Standardization of the Ethanol Extract of Mahkota Dewa Leaves (Phaleria macrocarpa (Scheff.) Boerl) Using Non-Specific Parameters

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ABSTRACT

Background*: Medicinal plant extracts have been widely developed for use in health services. Medicinal plant extracts derived from raw material can be used in the form of dry, viscous, and liquid extracts according to the active ingredients contained therein and the intended use. Traditional medicines circulating in Indonesia must meet quality, safety, and efficacy. One of the medicinal plants whose empirical use is widely known by the people of Indonesia is Mahkota dewa (Phaleria macrocarpa (Scheff.) Boerl).* ***Purpose****: It is to standardize the ethanol extract of Mahkota Dewa leaves to ensure its quality, safety, and pharmacological properties. The standardization carried out is non-specific parameters based on Indonesian Herbal Pharmacopeia.* ***Methods****: The leaves of Mahkota Dewa were collected from Parigi Moutong, Donggala, and Sigi Regon, and extracted using maceration method with ethanol. The ethanol extract was then tested for non-specific parameters including drying shrinkage, water content, total ash content, acid insoluble ash content, specific gravity, residual ethanol solvent, total plate number contamination yeast -mold number, Pb and Cd metal contamination* ***Results****: Based on the non-specific standardization parameter test results, the ethanol extract of Phaleria macrocarpa (Scheff.) Boerl leaves met the Indonesian herbal pharmacopeia standards; however, the Cd metal contamination test exceeded the established standards. Based on one-way ANOVA analysis, there were four standardization parameters that were differed significantly (sig <0.05), namely drying shrinkage, moisture content, total ash content, and determination of heavy metal content.*

Keywords: *mahkota dewa; medical plant ; non-specific parameter; phaleria macrocarpa (Scheff.) Boerl; standardization*

INTRODUCTION

Medicinal plants can be interpreted as types of plants in which part, all, and/or plant exudates are used as medicine, ingredients, or medicinal ingredients. Traditional medicinal plants are plant species that are known and trusted by the public to have medicinal properties and have been used as raw materials for traditional medicine (Wahyuni et al., 2016). The development of traditional medicine in Indonesia is aimed at improving health, preventing and curing diseases. However, the use of traditional medicines cannot be used like modern medicines, because tests

must be carried out on the efficacy, quality, and safety of herbal medicines (BPOM RI, 2005). The quality of a traditional medicinal raw material can be affected by soil conditions, cultivation, post-harvest, and processing of the raw material into an extract as well as during the extract storage process (Ulfah et al., 2019). To support this, it is necessary to have quality tests and standardization of extracts.

One of the plants used in traditional medicine is Mahkota Dewa (*Phaleria macrocarpa* (Scheff.) Boerl). Mahkota Dewa leaf showed several biological activities such as anti-inflammatory (Fariza et al., 2012) antibacterial, antioxidant, and increase the activity of the NKG2D (natural-killer group 2, member D) receptor which can prevent the growth of cancer cells (Altaf, 2013), analgesic effect (Tone et al., 2013), anti-inflammatory activity in the large intestine (Suprapti et al., 2014), inhibit the growth of the *Candida albicans* fungus in HIV/AIDS patients (Elianora et al., 2017), an inhibitor of inflammation in the rectal tissue (Putra et al., (2020), increase the expression of caspase-3 which can inhibit the growth of cells that are not needed by the body in the large intestine (Kusmardi et al's 2021).

The biological activities of the ethanol extract of Mahkota Dewa leaves is influenced by the number of active compounds it contains. The content of active compounds and the quality of a medicinal plant extract cannot be guaranteed to have the same levels because they can be influenced by climate and place of growth. Where a plant grows based on geographical location such as height above mean sea level (AMSL) will cause differences in weather and climate as well as temperature and humidity (Istiawan & Kastono, 2019). Several of these factors will affect the characteristics of a plant extract, therefore in this study samples of the crown of the gods were obtained from three different locations, namely Parigi Moutong with an altitude of 13 meters above sea level, Donggala with an altitude of 31 AMSL and Sigi with an altitude of 638 AMSL. Controlling the quality of the extract can be done by standardizing the extract. Standardization is needed to obtain uniform raw materials so as to guarantee the resulting pharmacological effects. In order to guarantee the quality of medicinal plant extracts, it is necessary to determine non-specific quality standards which include moisture content, ash content, acid-insoluble ash content, specific gravity, residual ethanol solvent, microbial contamination, and heavy metal contamination so that are standardized. The obtained extracts can meet the aspects of security and stability.

RESEARCH METHOD

This research is an experimental study that focuses on standardizing the ethanol extract of Mahkota Dewa leaves based on standardization parameters using the Indonesian Pharmacopoeia. The results of standardized parameter measurements were analyzed using one-way ANOVA.

Materials

The materials used in this study were the leaves of Mahkota Dewa (*Phaleria macrocarpa* (Scheff.) Boerl), distilled water, hydrochloric acid, nitric acid p.a, sulfuric acid, 70% ethanol (Onemed), 96% ethanol, aluminum foil, filter paper, spiritus, Physiological NaCl (Satoria Pharma), Potato Dextrose Agar (PDA) (Merck KGaA), Nutrien Agar (NA) (Merck KGaA) and cotton, Aqua Pro Injection (API) (Onemed).

Sample Preparation and Extraction

The Mahkota Dewa leaves were obtained from Tindaki Village, South Parigi District, Parigi Moutong Regency with a height of 13 meters AMSL, Sipi Village, Sirenja District, Donggala Regency with an altitude of 31 AMSL, and Berdikari Village, Palolo District, Sigi Regency with an altitude of 638 AMSL. The sample of the Mahkota Dewa was identified at the Biosystematics Laboratory of the Department of Biology, Faculty of Mathematics and Natural Sciences, University of Tadulako. The leaves of the Mahkota Dewa are sorted wet, then washed with running water, then cut into small pieces, and air-dried and dried. Dried Mahkota dewa leaves turned into powder form and macerated by using ethanol for 3×24 hours. The filtrate of each sample was concentrated using an evaporator to obtain condensed ethanol extract.

Non-Specific Parameter Testing (Indonesian Health Department, 2000)

1. Determination of Water Content

Five grams of the extract were weighed in a calibrated container. Dry at 105^{o}C for 5 hours, then weigh. Drying was continued and weighed every 1 hour intermittently until the difference between two consecutive weighing was not more than 0.25%.

2. Determination of Total Ash Content

Two grams of extract which had been crushed and weighed carefully were put into a porcelain crucible which had been ignited and then leveled. Incandescent slowly at 600ºC for ± 2 hours until the charcoal is used up, cooled, and weighed. If the charcoal cannot be removed in this way, then add hot water, then filter and ignite the remaining paper and filter paper in the same porcelain crucible.

3. Determination of Acid Insoluble Ash Content

The ash content obtained was boiled with 25 mL of dilute hydrochloric acid for 5 minutes, the acid-insoluble part was collected, filtered using ash-free filter paper, then washed with hot water, and ignited in a crucible to a constant weight, and then weighed.

4. Determination of Specific Weight

The liquid extract with a temperature of 20^{o}C was put into the pycnometer, the temperature of the pycnometer was set at 25^{o}C, and the remaining liquid extract was removed and weighed until a constant weight was obtained. The specific gravity is obtained by dividing the weight of the liquid extract by the weight of the distilled water and multiplying by the specific gravity of the water.

5. Determination of Microbial Determination

- Total Plate Numbers (TPN)

One milliliter of extract from dilutions 10 and 10^{-1}, 10^{-2}, 10^{-3}, and 10^{-4} was pipetted using a sterile pipette, then instilled in NA medium, and then incubated at 37^{o}C for 24 hours. Observe and count the number of colonies that grow.

- Mold and Yeast

One milliliter of extract from dilutions 10 and $10^{-1,}$ 10^{-2}, 10^{-3}, and 10^{-4} was pipetted using a sterile pipette, then instilled in a PDA medium, and then incubated at 25^{o}C for 3 days. The number of colonies that grow were observed and counted.

6. Residual Ethanol Solvent

The liquid is estimated to contain 30% ethanol or less. The concentrated extract was weighed as much as 2 g, then it was dissolved in water up to 25 mL, and put into a distillation flask with a temperature of 78.5^{o}C. Observe until the distillate is ± 2 mL smaller than the volume of the test liquid (distill for 2 hours or no longer drip). Added 25 mL of water, and determined the specific gravity of the liquid at a temperature of 25^{o}C. Then the percentage in the volume of ethanol in the liquid was calculated using a table of specific gravity and ethanol content (Saifudin et al., 2011).

7. Determination of Heavy Metal Limits

Determination of heavy metal limits by atomic absorption spectrophotometer (AAS) method through destruction. Destruction begins with weighing 1 g of extract and adding 10 mL of HNO_3, then heating with a heating mantle until dry or thick. The thick extract was added with 10 mL distilled water and 5 mL perchloric acid, heated until thick, then filtered into a 50 mL volumetric flask, and the volume was made up with distilled water. The 20 mg/mL filtrate was filtered, then put into the AAS tool and analyzed. The calibration curve for metal Pb is based on SNI 6989.8:2009, and the calibration curve for metal Cd is based on SNI 06-6989.16-2004.

DATA ANALYSIS

Non - specific parameter measurement results were analyzed using one-way ANOVA analysis and continued with the t-test if the p-value<0.05.

RESULT

a. Identification and Extraction of Mahkota Dewa leaves

The results of the identification stated that the plants used in this study were indeed the leaves of the Mahkota Dewa plant (*Phaleria macrocarpa* (Scheff.) Boerl) according to Figure 1. The yield of the ethanol extract of the leaves of the Dewa crown from Parigi Moutong was 7.322%, Donggala 10.02%, Sigi 10.920 % (attached to Table 1).

b. Non-Specific Parameters Testing Based on The Ministry of Health (2000)

The results of the non-specific parameter tests that have been carried out on samples of the ethanol extract of Mahkota Dewa leaves (*Phaleria macrocarpa* (Scheff.) Boerl) from three

different areas based on altitude, namely Parigi Moutong, Donggala, and Sigi, the ethanol extract of Mahkota Dewa leaves have met the Herbal Pharmacopoeia standards. Although, the detected cadmium (Cd) metal contamination was above the specified maximum limit. Non-Specific Parameter Testing Data is attached in the table.

DISCUSSION

The potential biological activity of Mahkota Dewa leaf extract requires standardization to ensure its quality and safety. In the future, it is hoped that Mahkota Dewa leaf extract can be used as a raw material for phytopharmaca.

Several factors that can affect the quality of an extract are biological factors which include species identity, growing location, harvesting period, self-life, and parts used. Based on this, one of the factors that influence the quality of the extract is the location of growth, so in this study, samples were obtained from three places with different heights, namely in Tindaki Village, Parigi Selatan District, Parigi Moutong Regency with an altitude of 13 masl, Sipi Village, Sirenja District, Donggala Regency. with an altitude of 31 masl and Berdikari Village, Palolo District, Sigi Regency with an altitude of 638 masl, Central Sulawesi Province.

Mahkota Dewa plant used in the nomenclature description, the parts of the plant used, and the Indonesian name of the plant is based on the standard literature by first identifying it at the Plant Biosystematics Laboratory, Department of Biology, Faculty of Mathematics and Natural Sciences, Tadulako University. The identity of the sample was verified by the results of identification which stated that the sample used was the leaf of Mahkota Dewa with the species *Phaleria macrocarpa* (Scheff.) Boerl.

The simplisia of Mahkota Dewa leaves was extracted using 96% ethanol solvent by the maceration method. The maceration method was chosen because it is the simplest method and is used for analytes that are neither heat resistant nor heat resistant. In this study the solvent used in the extraction process was 96% ethanol; the choice of this solvent was because ethanol is universal, causing ethanol to extract polar and nonpolar compounds. The universal properties of ethanol are influenced by the structure of its compounds. Ethanol has alkyl groups (CH_3) and hydroxy groups (OH), these two groups give universal properties to ethanol, the hydroxy groups help in extracting polar compounds and the alkyl groups help in extracting nonpolar compounds.

The extraction process is important in determining the yield percentage because the yield percentage describes the amount of simplicia needed for a number of extracts produced from the extraction process so that it can estimate the amount of simplicia needed to fulfill the required amount of extract in the test. The highest yield processed was obtained from the leaf extract of the crown god sample from Sigi 10.92% as much as 54.6 g of the total simplicial of 500 g. The amount of yield value also describes

the number of compounds extracted from the simplicia.

Determination of non-specific parameters carried out in this study was water content, total ash content, acid insoluble ash content, specific gravity, residual solvent, total plate count, yeast mold count, Pb and Cd metal contamination.

The determination of water content is a measurement of the water content in viscous extracts. Determination of water content aims to ensure the quality of an extract, where water is a medium for microbial growth, the presence of a microbe will affect and reduce the biological activity of the sample during the storage process. In determining the water content, the highest results were found in samples from Parigi Moutong at 21.7305% ±0.0913 and the lowest from Sigi Regency at 18.8378 ± 0.5630. According to Saifudin et al., (2011), the obtained results do not exceed a predetermined maximum limit of 5-30%. ANOVA and t-test analysis that is to determine the water content of the ethanol extract of Mahkota Dewa leaves from the three districts showed a significant difference (sig <0.05), this indicates that there is an effect of differences in the height of the place where it grows with the water content of the ethanol extract of Mahkota Dewa leaves.

Several factors can affect the sample's water content, namely differences in growing environments such as growing height, air humidity, and sunlight intensity (Rahmaniati et al., 2018).

The total ash content can describe the mineral content of a material, the higher the ash content, the higher the minerals contained in the material (Lestari et al., 2014). These minerals can be in the form of organic salts (oxalate, acetate, malic, and pectate salts) and inorganic salts (phosphate, carbonate, nitrate, chloride, and sulfate salts). The results of determining the total ash content with the highest value were obtained in samples from Donggala, namely 4.7056% ± 0.3370. The value does not exceed a predetermined maximum limit. ANOVA and t-test analysis showed that there were significant differences (sig<0.05) in the total ash content of the ethanol extract of Mahkota Dewa leaves from the three districts. So it can be concluded that the total ash content of a plant extract is influenced by the place where it grows.

According to Maryam et al (2020), the determination of the acid-insoluble ash content was carried out to evaluate the extract against contamination of siliceous materials such as soil and sand.

The results of determining the acid-insoluble ash content of the ethanol extract of Mahkota Dewa leaves with the highest value were found in the sample from Sigi 0.4079% ± 0.0979. This value does not exceed a predetermined maximum limit. Ash content that does not dissolve in acid indicates the presence of sand or other impurities. ANOVA analysis for determining the acid-insoluble ash content of the ethanol extract of Mahkota Dewa leaves showed no significant difference (sig>0.05) from the three samples of Mahkota Dewa

leaves with differences in where they grew.

Specific gravity describes the ratio of the density of a substance to the density of water with a comparison between the weight of the material and the weight of water at the same temperature and volume (Purwadi et al., 2017). The highest specific gravity determination value was obtained in the sample from Parigi Moutong 0.826 g/mL ± 0.005. ANOVA analysis to determine the specific gravity of extracts from three different districts of the ethanol extract of Mahkota Dewa leaves showed no significant difference (sig>0.05).

According to the Depkes RI (2000), the specific gravity test aims to provide a limit on the amount of mass per unit volume. Special parameters of liquid extracts to thick extracts can still be poured. The specific weight also gives an idea of the purity and contamination of the material.

Testing the residual ethanol solvent aims to determine the residual solvent contained in the extract which should not be present in an extract (European Medicines Agency, 2014). The highest results were found samples from Sigi 1.001 g/mL ± 0.008. Based on the specific gravity values, it can be seen that the percentage of ethanol content in extracts from the three districts is 0-2.7% (Conversion table in the Indonesian Pharmacopoeia). ANOVA analysis showed that there was no significant difference (sig>0.05) in the residual solvent contained in the ethanol extract of Mahkota Dewa leaves from the three districts. According to the European Medicines Agency (2014), the remaining allowable ethanol solvent is 5%. This shows that the samples from the three locations in this study still met the maximum residual solvent limit requirements that had been set.

Testing for microbial contamination is very important to ensure that the extract does not contain pathogenic and non-pathogenic microbes that exceed the maximum limit set because it can affect the stability of an extract and is toxic to the human body (Depkes RI, 2000). The results obtained in the Total Plate Count test were <1.0 × 101 colonies/g. On the Mold Yeast Number test, the highest results were obtained in samples from Sigi 11.3 × 101 colonies/g. According to BPOM RI (2019), the results obtained did not exceed the specified maximum limit, namely ≤ 5 × 107 colonies/g for bacteria and ≤ 5 × 105 colonies/g for molds. The low growth of this bacteria can be caused by the extract used, namely ethanol extract which can inhibit microbial growth in an extract (Tiwari et al., 2011).

Heavy metals are important elements needed by every living thing. Heavy metals in small amounts have a role to maintain the human body's metabolism such as copper (Cu), selenium (Se), iron (Fe), and zinc (Zn). The metals that are harmful to the human body are lead (Pb), mercury (Hg), arsenic (As), and cadmium (Cd) (Agustina, 2014). The metal contamination test was carried out using the atomic absorption spectrophotometer (AAS) method, this tool is based on the Lambert-Beer law,

namely the amount of light absorbed is directly proportional to the amount concentration of a substance. The highest levels of lead (Pb) were obtained in samples from Sigi, namely 8.4725 mg/kg ±0.2368. In the cadmium (Cd) metal contamination test, the highest Cd content was obtained in the sample from Parigi Moutong of 1.0025 mg/kg ± 0.0176. According to BPOM RI (2019), the limits for lead (Pb) and cadmium (Cd) contamination are respectively ≤ 10 mg/kg and ≤ 0.3 mg/kg. ANOVA and t-test analysis showed that there were significant differences (sig<0.05) in the content of Pb and Cd metals in the ethanol extract of Mahkota Dewa leaves from the three districts.

Based on the results of measurements of the metal content of Pb and Cd, it was found that the levels of lead (Pb) were below the maximum permissible level of metal contamination, while the levels of cadmium (Cd) were above the maximum limit of metal contamination that had been set. The high content of heavy metals in an extract can be caused by the type of soil and soil conditions, accumulation of dust, rain, soil erosion, and waste disposal (Ma'arif et al., 2020).

CONCLUSION

Based on the results of non-specific parameter testing that has been carried out on samples of the ethanol extract of Mahkota Dewa leaves (*Phaleria macrocarpa* (Scheff.) Boerl) from three growing places, namely Parigi Moutong, Donggala, and Sigi, it can be concluded that the ethanol extract of Mahkota Dewa leaves meets the Pharmacopoeial standards, even though the metal cadmium (Cd) contamination was above the maximum required limit. Based on one-way ANOVA and t-test analysis, there were three standardization parameters that differed significantly (sig <0.05), namely moisture content, total ash content, and determination of heavy metal content. The value of these four parameters is influenced by the place where the Mahkota Dewa plant grows.

SUGGESTION

It is necessary to test the specific parameters of the ethanol extract of the leaves of the Phaleria macrocarpa (Scheff.) Boerl to complete the standardization data for this plant.

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Table 1. Percent Yield of Mahkota Dewa Leaves Extract

Location	Raw material weight (g)	Extract weight (g)	Yield (%)
Parigi Moutong	500	36.61	7.322
Donggala	500	50.12	10.024
Sigi	500	54.60	10.920

Table 2. Water Content, Total Ash Content, Acid Insoluble Ash Content, Specific Weight and Residual Ethanol Solvent

Parameters	Parigi Moutong	Donggala	Sigi	sig	Requirements
Water Content (% ± DS)	21.7305 ± 0.0913	18.8378 ± 0.5630	19.5167 ± 0.4256	<0.05	5 – 30% (Saifudin et al., 2011)
Total Ash Content (% ± DS)	3.4926 ± 0.0451	4.7056 ± 0.3370	3.6630 ± 0.1525	<0.05	≤ 16.6% (Depkes RI, 2008)
Acid Insoluble Ash Content (% ± DS)	0.2742 ± 0.1098	0.2956 ± 0.0546	0.4079 ± 0.0979	>0.05	≤ 0.7% (Depkes RI, 2008)
Specific Weight (g/mL ± DS)	0.8260 ± 0.0050	0.8200 ± 0.0100	0.8200 ± 0.0100	>0.05	-
Residual Ethanol (g/mL ± DS)	0.9946 ± 0.0072	0.9956 ± 0.0066	1.0006 ± 0.0086	>0.05	5% (European Medicines Agency, 2014)

n = 3

Table 3. Results of Microbial Contamination Test Total Plate Number and Yeast Mold Number

Parameters	Parigi Moutong	Donggala	Sigi	Maximum Limit
Total Plate Number	$< 1.0 \times 10^1$	$< 1.0 \times 10^1$	$< 1.0 \times 10^1$	$\leq 5 \times 10^7$(BPOM RI, 2019)
Yeast Mold Number	2.6×10^1	0.6×10^1	11.3×10^1	$\leq 5 \times 10^5$(BPOM RI, 2019)

Table 4. Pb and Cd Metal Contamination Test Results

Parameters	Parigi Moutong	Donggala	Sigi	Maximum Limit
Pb metal contamination (mg/kg ± SD)	5.3975 ± 0.1166	5.8975 ± 0.1166	8.4725 ± 0.2368	≤ 10 (BPOM RI, 2019)
Cd metal contamination (mg/kg ± SD)	1.0025 ± 0.0176	0.9650 ± 0.0707	0.6475 ± 0.0530	≤ 0.3 (BPOM RI, 2019)

n = 2