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SPRAY DRIED AQUEOUS EXTRACT OF LEMONGRASS (*Cymbopogon citratus*) EXHIBITS IN VITRO AND IN VIVO ANTI HYPERGLYCEMIC ACTIVITIES

AKTIVITAS IN VITRO DAN IN VIVO ANTI HIPERGLISEMIA DARI EKSTRAK AIR SERAI (*Cymbopogon citratus*) YANG DIKERINGKAN DENGAN METODE SPRAY-DRYING

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ABSTRACT

Lemongrass was found to be a promising herb for anti-hyperglycemia treatment due to its activities to inhibit alpha glucosidase and alpha amylase in vitro activities and ability to improve blood glucose profile. Lemongrass potency through its anti-hyperglycemic ingredients requires evaluation of the functional stability during processing. In this study, the in vitro anti-hyperglycemic activities of spray-dried aqueous extract of lemongrass were determined by its inhibitory activity against rat intestinal glucosidase enzymatic hydrolysis of sucrose. In vivo activity was observed based on its ability to prevent blood glucose elevation in oral glucose, sucrose and maltose tolerance tests (OGTT, OSTT and OMTT). The in vitro evaluation showed that aqueous extraction, which involved stirring at 70 °C for 40 min, successfully increased the glucosidase inhibitory activity of lemongrass extract, while spray drying with inlet 130 °C had no significant impact to the activity tested in vitro. Spray-dried lemongrass powder was found to be effective for lowering blood glucose level in OGTT, OSTT and OMTT. This study provides support for further development of lemongrass extracts as functional ingredients for hyperglycemia treatment.

Keywords: *anti hyperglycemia, aqueous extract, lemongrass, spray-dried powder*

ABSTRAK

Serai diketahui memiliki aktivitas in vitro untuk menghambat enzim alfa glukosidase dan alfa amilase dan aktivitas in vivo untuk memperbaiki profil gula darah. Potensi serai untuk dikembangkan sebagai bahan baku fungsional dengan aktivitas anti hiperglisemia perlu dikaji dalam kaitannya dengan stabilitas aktivitas fungsionalnya. Pada penelitian ini, ekstrak air serai yang dikeringkan dengan metode spray-drying dikaji aktivitas in vitronya untuk menghambat hidrolisis enzimatis sukrosa oleh enzim glukosidase yang berasal dari usus tikus serta aktivitas in vivonya untuk menghambat kenaikan gula darah mencit setelah uji toleransi oral glukosa, sukrosa, dan maltosa (OGTT, OSTT and OMTT). Ekstraksi air yang dilakukan dengan teknik maserasi dan pengadukan selama 40 menit pada suhu 70 °C, meningkatkan aktivitas in vitro secara signifikan sedangkan pengeringan dengan metode spray drying pada suhu inlet 130 °C tidak memiliki dampak signifikan terhadap aktivitas in vitro. Bubuk yang dihasilkan dari pengeringan tersebut menurunkan tingkat gula darah secara efektif pada pengujian OGTT, OSTT and OMTT. Hasil penelitian ini diharapkan dapat mendukung pengembangan serai sebagai bahan baku fungsional untuk mengatasi hiperglisemia.

Kata kunci: *anti hiperglisemia, ekstrak air, serai, bubuk spray-dry*

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INTRODUCTION

Lemongrass potencies for diabetic treatment have been reviewed in previous studies (Shah et al., 2011; Geetha and Geetha, 2014), showing 125-500 mg/kg daily oral dosing of aqueous extract from fresh leaves could lower fasting plasma glucose in male Wistar rats after 42 days of treatment (Adeneye and Agbaje, 2007), though evaluation of its immediate impact to blood glucose has not yet been done. Lemongrass also recently had been extracted in several solvents and evaluated for its in vitro alpha glucosidase inhibitory activities (Santoso et al., 2016; Gunawan-Puteri et al., 2017), resulting in the finding of lemongrass extracted in methanol and ethyl acetate having more than 50% inhibition activity against sucrase at 0.02 mg/ml (Santoso et al., 2016). Aqueous extract of lemongrass was optimized and the selected extract was then pulverized using spray drying methods for the production of lemongrass powder for functional food ingredients (Gunawan-Puteri et al., 2017). Spray drying is widely used in the Food industry due to the affordability and effectiveness of the operation and process which are relatively flexible, produce a good quality product and can prolong the shelf life of liquid products as it turns into powder (Munin and Edwards-lévy, 2011). Despite the practicality of powder ingredients, impacts of the extraction optimization and further pulverization to produce spray-dried aqueous extract of Lemongrass on the sucrase inhibition activity in vitro and in vivo have not been observed.

METHODS

Materials

Sun-dried lemongrass was collected from Yogyakarta, Indonesia through the herbal supplier CV Sekar Utami. Rat intestinal acetone powder as a source of the glucosidase enzyme was acquired from Sigma-Aldrich, Singapore, while glucose kit C-II for glucose measurement was acquired from Wako, Japan. Potassium phosphate buffer pH 7.0 and ethylenediaminetetraacetic acid were acquired from Sinopharm Chemical Reagent Co., Ltd., China, while analytical grade methanol and maltodextrin were acquired from PT Bratachem, Indonesia. Aluminium oxide 60, sucrose (saccharose), maltose and D-(+)-Glucose anhydrous for biochemistry analysis, and other chemical reagents were acquired from Merck Millipore, Germany, unless stated otherwise.

Plant Samples Preparation

Sun-dried lemongrass was ground using a miller for 90 s to reduce the size. Maceration extraction methods were used with the ratio 3:5 (v/v) between dried lemongrass and water. The basic extraction was done for 24 h in room temperature while the optimized extraction was done for 40 min at 70 °C using stirring. Crude extracts were filtered using vacuum filtration and were subsequently concentrated using a rotary evaporator at reduced pressure at 50 °C and then stored in amber bottle glass at 4 °C prior to analysis or spray drying until the total soluble solid reached more than 10%. Selected samples underwent a spray drying process using 130 °C for the inlet temperature. The nozzle number of the spray dry machine was TD7-97 with the spray angle of 65°.

Rat intestinal glucosidase inhibitory activity assay

Glucosidase inhibitory activity was determined using methods described previously (Gunawan-Puteri and Kawabata, 2010; Ieyama et al., 2011; Arsiningtyas et al., 2014) with slight revision. Rat intestinal acetone powder was cold-ground and dissolved in 0.1 M potassium phosphate buffer (pH 7.0) containing 5 mM ethylenediaminetetraacetic acid and centrifuged at 11,000 rpm, 4 °C, for 60 min. The inhibitory activity against sucrose hydrolysis was measured by the following procedures. Two test tubes, as sample and control, containing 0.20 ml sucrose solution (56 mM) in potassium phosphate buffer (0.1 M, pH 7.0) and two test tubes, containing 0.40 ml potassium phosphate buffer (0.1 M, pH 7.0) as each blank were pre-incubated at 37 °C for 5 min. The control and control blank were defined as 100% and 0% enzyme activity, respectively. The working samples diluted in water (0.10 ml) were added to the sample and sample blank test tubes while 0.10 ml water was added to the control and control blank test tubes. Next, crude rat intestinal sucrase (0.20 ml) was added only to the test tubes containing sucrose solution (sample and control). The reaction was done at 37 °C for 20 min and stopped by adding Tris–HCl buffer (2 M, pH 6.3, 0.75 ml).

The reaction mixtures were then passed through a short column of Aluminium oxide 60 (1.5 g, 500 x 5 mm) for removing phenolics, which may interfere with the following glucose quantification. Each mixture (50 µl) was placed into a 96-well microplate and added with 200 µl

glucose kit and incubated at 37 °C for 15 min. The absorbance (Abs) was measured using a UV-Vis spectrophotometer at 492 nm wavelength.

Inhibitory activity was calculated by the following equation:

$$\text{Inhibitory activity (\%)} = \frac{(Abs_C - Abs_{Cb}) - (Abs_S - Abs_{Sb})}{(Abs_C - Abs_{Cb})} \times 100\ \% \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots(1)$$

with Abs = Absorbance, [c] = control, [cb] = control blank, [s] = sample, [sb] = sample blank

The experiments were done in triplicate for each concentration and the resulting sucrase inhibitory activity was plotted in the curve against concentration to derive the linear regression mathematical formula. Data were presented as IC_{50}, which was defined as lemongrass concentration that inhibits 50% of sucrose hydrolysis into glucose and fructose in the presence of crude extract of rat intestinal acetone powder.

Test animals and housing

All experiments were performed on adult male Swiss mice (20 - 30 g) obtained from the Imono Laboratory, Sanata Dharma University, Indonesia. The animals were maintained under standard laboratory condition. They were housed in standard cages at temperature 22 ± 2 °C and 12:12 h light dark cycle. Standard pelleted diet and water were given ad libitum. All procedures described were reviewed and approved with approval number KE/KF/0618/EC/2017 by the Health and Medical Research Ethics Committee Faculty of Medicine Universitas Gadjah Mada - Dr. Sardjito General Hospital, Yogyakarta Indonesia.

Sugar tolerance test

Anti-hyperglycemic activity of spray-dried aqueous extract of lemongrass was tested using carbohydrate loads in mice. Overnight fasted mice were used to perform oral glucose tolerance test (OGTT), oral sucrose tolerance test (OSTT) and oral maltose tolerance test (OMTT). Male Swiss mice were divided into fifteen groups (n=5) randomly (negative control, sugar [glucose/sucrose] control, positive control and dose groups).

For glucose control Group I received 2 g/kg BW glucose solution orally and Group II were given acarbose 0.08 g/kg BW for the positive control. Group III-V (treated-glucose groups) received 4.33; 6.67; 10 g/kg BW of spray-dried aqueous extract of Lemongrass respectively. After 30 min of treatment, glucose solution was administered to all mice of Group II-V at 2 g/kg BW (James et al., 2009; Pattanayak et al., 2009; Rathod et al., 2011; Ali et al., 2013).

Group VI (sucrose control) received 4 g/kg BW sucrose solution orally. Group VII (positive control) was treated with acarbose 0.08 g/kg BW. Group VIII-X (treated-sucrose groups) received 4.33; 6.67; 10 g/kg BW of spray-dried aqueous extract of Lemongrass respectively. After 30 min of treatment, the animals were administered sucrose solution 4 g/kg BW (Ali et al., 2013; Yusoff et al., 2015).

Group XI as maltose control received 3 g/kg BW orally. Group XII (positive control) was treated with acarbose 0.08 g/kg BW. Group XIII-XV (treated-maltose groups) received 4.33; 6.67; 10 g/kg BW of spray-dried aqueous extract of Lemongrass, respectively. After 30 min of treatment, the animals were administered maltose solution 3 g/kg BW (Wongnawa et al., 2014; Bae et al., 2015).

Blood collected from the tail vein of the mice and blood glucose levels were measured at 0, 15, 30, 60, 90 and 120 min using a glucometer (GlucoDr, All Medicus Co. Ltd) (Yeo et al., 2011; Wongnawa et al., 2014). Area under the blood glucose-time curve up to the last sampled time-point (AUC) was calculated using the trapezoid method formula (Eseyin et al., 2010; Jo et al., 2011; Yusoff et al., 2015).

Statistical analysis

Results are expressed as mean ± standard deviation (SD). Data were analyzed using Kruskal-Wallis analysis of variance followed by post-hoc Mann-Whitney tests using SPSS 22. A *p*-value <0.05 was considered statistically significant.

AUC (Area under the curve) was estimated by the trapezoid method formula (Hendra et al., 2017), as below:

$$AUC = \left(\frac{C1-C0}{2} \times t_1\text{-}t_0\right) + \left(\frac{C2-C1}{2} \times t_2\text{-}t_1\right) + \ldots + \left(\frac{Cn-Cn-1}{2} \times t_n\text{-}t_{n-1}\right) \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots(2)$$

with T= time, C= concentration of glucose.

Table I. The Glucosidase Inhibitory Activity of Lemongrass Extract and Powder

Samples	Treatments	Glucosidase IC_{50} (mg/ml)
LG Extract 1	Extraction: Maceration, room temperature, 24 h	132.89
LG Extract 2	Extraction: Maceration, stirring, 70 °C, 40 min	14.46
LG Powder	Extraction: Maceration, stirring, 70 °C, 40 min; Spray drying: Inlet 130 °C, spray angle 65°	18.22

Note: Values were presented as IC_{50}, defined as Lemongrass concentration to inhibit 50% of sucrose hydrolysis reaction *in vitro*.

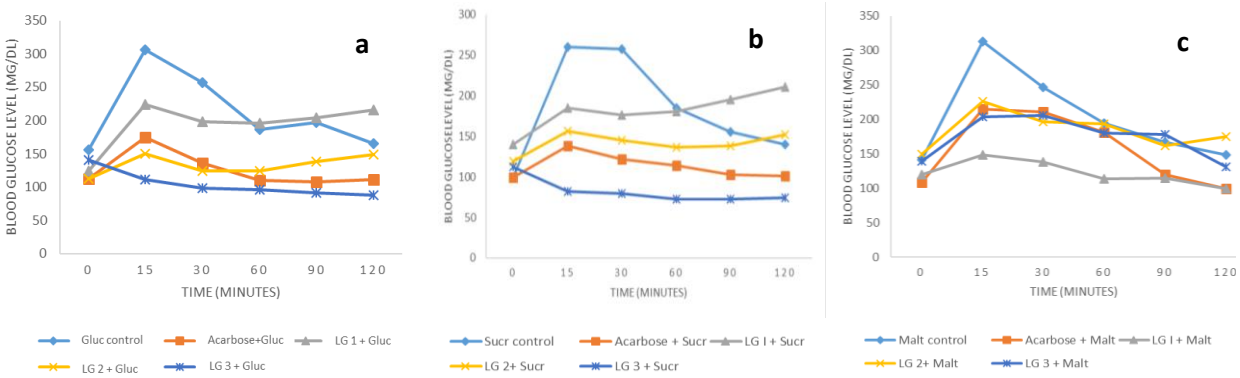

Figure 1. Effects of spray-dried lemongrass powder in oral glucose (a), sucrose (b), and maltose (c) loading test on mice. Values are expressed as mean (n=5). Gluc: glucose, Sucr: Sucrose LG: Spray-dried Lemongrass powder.

RESULT AND DISCUSSION

Our results showed that the optimized extraction method using water solvent at 70°C increased the glucosidase inhibitory activity of the lemongrass extract despite the very short extraction time (40 min) compared to the basic extraction at room temperature for 24 h (Table I). While further study is required to show the active compound responsible for the sucrase inhibitory activity, previous study showed positive correlation of phenolic content and alpha glucosidase inhibitory activity of Indonesian medicinal plants tested, including lemongrass (Santoso et al., 2016). Aqueous extract of lemongrass is known to contain phenolics, such as caffeic acid, chlorogenic acid, catechol, elimicin, and hydroquinone (Shah et al., 2011), and some of the aforementioned compounds, such as caffeic and chlorogenic acids, were already known for its alpha glucosidase inhibitory activity in vitro (Oboh et al., 2015). Previous observations of the effect of extraction solvents, temperature and time on the total phenolic content in *Salvia officinalis* L. showed that higher temperature in combination with polar solvent increased phenolic solubility and diffusion coefficient. Best extraction conditions according to the higher total phenolic content were acquired using 30% ethanolic extraction at 60 °C for 30 min, followed by aqueous extraction at 60 °C for 90 min and water extraction at higher temperature was shown as the most desirable extraction method to acquire more caffeic acid in other plants (Dent et al., 2012).

Sudden heat exposure in the spray drying process was seen to reduce 26.09% of the sucrase inhibitory activity. Previous study shown that the addition of both maltodextrin and combination of maltodextrin and Arabic gum seemed to reduce the inhibitory activity even more (Gunawan-Puteri et al., 2017). Encapsulation is a common practice in pulverization using spray drying due to its ability to protect products from heat and decrease sticking possibility inside the spray dryer (Nogueira et al., 2014). Maltodextrin of DE 20-21 has been found as the best encapsulation agent for anthocyanin, while the combination of maltodextrin and Arabic gum (3:2) was shown to be the best encapsulating agent of polyanilines (Munin and Edwards-Levy, 2011). However, both encapsulating agents are a polysaccharide carbohydrate and though it may protect the active compound in the Lemongrass extract, it may also hydrolyze by heat in spray drying process or enzymatic treatment in sucrase inhibitory activity analysis contributing to the higher content of glucose in the end of analysis (Parikh et al., 2014).

Table II. The Area Under Curve in Oral Sugar Loading Test after Administration Acarbose and Spray-Dried Lemongrass Powder on Mice

Treatment*	Area Under Curve (mg.min/dl)		
	OGTT	OSTT	OMTT
Sugar control	25530 ± 1924[a]	22739 ± 2343[a]	24349 ± 2878
Acarbose 0.08 g/kg BW	14624 ± 2001[b]	13568 ± 1270[c]	19303 ± 1812
LG 4.33 g/kg BW	23996 ± 745[a]	22191 ± 1021[a]	14472 ± 3205[d]
LG 6.67 g/kg BW	16034 ± 2045[b]	17037 ± 1875[c]	21817 ± 4248
LG 10 g/kg BW	11888 ± 1974[b]	9355 ± 1609[a,c]	21421 ± 3364

*Treatments were co-administered orally and respectively with glucose (2 g/kg BW) in OGTT test, sucrose (4 g/kg BW) in OSTT test and maltose (3 g/kg BW) in OMTT. Values are expressed as mean ± SD of five animals in each group; a: $p<0.05$ vs acarbose; b: $p<0.05$ vs glucose; c: $p<0.05$ vs sucrose; d: $p<0.05$ vs maltose. LG: Spray-dried Lemongrass powder.

In the in vivo study, sugar tolerance tests in mice were employed to observe the anti-hyperglycemic activity of spray-dried lemongrass powder. The blood glucose levels increased 15 min after administration of glucose (2 g/kg BW), consistent with previous results (Mustaffa et al., 2014) (Figure 1A). Similar patterns were observed in sucrose loading (4 g/kg BW) and maltose loading (3 g/kg BW) (Figure 1B and 1C).

Administration of lemongrass extract for 30 days caused a steady decrease in blood glucose levels in normal rats (Ademuyiwa et al., 2015). However, no sugar tolerance test has been reported yet. Spray-dried lemongrass powder with oral dose of 6.67 g/kg BW was found to be effective in lowering blood glucose level in glucose and sucrose tolerance tests, while a significant decrease in AUC at dose 4.33 g/kg BW was observed in the maltose tolerance test (Table II). This finding suggested that spray-dried lemongrass powder probably exerted its antidiabetic effect via suppressing postprandial hyperglycemia. The present study confirmed the result of our previous study that shown lemongrass had an inhibition activity against sucrase (Nivetha et al., 2016; Santoso et al., 2016; Gunawan-Puteri et al., 2017). Glucose derived from the diet and body synthesized needs transporters (SGLT, GLUT) to be transported into the bloodstream and cells (Wright et al., 2003), and before glucose is transported to the cells and stored for a source of energy, glucose exists in the bloodstream (Aronoff et al., 2004). There are several mechanisms to decrease the amount of glucose in the bloodstream, such as inhibition of glucose transporter and acceleration of the number of glucose transporters (Wood and Trayhurn, 2003). The effect of spray-dried lemongrass powder in prevention of blood glucose rise in OGTT test indicates the possibility that lemongrass might possess other anti-hyperglycemic activities than sucrase inhibitory activity.

The oral dose of 10.00 g/kg BW seemed to lower blood glucose to levels that are lower than acarbose treatment (Table II). Acarbose is a commercial anti-hyperglycemic medicine that has been used for more than 20 years to control hyperglycemia (Rosak and Mertes, 2012) and its ability to reduce hyperglycemia in sucrose tolerance tests has been proved (Ali et al., 2013). Nonetheless, the effect caused by the treatment of oral dose of 10.00 g/kg BW lead to the conclusion that the dose might not be suitable to be further observed in humans since it caused abrupt blood glucose lowering impact that may lead into hypoglycemia and subsequent drawbacks.

CONCLUSION

This study found that the aqueous extraction method, which involved stirring at 70 °C for 40 min successfully increased the sucrase inhibitory activity of lemongrass extract, while spray drying with inlet 130 °C did not have significant impact. The spray-dried lemongrass powder proved to be effective in lowering blood glucose level on OGTT, OSTT and OMTT.

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THE EFFECT OF HEALTH INSURANCE ON ASTHMA CONTROL IN RESPONDENTS WITH ASTHMA IN YOGYAKARTA, INDONESIA

PENGARUH ASURANSI KESEHATAN TERHADAP PENGENDALIAN ASMA PADA RESPONDEN ASMA DI YOGYAKARTA, INDONESIA

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ABSTRACT

Asthma is a chronic disease with recurrent breath shortness. Until now, there is no particular therapy to cure the disease and long-term treatment is needed to control the disease. Health insurance has the benefit to support the asthma therapy. This study aimed to assess the effect of health insurance on the asthma control based on Asthma Control Test (ACT) score. The study was done with a cross-sectional design on respondents with asthma who agreed to sign informed consent forms in Yogyakarta. The asthma respondents (n=36) were selected non-randomly, consisting of 23 respondents with health insurance, including universal health coverage or UHC (n=15), UHC and private insurance (n=7), and private insurance only (n=1). The ratio and categorical data were analyzed with the independent T-test or Mann-Whitney test and chi-square statistics, respectively. The study demonstrated that the profiles and number of medicines were similar between groups, except for lower smoking proportion among health insurance groups; the respondents with and without health insurance had the median ACT score at 22 (partial control) and 15 (bad control) respectively, though the scores were not statistically different. Conclusion: the asthma respondents with and without health insurance were not statistically different in the asthma control.

***Keywords**: asthma, asthma control, Asthma Control Test (ACT) score, health insurance*

ABSTRAK

Asma merupakan penyakit kronis dengan gejala serangan sesak nafas berulang yang belum ada penyembuhannya, dengan demikian diperlukan penatalaksanaan terapi jangka panjang yang efektif dan aman. Asuransi kesehatan bermanfaat mendukung terapi pasien asma. Penelitian ini dilakukan dengan tujuan mengevaluasi pengaruh asuransi kesehatan terhadap pengendalian asma berdasarkan skor Asthma Contol Test (ACT). Penelitian observasional ini dilaksanakan dengan rancangan potong lintang pada responden di Provinsi Yogyakarta yang pernah atau sedang mengalami asma serta bersedia mengisi informed consent. Responden dipilih menggunakan metode sampling nonrandom. Dari 36 responden asma, sebanyak 23 responden memiliki asuransi kesehatan yang meliputi JKN-BPJS (n=15), JKN-BPJS dan asuransi swasta (n=7), dan hanya asuransi swasta (n=1). Data rasio dianalisis dengan uji-T atau Mann Whitney, sedangkan data kategorikal dianalisis menggunakan uji chi-square. Hasil penelitian menunjukkan karakteristik responden dan jumlah obat asma responden tidak berbeda kecuali faktor merokok dengan proporsi yang lebih sedikit secara bermakna pada responden yang memiliki asuransi kesehatan. Responden dengan asuransi kesehatan memiliki median skor-asma ACT 22 (terkendali sebagian) dibandingkan tanpa asuransi dengan skor ACT 15 (pengendalian yang buruk) meskipun secara statistik berbeda tidak bermakna. Kesimpulan: responden dengan dan tanpa asuransi kesehatan memiliki pengendalian asma yang berbeda tidak bermakna secara statistik.

***Kata kunci**: asma, pengendalian asma, skor Asthma Control Test (ACT), asuransi kesehatan*

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INTRODUCTION

Asthma, a major non-communicable disease, has the clinical characteristics of chronic inflammation in the respiratory tract and recurrent breath shortness (WHO, 2017a). The prevalence of asthma in Yogyakarta Province in 2013 was 6.9%, and the incidence was higher than national data at 4.5% (BPDANP *Kesehatan Kemenkes* RI). The inflammation process in asthmatic patients involves increased numbers of cells and cell elements, including mast-cells, eosinophils, lymphocyte-T cells, macrophages, neutrophils, and epithelia cells. Until now, there are no primary cures nor prevention for asthma. Patients with asthma depend on a long-term asthma therapy, and they need therapy with efficacy and safety to control the disease or to prevent the exacerbations (Kelly and Sorkness, 2008). Uncontrolled asthma will lead to the increase in mortality rate among the patients and the mortality rate due to asthma at 80% happens in low and middle-low income countries (WHO, 2017b).

Financial support for long-term therapy is one of the important factors to control the disease among the subjects. Patients are concerned about the affordability aspect of the medicine; therefore, they expect to be able to communicate with healthcare providers for more effective and efficient therapy (Patel and Wheeler, 2014). Lack of health access contributes to the increase of hospitalization and mortality rate in asthma patients (Kelly and Sorkness, 2008). A study of therapy cost showed that the health burden of asthma is likely to affect the therapy outcome of the disease. Children whose parents believe that asthma therapy is an economic burden will have more emergency visits to health care and school absence due to the disease (Patel et al., 2012). Health financing support including health insurance is considered as a solution for most disease control including asthma.

Recently, the greatest health financing support system in Indonesia is the Universal Health Coverage (UHC) or according to the Indonesian terminology it is called as *Jaminan Kesehatan Nasional*. The UHC is managed by the social (health) insurance management agency or *Badan Pengelola Jaminan Sosial (BPJS) Kesehatan* with the principle of cooperation. Data in November 2017 indicated the UHC covered more than 183.5 million population and involved 21,771 health facilities. The UHC has the target of 100% coverage of the Indonesian population, and the UHC aims to support population welfare with qualified and continuous health care including for asthma patients. The UHC covers the management of asthma in the primary care and the secondary care (BPJS Kesehatan).

Besides the health financing support, the patients' knowledge contributes to asthma control. A cross-sectional study done in Cipto Mangunkusumo Hospital in Jakarta among uncontrolled asthmatic patients showed that patients' knowledge was the most influential factor on treatment adherence, whereas the health insurance and other factors had an insignificant effect on the disease control (Ferlani et al., 2015). Poor asthma control causes depression, frequently found in geriatric patients, and decreases patient's quality of life.

The Asthma Control Test (ACT) is a tool to measure asthma control (American Thoracic Association, 2017; GSK, 2017). Some studies using ACT demonstrated the correlation between ACT score and asthma control. A longitudinal study done in 1-year duration showed the increase of asthma control was equal to the increase of ACT score (Afandi et al., 2013). Another study on occupational asthma patients showed that the patients have statistically and clinically worse ACT score at work than the ACT score outside the work (Quirce et al., 2013).

Studies on the asthma control due to the disparity of health insurance in Yogyakarta population were not found during the literature review. Whereas, a study related to the health insurance in hypertension patients in Yogyakarta Province was found that showed patients with insurance had better awareness and higher therapy proportion than those without insurance. Nonetheless, the insurance was not successful to increase the blood pressure control (Suhadi et al., 2015). Based on the above description, a study was done among the population in Yogyakarta to evaluate the effect of the insurance ownership, therapy, and respondent profiles on asthma control using ACT.

METHODS

This study was an observational research conducted with the cross-sectional design with the study permit No. 070/01008 issued by *Dinas Penanaman Modal dan Perizinan Pemerintah Kota Yogyakarta.* The study protocol was approved by The Ethics Commission of the Medical Faculty, *Universitas Kristen Duta Wacana* with the Ethical Clearance No. 405/C.16/FK/2017. This study was part of the

main study about Improving the Role of the Indonesian Pharmacists on Asthma Management through "*Pelayanan Kefarmasian Pasien Asma* or *PKPA*" (Pharmaceutical Care on Asthma Patients).

Selection of the Subjects

The subjects were recruited from people who live in Yogyakarta Province. The inclusion criteria were those who were experiencing and/or recently suffered from asthma for both with or without routine therapy of asthma, and signed the informed consent for the willingness to participate in the study. The respondents were selected with non-proprietary sampling. Respondents were obtained from private clinics, hospitals, and community. Furthermore, some respondents were recommended by other respondents.

Procedures

The independent variable of the study was the ownership of health insurance for asthma therapy divided into the UHC, private/voluntary insurance, and without health insurance coverage, whereas the dependent variable was asthma control measured by ACT. Additional variables included sociodemographic profiles of age, gender, education background, and occupation; weight; medication history including non-pharmacology; etiology and history of asthma. Data collection was done by direct interview guided with open-ended questionnaire. The interview appointment was done at the time and place agreed by the respondents. The data collectors consisted of the interviewer and the note documenter who guided the respondents in answering the questionnaires. All interviews were recorded with a voice recorder. The ACT score was measured using ACT in the Indonesian version (Zaini, 2011). The children respondents were accompanied by their parents during the interview. The questionnaires for the interview have been translated into the Indonesian language. All data collectors were trained for their reliability in understanding the questions and the respondents' answers before the interview.

Data Analysis

The ACT scores were categorized based on clinical asthma outcomes into 3 levels, namely: uncontrolled asthma at ACT score less or equal to 19, partially controlled asthma at ACT score 20-24, and perfect controlled asthma at ACT score 25 (Zaini, 2011). The data analysis was done both in total respondents and categorical groups (with and without health insurance). Categorical data included gender, family history, history of hospitalization due to asthma, routine visit to health care facilities were analyzed using chi-square 2x2 statistics. Meanwhile, the smoking status of active, passive, and non-smoker was analyzed with Gamma test. The ratio data of age, age with the initiation of asthma, item of medicines administered by the respondents, and ACT score were analyzed for its distribution, followed by Mann-Whitney or T-test analysis depending on normal distribution of data. Statistical data analyses were done with 95% confidence level. The conclusions were drawn from both statistics and clinical outcomes.

RESULTS AND DISCUSSION

From 36 eligible asthma respondents, 23 were covered with health insurance, namely UHC or JKN-BPJS (n=15), both UHC and private insurance (n=7), and private insurance only (n=1). The total of respondents in this study had more females than males, but the gender characteristics were similar between groups. This finding was similar to the asthma prevalence in adults which is higher in females (Kelly and Sorkness, 2008). Profiles of respondents between groups were not significantly different except for lower smoking status in respondents with insurance (p=0.03). (Table I).

There were 4 respondents in the group with insurance making routine doctor visits for asthma therapy, whereas none from the without insurance group had this routine habit. In comparison, the routine therapy was not statistically different. This finding was similar with the result from a study that showed the effect of health insurance on the greater proportion of patients seeking chronic disease therapy in Sleman District of Yogyakarta Province (Suhadi et al., 2015). For the lower proportion of routine therapy among without insurance subjects, asthma will become health burden and they will likely have a poorer outcome in the future (Patel et al., 2012). Hospitalization due to asthma was not different between groups.

Table I. Comparison of asthma respondent's profiles in categorical data based on the ownership of health insurance/ financial support

Characteristics	Sub-group	Ownership of health insurance/ financial support Yes n=23 (proportion %)	 No n=13 (proportion %)	*p* value OR (95%CI)
Gender	Male Female	6 (26.1) 17 (73.9)	3 (23.1) 10 (76.9)	0.84 1.18(0.24-5.8)
Visit to health care sites	Routine Not-routine	4 (17.4) 19 (82.6)	0 (0) 13 (100.0)	0,11 n.a.
Family History of asthma	Yes No	13 (56.5) 10 (43.5)	5 (38.5) 8 (61.5)	0.30 2.08 (0.52-8.34)
Hospitalized experience due to Asthma	Yes No	8 (34.8) 15 (65.2)	5 (38.5) 8 (61.5)	0.83 0.85 (0.21-3.49)
Smoking status	Active Passive No	0 (0.0) 5 (21.7) 18 (78.3)	3 (8.3) 4 (30.8) 6 (46.2)	0.03*

Note: respondents with health insurance (n=23) including UHC or *JKN-BPJS* (n=15); UHC and private insurance (n=7); private insurance only (n=1); p-value with *Chi-square;* OR (95% CI) = *odds ratio* (95% *confidence interval*); *=gamma test; n.a.= *not applicable* cannot be calculated due to 0% in one group.

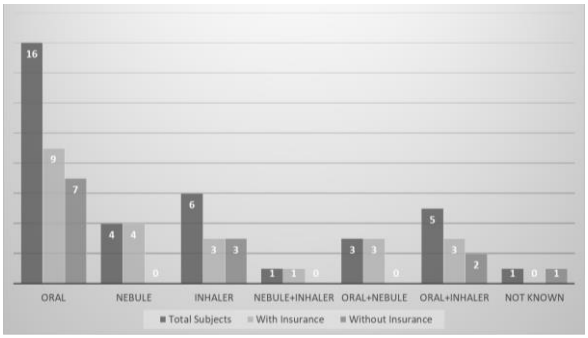

Figure 1. Profiles of dosage forms of the medicine used by the total asthma respondents, groups with and without health insurance

Respondents with health insurance had fewer smoking subjects than the without insurance subjects. The better smoking status was related to better awareness among the group with insurance. Smoking is an unfavorable factor for asthma control (Stapleton et al., 2011). Smoking status influenced the asthma control through the increase of anxiety and sensitivity among the asthma patients significantly (Avallone et al., 2015). Asthma has a close relationship with genetic factors or family history. Both groups of subjects had similar profiles for family history. Based on the ACT, both groups with and without insurance did not reach the ideal asthma control. This finding was likely related to smoking habit, both active and passive smoking, found in both groups of respondents. (Table II) Based on evidence-based medicine, it is crucial the smoking respondents become involved in the smoking cessation program for better asthma control (Saba et al., 2014).

Respondents in the groups of with and without health insurance were statistically similar in age, history of first asthma occurrence, items of asthma therapy, and ACT score. The ACT score indicates the asthma control, though the ACT score was not significantly different between groups, the respondents with insurance had ACT score at 22 (ACT 19-24) categorized as partial control of asthma. Meanwhile, the respondents without insurance had ACT score at 15 (ACT <19) categorized as poor control of asthma. Higher median ACT score among the respondents with insurance was related to the more frequent visits to health care center, therefore the appropriate therapy could prevent the asthma recurrence (Patel et al., 2012).

Respondents in with and without insurance groups had the median value of 1 and 2 items of medicine, respectively. Respondents with insurance had higher median ACT score with fewer items of medicine (Table II). The better ACT score was also supported by more proportion of subjects with routine therapy. Knowledge level of the subjects was also considered as an important factor in asthma therapy (Ferlani et al., 2015) but this factor could not be evaluated in this study because the subjects were from a wide age range from youth to elderly and thereby, the knowledge level was difficult to measure.

Table II. Comparison of age profile, asthma history, ACT score, and item of medicine among the total asthma respondents and within the group with and without health insurance

Characteristics	Subjects with health insurance		
	Yes	**No**	**p-value***
	n=23	**n=13**	***t-test***
	Mean ± SD (Median)	**Mean ± SD (Median)**	**(Mann-Whitney)**
Age (years)	31.0±17.5	35.0±19.0	0.53
	(27.0)	(27.0)	(0.67)
Asthma history (at years)	13.8±14.1	11.2±10.5	0.56
	(7.0)	(10.0)	(0.90)
Item of medicine	1.7±1.0	2.2±1.3	0.28
	(1.0)	(2.0)	(0.26)
ACT score	18.7±7.4	15.8±6.7	0.25
	(22.0)	(15.0)	(0.09)

Note**:** ACT: *Asthma Control Test;* fixed combination medicine was calculated as 1 single item;
**p*-value between subjects with and without health insurance analyzed with T-test and Mann-Whitney due to not normally distribution of data.

Drug selection was not further discussed in this study. The effect of drug selection and dosage form on the asthma control could not be evaluated in this study due to the variety of drug selection and limited subjects for each drug selection, furthermore some respondents did not recognize the composition of the medicine but they only knew the dosage form of the medicine used in the asthma therapy. The most frequently used dosage form of medicine in both with and without insurance groups was single oral preparation because oral single dosage form was more affordable (Figure 1).

Limitation of the study

The study showed the clinically better effect of the health insurance on ACT score. The result cannot be generalized to another population with different population setting because the baseline level of asthma severity of the respondents was not known. Asthma control is a result of multi-dimensions of patient, disease progress, medication, health-care provider, environment, and social background. The single factor of health insurance is likely not enough to affect the control of the disease. The study also has the limitation in the small number of respondents, therefore further research with more respondents is needed to confirm the results of the study.

CONCLUSION

The research of the asthma control in the respondents in Yogyakarta based on the ACT score can be concluded that the respondents with and without health insurance were not statistically different in asthma control.

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THE EFFECT OF NaOH CONCENTRATION IN DELIGNIFICATION PROCESS ON MICROCRYSTALLINE CELLULOSE FROM GREEN ALGAE (*Cladophora sp*.) AS THE RENEWABLE MARINE PRODUCT

PENGARUH KONSENTRASI NaOH PADA PROSES DELIGNIFIKASI TERHADAP SELULOSA MIKROKRISTAL DARI ALGA HIJAU (*Cladophora sp*.) SEBAGAI PRODUK BAHARI TERBARUKAN

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ABSTRACT

Research on marine natural resources as an excipient material of pharmaceutical product is still rare. One of the marine products is the green algae, Cladophora sp. High cellulose content causes Cladophora sp. which can be used as an alternative material of microcrystalline cellulose (SM). There are two stages to produce SM, namely delignification and hydrolysis. Delignification is the process of removing the lignin of complex compounds. The delignification process is carried out chemically in alkaline situation using a NaOH solution which dissolves lignin, carbohydrates, organic acids, and resins so that cellulose is released from its bonds. This is important because the presence of lignin may inhibit acid penetration prior to hydrolysis. Therefore, the purpose of this study is to investigate the effect of delignification by using NaOH solution at various concentrations (2, 4, and 6%) to cellulose content and physical character of microcrystalline cellulose from Cladophora sp. (SMC). In the hydrolysis process, 5% HCl solution was used. SMCs of various concentrations of NaOH were observed and the cellulose levels included alpha, beta and gamma levels. While the physical character observation is done on Scanning Electron Microscopy (SEM) test. Based on the cellulose content, the higher the concentration of NaOH used, the higher the alpha cellulose will increase. The opposite result occurs on the measurement of beta and gamma cellulose. Based on SEM test, it appears that there is no effect of increasing NaOH concentration on physical character of SMC.

Keywords: *Cladophora sp., delignification, microcrystalline cellulose, NaOH, SEM*

ABSTRAK

Penelitian mengenai pemanfaatan sumber daya alam bahari sebagai bahan eksipien sediaan farmasi masih jarang. Salah satu produk bahari adalah alga hijau Cladophora sp. Kandungan selulosa yang cukup tinggi menyebabkan Cladophora sp. dapat dijadikan sebagai alternatif bahan baku pembuatan selulosa mikrokristal (SM). Pembuatan SM dilakukan melalui dua tahapan yaitu proses delignifikasi dan hidrolisis. Delignifikasi merupakan proses penghilangan struktur lignin dari suatu senyawa kompleks. Proses delignifikasi dilakukan secara kimia dalam keadaan alkali menggunakan larutan NaOH yang berfungsi melarutkan lignin, karbohidrat, asam organik, dan resin sehingga selulosa terlepas dari ikatannya. Hal ini penting dilakukan karena adanya lignin dapat menghambat penetrasi asam sebelum dilakukan proses hidrolisis. Berdasarkan hal tersebut, tujuan penelitian ini adalah untuk mengetahui pengaruh penggunaan larutan NaOH pada berbagai konsentrasi (2; 4; dan 6%) terhadap kadar selulosa serta karakter fisik selulosa mikrokristal dari Cladophora sp. (SMC). Dalam proses hidrolisis, digunakan larutan HCl 5%. SMC dari berbagai konsentrasi NaOH dilakukan pengamatan kadar selulosa yang meliputi kadar alfa, beta dan gamma. Sedangkan pengamatan karakter fisik dilakukan berdasarkan pengujian Scanning Electron Microscopy (SEM). Ditinjau dari kadar selulosa, semakin tinggi konsentrasi NaOH yang digunakan, kadar alfa semakin meningkat. Hasil sebaliknya terjadi pada pengukuran kadar beta dan gamma selulosa. Berdasarkan pengamatan melalui uji SEM tampak bahwa tidak ada perbedaan karakteristik fisik seiring dengan peningkatan konsentrasi NaOH yang digunakan.

Kata kunci: *Cladophora sp., delignifikasi, selulosa mikrokristal, NaOH, SEM*

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INTRODUCTION

One example of Green algae, *Cladophora* sp., has a high growth rate. Uncontrolled growth can lead to "algae blooms" which can cause water ecosystem pollution characterized by changes in water color and produce unpleasant odor (Sze, 1993).

Mihranyan (2011) states that *Cladophora* sp. contains high cellulose. Cellulose is the main raw material of microcrystalline cellulose (SM). The dissolution of cellulose in strong alkali will produce alpha cellulose. The higher level of alpha cellulose will cause the higher purity level of microcrystalline cellulose that is produced (Gunam et al., 2010). The utilization of *Cladophora* sp. as the main raw source of cellulose has the advantage because this type of algae has not been widely used.

To be able to dissolve cellulose, lignin contained in the plant cell wall should be destroyed first. This process is called delignification. The current research on delignification process was carried out on rice straws. Prasetia et al. (2015), state that the use of NaOH solution in a delignification process can dissolve cellulose in to produce alpha cellulose. In the Mansur variety rice straws, the Balinese local rice, the use of 7.5% of NaOH is able to purify cellulose up to 82.96%. 15% of NaOH is required for rice straws IR-64 variety until 98.0% of alpha cellulose is obtained (Prasetia and Dewantara Putra, 2015). Different result is obtained by Dewantara Putra et al., 2016, where 5% of NaOH is required for the delignification process of Balinese local red rice straw. The different characteristics of plant cell wall will cause different solution of NaOH in the delignification process.

Based on this research, the researcher would like to examine the influence of using NaOH solution on various concentrations (2; 4; and 6 %) to the cellulose content and the physical characteristics of microcrystalline cellulose from *Cladophora* sp. (SMC).

METHODS

Material

Green algae of *Cladophora* sp. is obtained in Jimbaran coastal area in Badung Regency. The materials are NaOH (Pharmaceutical Grade, Bratachem), HCl (Pharmaceutical Grade, Bratachem), indicator of Ferroin (Pharmaceutical Grade, PT. Nusa Indah), potassium dichromate (Pharmaceutical Grade, Merck), ferrous ammonium sulfate (Pharmaceutical Grade, Merck) and distilled water (Pharmaceutical Grade, Waterone).

Equipment

The equipment used includes an analytical balance (*Adam® AFP-360L*), a desiccator, pH meter (*Oakton pH 510 series*), glass tools, mesh 60, a water bath (Memmert), an oven (Binder), SEM test equipment (JEOL-2200).

Sample Collection

The sample that is used is Cladophora sp. algae obtained in the coastal area in Jimbaran, Badung regency, Bali.

Plant Identification

The determination process was conducted in the Laboratory of the Department of Pharmacy Biology, Gadjah Mada University, Yogyakarta.

Sample Processing

The sample is sorted then baked in the oven at 60°C for 24 hours.

Delignification Process

One gram of sample is dissolved in 12 ml of NaOH into various concentrations of NaOH (2; 4; and 6%) at 60°C for 24 hours and then the result is filtered. The pulp is then separated and washed with distilled water until a neutral pH is obtained. Afterwards, the desiccation is conducted at room temperature for 24 hours (Mihranyan, 2011).

Hydrolysis Process

One gram of each formula is then soaked in 20 ml of 5% of HCL at 92°C. After that, let the pulp settle overnight at the room temperature. The pulp obtained is then filtered and washed with distilled water until the neutral Ph is reached. After the desiccation process is conducted at 60°C for 12 hours, the sample is sieved with a 60mesh sieve (Mihranyan, 2011).

Microcrystalline Cellulose Evaluation

SMC from various concentrations of NaOH is observed for identifying the cellulose content which includes alpha, beta and gamma content based on the method listed in the Indonesian National Standard (SNI) 2009. Meanwhile, the physical character observation is conducted based on the Scanning Electron Microscopy (SEM) test.

RESULT AND DISCUSSION

Cellulose Content Test

Cellulose content test was conducted by using the titration method which is marked by the formation of purple color (SNI, 2009). Alpha-cellulose is a long-chain cellulose with 600-1500 degree of polymerization and insoluble in 17.5% of NaOH solution or strong alkaline solution. Alpha-cellulose is used to determine the level of cellulose purity. Beta-cellulose is a short-chain cellulose with 15-90 degree of polymerization, can be dissolved in 17.5% of NaOH or strong base, can precipitate when it neutralized. Gamma-cellulose is a short-chain cellulose with polymerization degree less than 15, can be dissolved in 17.5% of NaOH or strong base and the main content is hemicellulose (Sumada et al., 2011). Gamma-cellulose test aims to identify hemicellulose contained in microcrystalline cellulose. The content of cellulose can be seen in the Table 2.

Figure 1 shows that alpha cellulose obtained is significantly increasing with the increasing NaOH that is used in the delignification process. However, the content of beta and gamma-cellulose produced is decreasing. The highest content of alpha-cellulose is produced in SMC-6. Conversely, with the same formula, the lowest price of beta and gamma-cellulose is obtained when compared to other SMCs.

Based on these data, an increase in NaOH concentration can increase alpha-cellulose content on microcrystalline cellulose produced. The higher concentration used, the higher the ability to damage lignin and cellulose. In addition, it also can cause the cellulose to be easily hydrolyzed so that the content of alpha-cellulose is getting higher (Gunam et al., 2010). The use of strong alkaline, NaOH, will be able to break the structure of hemicellulose and dissolve it. The more NaOH is used, the more hemicellulose content can be dissolved so that alpha-cellulose content increases.

Scanning Electron Microscopy (SEM) Test

The analysis of physical characteristics and surface morphology of a sample can be observed by using Scanning Electron Microscopy (SEM) method. The result can be seen in Figure 2. SEM from SMC-2, SMC-4 and SMC-6 shows that the fibrils intertwined with a smooth surface. It indicates that the morphologies produced are similar (Camacho et al., 2011). Therefore, in terms of physical characteristics, the increase in NaOH concentration has no significant effect.

Table I. NaOH Variations on Delignification Process in Making Microcrystalline Cellulose *Cladophora* sp.

Formula	NaOH Concentration (%)
SMC-2	2
SMC-4	4
SMC-6	6

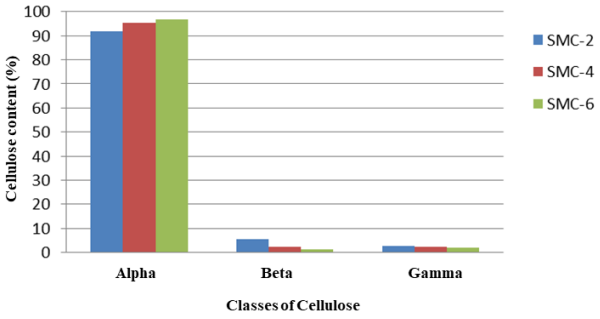

Figure 1. Graph of cellulose content in various SMCs

Table II. Observation Result of Cellulose Content in Various SMC Formula

Formula	Cellulose Content (%)		
	Alpha	Beta	Gamma
SMC-2	91.75 ± 0.55	5.60 ± 0.49	2.65 ± 0.06
SMC-4	95.41 ± 0.59	2.33 ± 0.56	2.25 ± 0.08
SMC-6	96.68 ± 0.36	1.32 ± 0.24	2.00 ± 0.19

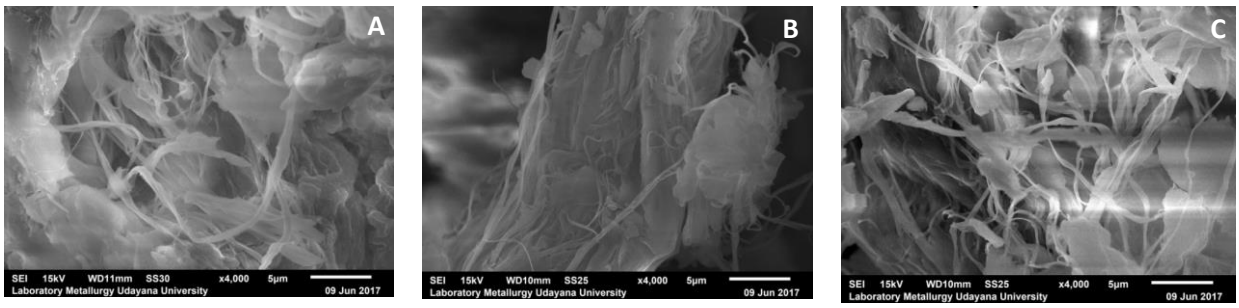

Figure 2. The SEM test result with 4000 times enlargement with various SMCs (A=SMC-2; B=SMC-4; and C=SMC-6)

CONCLUSION

Various concentrations of NaOH in the delignification process on *Cladophora* sp. affect the cellulose content that is produced but it does not affect the physical characteristic formed. This finding is based on the result of cellulose content test and SEM test.

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COMPOUNDING STERILE PREPARATIONS FOR INTENSIVE CARE UNIT PATIENTS (ICU) IN ONE PRIVATE HOSPITAL IN SEMARANG

PERACIKAN SEDIAAN STERIL UNTUK PASIEN INTENSIVE CARE UNIT (ICU) DI SALAH SATU RUMAH SAKIT SWASTA DI SEMARANG

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ABSTRACT

Sterile preparations for intravenous injection probably cause greater risk of errors than other preparation treatment routes due to their complex preparation steps. Errors in preparation and compounding stage will affect the quality and stability of the pharmaceutical product obtained. The aim of this study was to evaluate the process of compounding and assess both quality and stability of the parenteral preparations products that resulted from the compounding process for ICU's patients in one private hospital in Semarang, Central Java, Indonesia. This observational analytic study was conducted using accidental sampling technique. The descriptive study results showed that sterile preparation in hospital "X" was not performed according to the Guidelines for Drug Injection and Handling of Cytostatic Preparations. In order to evaluate the quality of the sterile preparations, three different drugs with the highest prevalence of use: namely ceftriaxone, meropenem and omeprazole were evaluated. It was found that the pH value of omeprazole was not acceptable due to the use of an appropriateness solvent. The sterility tests showed that the preparation products prepared by the nurses were free from microorganisms.
Keywords: *dispensing errors, intensive care unit, intravenous preparations, patient, sterile compounding*

ABSTRAK

Pemberian obat secara intravena memiliki resiko kesalahan yang lebih besar dibandingkan dengan rute pengobatan lain karena tahap preparasi dan peracikan yang lebih kompleks. Kesalahan pada preparasi dan peracikan akan berpengaruh pada kualitas hingga stabilitas sediaan parenteral yang diracik. Tujuan dari penelitian ini adalah mengevaluasi proses peracikan, kualitas serta stabilitas sediaan parenteral yang dihasilkan dari proses peracikan untuk pasien Intensive Care Unit (ICU) salah satu rumah sakit swasta (RS "X") di Semarang. Penelitian ini merupakan penelitian observasional analitik dengan teknik pengambilan data secara accidental sampling. Subyek penelitian terbagi menjadi dua macam yaitu subyek penelitian deskriptif dan subyek penelitian analitik. Hasil deskriptif menunjukan preparasi hingga peracikan yang dilakukan di ICU RS "X" belum dilakukan sesuai Pedoman Pencampuran Obat Suntik dan Penanganan Sediaan Sitostatik. Kualitas sediaan racikan yang dievaluasi adalah tiga macam obat dengan prevalensi penggunaan tertinggi yakni; ceftriaxone, meropenem dan omeprazole. Pengujian menunjukan terdapat perbedaan nilai pH sediaan injeksi omeprazol yang diracik di rumah sakit karena penggunaan pelarut yang tidak tepat. Hasil uji bebas kuman menunjukkan pada sediaan yang diracik tidak terdapat pertumbuhan mikroorgannisme.
Kata kunci: *dispensing error, intensive care unit, sediaan parenteral, pasien, peracikan sediaan steril*

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INTRODUCTION

Parenteral preparations are described as preparations intended for injection, infusion or implants in the body. Parenteral administration has several benefits such as its fast onset and effect, avoiding the first pass effect, predictability of drug amount in the blood, avoiding the drug degradation in the gastrointestinal system, and its possibility to treat an emergency and unconscious patients (Shargel et al., 2005).

It is should be considered that parenteral administration of drugs may have higher risk of medication errors compared to other administration routes. The complex steps during preparation, compounding, storage, and administration lead to the possibility of medication errors. Several drugs which are unstable in the form of solution need to be reconstituted before administration due to their solid form. Dose adjustment should be done for several drugs to provide specific medication dose for patients. The possibility of medication errors is becoming more important since the stricter requirement of drug carriers and the toxicity issues for several parenteral administration drugs (Agoes, 2009).

According to the Indonesian Ministry of Health (2009; 2009) sterile preparations compounding should be done by pharmacists at the Pharmacy Installation. Sterile preparations compounding requires special techniques with a background in knowledge of sterility, physicochemical properties, drug stability, drug incompatibility and the risk of dangerous exposure to drugs such as for antibiotics (Nguyen et al., 2015). In addition, special facilities and infrastructure are needed to support the whole compounding work to achieve the sterility and drug stability.

Previous studies have been conducted to evaluate the compounding process of sterile preparations compared to the Guideline for I.V. Admixture and Handling Cytostatic and Basic Guidelines of Sterile Dispensing (Ministry of Health of the Republic of Indonesia, 2009; Ministry of Health of the Republic of Indonesia., 2009). The studies showed that some critical aspects in sterile preparations did not meet the requirements according to the guidelines, such as personnel, facilities, infrastructures and aseptic process (Putri and Yuliani, 2018; Sudianto et al., 2018).

Previous research in order to assess the compatibility of intravenous drugs for ICU patients has been conducted in a hospital in Surabaya. The results showed that 30.16% of sterile preparations compounding were done without considering the compatibility of the drug compounded (Dwijayanti et al., 2016). Research related to compatibility evaluation also concluded that incompatibility of sterile preparations was one of the real problems that occurred in patients' medication in the ICU. The percentage of occurrences for incompatibility incidents were reported in the range of 0.30% to 18.70% (Fahimi et al., 2008). A systematic review study conducted by Salmasi et al. (2015) found that the common errors that occur during preparation handled by pharmacists and nurses in Malaysia and Vietnam were wrong techniques and wrong solvent types. A study conducted by Ong and Subasyimi (2013) at Selayang Hospital Malaysia showed that there were 341 errors identified from 349 preparations and administration stages. Research conducted by Strbova et al. (2015) found that unclear drug labels increase the risk of medication errors. Hence, it is necessary to assess the conformity of the procedures for parenteral preparations compounding.

Research related to the compounding of sterile preparations in the ICU has never been done at the hospital where the data was collected. The aim of this study was to evaluate the compounding process as well as assess the quality and stability of the parenteral preparations for ICU's patient in one of the private hospitals in Semarang, Cental Java, Indonesia. The results from this study will be useful in order to improve the pharmaceutical care implementation in the hospital.

METHODS

Study design

This research was a non-experimental study with descriptive and analytical design conducted by observing prospectively a type C private hospital in Semarang with the research permission number of 748.2/RSX/LP/DIKLAT/ VIII/2017. Data collection was done every Saturday and Sunday during September to October 2017 with accidental sampling technique. The independent variables in the descriptive study were the personnel, compounding process, and the results of sterile preparations, while the dependent variables were the conformity according to the Guideline for I.V. Admixture and Handling Cytostatic (Ministry of Health of the Republic of Indonesia., 2009).

Analytical study was conducted at the Pharmacy Laboratory of Universitas Sanata Dharma in October 2017 with a purposive

sampling technique. The independent variable in this study was the process of compounding the preparation, while the dependent variables were pH and the presence or absence of microbial growth.

Instrumentations

The research instrument used in this descriptive study was a set of observational sheets according to the Guideline for I.V. Admixture and Handling Cytostatic and Basic Guidelines of Sterile Dispensing (Ministry of Health of the Republic of Indonesia, 2009). The instrument used for analytic study was a pH meter.

The observational sheet includes several aspects as follows: 1) facilities, infrastructure and supporting system (including compounding personnel, compounded sterile rooms, laminar air flow, pass boxes, special waste bags); 2) compounding preliminaries (including right patient, right medication, right dosage, right route, right administration time, checking the drug name, checking product expiration date, checking product batch number, accuracy of solvent / diluent, accuracy of the amount of solvent); 3) compounding process (including washing hands before compounding work, use gloves and masks, hand disinfection, ampule/vial disinfection before opened, sample transfer techniques, use of single-use needles); and 4) results of sterile preparations (clarity, stability, labelling, complete information on label).

Observation

Observation data were collected by observing the preparation process and compounding process of sterile preparations. The inclusion criteria of the study subjects were compounding parenteral preparations for the "X" Hospital ICU patients done during the observation period. All samples that met the inclusion criteria for conformity were immediately evaluated for compounding errors during the compounding preliminaries and process of parenteral preparations according to the guidelines. In this study, there were no exclusion criteria because all existing samples were evaluated.

Test of Sterile Preparation Quality

Quality evaluation of sterile preparations was done on all samples which met the inclusion criteria. The inclusion criteria were defined as the three drugs with the highest frequency of use for ICU patients in Hospital "X" based on observations. The three drugs were formulated twice (duplo); one sample was formulated based on the compounding procedure in the hospital with the worst case condition (worst case criteria based on observations), while one other sample was formulated according to the Guideline for I.V. Admixture and Handling Cytostatic and Basic Guidelines of Sterile Dispensing (Ministry of Health of the Republic of Indonesia, 2009). Analytical data collection was done by measuring the pH suitability using a pH meter. The germ-free test was done at the Semarang Health Center by inoculating samples of sterile preparation into a universal medium for bacteria, then observing the presence or absence of microbial growth.

Data analysis

Data analysis was done by verifying the observations listed in the Observational Sheet with the reference literature used, Guideline for I.V. Admixture and Handling Cytostatic and Basic Guidelines of Sterile Dispensing. Analysis of observation data was done by calculating the percentage form of errors in each aspect using the equation:

$$\%\, nonconformity = \frac{number\ of\ nonconformity}{total\ of\ observation\ sample} \times 100\% \quad \text{.....(1)}$$

If the result for % nonconformity is 0%, it can be concluded that the aspect in compounding preliminaries and process was meeting the requirements as mentioned in the Guideline for I.V. Admixture and Handling Cytostatic and Basic Guidelines of Sterile Dispensing.

RESULTS AND DISCUSSION

Observations were conducted for 25 patients in ICU consisting of 24 adult patients and 1 pediatric patient. During the observation, 119 sterile preparations were provided (Figure 1). The results showed that sterile preparations with highest frequently prepared were omeprazole injection, meropenem injection, and ceftriaxone injections.

Critically-ill patients have high potential of getting stress-related mucosal disease (SRMD). Omeprazole is a proton pump inhibitor (PPI). It is an effective agent to decrease gastric acid secretion. Omeprazole is often used with critically ill patients because it is more effective than histamine 2 receptor antagonists in preventing clinically important and overt upper gastrointestinal bleeding (Alhazzani et al., 2013; Barkun et al., 2012). It can explain why omeprazole injection was the most frequently prepared in ICU.

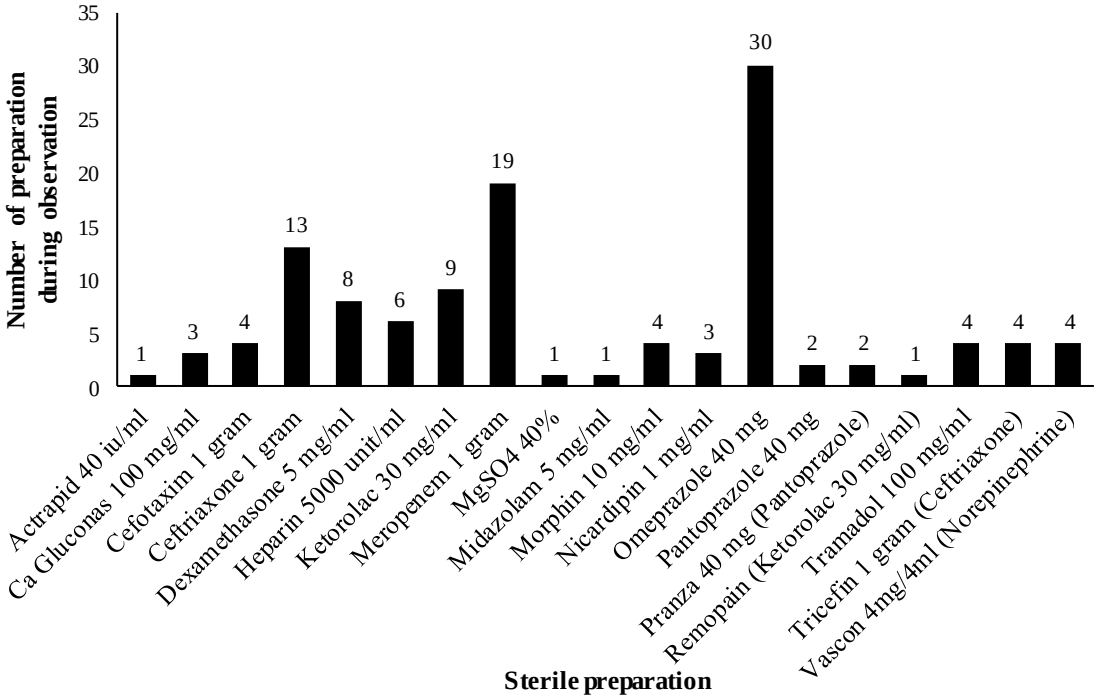

Figure 1. Sterile preparation during observation

Infections are common in patients in contemporary ICUs, and risk of infection increases with duration of ICU stay so that they get antibiotics (Vincent et al., 2009). Meropenem and Ceftriaxone are in the family of β-lactam type of antibiotics. Both are frequently used in ICUs for severe infection or to prevent another infection (Wong et al., 2014). Ceftriaxone is a well tolerated third generation cephalosporin with a broad spectrum activity against gram positive and gram negative bacteria, commonly used in intensive care units (ICU) for the empirical or documented treatment of a wide range of infections, such as pulmonary, urinary, intra abdominal and central nervous system infections (Garot et al., 2011). Meropenem has a good potential to prevent nosocomial infection from becoming worse and as therapy for bacteremia conditions (Trisnadewi and Widodo, 2014). It also explains why these two antibiotics were commonly used for ICU patients.

Facilities, Infrastructure and Supporting System

The observation results for Facilities, Infrastructure and Supporting System are shown in Table I. Regulations in Indonesia state that compounding of sterile preparations is under the responsibility of a certified pharmacist in the Hospital(Ministry of Health of the Republic of Indonesia, 2016; Ministry of Health of the Republic of Indonesia., 2009; Ministry of Health of the Republic of Indonesia, 2009; Webster, 2015). Compounding of sterile preparations for ICU patients in Hospital X were done by nurses. The lack of the pharmacist's role in compounding sterile preparations in the ICU is due to the limited number of pharmacists with overloaded duty for pharmacy service in the hospital.

The process of preliminaries and compounding of sterile preparations must be done by personnel/staff who have been trained under the responsibility and supervision of pharmacists in Hospital Pharmacy Installation because Pharmacists have the knowledge and skills in dispensing drugs, both in terms of mixing techniques, related to aspects of sterility, and to the stability aspects of the sterile preparation. If indeed compounding cannot be done by pharmacists, then the short-term solution that can be done is by increasing the capacity of personnel in the field of sterile preparations as continuing education activities for hospital health workers to improve patient services as a form of Pharmaceutical Care and Interprofessional Education (Maharani et al., 2013; Putri and Yuliani, 2018).

Facilities and infrastructure for compounding sterile preparations in the ICU of Hospital “X” did not conform to the guidelines. In the Hospital "X"

compounding parenteral preparations for ICU patients were done in the ward, where there were no sterile rooms or special equipment to support the compounding process. The nurse performs a compounding process on the table that is used to mix parenteral and non-parenteral preparations. Before compounding sterile preparation, the nurses have to make sure that table is clean and there are no ingredients other than those used for compounding. The table is placed in the nurse's room next to the administration desk and doctor's table. The compounding process is carried out without Laminar Air Flow (LAF), without completing the compounding document and does not include medical devices used for compounding, labeling, and drugs that will be mixed or compounded into a sterile space through a pass box.

Based on the Basic Guidelines for Dispensing Sterile Preparations, compounding sterile preparations should be done in a sterile room, in LAF. All tools and material that are needed should be taken to a sterile room via a pass box. If there are no sterile room facilities and LAF, the short-term solution for compounding parenteral preparations can be carried out in special conditions by paying attention to various aspects such as the compounding space used must be clean, separate and special for sterile preparations only because the procedure performed must be aseptic. Special tables that are routinely cleaned and sterilized can be used instead of LAF for short term solutions.

Table I. Results of the descriptive study on several aspects (n= 119)

Aspects	Nonconformity (%)
Facilities, infrastructure and supporting system	
Conducted by pharmacist	100.00
Sterile room availability	100.00
LAF availability	100.00
Pass box availability	100.00
Special waste bag availability	0
Compounding preliminaries	
Right patient, right medication, right dosage, right route, right administration time	0
Checking the drug name	0
Checking product expiration date	0
Checking product batch number	100.00
Appropriateness of solvent	25.21
Solvent volume accuracy	32.77
Compounding process	
Washing hands before compounding work	33.00
Usage of gloves and masks	100.00
Hand disinfection	0
Ampule/vial disinfection before opened	31.09
Sample transfer techniques	0
Usage of single-use needles	0
Result of sterile preparations	
Clarity	10.08
Stability	2.52
Labelling	0
Complete information on label	0

Table II. pH evaluation of sterile preparation

No.	Sterile preparation	Theoretical pH	pH sample A	pH sample B
1.	Ceftriaxone 1 gram	6-8	6.5	6.4
2.	Meropenem 1 gram	7.3-8.3	7.5	7.7
3.	Omeprazole 40 mg	8.8-10	8.3	8.6

Note:
Sample A is sterile preparation compounded in Hospital X with worst case
Sample B is sterile preparation compounded based on Basic Guidance of Sterile Dispensing

Special waste bags for sterile preparations are needed to prevent accident. Sterile preparation involving the use of syringes and ampules are categorized as risk or hazardous waste (Amin et al., 2013; Chartier, 2014). All of the sterile preparation waste in ICU Hospital X have been separated from general waste. There were some special bags to collect the hazardous waste.

Compounding preliminaries

Compounding preliminaries involve a number of activities, including checking that the patient's name, drug, dosage, route and administration time is correct, product's expired date, and product's batch number. Other important steps to do are calculating dosage suitability, using appropriate solvents, calculating solvent volume, making labels and completing compounding documents to prevent medication errors that can harm patients (Cousins et al., 2005).

Conformity profile of preliminaries phase before compounding sterile preparations in ICU in Hospital X is shown in Table I. Personnel who performed preliminaries had checked the patient, medications, dosage, route, administration time, and product's expired date before they compounded. This is a good practice that must be maintained to reduce the risk of medication errors. Meanwhile, the batch number of the drug were not checked even once. The batch number of the product must be observed and recorded in the compounding document as an archive, so that if one day medication error is found that arose in the preparation caused by the initial product it can be traced and reported to the manufacturer (Collins, 2014).

A total of 25.21% of drugs were done using appropriateness solvents (compared with solvent in Handbook of Injectable Drugs). In ICU Hospital X, most of the sterile preparations (Figure 1) were formulated or reconstituted with Aqua Pro Injection and given through a syringe pump, except ketorolac and tramadol preparations that were using 0.9% NaCl as a solvent and given by i.v. drip. There are limited information about incompatibility of some product with several solvents (Dwijayanti et al., 2016; Kanji et al., 2010). This gap becomes a difficulty in assessing the potential incompatibility of a drug with a solvent. The safest way that can be done is to use solvents that have been known to be compatible with the drug based on several trusted literature such as the current Handbook of Injectable Drugs (FASHP, 2012).

A total of 32.77% of drugs were dissolved with inaccuracies in volume of solvent (compared with volume suggested in brochure). The main guideline used to see the volume of drug solvents is the drug packaging leaflet. If there is no information how much the volume of solvents recommended in the drug packaging leaflet, the researchers recommend other guidelines such as the Handbook on Injectable Drugs 16th Edition (FASHP, 2012) or the Guideline for I.V. Admixture and Handling Cytostatic (Ministry of Health of the Republic of Indonesia., 2009).

An example of the inaccuracy volume of solvent that was observed is the compounding of ceftriaxone injection. The leaflet states that each 1 gram of ceftriaxone powder for injection is dissolved with 10 mL of water for injection. At the time of observation, ceftriaxone reconstitution was done with a variety of solvent volumes: 5 mL, 8 mL; up to 20 mL. The difference in the amount of solvent can affect the solubility rate of ceftriaxone injection in solvents and the tonicity of the solution (Putri and Yuliani, 2018).

Compounding Process

The observation results show that some aseptic techniques were not implemented well in ICU Hospital X (Table I). Implementation of aseptic techniques must be carried out in compounding sterile preparations. One procedure that must be done in aseptic techniques before compound preparations is personnel must wear a complete personal protective equipment (PPE), which is done to prevent possibilities of contamination from personnel to preparations that are formulated and also prevent exposure to the drugs formulated to personnel. In addition, hand washing or hand disinfection is a mandatory activity to fulfill aseptic procedures (Ministry of Health of the Republic of Indonesia, 2009) Surprisingly, all of the compounding sterile preparations (100%) observed were performed without wearing handscoon and mask while 33% did not involve washing hands, although at least they have disinfected hands before compounding the sterile preparations.

If compounding were not done aseptically, it is likely that contamination will occur and can threaten patients' safety and cause medication errors (Agyemang and While, 2010). Factors that can cause nurses to not follow the procedure of aseptic techniques are high workloads or the low ability or lack of knowledge about basic guidelines in compounding sterile preparations (Keers et al.,

2015). One short-term solution that can be done is by conducting training on good compounding sterile preparations (aseptic technique), in order to improve the ability of (Maharani et al., 2013).

Aseptic techniques should be implemented to reduce risk of contamination. Right transfer technique and using single needle/syringe to collect the drug can optimize this important goal (Ministry of Health of the Republic of Indonesia, 2009). All compounding sterile preparations in ICU Hospital X were performed with a good transfer technique and always uses single needle/syringe.

Results of sterile preparations

The observation results of sterile preparations are shown in Table I. We found that 10.08% of sterile preparations had turbidity after being compounded and then a few moments later turbidity disappeared. It happened in ceftriaxone injections dissolved with 5 mL. However, turbidity indicates the presence of powdered drug particles that are still visible in the solution. It can become harmful to the patients because it can cause embolism if it has not been completely dissolved when administered (Langille, 2013).

The stability of sterile preparations must also be a concern. Stability of stocks includes physical, chemical, and microbiological stability. Changes in physical stability can be identified if there is a change in color, appearance, clarity, and consistency of the preparation. Changes in chemical stability are indicated by product degradation. There are several factors that affect product degradation, such as light, metal, oxygen, water, etc. (Falconer and Steadman, 2017; Srivastava and Kumar, 2017).

The results of the observation showed that there was potential for instability that might occur as much as 2.52% in nicardipine injection preparations. According to (FASHP, 2012) nicardipin injection is one of the photosensitive drugs, but in ICU Hospital X, nicardipin injections were not protected from light, while in the storage instructions printed on the label, it states it must be kept away from direct light. The possibility that can occur if photosensitive preparations exposed to light is a decrease in stability. One short-term solution that possibly can be done according to the Guideline for I.V. Admixture and Handling Cytostatic (Ministry of Health of the Republic of Indonesia, 2009) is to protect the solution using aluminum foil or black bags to protect photosensitive drugs from light.

Sterile preparations should be labelled after compounded. Right labelling can prevent medication error (Merali et al., 2008). In ICU Hospital X, the sterile preparation were not labelled after compounded, which means that there was no information about the products. The reason from the personnel is because the sterile preparations were directly administered to patients and the hospital did not provide labels for the sterile preparations.

Standard labels for sterile preparations in Guideline for I.V. Admixture and Handling Cytostatic (Ministry of Health of the Republic of Indonesia, 2009) should contain important information such as: Patient's name, medical report number, room, drug, concentration/dose, administration route, compounding date and time, beyond use date, storage procedure. One short term solution that can possibly be done is providing labels for sterile preparations. Pre-printed or peel-off flag labels on ampules and vials can facilitate correct labelling (Merry et al., 2011).

Physical quality of sterile preparations

Physical quality tests were done on 3 drugs with the highest frequency of use, i.e. Ceftriaxone 1 gram, Meropenem 1 gram and Omeprazole 40 mg. Evaluations carried out included pH test and germ free test. Evaluation was done on sterile preparations compounded by following the Basic Guidance of Sterile Dispensing and sterile preparations compounded by the hospital based on the worst conditions observed, i.e. not using PPE, not washing hands, and done at the nurse's desk.

An important component that must be considered in dispensing sterile preparations is the pH of the compounded drugs which will have an impact on incompatibility (Newton, 2009). The pH test was done on two groups of test subjects and the results are listed in Table II. Chemical incompatibility describes the chemical degradation of one or more drugs compounded, causing therapeutic toxicity or inactivation. Degradation is not always observable. Specific pH values or a narrow range of pH values are needed to maintain drug stability after being mixed (Newton, 2009).

The pH of Sample A and Sample B for Ceftriaxone 1 gram and Meropenem 1 gram that was dissolved in water for injection, conformed with theoretical pH. Meanwhile pH of Sample A Omeprazole injection had a pH below theoretical pH. It possibly happened because omeprazole in ICU Hospital X was dissolved using water for injection instead of the appropriate solvent provided from the manufacturer. It is especially

important to always use the right solvent to get the right pH.

A germ-free test was conducted on samples produced from compounding in the ICU Hospital "X". Sterile means that the preparation meets the criteria free of microorganisms, pathogens and particles. In this study, the researchers defined the term, sterile is to be free of germs or microorganisms and proved by testing in the laboratory of Semarang Health Center. The test results show that the preparations produced from Hospital X are germ-free. It might happen because two of the samples tested are antibiotics while the process of inoculating samples to universal media was done without inactivating the ability to inhibit bacteria. In addition, other factors that can be influential are the products might contain preservatives, so microorganisms cannot contaminate them (Pramanick et al., 2013).

CONCLUSIONS

Based on the research conducted, it can be concluded that the compounding process carried out for patients in the Intensive Care Unit "X" Hospital is largely not in accordance with the Guidelines for Compounding Syringes and Cytostatic Treatment. The quality of 3 sterile preparations was free of bacterial growth. The pH measured of Ceftriaxone and Meropenem was still in the pH range based on the literature. Meanwhile pH of Omeprazole injection that was dissolved using appropriateness solvent had a pH below theoretical pH. It is especially important to always implement The Guideline for I.V. Admixture and Handling Cytostatic and The Basic Guidelines of Sterile Dispensing to prevent medication errors that can harm the patient.

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STANDARDIZATION OF EXTRACT AND CHARACTERIZATION OF EMULGEL FORMULA OF LENGKUAS (*Alpinia galanga* (L.) Willd) RHIZOME EXTRACT

STANDARDISASI EKSTRAK DAN KARAKTERISASI FORMULA EMULGEL EKSTRAK RIMPANG LENGKUAS (*Alpinia galanga* (L.) Willd)

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ABSTRACT

The lengkuas rhizome has an antifungal activity. The non-specific parameters for extracts of lengkuas rhizome need to be standardized to obtain the extracts with consistent good quality. The lengkuas rhizome extract emulgel topical preparations are easily mixed with active substances that are hydrophobic or hydrophilic. This study aims to obtain a lengkuas rhizome extract emulgel formula that has good quality and good physical properties. Extraction of lengkuas rhizome was obtained using a maceration method with 96% ethanol solvent. The extract is standardized by non-specific parameters. After that, the extract was formulated in the form of emulgel preparation with 10% concentration. The physical properties of emulgel were evaluated. The results of the study showed that the extract yield is of (14.66±0.056)%; powder drying shrinkage (8.63±0.134)%; extract water rate (5±0)%; powder total ash rate (3.24±0.017)%; and extract (1.30±0.035)%; acid-insoluble ash rate powder (2.66±0.10)%; and extract (0.87±0.031)%; extract type weight 1.01; and the physical properties of emulgel preparations were homogeneous emulgel, semisolid form, light brown color, distinctive smell of lengkuas rhizome extract, stable at 5^{o}C and 25^{o}C for 24 hours; pH 7; spreadability (2.45±0.03) g.cm.s-1; stickiness (8.80±0.72) seconds; o/w emulsion type; and viscosity (1.37±0.22) Pa.s. This study obtained extracts of lengkuas rhizomes that meet the requirements of non-specific parameter standardization in general and the formulation of lengkuas rhizome extract emulgel had good physical properties.

Keywords: *lengkuas rhizome extract, non-specific parameter standardization, emulgel*

ABSTRAK

Rimpang lengkuas memiliki aktivitas sebagai antifungi. Ekstrak rimpang lengkuas perlu dilakukan standardisasi parameter non spesifik untuk memperoleh sediaan yang terjamin mutunya secara konsisten. Sediaan topikal emulgel ekstrak rimpang lengkuas merupakan sediaan yang mudah bercampur dengan zat aktif yang bersifat hidrofob atau hidrofil. Penelitian ini bertujuan untuk mendapatkan formula emulgel ekstrak rimpang lengkuas yang memiliki mutu yang baik serta sifat fisik yang baik. Ekstraksi rimpang lengkuas diperoleh dengan menggunakan metode maserasi dengan pelarut etanol 96%. Ekstrak distandardisasi dengan parameter non spesifik. Selanjutnya ekstrak diformulasikan dalam bentuk sediaan emulgel dengan konsentrasi 10%. Emulgel dievaluasi uji sifat fisik. Hasil penelitian diperoleh rendemen ekstrak (14,66±0,056)%; susut pengeringan serbuk (8,63±0,134)%; kadar air ekstrak (5±0)%; kadar abu total serbuk (3,24±0,017)%; dan ekstrak (1,30±0,035)%; kadar abu tidak larut asam serbuk (2,66±0,10)%; dan ekstrak (0,87±0,031)%; bobot jenis ekstrak 1,01; dan uji sifat fisik sediaan emulgel diperoleh emulgel homogen, bentuk semisolid, berwarna coklat muda, bau khas ekstrak rimpang lengkuas, stabil pada suhu 5^{o}C dan 25^{o}C selama 24 jam; pH 7; daya sebar (2,45±0,03) g.cm.s-1; daya lekat (8,80±0,72) detik; tipe emulsi o/w; dan viskositas (1,37±0,22) Pa.s. Penelitian ini diperoleh ekstrak rimpang lengkuas yang memenuhi persyaratan standardisasi parameter non spesifik secara umum dan formulasi emulgel ekstrak rimpang lengkuas mempunyai sifat fisik yang baik.

Kata kunci*: ekstrak rimpang lengkuas, standardisasi parameter non spesifik, emulgel*

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INTRODUCTION

The use of plants can be used as a treatment for various types of diseases, one of which is a disease caused by fungi. Diseases caused by fungi are still very common, because Indonesia has a tropical rain, climate which leads to high air humidity (RH> 80%) with an average temperature of 28 - 33ºC (Sundarim and Wiem, 2001). Natural ingredients that have anti-fungal activity are *lengkuas*, a plant that has long been used by the Indonesian people as a medicinal ingredient for stomach ailments, scabies, tinea versicolor, and eliminating bad breath (Kusumaningtyas et al., 2008). *Lengkuas* rhizome extract can even function well on molds and yeasts that are resistant to amphotericin B and ketoconazole (Ficker et al., 2003). The research of Fakhrurrazi et al. (2012) revealed that *lengkuas* was able to inhibit the growth of Candida albicans at the 10% concentration, and from Silvina's research, 2006, *lengkuas* rhizome extract at the 10% concentration was more effective to inhibit C. albicans in vitro compared to ketoconazole 2%.

Lengkuas rhizome extract is the active ingredient in this study, so standardization is needed to obtain extracts with guaranteed consistent quality. Standardization is conducted so that the same raw ingredients can be obtained which can guarantee the pharmacological activity of the plant. Standardization is the process of guaranteeing the final product (simplicia, extracts, products or herbal products) in order to have a certain constant parameter value (Zainab et al., 2016).

The *lengkuas* rhizome extract has an active compound component that is hydrophilic and hydrophobic, so a formulation that can dissolve both components is needed. In emulgel preparations, the emulsion incorporated into the gel formula will help increase the solubility of the ingredient that is hydrophobic (Haneefa, et al., 2013). Preparations that have shorter spreading distances show better dispersion coefficients (Gupta and Gaud, 2005) and the higher the stickiness, the longer the gel attaches to the skin and the longer the therapeutic effect will be (Arikumalasari et al., 2013).

METHODS

Materials and Instrumentations

The materials used in this study are *lengkuas* rhizome extract, 96% alcohol (pharmaceutical), hydroxypropyl methylcellulose (pharmaceutical), liquid paraffin (pharmaceutical), tween 80 (pharmaceutical), span 80 (pharmaceutical), propylene glycol (pharmaceutical), methyl paraben (pharmaceutical), propyl paraben (pharmaceutical), toluene (pa) (E-Merck), aqua destilata (pharmaceutical), dilute hydrochloric acid (pharmaceutical, and concentrated hydrochloric acid (pharmaceutical) (E-Merck).

The instrumentations used in this study were waterbath (Memmert), rotary evaporator (Buchi Rotavapor R-200), universal pH (Merck), analytical scales (Ohaus TM AR2140), vacuum (Gast Manufacturing), furnace (benchtop muffle Ney Vulcan D- 130), distillation apparatus (Dean-Stark), Halogen Moisture Analyzer HB43, piknometer (Duran), oven, sticky power tester, distribution power tester, and viscosity tester (viscosimeter Rheosys Merlin VR parallel spindle; 30 mm parallel plate).

Ingredients Preparation

The *lengkuas* rhizome was obtained from Beringharjo Market, Special Region of Yogyakarta, then sorted wet, washed, cut by 2 mm transversely, dried using an oven with a temperature of 40ºC until dry, sorted dry, and then pollinated (Purwani et al., 2012).

Extraction

Simplicia was macerated with 96% alcohol solvent with a ratio of 1:10 for 24 hours with 2x remaceration, filtered to get the macerate, then evaporated by using waterbath until thick extract was obtained (Dwi, 2017).

Non-Specific Parameter Setting

Powder Drying Shrinkage Setting

Five grams of dried *lengkuas* rhizome powder were put in the Halogen Moisture Analyzer using aluminum foil, and then the Moisture Rate was measured at 105ºC temperature until the weight was constant, so that the drying shrinkage in the simplicia powder was obtained. It is said to be eligible if the value of Moisture Rate is less than 10% (Depkes RI, 1994).

Total Ash Rate Setting

Three replications of powder and extract are weighed 2 grams each, and then put into the silicate exchange rate, which has been anchored and slowly spawned by increasing the temperature gradually to 600ºC until they are carbon free. After that, they are cooled gradually until they reach the room temperature, and then put into the desiccator and weighed until they reach a constant weight.

The ash rate is calculated in percentage towards the weight of the test ingredients that are expressed in %, b/b, using the formula in (1) (Depkes RI, 2008).

$$\text{Ash rate (\%)} = \frac{\text{ash constant weight (g)}}{\text{extract weight (g)}} \text{ x } 100\% \quad \text{.....(1)}$$

Acid-Insoluble Ash Rate Setting

Ash was obtained from the setting of the total ash rate, which was boiled with 25 mL of LP dilute hydrochloric acid for 5 minutes, the acid-insoluble part was collected and filtered until they were ash-free, washed with hot water and heated in the exchange rate until they reached a constant weight. The acid-insoluble ash rate is calculated towards the test ingredients that are expressed in % b/b, using the formula in (2) (Depkes RI, 2008).

$$\text{Acid-Insoluble Ash Rate (\%)} = \frac{\text{acid-insoluble ash constant weight (g)}}{\text{extract weight (g)}} \text{ x } 100\% \quad \text{.....(2)}$$

Water Rate Setting

Two grams of the extract are weighed carefully and then put in a dried pumpkin. Approximately 200 mL of toluene saturated water was poured into the pumpkin and 2 mL of aquadestilata was added. After that, a series of tools were attached. Water-saturated toluene was added into the receiving tube through the cooler until the container's neck. The pumpkin is heated carefully for 15 minutes. After the toluene starts boiling, the distillation is set at a speed of less than 2 drops per second, until most of the water is distilled, and then the distillation speed is increased to 4 drops per second. The distillation continued for 5 minutes. The receiver is cooled to room temperature. The volume of water is obtained after the water and toluene separate completely. The water rate is calculated in % v/b, using the formula in (3) (Depkes RI, 2008)

$$\text{Water Rate (\%)} = \frac{\text{final volume (mL)} - \text{initial volume (mL)}}{\text{extract weight (g)}} \text{ x } 100\% \quad \text{.....(3)}$$

Extract Type Weight Setting

The extract type weight was set towards the results of 10% extract dilution in ethanol solvents with the pycnometer tool (Anam et al., 2013). The pycnometer used was clean, dry, and calibrated by setting the pycnometer weight and the newly-boiled water weight at the temperature of 25°C. The temperature of the pycnometer which has been filled with liquid extract is approximately set to 20°C, and then put into the pycnometer. The pycnometer which has been filled with liquid extract is then adjusted to the temperature of 25°C. The excess of the liquid extract is removed and weighed. The empty pycnometer weight was subtracted from the weight of the filled pycnometer. The type weight is obtained by dividing the extract density to the water density in the pycnometer at the temperature of 25°C. (Depkes RI, 2000), using the formula in (4):

$$\text{Extract Type Weight} = \frac{\rho \text{ of extract at T25°C}}{\rho \text{ of ethanol at T25°C}} \quad \text{.....(4)}$$

Phenol Compound Screening Test

A number of samples (0.1 g) were extracted with 20 mL of 70% methanol. 1 mL of the produced solution was taken and then 2 drops of 5% $FeCl_3$ solution were added. Positive reactions are indicated by the formation of green or yellowish green color (Nugrahani et al., 2016).

Table I. Emulgel Base Formulation

Ingredients	Concentration (%)
HPMC	2.5
Liquid Paraffin	5
Tween 80	1.08
Span 80	0.42
Propylene glycol	10
Methyl paraben	0.03
Propyl paraben	0.01
Distilled Aqua	100

Table II. Non Spesific Parameter Standardization Results

Parameter	Results	Requirements	Reference
Drying Shrinkage(%)	8.63 ± 0.134	<10 %	FHI
Water Rate (%)	5 ± 0	<10%	FHI
Powder Ash Rate (%)	3.24 % ± 0.017	<3.9%	FHI
Extract Ash Rate (%)	1.30 ± 0.035	-	-
Powder Acid Insoluble Ash Rate (%)	2.66 ± 0.10	<3.7%	FHI
Extract Acid Insoluble Ash Rate (%)	0.87 ± 0.031	-	-
Extract Type Weight	1.01	-	-

Emulgel Formulation

The Lengkuas Rhizome Extract Emulgel Formula in this study can be seen in Table I (Yenti et al., 2014). Firstly, each Emulgel base ingredient was weighed. After that, the emulgel base is made as the following steps. The oil phase is made by mixing span 80 with Liquid paraffin at 70ºC, the water phase is made by mixing tween 80 and some water at 70ºC. The oil phase is added to the water phase at 70ºC while still being stirred until the emulsion is formed. The gel is made by dispersing the HPMC little by little into hot water at 80ºC, and crushed until the gel base is formed. Methyl paraben and propyl paraben are dissolved in propylene glycol, and then mixed with gel. After that, the emulsion and gel that have been formed are mixed with the Homogenizer at a speed of 700 rpm for 45 minutes until emulsions are formed. 10% of lengkuas rhizome extract were put into the mouth gradually is added and then crushed until it is homogeneous. At last, each formula is stored in an emulgel container (Yenti et al., 2014).

Emulgel Physical Properties Test

Organoleptic Test

Organoleptic observation includes: form, smell and color which have been conducted every week for 6 weeks at the room temperature (Yenti et al., 2014).

Homogeneity Test

0.1 g of Emulgel are weighed and then applied evenly and thinly on transparent glass, the preparation must show a homogeneous arrangement and coarse grains should not be visible (Yenti et al., 2014).

Stability against Temperature Test

Cold Temperature

Five grams of emulgel are weighed and put into an emulgel container, and then placed in a refrigerator at 5ºC temperature and left for 24 hours. After that, it is taken out of the refrigerator and observed on whether or not there is a separation (Yenti et al., 2014).

Room Temperature

Five grams of emulgel are weighed and put into an emulgel container, and then placed in a refrigerator at 25ºC temperature and left for 24 hours. After that, it is observed on whether or not there is a separation (Yenti et al., 2014).

pH Setting

A half gram of emulgel is diluted with 5 mL of aquadest, then the pH is checked using the universal pH (Naibaho et al., 2013).

Spreadability Test

A half gram of emulgel is placed on a round glass scale and covered with another round glass and then left for 1 minute, after that it is added with 150 g ballast and then the distribution diameter is recorded every 1-minute interval (Garg et al., 2002). Distribution power is calculated using the formula of (5):

$$S = m \times \frac{l}{t} \quad \text{.....(5)}$$

Note:
S = Spreadability
m = Burden weight (150 g)
L = diameter when constant (cm)
T = constant time (second)

Stickiness Test

A quarter gram of emulgel are placed on a predetermined glass object. After that, another glass object is placed on top. The glass object is then attached to the test apparatus and is given a load of 1 kg for 5 minutes. Then, it is released with 80 g load weight. The time is recorded until the two glass objects were detached (Naibaho et al., 2013).

Emulsion Type Setting

The emulsion type is evaluated by applying the prepared preparation in a petri dish, and then added with the drops of blue methylene solution and stirred evenly. If the blue methylene solution is immediately dispersed throughout the preparation, then it has the M/A type of emulsion (Suryani et al., 2014).

Viscosity

The viscosity measurement is done by using Rheosys Merlin VR II Viscometer. The viscosity was measured by a Viscometer equipped with a 30 mm parallel spindle, using 10 points with rotating speeds of 0.1 - 20.0 RPM with a delay time of 30 seconds and integration time of 1 second and carried out in an Integrated Research Laboratory in the Faculty of Pharmacy of Ahmad Dahlan University.

RESULT AND DISCUSSION

Formulation of *Lengkuas* Rhizome Extract (*Alpinia galanga* (L.) Willd)

The *lengkuas* rhizome extract was made using the maceration method using 96% ethanol solvent. Maceration is an extraction method in which the finer material is soaked in a suitable solvent so that it seeps in and softens the cell arrangement so that substances easily dissolve (Ansel, 2005).

The solvent liquid used to be 96% ethanol because it refers to the study conducted by Dwi (2017) which used the same solvent for making lengkuas rhizome extract and obtained a large yield of 17.06%. In addition, ethanol is a universal solvent that attracts most of the chemicals contained in herbs (Runadi, 2007). Another consideration is ethanol as a solvent because it is more selective, so that it is difficult for molds and germs to grow, non-toxic, neutral, and the heat needed for thickening is relatively less (Depkes RI, 1986). Ethanol also does not cause cell membrane swelling and improve the stability of dissolved medicinal substances. Other advantages of ethanol the ability to precipitate albumin and inhibit the action of enzymes (Voigt, 1994). During the maceration process, the diffusion process occurring will affect the degree of difference in concentration, thickness of the boundary layer, and diffusion coefficient. The degree of difference in concentration will affect the stirring process to flatten the concentration of the solution outside the simplicia powder, so that stirring will maintain the degree of difference in the smallest concentration between the solution in the cell and the solution outside the cell (Depkes RI, 1986).

A comparison in percentage states the value of the extract. The yield of the lengkuas rhizome extract was 14.66%, while the results of the study by Dwi (2017) using the maceration method and the same solvent obtained the yield of 17.06%. The difference in yield results could be caused by differences of the growing place of the lengkuas rhizomes, length of drying time, length of the extract thickening time until a smaller yield is produced.

Non Specific Parameter Standardization

The non specific parameter standardization results of the lengkuas rhizome extract can be seen in Table II.

The powder drying shrinkage is one of the parameters of the quality of the simplicia. The aim of drying shrinkage is to provide maximum limits (ranges) on the amount of compounds lost in the drying process and to meet water standards in the dried simplicia with the requirement of not more than 10% (Depkes RI, 2008). High water content or more than 10% can be a medium for growth of molds and fungi that can reduce the quality of simplicia. In addition, it is also to get simplicia that is not easily damaged so that the material's resistance in the storage process is longer (Depkes RI, 1986).

The setting of drying shrinkage of lengkuas rhizome powder using a Halogen Moisture Analyzer of 8.63% was obtained from an average of 3 replications. The drying shrinkage obtained which is smaller than the requirements from the Indonesian Herbal Pharmacopoeia (no more than 10%) can be influenced by the length of simplicia drying in the oven, which makes the simplicia completely dry so that the water rate in the simplicia is small. While the results of the

study by Rosanti (2007) found that the shrinkage drying of lengkuas powder were 2.69% in this case there were differences in the results of drying shrinkage, which was caused by differences in the growing place of the lengkuas rhizomes and the length of drying time as stated by Rosanti in 2007 that it requires a drying time of 8 days, while in this study, it is only until the simplicia is dried, which only need 2-3 days, resulting in a higher shrinkage drying value than what was found in the study conducted by Rosanti in 2007. The measurement results of the drying shrinkage in this study indicate that simplicia fulfills the predetermined requirements so that simplicia can be declared to have good quality.

The setting of water rate is a measurement of the water content contained in the extract expressed in% v/b. The purpose of setting the water content of the lengkuas rhizome extract is to determine the amount of water content in the extract, related to the purity and contamination that may occur in the process of making the extracts (Depkes RI, 2000). The water rate can affect storage time and can also cause susceptibility to microbial activity. The less the water rate, the less likely the extract is to be contaminated by fungal or mold growth (Depkes RI, 1986).

The method used for setting the water rate as stated in the Indonesian Herbal Pharmacopoeia was the toluene distillation method. The toluene used is the toluene saturated water so that the water obtained does not bind with the toluene so that the actual water rate is obtained (Agustin, 2017). The principle of setting the water rate by

toluene distillation is to evaporate water with chemical liquid carriers that has lower type weight than water.

The water rate of lengkuas rhizome extract is 5.0%, the water rate in traditional medicinal preparations including extracts should not exceed the limit of 10% (Depkes RI, 2008). In the study of Hernani et al. (2007), the water rate of the lengkuas rhizome extract was 7.80%. The water rate obtained in this study is smaller than the results of the study of Hernani et al. (2007) and the requirements of Indonesian Herbal Pharmacopoeia. This can be influenced by the differences in the length of simplicia drying time, solvent evaporation process and extracts thickening time, so that thick extracts are obtained with smaller water rate. Water rate will affect the active substance which is obtained. The high water rate indicates that mold or fungus can easily grow on them, which will affect the stability of the extract, and thus causing a low quality of the extract (Depkes, 1986). The measurement results in this study indicate that the lengkuas rhizome extract fulfills the predetermined requirements, namely the water rate of the extract is not more than 10%.

The setting of total ash rate has the purpose of providing an overview of internal and external mineral content which comes from the initial process to the formation of the extracts. It is carried out by spreading the powder and the extract in the kurs in the furnace at a temperature of 600oC until the charcoal runs out (for 6 hours), followed by weighing to constant weight. In this test, heating of the material occurs at high temperatures where organic compounds and their derivatives are decomposed and evaporated, so that only the mineral and inorganic elements will remain (Depkes RI, 2000).

The ash rate and its' composition depends on the type of material and the method of ignition. Ash content is related with the minerals in an ingredient. The minerals contained in an ingredient are two kinds of organic namely organic salts (salts of malic acid, oxalate, acetate, pectar, etc.) and inorganic salts (phosphates, carbonates, chlorides, sulfates, nitrates and alkali metals) (Agustin, 2017). The setting of total ash rate can be used for various purposes including determining whether or not a processing is good, knowing the type of ingredients used and setting the parameters of nutritional value in food ingredients (Pine et al., 2015). The ash rate is calculated against the weight of the test ingredients stated in % b/b.

The results of this study obtained that the powder total ash rate is 3.24% and the powder total ash rate is 1.30%. The difference in the results of ash rate in the powder which is higher than that of the extract caused by the extract of the lengkuas rhizome which has gone through the processing, so that it can minimize the amount of sand or soil attached to the lengkuas rhizome. In the Khoerunnisa (2015) study, the extract ash rate was 7.53%. The total ash rate that meets the requirements from the Indonesian Herbal Pharmacopoeia is that for lengkuas rhizome powder to be no more than 3.9%. The difference in the results of the ash rate in each study can be caused by the differences in the growing place of simplicia and the extract processing process.

The high ash rate value indicates mineral and inorganic contamination found in powder and extract. This contamination can occur related to the place of growing or during the process of making extracts that are less clean. The higher the rate of ash, the lower the quality of the powder or extract (Agustin, 2017). The results of the measurement of total ash rate in this study showed that results that the lengkuas rhizome powder and extract fulfilled the stipulated requirements.

The levels of acid insoluble ash rate obtained in this study is 2.66% in the lengkuas rhizome powder and 0.87% in the lengkuas rhizome extract. The difference in the results of acid insoluble ash rate in the powder which is higher than that of the extract is caused by the lengkuas rhizomes extracts which have gone through the processing process, so that it can minimize the amount of sand or soil attached to the lengkuas rhizome. Soil and sand are silicate compounds that do not burn so that they are components of acid-insoluble ash. In Khoerunnisa's study (2015) the results of acid insoluble ash rate were 2.93%. The rate of acid insoluble ash can be stated as fulfilling the requirements from the Indonesian Herbal Pharmacopoeia if the rate in the powder is not more than 3.7%. The difference in the results of acid insoluble ash rate can be caused by differences in the place of growth of simplicia and extract processing process. The results of the acid insoluble ash rate and lengkuas rhizome extract rate in this study can be declared as fulfilling the requirements stated in Indonesian Herbal Pharmacopoeia.

The test results for determining the type weight of lengkuas rhizome extract were 1.01. Measuring the type weight of thick extracts can be done as long as the extract can still be poured. The weight of the type of extract type is related to the

purity and contamination of the extract. The results obtained was that the type weight of the lengkuas rhizome extract is >1, which means small extract contamination, because the extract is a thick extract containing little water (Haryani et al., 2013).

Phenol Compound Screening Test

The phenol compound screening test was chosen because Fitriati (2007) stated that some of the antifungal active compounds in lengkuas are phenolic compounds. Therefore, this test can show the presence of active compounds which are antifungal in the lengkuas rhizome extract, the presence of phenol compounds which is indicated by yellowish green discoloration (there is a change in color) when $FeCl_3$ is added. The reactions that occur are expressed as follows: $FeCl_3$ (aq) + 6 ArOH (s) → $6H^+ + 3Cl^- + [Fe (Oar) 6]^{3-}$ (aq) (Nugrahani et al., 2016). In this study, there was a change in color. Thus, there was a class of active phenolic compounds which were anti fungal in the lengkuas rhizome extract.

Emulgel Physical Properties Test

The results of the physical properties test of lengkuas rhizome extract emulgel in this study can be seen in Table III.

Spreadability testing aims to see the ability of the emulgel to spread when applied, the emulgel preparation is expected to be able to easily spread when applied to the skin of the desired part of the body. Spreadability is related to how large the surface of the skin is in contact with topical preparations when applied (Pratama and Zulkarnain, 2015). Preparations that have shorter spreading distances show better dispersion coefficients (Gupta and Gaud, 2005). Spreadability test on emulgel preparation is 2.45 g.cm.s-1, using a load of 150 g and the time when the spread diameter is constant at 480 seconds.

Stickiness is the ability of a preparation to stick for a long time when applied. The longer the stickiness of a preparation, the longer the penetration time of the medicine into the skin so that the absorption of the medicine becomes optimal (Ansel, 2005). Topical preparations are expected to have long stickiness, so that the medicine will be in contact with the skin for longer time, so that the effect of the medicine will be more optimal. The stickiness test on emulgel preparations was 8.80 seconds. The stickiness in this study meets the requirements of good stickiness, which is more than 4 seconds (Ulaen et al., 2012)

Viscosity is a statement to flow from a system with a thicker liquid. The thicker the liquid, the bigger the power required by the liquid to flow (Martin et al., 1993). Viscosity measurement with Rheosys Merlin VR II Viscometer is equipped with 30 mm parallel spindle, using 10 points with rotating speed from 0.1 to 20.0 RPM with 30 seconds delay time and 1 second integration time. The viscosity test showed that at 15.6 RPM, the emulgel viscosity is about 1.37 Pa.s ± 0.22.

In addition to getting the viscosity value, using the Rheosys Merlin VR II Viscometer also obtained a graph that shows the flow properties of preparations (Hendriana, 2016), Graphs were obtained in the emulgel which follows the type of non-Newtonian flow, then linear regression calculations between shear stress (x) vs shear rate (y) and log shear stress (x) vs. log shear rate (y) were conducted. Then in the log shear stress (x) vs log shear rate (y) equation of the three replications, the R square results closest to 1 were obtained, so that the flow type of the emulgel preparation was non-Newtonian pseudoplastic type. This result is in accordance with the theory presented by Martin et al., 1993 which states that generally, semisolid preparations have non-Newtonian flow properties and polymer-based pharmaceutical preparations such as emulgel preparations showing pseudoplastic flow. The graph of the viscosity test results can be seen in Figure 1.

Tabel III. Emulgel Physical Properties Test Results

Parameter	Results	Requirement
Spreadability (g.cm.s-^{1})	2.45 ± 0.03	-
Stickiness (s)	8.80 ± 0.72	> 4 seconds (Ulaen *et al*., 2012)
Viscocity (Pa.s)	1.37 ± 0.22	-
Flow Type	Non-Newton - Pseudoplastic	Pseudoplastis (Martin *et al*., 1993)
pH	7	5-7 (Swastika *et al*., 2013)
Emulsion Type	m/a or o/w	-
Organoleptis	Stabil (semisolid form, light brown color, distinctive smell of the lengkuas rhizome)	-
Homogeneity	Homogeneous	-
Stability towards Temperature	No changes (Stabil)	-

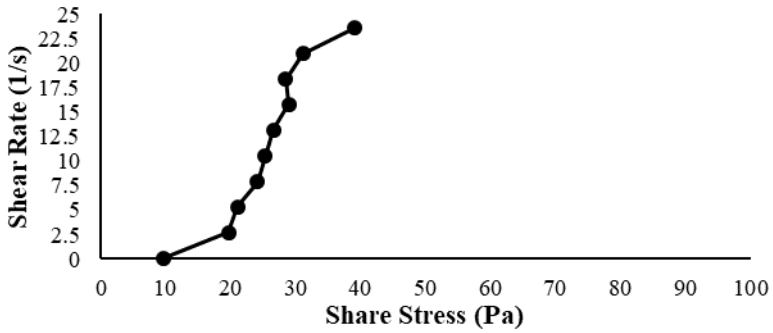

Figure 1. Viscosity Test Results Graph

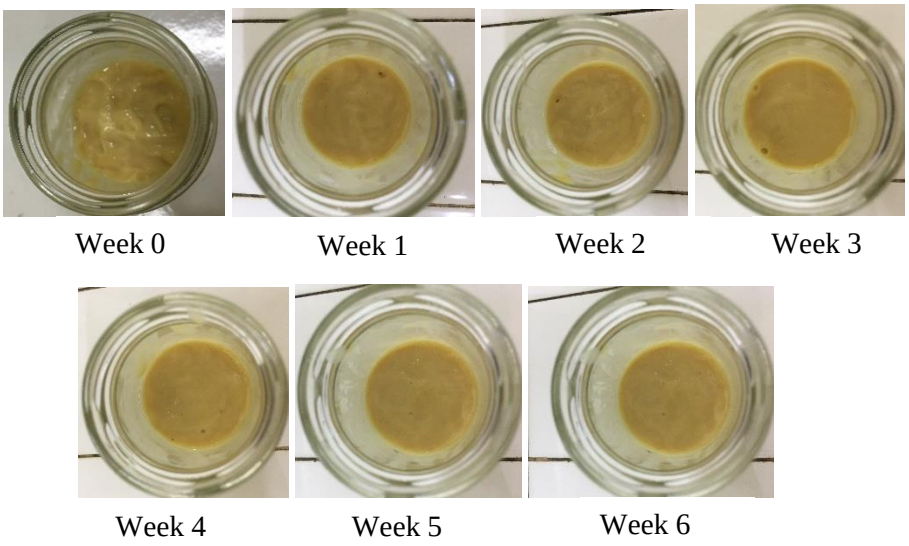

Figure 2. Organoleptic Observation Results

The higher the viscosity value, the higher the thickness level of the substance (Arikumalasari et al., 2013). Viscosity is related to the spreadability and stickiness of a topical preparation. Spreadability is inversely proportional to the viscosity and stickiness of the preparation, so the greater the viscosity of a preparation, the greater the stickiness and the smaller the spreadability produced (Setyaningrum, 2013).

Setting of pH on emulgel preparations is useful to figure out the pH of emulgel preparations. The pH test of the preparation aims to determine the safety of emulgel preparations when used so as not to irritate the skin, skin preparations should have a pH that is more or less the same as the pH of the skin so that it does not easily irritate the skin which is between 5-7 (Swastika et al., 2013). If the pH of the preparation is lower than the physiological pH of the skin, it will result in skin irritation. Preparations with a higher pH, resulting in irritation and dry skin (Young, 2002). The pH test is carried out by using universal pH paper, and based on the pH test results, the emulgel preparation has a pH of 7, so that the emulgel preparation has a pH that matches the pH range of the skin (5-7).

Emulsion type tests are carried out to ascertain whether the emulsion type of emulgel is as expected, that is typed O/W. This test is carried out using methylene blue liquid, if the blue color spreads evenly, then the emulsion type is O/W. In this study, when drops of methylene blue solution are added on the emulgel, blue color is spread evenly, so that the type of emulsion is in accordance with the expected type O/W. O/W type is more acceptable because it is easily applied to the skin and leaves a feeling of comfort compared to the W/O type (Dipahayu et al., 2014).

Organoleptic observations were carried out by observing the shape, smell and color of the

emulgel preparation, observing the 0, 1, 2, 3, 4, 5, 6 weeks so that the observations were carried out for 6 weeks. Organoleptic tests were carried out to see the physical appearance of the preparation by observing the shape, color, and smell of the preparations that had been made (Allen, 2002). The organoleptic observations on emulgel preparations found that the shape of the preparation is semisolid, then the distinctive smell of lengkuas rhizome extract, and light brown color. During the 6-weeks-storage with room temperature, the emulgel preparation did not experience changes in shape, smell or color so that it could be said that the emulgel had good stability, and was stable in storage at room temperature within 6 weeks, this could prove that the emulgel preparation could maintain the stability of active compounds contained in lengkuas rhizome extract which are phenolic compounds, whereas phenolic compounds are easily oxidized which is known as auto-oxidation, which is a reaction caused by the presence of light and oxygen (Setyaningtyas et al., 2018). The observation results can be seen in Figure 2.

Homogeneity examination is related to the therapeutic effects produced by emulgel preparations. If the emulgel is not homogeneous, then the active substance is not evenly distributed on the emulgel base, so that the part of the emulgel which does not contain active substances makes the therapeutic effect produced from emulgel preparations less. Observations were conducted by applying emulgel on transparent glass. Based on observations of the emulgel, there is no visible coarse grains on transparent glass so that the emulgel can be said to be homogeneous. This proves that emulgel preparations can mix well and homogeneously with lengkuas rhizome extract that has hydrophobic or hydrophilic properties.

Observation of emulgel stability on temperature aims to see the stability of the emulgel when stored at a certain temperature. This test was observed at two different temperatures, namely cold temperature (5ºC) and at room temperature (25ºC) and observations were made with 24-hour storage. After being stored for 24 hours at a predetermined temperature, it is then observed whether there is a phase separation that occurs in the emulgel. The results of this observation found that emulgel preparations that were stored for 24 hours at cold and room temperature did not separate. There is no change in the emulgel form. This proves that the emulgel formula can mix with *lengkuas* rhizome extract so that there is no cracking in the preparation.

CONCLUSION

The non-specific parameter standardization of lengkuas extract obtained the results of extract yield (14.66 ± 0.056) %; powder drying shrinkage (8.63 ± 0.134) %; extract water rate (5 ± 0) %; powder total ash rate (3.24 ± 0.017) %; and extract (1.30 ± 0.035) %; powder acid-insoluble ash rate (2.66 ± 0.10) %; and extract (0.87 ± 0.031) %; extract type weight 1.01. The test results of physical properties of emulgel obtained the spreadability of (2.45 ± 0.03) g.cm.s-1; stickiness (8.80 ± 0.72) seconds; viscosity (1.37 ± 0.22) Pa.s; pseudoplastic flow type; pH 7; emulsion type m/a; stable emulgel at 6 weeks stored in the semisolid form, light brown color, distinctive smell of lengkuas rhizome extract; homogeneous emulgel; and stable at 5ºC and 25ºC for 24 hours.

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FORMULATION OF SUNSCREEN CREAM OF PARIJOTO FRUIT EXTRACT (*Medinilla speciosa* Blume) AND IN VITRO SPF VALUE TEST

FORMULASI KRIM TABIR SURYA EKSTRAK BUAH PARIJOTO (*Medinilla speciosa* Blume) DAN UJI NILAI SPF SECARA IN VITRO

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ABSTRACT

Sunscreen preparations are cosmetic preparations used as a protection to reduce the impact of sun exposure whose formulations contain active ingredients to absorb or diffuse sunlight, especially in areas of ultraviolet and infrared wave emissions. One of the potential natural ingredients for a sunscreen is parijoto fruit (Medinilla speciosa Blume). It contains flavonoid compounds that are able to prevent the harmful effects of UV rays. The objective of this research is to find out the formula of sunscreen cream of parijoto extract that meets the good physical quality of cream and to find out the result of SPF value test of parijoto fruit extract as sunscreen cream preparation in Vitro. The design of the study was experimental research conducted in the laboratory. The sample used in this research was parijoto made into thick extract by maceration method. Further, the viscous extract obtained was made to be a sunscreen cream and then tested either its physical evaluation or calculation of SPF value. The results of this study indicate that the preparation of sunscreen cream of parijoto fruit extract included in the extra protection category with the value is 6.66 and can be made into the good and stable preparations. The sunscreen cream of parijoto fruit extract has good physical properties and also has activity as UV protection in vitro.
Keywords: *cream, parijoto fruit (Medinilla speciosa Blume), SPF, sunscreen*

ABSTRAK

Sediaan tabir surya adalah sediaan kosmetika yang digunakan sebagai salah satu perlindungan untuk mengurangi dampak paparan sinar matahari. Formulasinya mengandung zat aktif untuk menyerap atau menyebarkan sinar matahari terutama daerah emisi gelombang ultraviolet dan inframerah. Salah satu bahan alam yang memiliki potensi sebagai tabir surya adalah buah Medinilla speciosa (Medinilla speciosa Blume) yang mengandung senyawa flavonoid yang mampu mencegah efek berbahaya dari sinar UV. Tujuan dari penelitian ini adalah untuk mengetahui formula sediaan krim tabir surya ekstrak buah Medinilla speciosa yang memenuhi persyaratan mutu fisik krim yang baik serta mengetahui hasil uji nilai SPF secara in vitro ekstrak buah Medinilla speciosa. Sampel yang digunakan pada penelitian ini yaitu buah Medinilla speciosa yang dibuat menjadi ekstrak kental dengan metode maserasi. Ekstrak kental yang diperoleh kemudian dibuat menjadi sediaan krim tabir surya kemudian dilakukan uji evaluasi fisik dan perhitungan nilai SPF. Hasil penelitian ini menunjukkan bahwa sediaan krim tabir surya esktrak buah Medinilla speciosa termasuk dalam kategori proteksi ekstra dengan nilai 6,66 serta dapat dibuat menjadi sediaan yang baik dan stabil. Krim sunscreen ekstrak buah Medinilla speciosa mempunyai sifat fisik yang baik dan juga memiliki aktivitas sebagai perlindungan sinar UV secara in vitro.
Kata kunci: *krim, buah parijoto (Medinilla speciosa Blume), SPF, tabir surya*

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INTRODUCTION

Indonesia is a country with high exposure of sunlight. Human beings need sunlight to create vitamin D which is very useful to the bones. However, if an individual is excessively exposed to sunlight, it can cause the skin epidermis layers unable to guard from the generated negative effect ranging from light dermatitis to the skin cancer (Chiari et al., 2014).

One of the chemical protections which can be taken to help reduce the effect of sunlight exposure is using the cosmetic preparation of the sunscreen by applying it before being exposed to the sunlight. The sunscreen cream can absorb at least 85 % of the sunlight at the wavelength of 390-320 nm for UVB, while for UVA can absorb the light at the wavelength of 320 (Suryanto, 2012).

Medinilla speciosa plant is one of the particular plants that is found in Colo village in Kudus District, Central Java which has not been explored concerning its benefits. Therefore, the extract of *Medinilla speciosa* was chosen as the material used for sunscreen cream formulation. The *Medinilla speciosa* fruit contains some phenolic compounds, among others, the flavonoids, saponins, and cardenolin (Tussanti et al., 2014). Flavonoid has been identified to be functional as the antioxidant. The flavonoid can prevent the harmful effect or UV rays or can reduce the skin distraction (Mokodompit et al., 2013). The flavonoid compound found in the *Medinilla speciosa* fruit has been known to be able to give protection against the exposure of the sunlight hence it was determined to be the background of this research, concerning the preparation formulation of the sunscreen cream of the *Medinilla speciosa* extract. The solvent used in the formulation of *Medinilla speciosa* extract was the ethanol 70% because it had some advantages. Some of them were that it was very effective in producing optimal active ingredients, and also the polar solvent such as ethanol was the more effective solvent that could be used for the natural antioxidant extraction. It was chosen as the cream preparation because of its spreading ability which was good for the skin, easy to wash with water, and delivers the good medicine (Voight, 1994). To identify the effectiveness for the preparation of sunscreen cream based on *Medinilla speciosa* ingredient, it was necessary to test the physical quality and in vitro testing of the SPF values of the sunscreen cream preparation which was carried out using the spectrophotometry of UV-VIS.

The aim of this research is to identify the formula of the preparation of the sunscreen cream which was determined from the extract of *Medinilla speciosa* to able to fulfill the physical qualification of the cream and to identify the result of the SPF value test in vitro contained in the extract of *Medinilla speciosa* fruit for the preparation of sunscreen cream.

METHODS

Instrumentations and Materials

The instrumentations used in this research were waterbath, chemical glass, pH indicator, spreadability test apparatus, porcelain cup, drop pipette, cream pot, oven, filter paper, analytical scales, Brookfield viscometer, spectrophotometry UV-Vis. The materials used in this research were, the *Medinilla speciosa* fruit, aquadest, ethanol 70% (technical), cream base which includes cetyl alcohol (Brataco Chemical, Indonesia), mineral oil (technical), tween 80 (technical), glycerin (Brataco Chemical, Indonesia), span 80 (technical), methyl paraben (technical), propyl paraben (technical), and stearate acid (technical).

The Collecting and Identification of the Plant

The selected *Medinilla speciosa* fruit had the specification of which had purplish pink color. The selected *Medinilla speciosa* fruit was sorted first to clean it from the dust, dirt and the insects so that it was free from the pollutants which could reduce its quality. Then, the *Medinilla speciosa* fruit was separated from its stalk. Next, the *Medinilla speciosa* fruit was chopped up to make the dry process easy which was done in the oven at the temperature of 50°C until it become dried simplicia (Wulandari et al., 2017).

The Extract Production

The extract of *Medinilla speciosa* fruit was made using the maceration method, that is, the dried *Medinilla speciosa* fruit was extracted using ethanol 70% as long as 3 x 24 hours. The result of extraction, then was evaporated using the waterbath so that the viscous extract could be obtained (Sharon et al., 2013).

The Characterization of the Extract

The characterization of the extract was seen by using the organoleptic, measuring the extract pH, and by testing the phytochemical compound content.

Organoleptic Properties

Organoleptic properties of extract was tested by using the human senses, starting from the shape, smell, and color.

pH

The pH of the extract was measured using pH indicator, that is, by immersing the indicator into the extract of *Medinilla speciosa* fruit. Then, the change of the color was observed and adjusted to the color spectrum in that indicator.

The Phytochemical Content Testing

Preparation of phytochemical test solution

As many as 0.5 gram of ethanol extraction of the *Medinilla speciosa* fruit was dissolved with the 50 mL of methanol, then they were shaken until they were homogeneous. Next, they were divided into three test tubes (Artini et al., 2008).

The Examination of Flavonoids

It took 1 mL of test solution; it was added with little powder of Mg and 1 mL of concentrated HCl, then, they were shaken. The positive testing was marked by the formation of the red color, pink, or purple (Marliana and Saleh, 2011).

The examination of Saponin

It took as many as 1 mL of test solution; it was poured into the test tube, then, was shaken strongly for 10 seconds. The formation of the foam about 1-10 cm high which was stable for no less than 10 minutes, indicated the existence of the saponin. On the addition of 1 drop of HCl 2N, the foam did not disappear (Artini et al., 2008).

The examination of Tannin

It took 1 mL test solution and was poured into the test tube and was added with 3 drops of $FeCl_3$ 1%. The sample contained tannin if the color changed to be blackish green (Arief et al., 2017).

Formulation of Sunscreen cream of *Medinilla speciosa* fruit Extract

The cream was made by modified formula from Hastuti (2016) and can be seen in Table I. The phase of oil was heated in the waterbath at the temperatures of 65-75ºC. At the same time, in the different way, the phase of water was heated in the waterbath at the temperatures of 65-75ºC. The phase of oil was poured into the mortar while being stirred. The phase of water was added to the phase of oil in the condition of being heated, drop by drop while it was continuously stirred. The cream was cooled while being stirred until it was homogeneous.

The evaluation of the physical properties of cream

Organoleptic

The organoleptic test was conducted using the five senses, starting from the shape, the smell, and the color. The parameter of quality of the physical properties of cream was that there were no changes in the form, color, and the smell since the beginning of the production, storage, up to the usage. The organoleptic compared the sunscreen cream base with the sunscreen *Medinilla speciosa* fruit extract base.

pH

The pH of the preparation was measured using the pH indicator by immersing the pH indicator into the sunscreen cream preparation. Then, the color change was observed and adjusted to the color spectrum in the indicator tool. The pH of the sunscreen cream *Medinilla speciosa* fruit extract should also be compared with the sunscreen cream base.

Viscosity

The test was conducted using the Brookfield viscometer and utilizing 64 spindles. Afterward, the cream was placed in a container, then, the spindle which had been installed was pulled down until the spindles was immersed.

Spreadability

The cream was placed on the glass plate and was left alone for 1 minute, then, the diameter of the cream spread was measured. Next, the load was added by 50 mg. It was left alone for 1 minute, then, diameter of the cream spread was measured. That same thing should be done again and again until the constant diameter of the cream spread was obtained. (Rindiyantoko and Hastuti, 2017).

Homogeneity

The homogeneity test was conducted by smearing the preparation to the surface of the object glass, then, it was spread to the other object glass to find the homogeneous surface. The cream could be said homogeneous if the particle structure did not cause to clot or was not mixed (Wulandari et al., 2017).

Freeze-Thaw Cycling

The freeze-thaw test was conducted by keeping each of the cream formula in the storage in the temperatures of -10°C and 30°C for 24 hours in 3 cycles. The cream that passed through the freeze-thaw was observed organoleptically and was identified whether the change of the phase occurred (Yuliani et al., 2016).

The Determination of the SPF (Sun Protection Factor) Value

The determination of the effectiveness of the sunscreen was carried out by determining the SPF value in vitro using the spectrophotometer UV-Vis. The cream was diluted in 4000 ppm by taking out 0.1 gram of the *Medinilla speciosa* fruit extract being dissolved in the 96% ethanol as many as 25 mL and being mixed up until it became homogeneous (Mokodompit et al., 2013). Before the spectrophotometer was calibrated using ethanol 96%, by way of 1 mL of ethanol was poured into the cuvette in the wavelengths between 290-320 nm, utilizing the ethanol 96% as the blank. Then, the absorption average (Ar) was determined in the interval of 5 nm. The result of the absorbance was recorded, then, the SPF value was calculated by applying the following formula (Rauf et al., 2017):

$$AUC = \left(\frac{Aa + Ab}{2}\right)(dPa - b)$$

$$\Delta AUC = AUC_1 + AUC_2 + AUC_3 + AUC_4 + AUC_5 + AUC_6$$

$$\text{Log SPF} = \left(\frac{\Delta AUC}{\lambda_n - \lambda_1}\right) x\ 2$$

SPF = antilog SPF

With Aa: Absorbance in wavelength a nm; Ab: Absorbance in wavelength b nm; dPa-b: the difference between wavelengths a and b; λn: the biggest wavelength (320 nm); λ1: the smallest wavelength (290 nm); AUC: Area Under Curve; ΔAUC: Total AUC.

The effectiveness of the sunscreen cream preparation based on the SPF values were presented in Table II.

Table I. Cream Formula

Composition	Quantity (%)
Extract	500 mg
Cetyl alcohol	4
VCO	10
Tween 80	2,204
Glycerin	10
Span 80	2
Methyl paraben	0,2
Propyl Paraben	0,1
Stearate Acid	3,796
Aquadest	Add 100

Source: (Hastuti, 2016)

Table II. Effectiveness of the Sunscreen Cream Preparation

SPF	Category
2-4	Minimum Protection
4-6	Medium Protection
6-8	Extra Protection
8-15	Maximum Protection
≥15	Ultra-Protection

Table III. The Result of Characterization of *Medinilla speciosa* fruit Extract

Type of Characterization	Result
Organoleptic	
Color	Dark Brown
Form	Concentrated Extract
Smell	Particular Extract
pH	4
Phytochemical Test	
Flavonoids	+
Saponin	+
Tannin	+

Table IV. The Result of characterization test of the Physical properties of cream

Characterization of physical properties of cream	Base sunscreen cream	*Medinilla speciosa* fruit Extracted cream
Organoleptic		
Color	White	Brown
Form	Cream, smooth, not sticky	Cream, smooth, not sticky
Smell	Particular base	Particular extract
pH	5	5
Homogeneity	Homogeneous	Homogeneous
Viscosity (cP)	Average of SD 3451.13 ± 41.491	Average of SD 578.15 ± 24.614
Spreadability	Average of SD 1.09 ± 22.275	Average of SD 1.03 ± 14
Freeze-thaw	-	+

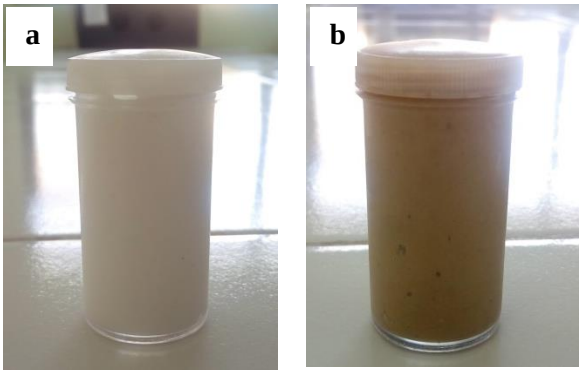

Figure 1. Physical appearance of Sunscreen cream Medinilla speciose fruit extract (a) and base sunscreen cream (b)

RESULTS AND DISCUSSION

The Rendemen Result of *Medinilla speciosa* fruit Ethanol Extract

The production process of *Medinilla speciosa* fruit extract was done using maceration method applying the solvent of ethanol 70%. The maceration was conducted as long as 3 x 24 hours by stirring occasionally and was strained using the filter paper, then, the dregs was macerated by applying the same solvent until it produced clear macerate. The liquid extract obtained from the maceration result was, then, concentrated by using the waterbath at the temperature of 40ºC so that the concentrate extract was gained. From the result of the extraction, it was obtained 10.95% macerates. The obtained extract with the bigger solubility in the water was compared with the solubility in the oil.

Characterization of the Extract

The characterization of extract can be showed by Table III. According to Wachidah (2013), the total of flavonoids grades of the *Medinilla speciosa* fruit was as many as 164 mg RE/g of extract. This flavonoids compound was exactly used as the active content of the sunscreen.

The Cream Formulation

The cream formula was the formula by Hastuti (2016), which was modified with which the applied base was cetyl alcohol, mineral oil, tween 80, glycerin, span 80, methyl paraben, propyl paraben, and stearate acid. Those which were included in the water phase were the tween 80, glycerin, methyl paraben, aquadest, and *Medinilla speciosa* fruit extract. While the ingredients that were included in the oil phase were span 80, cetyl alcohol, mineral oil, propyl paraben, and stearate acid.

The Evaluation of the Physical properties of cream

The result of characterization test of the Base Sunscreen cream and *Medinilla speciosa* fruit extracted cream are presented in Table IV and Figure 1.

The organoleptic test was conducted by observing the cream visually on the form, color, and the smell which was meant to see the physical appearance of a preparation. Then, the base cream was compared with the extracted cream. The result showed that the base cream was white while the extracted cream was brown because there was extract addition which was dark brown in color.

The measurement of pH was implemented using the pH indicator by way of immersing the pH indicator into the cream preparation, then, the color was checked with the color spectrum in the indicator tool (Mailana et al., 2016). The result of pH examination indicated that the comparation between the base cream and the extracted cream had same pH score, that is, 5. The score of pH base cream preparation and the extracted cream was still in the range of normal skin pH, that is, between 4 – 6 (Zulkarnain et al., 2015). Hence, that cream was classified safe if it was applied on the skin.

The objective of homogeneity test is to observe and identify the mixing of the ingredients of the cream preparation (Setyowati et al., 2013). The homogeneity of cream preparation was tested using the object glass by way of smearing the cream on the glass and the existence of coarse grain was observed. The result of the homogeneity test to the base cream and extracted cream indicated good result, that is, the cream was dispersed evenly and there was no particle clod which could be observed visually.

The viscosity is a statement on the endurance of a liquid to flow. The higher is the volume of the preparation, its viscosity is also higher, hence, the preparation will get more stable because the movement of the particle is likely difficult as the preparation gets thicker (Mailana et al., 2016).

The result showed that the viscosity between the base cream and the extracted cream had fulfilled the standard. According to Gozali et al. (2009), the ideal viscosity score of the cream is more than 5000 cP. While according to the Indonesian Nasional Standard SNI 16-4399-1996 about the quality standard of the sunscreen cream, the good viscosity of the preparation ranges between 2000 - 50.000 cP.

The spreadability test is used to identify how wide the cream can spread on the skin. The bigger the spreadability of the cream, the more active substance of the cream can be delivered into the skin layer (Voight, 1994). The obtained result of the spreadability test was, then, examined by T-test using the SPSS and the result of the T-test was Sig. 0.001 < 0.05 which could be defined that there was difference, as the result of the spreadability test, between the base sunscreen cream and sunscreen cream from the *Medinilla speciosa* fruit extract.

Freeze-thaw test was conducted to identify the stability of the physical properties of cream. The test can be seen by the absence or presence of phase separation during the storage in the extreme temperature, i.e. -10°C dan 30°C. The testing was done in three cycles. The results obtained were that the base cream did not undergo a phase change during 3-cycled storage. In contrast, in Medinilla fruit extract, cream extract undergoes phase changes in the second cycle. This can be caused by the addition of *Medinilla speciosa* fruit extract which causes physical properties of cream instability.

Determining the SPF Value

The tests of the UV light treatment for *Medinilla speciosa* fruit extract cream in vitro were carried out using a UV-Vis spectrophotometer in the range of wavelengths between 290-320 nm. The wavelength is included in the wavelength for UV A which can continue light on the 320 nm and UV B wavelengths that can absorb sunlight in the wavelength of 290-320 nm (Suryanto, 2012). Then, the value of SPF cream Medinilla specimen fruit extract was 6.66 which was categorized as extra protection. The SPF value determines the ability of sunscreens to protect the skin and prevent sun exposure. The higher the SPF value on sunscreen preparations, the better the ability of protection (Rahmawanty and Fadhillaturrahmah, 2014). Sunscreen preparations can be said to provide protection if they have an SPF value of at least 2 and a good sunscreen assessment category if sunscreen preparations have an SPF value above 15 (Rosniah et al., 2016)

CONCLUSION

The formula for the preparation of sunscreen cream based on *Medinilla speciosa* fruit extract meets the physical properties of good cream. The test results of in vitro SPF value of Medinilla specimen fruit extract sunscreen cream were 6.66%. It is categorized as extra protection.

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THE EFFECT OF EDUCATIONAL SELF-MEDICATION FOR DYSMENORRHEA TREATMENT USING OVER THE COUNTER DRUGS

PENGARUH EDUKASI SWAMEDIKASI TERHADAP PENANGANAN DISMENORE DENGAN OBAT BEBAS - BEBAS TERBATAS

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ABSTRACT

Self-medication is an attempt to treat the disease felt by using the over-the-counter drug (OTC) which is based on knowledge about the safe and rational treatment. The implementation of the self-medication drug use tends to be misused. The ease in self-medication treatment in community shows the importance of education in the use of medications safely and rationally. Education is carried out appropriately with effective methods and media. This research used quasi-experimental design approach with one group pretest – posttest design. The sample of this research was 34 female students from Frateran High School Malang selected using a purposive sampling. The data was analyzed using Paired T-Test. The results of comparison of self-medication treatment using OTC drugs before (pre) and after (post) education provided the significance value obtained 0.000 which is smaller than alpha 0.05. The null hypothesis (H_0) can be rejected and concluded that there is a different score in the self-medication treatment using OTC drugs before (pre) and after (post) education. It can be concluded that the education can affect the improvement of knowledge of the students for effectiveness of lowering OTC drugs abuse.

***Keywords**: dysmenorrhea, education, over-the-counter drugs, self-medication*

ABSTRAK

Swamedikasi adalah upaya mandiri untuk mengobati penyakit yang dirasakan dengan menggunakan golongan obat bebas – bebas terbatas, yang dilandasi dengan pengetahuan tentang pengobatan rasional dan aman. Pada pelaksanaan swamedikasi cenderung terjadi penggunaan obat secara tidak benar. Kemudahan dalam melakukan pengobatan mandiri dalam masyarakat, merupakan sarana bagi Apoteker untuk secara kontinu melakukan edukasi dalam penggunaan obat secara rasional dan aman. Jenis penelitian ini adalah quasi eksperimental dengan pendekatan the one group pra-post test design. Sebagai sampel penelitian adalah 34 siswi SMAK Frateran Malang, yang dipilih secara purposive sampling. Data dianalisa dengan menggunakan Uji T-Test Berpasangan. Berdasarkan hasil perbandingan skor pengetahuan tentang penanganan swamedikasi penggunaan obat bebas – bebas terbatas sebelum (pre) dan setelah (post) diberikan edukasi diperoleh nilai signifikansi sebesar 0.000 yang lebih kecil dari alpha 0.05. Hal ini menunjukkan terdapat perbedaan skor pengetahuan tentang penanganan swamedikasi penggunaan obat bebas – bebas terbatas yang signifikan pada siswa antara sebelum (pre) dan setelah (post) diberikan edukasi. Dengan demikian disimpulkan bahwa pemberian edukasi dapat mempengaruhi peningkatan pengetahuan siswa, sehingga efektif untuk menurunkan penyalahgunaan obat bebas – bebas terbatas.

***Kata kunci:** dismenore, edukasi, obat bebas-bebas terbatas, swamedikasi*

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INTRODUCTION

Health development aims to increase awareness, willingness and an ability to live healthy life for everyone so that the highest level of public health can be achieved. The increase in public health is required in accordance with the health development for Healthy Indonesia 2020 which is to increase independence of community and family in the maintenance of health (Moeloek, 2015).

The independence of community and family in maintaining health is related to treatment efforts when they are sick or if there are any health complaints. Easy health complaints can be overcome with self-medication or independent treatment by ourselves or family members.

Independent treatment effort to treat someone's diseases may use the over-the-counter drugs, based on people's knowledge on safe and rational treatment (Info POM, 2014). Safe and rational treatment according to the Kementerian Kesehatan Republik Indonesia (2011) includes the right diagnosis, exact indication of disease, right selection of drugs, right dosage, appropriate method of administration, exact time interval for administration, proper duration of administration, alert to side effects, precise assessment on patient's condition, precise information, patient compliance with treatment, warranted quality of drug provision, affordable prices, and effective and safe quality. Security in using drugs is an absolute requirement in self-medication because it is closely related to drug misuse, improper use of drugs. Drug abuse that often occurs indicates a wrong treatment, wrong method of using the drug, drug incompatibility with disease / disease symptoms, inappropriate drug dosages and not in patients (Departemen Kesehatan Republik Indonesia, 2008).

Therefore, efforts in avoiding errors in drug use are required. Based on the research conducted by Latifah (2013) as cited in Akhmad (2017), it is mentioned that the community of Santan Sumberejo, Magelang Regency, choose self-medication because: (1) the types of drugs are cheaper (50%); drugs are sold on the market (28%); they are more convenient (22%); over-the-counter (OTC) drugs are used to relieve headaches (46.1%). Rustam (2014) states in his research that 40% of students of STIFARM Padang choose the OTC drug to reduce pain during menstruation, which is able to quickly relieve pain (97.83%). Based on the preliminary study on one of the students in Frateran Catholic High School Malang, the student took mefenamic acid drugs to reduce and remove the pain when menstruation occurred (dysmenorrhea). This drug consumption is done without considering the time interval for administration. When the pain came within 1 (one) hour after the first administration, the student retook the drug even though it was not the right interval. Mefenamic acid is a pain reliever in hard drug category that includes in the pharmacy mandatory drugs that can be purchased without using a prescription but can be given by Pharmacy Management Pharmacist (APA) to the public.

Anti-pain drugs (analgesics) can increase the risk of kidney disease if the term of use is inappropriate. It is in accordance with the research by Curhan et al. (2004) as cited in Akhmad (2017) that there is a decrease in kidney function (glomerular filtration rate/GFR) in the misuse of Nonsteroidal Anti-Inflammatory Drugs (AINS), paracetamol and aspirin. Providing health counseling is one of the health education forms that aims to convey health messages to the community for better changes. One of the changes is by health counseling influenced by knowledge (Wawan and Dewi, 2011). Providing education through health counseling is expected to help in increasing self-medication knowledge of the use of OTC by female students to reduce menstruation pain (dysmenorrhea), so that they are able to handle pharmacology with an appropriate, safe and rational treatment.

In this research, the influence of self-medication education of dysmenorrhea treatment using over the counter (OTC) drugs to the student of Frateran Catholic High School Malang was analyzed.

METHODS

Stages of Research

This research consists of three stages, namely: Stage I: Distribute questionnaires to students of Frateran Catholic High School Malang before conducting self-medication education for dysmenorrhea treatment using OTC drugs; Stage II: Provide self-medication education for dysmenorrhea treatment using OTC drugs through leaflet and power point media to the female students of Frateran Catholic High School Malang; Stage III: Distribute questionnaires to students of Frateran Catholic High School Malang after conducting self-medication education for dysmenorrhea treatment using OTC drugs.

Research Instrument

This research used leaflets and power point media in providing self-medication education for dysmenorrhea treatment to the students of Frateran Catholic High School Malang. The questionnaires were used to determine distribution frequency of dysmenorrhea treatment to the students of Frateran Catholic High School Malang before and after conducting self-medication education. The questionnaires consist of statements containing the appropriate, safe and rational self-medication of dysmenorrhea treatment that includes appropriate indications by knowing and understanding the contradictions to the use of dysmenorrhea drugs; right selection of drugs which is the types of menstruation pain medication (dysmenorrhea) both OTC drugs and hard drugs. Those things include in the questionnaires in order to find out appropriate and inappropriate dysmenorrhea treatment by the students of Frateran Catholic High School Malang.

The categories are appropriate dosage; appropriateness in administering drugs; exact time interval for drugs administration in the form of the term of use; appropriate duration of drug administration (how long it is considered safe and rational to take the menstruation pain (dysmenorrhea) drugs) whether during menstruation or just when feeling pain; precise information about attention and warning of using dysmenorrhea drugs and the information about dysmenorrhea drugs storage; appropriate follow-up which becomes the possibility of unwanted side effects and the possibility of patients who do not recover with the treatment, those must be known and considered when doing dysmenorrhea therapy using menstruation painkiller drugs.

Therefore, the follow-up effort can be well prepared. The questionnaires used in this study have been tested for validity and reliability by using SPSS. Based on the validity test, R counting value on each question is greater than R table, and the reliability test result have Cronbach's α 0.985 value.

Data Analysis

The analysis was done through two stages, the first stage is univariable analysis. In this analysis, the research variable was analyzed descriptively to obtain the distribution overview of dysmenorrhea by respondents. Furthermore, the analysis was done to find out the influence of the independent variable to the dependent variable. The second stage is analyzed the influence of self-medication education to dysmenorrhea treatment using OTC drugs by using the parametric test with paired T-test.

The result of paired sample test shows that Sig. (2-tailed) has a value of 0.000 < 0.05 which means that the score of dysmenorrhea treatment using OTC drugs after (post) self-medication education shows an increase, compared to the score of dysmenorrhea treatment using OTC drugs before (pre) self-medication education.

RESULTS AND DISCUSSION

To find out the influence of self-medication education of dysmenorrhea using OTC drugs to the students of Frateran Catholic High School Malang, the identification on dysmenorrhea using OTC drugs was firstly done before self-medication education was given and it was compared to dysmenorrhea treatment using OTC drugs after conducting self-medication education.

Table I. Dysmenorrhea Treatment using OTC Drugs before Conducting Self-medication Education (Pre-Test)

Dysmenorrhea Treatment (*pre*)	Frequency	Percentage (%)
Appropriate	5	14.7%
Inappropriate	29	85.3%
Total	34	100%

Source: Research's Primary Data 2017

Table II. Dysmenorrhea Treatment using OTC Drugs after Conducting Self-medication Education (Post Test)

Dysmenorrhea Treatment (*post*)	Frequency	Percentage (%)
Appropriate	34	100%
Inappropriate	0	0%
Total	34	100%

Source: Research's Primary Data 2018

Table III. Statistic Analysis Using Paired T-Test to Find Out The Difference in The Average of Dysmenorrhea Treatment Using OTC Drugs Before and After Self-Medication Education

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Pre-Test - Post Test	-38.000	8.845	1.517	-41.086	-34.914	-25.050	33	.000

Source: Research's Primary Data 2018

Based on Table I, the result conducted on 34 female students of Frateran Catholic High School Malang, it shows that there are 29 students (85.3%) who had inappropriate dysmenorrhea treatment using OTC drugs (drugs used were not in accordance with the instructions, at inappropriate time and within inappropriate period time of therapy based on the recommendation). Meanwhile, the rest of the respondents (14.7%) shows that they had appropriate dysmenorrhea treatment using OTC drugs (drugs used were in accordance with the instructions, at appropriate time and within appropriate period time of therapy based on the recommendation). The inappropriate self-medication of dysmenorrhea can be caused by a lack of appropriate information and the information given is not from a competent source has knowledge about self-medication of dysmenorrhea. This is in accordance with the research by Harahap et al. (2017) who state that self-medication drugs sold in food stalls are 55.8%, in drug stores are 8.5%, in supermarkets are 4.4% and other are 1.5% such as from neighbors or respondent's family.

The research result shows that the place where people get drugs for self-medication is more than 50% from food stalls, drug stores, supermarkets and so on. It indicates that the respondents do not receive drugs from the place that can ensure the availability of appropriate drugs information. Therefore, this can influence inappropriate self-medication.

Based on Table II, the result conducted on 34 female students of Frateran Catholic High School Malang, there are 34 students (100%) who had appropriate dysmenorrhea treatment using OTC drugs (drugs used were in accordance with the instructions, at appropriate time and within appropriate period time of therapy based on the recommendation). Meanwhile, there is no respondent who had inappropriate dysmenorrhea treatment using OTC drugs (drugs used were not in accordance with the instructions, at inappropriate time and within inappropriate period time of therapy based on the recommendation). The appropriateness of respondents in dysmenorrhea using OTC drugs can be obtained after conducting self-medication education or health education through leaflet by using method of lecture, question and answer and discussion by competent health personnel such as a pharmacist and a nurse, so that the appropriate information required by the respondents can be obtained as well as the level of trust of the respondents in the information provided by the expert. This research result is in accordance with the research result by Utari (2015), who suggests significant changes after providing health education using method of lecture and discussion with leaflet media that can be brought and stored by the respondents about handling heal problems.

The test result using paired T-test (paired sample T-test) to find out the difference in the average of dysmenorrhea treatment using OTC drugs before and after self-medication education, can be presented in Table III.

The result of score comparison of dysmenorrhea treatment using OTC drugs before (pre) and after (post) conducting self-medication education shows significant value of 0.000 which is smaller than alpha 0.05, so Ho is rejected. The difference is indicated by the score of dysmenorrhea treatment using OTC drugs after (post) conducting self-medication education shows an increase compared to the score of dysmenorrhea treatment using OTC drugs before (pre) conducting self-medication education. This indicates that providing health education can change the way of dysmenorrhea treatment by the students of Frateran Catholic High School Malang using OTC drugs. In addition, this is also in accordance with Ningsih's statement (2011), in which the low education in terms of health information is directly proportional to the inappropriate behavior in dysmenorrhea treatment. This is also similar to Sitorus and Yuli's research (2015) that states a relationship between education and behavior in dysmenorrhea treatment. The

result is also in line with Utari's research (2015) which states the different behavior in students' pretest and posttest regarding dysmenorrhea treatment. In the intervention group, the p-value is 0.000 ($p<0.05$) and the control group is 0.028 ($p<0.05$) which means that health education influences healthy behavior in dealing with their own health problem in Pleret Public Junior High School 1.

Providing self-medication education can change the mindset and the way to treat dysmenorrhea up to 100%. This can be changed when the educator emphasizes the benefits of having appropriate behavior to handle dysmenorrhea with self-medication using OTC drugs. In addition, the educators may describe the fatal risk of side effects when dysmenorrhea is treated with inappropriate drugs, term of use and types. Besides, the educational materials are emphasized in how to select and take appropriate safe and rational drugs for dysmenorrhea treatment experienced by the female students. This is in line with the Kementerian Kesehatan Republik Indonesia (2016) in the health promotion material stating that behavioral intervention effort can be in a form of pressures and sanctions or exposure of a risk if the health education material is not implemented as well as persuasive and aware education so that the changes in behavior can occur. The way to deliver health material using power point and leaflet media and suing the method of lecture, question and answer, and discussion on dysmenorrhea treatment using OTC drugs triggers the students' enthusiasm. The new topic is presented by competent expert which is about dysmenorrhea that is often experienced by the female students. Students provided good response. The students' change of mindset and behavior in self-medication education of dysmenorrhea treatment using appropriate, safe and rational OTC drugs is influenced by the expert who is a new person in the school environment and the interesting topics to motivate students. This is in line with the health promotion material by the Kementerian Kesehatan Republik Indonesia (2016) which states that health education in health promotion can change "voluntary" behavior due to awareness and trust.

Providing education using leaflet media proved to be effective in increasing the respondents' knowledge and skills. It is stated by Notoadmojo (2010) that leaflet is a media or props that can be stored for a long time, used as a reference, used for information the target in remote location, used as a complement o other media and the content of the leaflet can be reprinted for discussion. Purnama (2016) also states that health promotion media has an important role in conveying material ideas or ideas in health promotion.

CONCLUSION

Based on the research that has been conducted with 34 respondents of the students of Frateran Catholic High School Malang, it can be concluded that the Dysmenorrhea treatment using OTC drugs by students of Frateran Catholic High School Malang (n=34) before conducting self-medication education is categorized as inappropriate, with 29 respondents (85.3%). Dysmenorrhea treatment using OTC drugs by students of Frateran Catholic High School Malang (n=34) after conducting self-medication education is categorized as appropriate, with 34 respondents (100%). Self-medication education in dysmenorrhea treatment using OTC drugs to the students of Frateran Catholic High School Malang.

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