood. It grows 10-1,200 m above sea level with a productive age that ranges from 10 to 20 years. The leaves are green and tapering with length and width ranging from 7 cm to 10 cm and 3-5 cm respectively. The flowers make a compound of 2-4, with color from green to maroon. Pit is round, white and poisonous [3] and fruit is of eclipse shape with a diameter of 3 cm. Fruits are green when un-ripened and become red on ripening [4]. Seeds exist as 1-2 seeds per fruit and are brown, ovoid and anatropous. Although the herb is being used in both un-processed and processed form, however, the former can be poisonous and toxic [5]. P. macrocarpa is being considered generally as a treatment of life style diseases [6].

The Antiinflammatory Power Effect of Dewa Leaves Infant *(Phaleria macrocarpa (Scheff.) Boerl)* has been done in Male Rat (Rattus norvegicus). The results of the study showed that the infusion of the crown leaf of the god has potential as anti-inflammatory [7].

The pericarp and mesocarp extract of fruit have shown moderate anti-inflammatory activity while seed extract has shown weak activity [4]. Cytokines by binding with macrophages up-regulate nitric oxide synthase enzyme which forms NO (nitric oxide) from l-arginine. NO plays an important role in inflammation [9]. Extracts of *P. macrocarpa* inhibit NO production in a dose dependent manner thus inhibiting inflammation [8].

P. macrocarpa is frequently used as a therapeutic healing alternative in health system of the Indonesians and lower course of Malaysia (Ali). All parts of this plant including fruits, seeds, stems and leaves have well known therapeutic properties and have been extensively used in traditional medicine [9,10].

This is what prompted the study of antipyretic effect of infuri leaf of god's crown to prove the efficacy of god's crown leaf in overcoming fever. Because the crown of the gods has anti-inflammatory properties, it is most likely that the crown of gods also has the potential to have analgesic and antipyretic properties because the inflammatory/ inflammatory mediators, fever and pain are the same, ie prostaglandins. The purpose of this study was to prove the antipyretic effect of the crown of the gods crown and its effect strength. The results of the research is expected to be useful and useful generally for people in the world of health.

II. METHOD AND PROCEDURE

Method:

This research is a study of the antipyretic effect of dermatologies leaf infusion *(Phaleria macrocarpa (Sheff.) Boerl).* In this effect test the effect of the infusion of the crown of the god *(Phaleria macrocarpa (Sheff.) Boerl)* to the decrease of

body temperature, when the artificial fever is caused by injection or induction of a filling solution. The solvent used is 5% peptone. The antipyretic effect generated by the crown of the god *(Phaleria macrocarpa (Sheff.) Boerl)* was measured before administering the fever solution until after the solvent solution was performed at minute 0, 30, 60, 90, 120, and 180. The presence of antipyretic effect was indicated by Different temperature drops were statistically significant between the test groups compared to the positive control group. The temperature drop data were analyzed statistically using Annova (Variant Analysis) and LSD (Least Significant Different) [11].

Thermometer, stopwatch, digital scales, 2 ml injection, beaker, mortar, stamper, electric stove, stirrer, reaction tube, dropper, infusion pot, batik cloth and other glassware.

Material:

Simplicia *(Phaleria macrocarpa (Scheff.) Boerl)*, distilled water, 5% pepton, tragakan, CHCl3, Dragendorf, Mayer reagent, HCL 10%, alcohol, FeCl3, H2SO4, NaOH 30%, anhydrous acetic acid, Mg powder, 25% ammonia, Steasny reagent, Lieberman-Buchard reagent, gelatin solution, benzene, ether, and amyl alcohol. Wistar mice with weights between 100-200 g obtained from the Inter-University Center, Bandung Institute of Technology.

Material storage includes material collected, determination and processing of materials into simplicia. The research material is the crown of the god *(Phaleria macrocarpa (Sheff.) Boerl)* collected at Singajaya. Determination of the material is done with the purpose of ensuring the identity of the materials collected. Determination is done at Herbarium Bandungense, School of Life Sciences and Technology Istitut Teknologi Bandung.

(Phaleria macrocarpa (Sheff.) Boerl) is cleansed of impurities with water, sliced, and dried in the sun with a black cloth, then rinsed in a way in the be lender. To make an infusion with a concentration of 12% w / v, which is 12 grams of crown of god, 100 ml of water is added and then heated above the bath for 15 minutes from the temperature 90 0C while stirring occasionally. Serkai while hot through flannel, then added hot water through the dregs until obtained 100 ml volume. Subsequently prepared series of concentrations of 6% w / v and 3% w / v by means of dilution [12].

Procedure:

Different parts of the fruits of *P. macrocarpa* were screened for their anti-inflammatory activity using the nitric oxide (NO) synthesis in macrophage RAW 264,7 cell lines induced by the LPS/IFN-γ assay. Extracts from the pericarp and mesocarp showed notable anti-inflammatory effect with percentage of inhibition of 63,4% and 69,5%, respectively [13]. Study on anti-inflammatory activity was performed on the major compound from the fruits identified as phalerin. This compound showed low

inflammatory effect since it decreased the inflammation twice lower than the standard, Napoxen at dose of 22,5 mg/kg body weight [14]. Anti-inflammatory activity of phalerin was also determined by using the lipoxygenase (LOX), hyaluronidase (HYA) and xanthine oxidase (XO) assays. The results showed that phalerin had mild anti-inflammatory properties in the XO and LOX assays with percentage of inhibition 34,8% and 23,5%, respectively. Meanwhile, phalerin did not exhibit any inflammatory effect in the HYA assay [15].

The general toxicity of 29-norcucurbitacin derivatives; desacetyl-fevicordin A (14), fevicordin A (15), fevicordin A glucoside (16) and fevicordin D glucoside (17), isolated from this plant was evaluated by the brine shrimp (Artemia salina) lethality assay. All compounds showed variable general toxicity with LD50 values ranging from 3 – 12 ppm [16].

1. Division of animal experimental groups

   Mice were divided into 5 groups of animals in which rats were selected randomly, then the weight of each rat was weighed and then numbered to facilitate the administration of the preparation. Group 1 was a positive control group in which the group was heat-induced only without a test or comparison preparation, then group 2 was the comparison group in which this group after heat-induced was given a comparative form of paracetamol suspension at a dose of 45 mg / kg. The next group is group 3 is the dose I test group (infused leaf of the 3% concentration of the gold crown) which will be given a low dose, group 4 is the dose II test group (Infusa leaf crown of the god of concentration 6%) to be given the medium dose, and the group 5 is a dose III test group (Infusa leaf crown of the god of concentration 12%) which at the time of testing was given a higher test of dose.

2. Calculation of dose and preparation of test preparation

   2.1 Comparison

   The dose of paracetamol given at 45mg / kg body weight, then the desired weight given dosage weighing 200 g then the dose given to rats of Dose paracetamol given for 45mg / Kg BB, the weight given given 200g dosage then the dose given on:

   Dose in Mice = $\frac{200}{1000}$ x45 mg = 9 mg/mL

   2.2 Preparation of dosage test infusa *P. macrocarpa*

   Test dose III

   The volume of administration to be given to mice is 1 ml so that the concentration of the dosage given to group 5 is 120 mg/ml.

   The method of preparation of the dosage test of III as follows, preparing a mixture of simplex with a fine degree of 12 grams in a pan with water as much as 100 ml of water for 15 minutes starting from a temperature of 90 ºC while stirring occasionally. Serkai while

hot through flannel, add enough hot water through the dregs to obtain 100 ml of infusion volume.

a. Test dose II

The volume of administration to be given to mice is 1 ml so that the concentration of preparations given to group 4 is 60 mg / ml.

Furthermore, to prepare dosage with concentration 60 mg / ml performed with dilution dose III as much as 50 ml was added with aquadest to 100 ml.

b. Test dose I

The volume of administration to be given to mice is 1 ml so that the concentration of the dosage given to group 3 is 30 mg / ml.

Furthermore, to prepare the dosage with a concentration of 30 mg / ml was treated with a 50 ml dose II dilution was administered with aquadest to 100 ml.

III. RESULT AND DISCUSSION

Testing of antipyretic activity in Swiss Webster's Swiss strain mice was performed using a crown leaf of a god who had undergone a process of starting from washing to drying, then drying into a powder of simplicia until it was made into an infusion preparation.

Based on the results of determination conducted at the Herbarium Bandungense School of Life Sciences and Technology Bandung Institute of Technology, said that the plant in this antipyretic test is the true crown of the god who has Phaleria macrocarpa species (Sheff.) Boerl. which belongs to the Thymelaeaceae.

NSAIDs (Non Steroidal Anti-Inflamatory Drug's) is antiinflamasi drug, analgesic and antipyretic which are heterogeneous, even some of the drugs are very different chemically. The main principle of the therapeutic effects of NSAIDs known through its ability to inhibit the production of prostaglandins. The first enzyme in the synthesis of prostaglandins is the enzyme prostaglandin G/H synthase, or better known as cyclooxygenase (COX).

The research says that the gods Crown contains active compounds in the form of alkaloids, tannins, saponins, phenols, flavonoid, Lignans and sterols, asiri oils. Effect of antiinflamasi is the biological effects of flavonoid who has long researched in Chinese medicine and develop of the cosmetic industry. Flavonoids inhibit enzymes work with producers of eicosanoid including phospholipase A2, siklooksigenase and lipooksigenase and also reduce the concentration of prostanoid and leukotrienes. Compared with previous research, it turns out that in addition to the ethanol extract, preparations in the form of infusion also have the effect of antiinflamasi [17].

Test preparations are used to lower fevers in this research is the gods Crown infuse disari infundasi method. This method is similar to the use of vegetable ingredients

as traditional medicine is to boil the ingredients and take concentrate to drink so that equality of treatment is the use of traditional and treatment in research identical. The Crown of God that are used in this research in the form of simplicia. Chemical compounds contained in fruits Crown God, among other classes of alkaloids, tannins, flavonoids, phenols, saponin, lignin, essential oils and sterols [18].

Pepton used as induction of fever. Before the rats induced pepton, weight of mice weighed in the past to figure out the volume of the giving of the preparations corresponding to the weight of the rat rat body temperature, measured at normal temperature to know of any increase in temperature or not After injecting pepton. Pepton disuntikan subcutaneous skin in the neck. Granting of pepton in subcutaneous aims so pepton diabsorpsi in quite a long time, so as to extend the performance of pepton and cause the condition in mice induced fever be survive long enough. The volume of the granting of pepton for all mice of 0,6 mails without looking at the weight of mice. After inducing rat left for 2 hours in order to provide a period of time so that the body can be active pepton mice, rats measured body temperature then back to know whether rat fever or not. If fever, rats were given sodium orally administering in accordance with volume weight of the mice and measured the temperature after 30, 60, 90, 150, 210 minutes. A thermometer used to measure the body temperature of rats is calibrated in advance before the rat was inserted into the rectum.

Table 1.
The magnitude of the body temperature of mice before and after treatment

Group	No Mice	Body temperature of mice at the time of observation (°C)						
		Normal	Fever	T0	T30	T60	T120	T180
Control (tragakan 1%)	1	35,5	37,3	37,6	38	38,3	38,1	37,9
	2	35,8	37,4	37,5	37,6	37,8	38	37,7
	3	35,8	37,5	37,7	37,6	37,9	38	37,6
	Average	35,7	37,4	37,6	37,73	38	38,03	37,73
	SD	0,17	0,1	0,1	0,23	0,26	0,05	0,15
Comparison (parasetamol 45mg/KgBB)	1	35,4	37,2	37	36,4	36,1	36	35,8
	2	37,8	39,8	39,5	39	37,2	36,4	36
	3	37,6	38,5	37,9	37.4	36,9	36,1	34,9
	Average	36,93	38,5	38,13	37,6	36,73	36,16	35,56
	SD	1,33	1,3	1,26	1,31	0,56	0,21	0,58
Infusa *P. macrocarpa* 3%	1	35,2	37,1	37,7	37,2	36,5	36	35,2
	2	35,9	37,8	38,1	37,8	37	36,3	35,4
	3	36,8	38,5	38,3	37,9	37,6	37,3	36,6
	average	35,96	37,8	38,03	37,63	37,03	36,53	35,73
	SD	0,8	0,7	0,31	0,37	0,55	0,68	0,75

Infusa *P. macrocarpa* 6%	1	36	37,6	37,4	37	36,7	36,1	34,2
	2	36,4	36,8	37,6	37,2	36,9	35,9	33,9
	3	36,4	37,6	38,4	38	37,7	36,9	35
	rata-rata	36,26	37,33	37,8	37,4	37,1	36,3	34,36
	SD	0,23	0,46	0,52	0,52	0,52	0,52	0,56
Group	No Mice	Body temperature of mice at the time of observation (°C)						
		Normal	Fever	T0	T30	T60	T120	T180
Infusa *P. Macrocarpa* 12%	1	35,6	37,6	37,4	37,1	36,8	35,8	33,4
	2	36,3	37,1	36,3	36,2	35,9	34,7	33,3
	3	35,7	37,8	37,5	37,3	36,9	35,7	33,6
	average	35,86	37,5	37,06	36,86	36,53	35,4	33,43
	SD	0,37	0,36	0,66	0,58	0,55	0,61	0,15

Body temperature measurement results data can be seen in table 1. above where the body temperature of mice in normal circumstances, a State of fever either at the time of 30 minutes, 60 minutes, 90 minutes, 120 minutes and 210 minutes. A comparison using paracetamol. Whereas infusa p. Macrocarpa with a concentration of 3%, 6% and 12%.

Table 2.
The average body temperature of mice before and after Treatment

Group	The average body temperature of mice (°C)						
	Normal	Fever	T0	T30	T60	T120	T180
Control	35,7±0,17	37,4±0,1	37,6±0,1	37,7±0,23	38±0,26	38,03±0,05	37,73±0,15
Comparison	36,93±1,33	38,5±1,3	38,13±1,26	37,6±1,31	36,73±0,56	36,16±0,21	35,56±0,58
dose 1	35,96±0,8	37,8±0,7	38,03±0,31	37,63±0,37	37,03±0,55	36,53±0,68	35,73±0,75
dose 2	36,26±0,23	37,33±0,46	37,8±0,52	37,4±0,52	37,1±0,52	36,3±0,52	34,36±0,56
dose 3	35,86±0,37	37,5±0,36	37,06±0,66	36.86±0,58	36,53±0,55	35,4±0,61	33,43±0,15

Table 3.
The difference in body temperature of mice after Treatment

Group	No Mice	The temperature difference between the temperature at the time against fever observations (°C)				
		T0	T30	T30	T120	T180
Control (tragakan 1%)	1	-0,3	-0,7	-1	-0,8	-0,6
	2	-0,1	-0,2	-0,4	-0,6	-0,3
	3	-0,2	-0,1	-0,4	-0,5	-0,1
	Average	-0,2	-0,3	-0,6	-0,47	-0,25
	SD	0,1	0,32	0,34	0,15	0,25
Comparison (parasetamol 45mg/KgBB)	1	0,2	0,8	1,1	1,2	1,4
	2	0,3	0,8	2,6	3,4	3,8
	3	0,6	1,1	1,6	2,4	3,6
	Average	0,36	0,9	1,76	2,33	2,93
	SD	0,21	0,17	0,76	1,11	1,33
Infusa *P.*	1	-0,6	-1	0,6	1,1	1,9

macrocarpa	2	-0,3	0	0,8	1,5	2,4
3%	3	0,2	0,6	0,9	1,2	1.9
	Average	-0,23	-0,13	0,76	1,26	2,06
	SD	0,40	0,81	0,15	0,21	0,28
Infusa *P.*	1	0,2	0,6	0,9	1,5	3,4
macrocarpa	2	-0,8	-0,4	-0,1	0,9	2,9
6%	3	-0,8	-0,4	-0,1	0,7	2,6
	Average	-0,46	-0,06	0,23	1,03	2,96
	SD	0,57	0,57	0,57	0,41	0,40
Infusa *P.*	1	0,2	0,5	0,8	1,8	3,4
macrocarpa	2	0,8	0,9	1,2	2,4	3,8
12%	3	0,3	0,5	0,9	2,1	4,2
	average	0,43	0,63	0,96	2,1	3,8
	SD	0,32	0,23	0,21	0,3	0,4

Comparison group who were given paracetamol can be seen in table 6. that from the minute T0 to T180 shows temperature change over time increasingly large where on the drop in temperature of T0 0.36 ° C but showed no meaningful difference against the checklists, while from a T30 with a decrease in temperature of 0.9 ° C has shown a decrease in the temperature of different means towards the positive control group (p 0.05). On a T60 until T180 statistically meaningful difference shows. The method of testing the effect of antipyretic studies conducted have been valid. As for the mechanism of action of contrast (paracetamol) is inhibiting prostaglandin synthesis which is a mediator of fever so the rat body temperature can be decreased.

Table 4.
Changes of body temperature of mice after Treatment

Group	The average body temperature of mice (°C)				
	T0	T30	T60	T120	T180
Control (suspension tragakan 1 %)	0,2±0,1	-0,3±0,2	-0,6±0,34	-0,47±0,15	-0,25±0,25
Comparison (parasetamol 45mg/KgBB)	0,36±0,21 **(p=0,085)**	**0,9±0,17*** **(p=0,011)**	**1,76±0,76P*** **(p=0,00)**	**2,33±1,11*** **(p=0,00)**	**2,93±1,33*** **(p=0,00)**
dose 1 (infusa *P. macrocarpa* 3%)	-0,23±0,40 (**p=0,057)**	-0,13±0,81 **(p=0,624)**	**0,76±0,15*** **(p=0,005)**	**1,6±0,21*** **(p=0,002)**	**2,06±0,28*** **(p=0,001)**
dose 2 (infusa *P. macrocarpa* 6%)	-0,46±0,57 **(p=0,388)**	-0,06±0,57 **(p=0,515)**	0,23±0,57 **(p=0,055)**	**1,03±0,41*** **(p=0,004)**	**2,96±0,40*** **(p=0,00)**
dose 3 (infusa *P. macrocarpa* 12%)	0,43±0,32 **(p=0,912)**	**0,63±0,23*** **(p=0,035)**	**0,96±0,21*** **(p=0,002)**	**2,1±0,3*** **(p=0,00)**	**3,8±0,4*** **(p=0,001)**

A group of mice given infused *P. macrocarpa* with a concentration of 3% at T0 and T30 showed an increase in body temperature, after a minute T60 decline meaningfully different body temperature against the positive control (p 0,05) so that from testing statistics can be expressed that infused *P. macrocarpa* with a concentration of 3% has the ability as an antipyretic or reliever fever. On the Group of mice given infused *P. macrocarpa* with a concentration of 6% at T0 and T30 showed an increase in body temperature, after hours decline T60 body temperature but the magnitude of the drop in temperature did not differ meaningfully towards the positive control (p 0,05), new from minute T120 decline T180 and body temperature of rats successively 1,03°C and 2,96°C different means towards the positive control (p 0,5).

Infuse *P. macrocarpa* with a concentration of 12% from the initial minutes has shown a decrease in body temperature. At the minute T0 a temperature drop of 0,32°C but no significant difference to the positive control group (p 0,05), while from T30 with a temperature drop of 0,63°C has shown a significantly different temperature drop to the positive control group (p 0,05). The 3%, 6%, and 12% concentration of celestial leaf crown infections exhibited antipyretic activity. The crocodile leaf infused with a concentration of 12%, shows the best antipyretic activity with faster onset of action and the longest duration of action.

IV. CONCLUSION

Infuse *P. macrocarpa (Phaleria macrocarpa (Scheff) Boerl.)* With concentrations of 3%, 6%, and 12% all showed antipyretic activity. The crocodile leaf infused with a concentration of 12%, shows the best antipyretic activity with faster onset of action and the longest duration of action.

REFERENCES

[1] Ditjen POM., 1999. *Obat Tradisional*. http://repository.usu.ac.id/bitstream/123456789/14726/1/09E02836.pdf [21 nov 2014].

[2] Gurib-Fakim A. Medicinal plants: *Traditions of yesterday and drugs of tomorrow*. Mol Aspects Med ;27: pp. 1-93. 2006.

[3] Sufi A. Mataram: Heinrich-Heine-University Dusseldorf. *Lignans in* Phaleria macrocarpa *(Scheff.) Boerl and in Linum flavum var compactum L*. Faculty of Mathematics and Natural Sciences; p. 104. 2007.

[4] Hendra R, Ahmad S, Sukari A, Shukor MY, Oskoueian E. *Flavonoid Analyses and Antimicrobial Activity of Various Parts of* Phaleria macrocarpa *(Scheff.) Boerl Fruit.* Int J Mol Sci. 2011;12:3422–31. [PMC free article] [PubMed]

[5] Yosie A, Effendy MAW, Sifzizul TM, Habsah M. *Antibacterial, radical scavanging activities and cytotoxicity properties of* Phaleria macrocarpa *(Scheff.) Boerl leaves in HepG2 cell lines*. Int J Pharm Sci Res. 2011 ;2: pp. 1700–1706.

[6] Hendra P, Fukushi Y, Hashidoko Y. *Synthesis of benzophenone glucopyranosides from* Phaleria macrocarpa *and related benzophenone glucopyranosides***.** Biosci Biotechnol Biochem. 2009; 73:2172–82.

[7] Goodman, A.G., *Goodman & Gilman's The Pharmocological Basis of Therapeutics,* 10□ □ ED, The McGraw-

Hill Companies.Inc., New York, 690-693, 696-704, 2001.

[8] Wu CC. Nitric Oxide and Inflammation. *Current medicinal chemistry-antiinflammatory and antiallergy agents:* Bentham Science Publishers; 2004;3:217–22.

[9] Tjandrawinata RR, Arifin PF, Tandrasasmita OM, Rahmi D, Aripin A. DLBS1425, *a* Phaleria macrocarpa *(Scheff.) Boerl. extract confers anti proliferative and proapoptosis effects via eicosanoid pathway*. J Exp Ther Oncol. 2010;8: pp. 187–201.

[10] Winarno H and Katrin WE. *Benzophenone glucoside isolated from the ethyl acetate of the bark of mahkota dewa (Phaleria macrocarpa (Scheff.) Boerl.) and its inhibitory activity on leukemia L1210 cell line*. Indo J Chem. 2009;9:142-145.

[11] Syofian S., *Metode Penelitian Kuantiatif Dilenkapi Perbandingan Perhitungan Manual dan SPSS.* Jakarta: Kencana Prenada Media Group, pp : 202-203. 2003.

[12] Depkes RI. *Farmakope Indonesia*, ed 4, Depkes RI, Jakarta, hlm 30, 649. 1997

[13] Hendra R, Ahmad S, Sukari A, Shukor MY and Oskoueian E. *Antioxidant, anti-inflammatory and cytotoxicity of Phaleria macrocarpa (Boerl.) Scheff fruit.* BMC Complement Altern Med. 2011;11:1-10.

[14] Mariani R, Wirasutisna K, R, Nawawi A and Adnyana IK. *Antiinflammatory activity of dominant compound of mahkota dewa fruit Phaleria macrocarpa (Scheff.) Boerl*. Indonesian J Pharm. 2010;21:129-133.

[15] Fariza IN, Fadzureena J, Zunoliza A, Chuah AL, Pin KY and Adawiyah I. *Anti-inflammatory activity of the major compound from methanol extract of Phaleria macrocarpa* leaves. J Appl Sci. 2012;12: pp.1195-1198

[16] Kurnia D, Akiyama K and Hayashi H. *29-Norcucurbitacin derivatives isolated from the Indonesian medicinal plant, Phaleria macrocarpa* (Scheff.) Boerl. Biosci Biotechnol Biochem. 2008;72: pp.618-620.

[17] Mariani, R. *Telaah Kandungan Kimia dan Aktivitas Antiradang Buah Mahkota Dewa (Phaleria Macrocarpa [Scheff.] Boerl* [Abstrak]. Disertasi. 2005.

[18] Hendra, R. et al., Antioxidant, anti-inflammatory and cytotoxicity of Phaleria macrocarpa (Boerl.) Scheff Fruit. *BMC complementary and alternative medicine*, 11(1), p.110. 2011