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Antioxidant Activity Test And Permeability Test of Antioxidant Cream Preparation of 96% Ethanol Extract of Kaffir Lime Fruit Peel (*Citrus hystrix*) With The Addition of Enhancer

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ABSTRACT

This study aimed to determine the antioxidant activity, levels contained in kaffir lime peel extract, and penetration test on the antioxidant cream preparation of kaffir lime peel extract. This research method is experimental with descriptive analysis and SPSS. This extract was obtained by maceration using 96% ethanol and then standardizing the specific and non-specific extracts. The dosage form made is a cream with an extract concentration of 15% and modified enhancer variations F0 (without enhancer), F1 (10% propylene glycol), F2 (10% oleic acid), and F3 (5% propylene glycol and 5% oleate). The cream preparation was tested for physical evaluation of the preparation, % inhibition antioxidant activity using the DPPH technique and permeability test activity using Franz diffusion. The results showed that there were hesperidin levels of 25.34 mg/g, naringin 1.94 mg/g. Physical evaluation tests show that the cream fulfill all appropriate physical requirements, including homogeneity and organoleptic, pH, viscosity, spread ability, stickiness, cream type. The antioxidant activity of vitamins based on the inhibition percentage value is greater when compared to antioxidant cream, namely 41.604. The SPSS test uses One Way Anova, and the permeability test results of the largest cumulative amount and flux value were found in F2 with values respectively 341.983 µg/cm2, 0.928 µg/cm^2/minute. It can be concluded that the cream preparation made has antioxidant activity and permeability with the addition of 10% oleic acid enhancer which can influence penetration into the skin.

INTRODUCTION

The skin is the outermost organ, so any changes to the skin will be clearly visible, one of which is the aging process. Skin aging can be influeces by extrinsic and intrinsic influences including exposure to free radicals (Yusharyahya, 2021). However, as we age, the accumulation of ROS (*Reactive Oxygen Species*) increases, additional antioxidant from outside are needed, namely one of the potential sources of natural antioxidants, namely kaffir lime fruit peel (*Citrus hystrix*) (Silalahi, 2022). Kaffir lime peel extract (KLPE) is recognized as a food source by the community. Unfortunately, kaffir lime fruit peel is often ignored and only considered waste that is not maximally utilized, due to the lack of information about the benefits contained in kaffir lime peel. However, some studies mention kaffir lime fruit peel has potential as an antibacterial, antiviral, and antioxidant (Warsito et al., 2018). Natural phenolic chemicals known as flavonoids have biological activities that can be used for medicine and as antioxidants. However, based on the antioxidant strength test, it is known that kaffir

lime peel extract contains active components included in the flavonoid group, namely hesperidin and naringin (Jessica et al., 2022). The research conducted is in line with (Latifah et al., 2023) IC_{50} stated that the ethanol extract of kaffir lime peel tested with DPPH technique possesses a moderate level of antioxidant activity and an IC_{50} of 146.06 µg/ml.

This research was conducted to increase the effectiveness of using KLPE in the form of a cream as an antioxidant and permeability. Creams have the advantage of being easy to use, non-sticky, easy to wash with water, the obstacle faced in this study is that the active substance in the cream preparation formulation has difficulty in penetrating into the skin layer due to the presence of skin defense mechanisms. Therefore, the cream preparation formulation was modified by adding enhancers. Enhancer is a compound that has the ability to increase drug penetration so that it can penetrate the stratum corneum of the skin (Kurniawan et al., 2018). The existence of antioxidant activity in KLPE, then the development of pharmaceutical preparation is carried out by unutilizing kaffir lime peel to add value as an active ingredient in antioxidant cream preparations and conducting permeability or drug penetration tests so that the cream can penetrate into the stratum corneum skin.

MATERIALS AND METHODS

Tools

Analytical balance (Mettler toledo®, Indonesia), stirring rod, micropipette (Dragon lab®), glassware (Pyrex®), water bath (Grant®), pH meter (OTC®), viscometer (Lamy rheology®), diffusion cell apparatus (Orchid scientific®, India), HPLC (Shimadzu® LC 20. AD), UV-Vis spectrophotometry (Shimadzu® UV-1900i).

Material

Kaffir lime peel as active ingredient was obtained from Cipadang village RT. 11/RW.04. Benteng village, Cempaka sub-district, Purwakarta district, West Java. Stearic acid (Sumi asih®, Indonesia), liquid paraffin (Fagron®, Greece), glycerol (P&G®, Singapore), cetyl alcohol, tween 80 (Avantor®, Malaysia), Nipagin, nipasol (Alpha chemika®, india), aquadestilata (Smart lab®, india), KH2PO4, menthanol, NaOH span 80, TEA from Merck®, germany. DPPH, vitamin c, hesperidin, naringin from Sigma aldrich®, Amerika.

Characteristics of Experimental Animals

Experimental animals used was a male white rat strain Sprague Dawley aged 2-3 months, weighing 150-200 grams obtained by animal facility and modeling provider (IRatco). Number of animals try using 5 of them.

Methods

Preparation and Standardization of KLPE

Do wet sorting, then peel the kaffir lime fruit peel take the outer skin, then dry it with an oven at 50°C, do dry sorting then blend and sift using mesh No.40. weigh the powder obtained and record it. Test spesific parameters such as moisture content, ash content and drying shrinkage (Jessica et al., 2022).

Preparation of KLPE

Soak 1000 grams of kaffir lime fruit peel simplicia with 10 liters of 96% ethanol solvent for about three days (stirring every day), then filtered then obtained maceration 1 and pulp, the pulp is soaked again in the remaceration process for 2 days with 5 liters of solvent obtained macerate 2, combine macerate 1 and 2 concentrate using a rotary evaporator until a thick extract is obtained. Test spesific parameters in the form of organoleptic and non-spesific parameters in the form of water content, ash content, residual solvent. Remaceration is done to get more active chemicals and to improve the extraction process because some compounds remain that haven't been extracted yet (Saputra et al., 2023).

Determination of Efficacious Compound Profile And Determination of Naringin and Hesperidin Content In KLPE

Determination of the profile of active compounds naringin and hesperidin using HPLC. The analysis process used mobile phases: Isocratic methanol: mixture (Ammonium acetate 25 mm: Citric acid 75 mM), 40:60 and stationary phase: 18 zorbax exclipse column (4.6 x 150

mm). The sample was sonicated as much as 0.1 gram with methanol for 1 hour that point poured into a 10 mL. Solution was filtered using 0.45 micrometer filter paper and after that,20 µL was injected onto HPLC. Standard concentration of 10 µg/mL in methanol was used (Buyuktuncel, 2017).

Antioxidant Cream Formula Of KLPE

The formula in this study refers to (Khumaidi, 2015). by using 15% extract and modifying the addition of enhancers (Kurniawan et al., 2018). Modification in F0 (without the addition of enhancer), F1(10% propylene glycol enhancer), F2(10% oleic acid), F3(5% propylene glycol and 5% oleic acid) (**Table 1)**.

Table 1. Formulation of Modified Kaffir Lime Peel Extract Antioxidant Cream

Ingredients	Formula (%)			
	F0	F1	F2	F3
Kaffir Lime Peel Thickened Extract	15	15	15	15
Stearic Acid	5	5	5	5
Liquid Paraffin	5	5	5	5
Glycerin	15	15	15	15
Cetyl Alcohol	5	5	5	5
Tween 80	5	5	5	5
Span 80	5	5	5	5
TEA	2	2	2	2
Methyl Paraben	0.18	0.18	0.18	0.18
Propyl Paraben	0.02	0.02	0.02	0.02
Propilen Glycol	-	10	-	5
Oleic Acid	-	-	10	5
Aquadest	Add 100			

Physical Evaluation Of Cream Preparations

Physical tests of cream preparations include organoleptic, homogeneity, pH, viscosity using a lamy rheology viscometer spindle L4, spreadability test and stickiness test (Saryanti et al., 2019).

Antioxidant Activity Using DPPH Method

Preparation of 0.05 mM DPPH Solution

1.97 mg of DPPH was put into a 100 ml volumetric flask, add methanol until the limit mark, so as to obtain a concentration of 0.05 mM DPPH solution. Then 4 mL was taken and measured with a visible spectrophotometer at a wavelength of 400 - 800 nm. Then the operating time is determined at the maximum wavelength of the measurement results. (Mulangsari et al., 2017).

Measurement of Antioxidant Activity of Cream Preparations

The comparison sample used was vitamin c. The antioxidant cream preparations tested consisted of 3 formulas with extract ratios of 5%, 10%, 15%, made by dissolving 10 mg of the preparation in 10 mL of methanol p.a. Then a concentration series of 10, 20, 30, 40, 50 µg/mL was made into a 10 mL volumetric flask. Then 2 mL of sample solution was taken, 2 mL of 0.05 mM DPPH solution was taken into a test tube, then incubated in a dark room for 25 minutes and the absorbance was measured using a UV-Vis Spectrophotometer (Mulangsari et al., 2017).

Determination of % inhibition and IC50

$$\% \text{ Inhibition} = \frac{\text{Absorbance (control} - \text{sample)}}{\text{Control absorbance}}$$

Permeability Test

This penetration test research has received a certificate of passing ethical review (ethical approval) with number 022310124 Ahmad Dahlan University, Yogyakarta, rat were anesthetized using sevoflurane drug then shaved, then dissected on the abdomen and subcutaneous fat was taken. Place the rat skin in the donor compartment then 1 gram of cream preparation is placed in the donor compartment. The receptor compartment was filed using PBS liquid pH 7.4. Set the temperature at 37± 0.5 °C with a magnetic stirrer stirring speed of 500 rpm. Testing was carried out for six hours with sampling at intervals of 10, 30, 60, 90, 120, 180, 240, 300 and 360 minutes. Sampling liquid as much as 1 ml, then refill PBS solution pH 7.4 a number of size that have been taken. The sample liquid was then measured for absorbance using the maximum wavelength of the antioxidant cream by UV-Vis spectrophotometry. The sampe procedure was repeated 3 time for all formulas. Drug penetration rate per unit time as flux. The wavelength was obtained using the marker compound hesperidin with PBS solution pH 7.4. Used the marker compound hesperidin because the results had the highest levels compared to naringin (Sapra et al., 2021)

RESULT AND DISCUSSION

Preparation and Standardization of Kaffir Lime Fruit Peel (*Citrus hystrix*) Simplicia

Kaffir lime is taken from the skin of the fruit from the outer skin to the skin around the fruit. The manufacturing process is washig, wet sorting, chopping, drying, dry sorting, pulverizing and packing. The results of the quality parameters of kaffir lime peel simplicia can be seen in **Table 2.**

Preparation of KLPE

Carried out Using the technique of maceration, the simplisia powder was soaked in 96% ethanol for three days and then remacerated for two days. From 1000 grams of simplisisa powder, a thick extract of 204.993 gram. The results of the quality parameters of kaffir lime peel extract can be seen in **Table 3**.

Determination of Efficacious Compound Profile and Determination of Naringin and Hesperidin Content in Thick Extract of KLPE

The following is an image of the standard chromatogram of naringin and hesperidin which can be seen in **figure 1A** and **figure 1B**. It can be seen in figure 1 that the retention time/Rt of standard naringin obtained is 5.806 and the area obtained is 173392. Meanwhile the retention time of hesperdin can be seen in **figure 1B**. Retention time obtained was 6.436 and the standard area obtained was 175541. In **Figure 1C** Peak chromatograms of naringin and hesperidin in KLPE (*Citrus hystrix* DC) showed a naringin retention time of 4.71 minutes and a hesperidin retention time of 5.31 minutes. This shows that the retention time results obtained are not much different. The chromatogram peaks of naringin and hesperidin appeared at retention times/Rt 5.803 and 6.317 minutes. Naringin and hesperidin in KLPE extract were seen from the retention time obtained which was close to the standard. However, based on research (Pereira et al., 2017). The retention time for naringin appeared at 4.71 minutes and for hesperidin the retention time appeared at 5.31 minutes. The retention time results obtained were not much different due to differences in column type, mobile phase composition, pH. Then the results of naringin and hesperidin levels can be seen in **Table 4**. The naringin levels obtained were 1.93 mg/g and the hesperidin levels obtained were 25.34 mg/g. It can be concluded that the hesperidin levels in KLPE are greater than the naringin levels obtained.

Based on the organoleptic of all cream formulas during 4 weeks of storage, the shape, color and odor were relatively consistent, there was no change in the cream preparation.

Table 5 displays the pH test results. That F1 with the addition of 10% propylene glycol enhancer, the pH value is increasing. This is consistent with studies (Putri et al., 2019). The more concentration of propylne glycol used, the pH value obtained is still in accordance with the skin pH range based on SNI 16-4399-1996 between 4.5-8. So that the antioxidant cream made is anticipated not to cause irritation to the skin.

The highest viscosity value was obtained in F0 without enhancer, followed by F1, F3, F2. It can be cocluded that F2 has the smaless viscosity value so that it can cause the speed of diffusion of the preparation towards the skin surface and can accelerate the drug to penetrate the stratum corneum skin. The results obtained have met the requirements for viscosity in semi solid preparations, namely 4000-40.000 cPs (Tasman et al., 2023).

Based on **Table 5**, the results of the spreadability test on the F2 cream preparation had the widest spread area followed by F3, F1,F0. This can happen because the wider the distribution area, the wider the membrane available to facilitate the diffusion of the drug into the skin. As a result, the amount of substances that can penetrate the skin becomes more optimal. The optimal requirement for testing the spreadability of a cream preparation is 5-7 cm. Based on research findings, it shows that the spreadability of antioxidant cream still meets the requirements (Forestryana et al., 2020).

The adhesion test findings on F0 without the use of enhancing agents had the longest

adhesion time, followed by F1 with the addition of 10% propylene glycol enhancing agent, F3 with 5% propylene glycol enhancing agent and 5% oleic acid and F2 with the addition of 10% propylene glycol enhancing acid). In line with research (Safitri & Yuwono, 2014). Because the characteristics of the cream expanded beside the increase in concentration in the addition of enhancers. The signaling of all formulations has met the requirements of the perfect adhesion standard, which is not less than 4 seconds. The results of the characteristics of the antioxidant cream preparation formula of 96% ethanol KLPE and the physical evaluation of the antioxidant cream preparation can be seen in **Table 5**.

Table 2. The results of quality parameters of kaffir lime fruit peel (*Citrus hystrix*) simplicia (n=3)

Simplicia quality parameters	Characteristics	Results± SD	Terms	
			Terms	Reference
Spesific	Organoleptic			
	Shape	Powder		
	Color	Yellow	-	-
	Smell	Typical orange peel		
	Taste	Bitter		
Non-spesific	Water Content	6.023 ± 3.357%	<10%	(Depkes RI, 1997)
	Ash Content	5.42 ± 0.389%	<7%	(Depkes RI, 2017)
	Drying Shrinkage	6.6 ± 0.29%	<10%	(Depkes RI, 2017)

Description: The data on water content, ash content, and drying loss listed are avergae values ±SD

Table 3. The results quality parameters of KLPE (n=3)

Extract quality parameters	Characteristics	Results ± SD	Terms	
			Terms	Reference
Spesific	Organoleptic			
	Shape	Condensed extract	-	-
	Color	Chocolate		
	Smell	Typical kaffir lime		
Non spesific	Water content	9.981 ± 1.179%	<10%	(Depkes RI, 2008)
	Ash content	6.41 ± 0.075%	<6,6%	(Depkes RI, 2017)
	Drying shrinkage	0.06%	<1%	(Depkes RI, 2000)

Note: The water content and ash content data listed are average values ± SD

Table 4. levels of naringin and hesperidin compounds in KLPE

Compound	Sample weight (g)	Dissolved in a volumetric flask (mL)	Diluting factor	Standard area	Standard (µg/mL)	Area sample	Inject (µg/mL)	Level in sample (mg/g)
Naringin	0.1009	10	20	173392	10	16968	0.9786	1.9397
Hesperidin	0.1009	10	20	175541	10	224444	12.7858	25.3436

Table 5. Results of physical evaluation of antioxidant cream preparations

Physical Evaluation	Week 1	Week 2	Week 3	Week 4	Mean± SD
pH test					
F0	5.80	5.76	5.60	5.54	5.675 ± 0.124
F1	6.64	6.54	6.47	6.39	6.51 ± 0.106
F2	6.54	6.47	6.43	6.36	6.45 ± 0.075
F3	6.52	6.49	6.45	6.38	6.46 ± 0.060
Viscosity (cPs)					
F0	6961	6873	6805	6702	6835.25± 109.405
F1	6574	6529	6458	6254	6453.75 ± 141.469
F2	6510	6276	6180	6089	6263.75 ± 181.053
F3	6529	6514	6507	6136	6421.5 ± 190.554
Spreadability (cm)					
F0	5.20	5.23	5.25	5.28	5.24 ± 0.033
F1	5.31	5.34	5.58	5.60	5.457 ± 0.153
F2	5.59	6.10	6.12	6.29	6.025 ± 0.302
F3	5.34	5.48	5.42	5.74	5.495 ± 0.173
Stickiness					
F0	09.60	09.32	09.24	08.24	9.1 ± 0.593
F1	08.22	08.14	07.36	08.04	7.94 ± 0.393
F2	06.47	06.33	06.25	06.22	6.317 ± 0.111
F3	08.14	07.85	07.49	07.16	7.66 ± 0.426

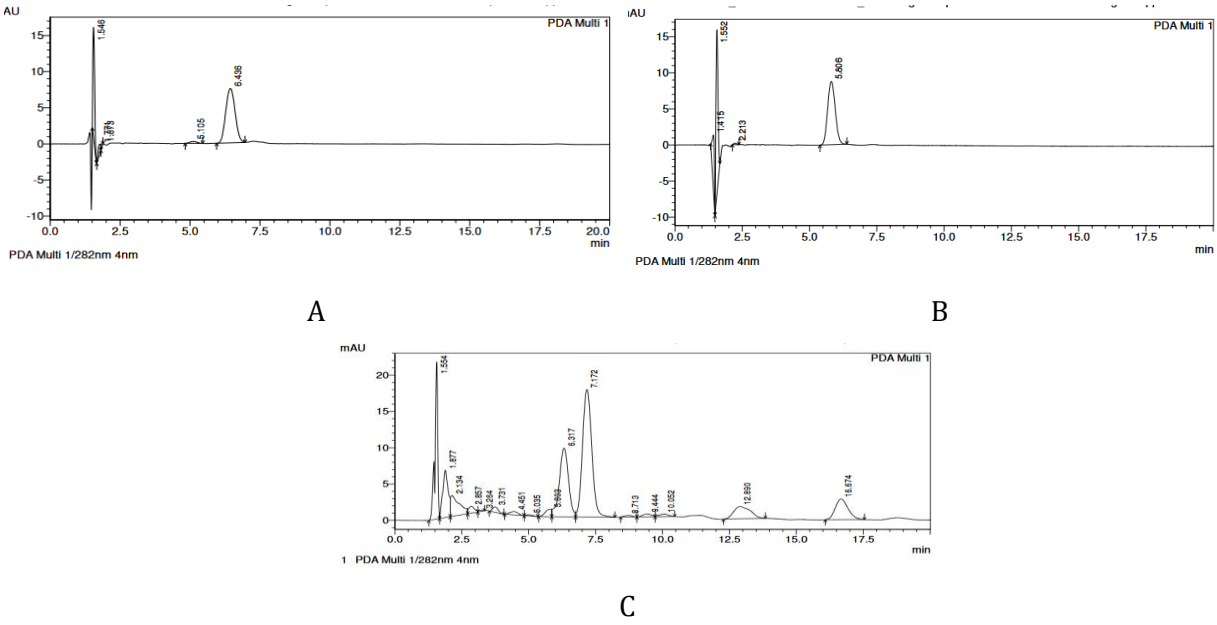


Figure 1. Profile Chromatogram of (A) standard naringin 10 (µg/mL), (B) standard hesperidin 10 (µg/mL), (C) naringin and hesperidin in KLPE

Antioxidant Activity Test

The method used is DPPH (1,1-diphenyl-2-picrylhydrazyl). The advantages of this method are simple, easy, fast, and do not require many samples. The advantages of this method are that it is simple, easy, fast and does not require a lot of samples. Percent inhibition (% antioxidant activity) is one parameter that shows the ability of an antioxidant to inhibit free radicals. Percent inhibition increases as the sample concentration

increases because there are more compounds in the sample that inhibit DPPH free radicals. Based on **Table 6**, the antioxidant activity of vitamins based on the inhibition percentage value is greater when compared to antioxidant cream, namely 41.604. The results of measuring the % inhibition value of vitamin C preparations and cream can be seen in **Table 6.**

Table 6. Measurement results of % Inhibition values of vitamin c and cream preparations

Sample	Concentration (µg/mL)	% Inhibition	Mean ± SD
Vitamin C	10	41.604	41.604 ± 0.00
Antioxidant cream 15% extract	10	34.038	34.038 ± 0.00

Note: The % Inhibition data listed is the mean value ± SD

Permeability Test

The purpose of the permeability test is to determine the amount of antioxidant cream that penetrates the membrane at each time period. The receptor liquid was then analyzed using UV-Vis spectrophotometry 285.80 nm is the wavelength at which the concentration of hesperidin in the receptor liquid was calculated using the equation Y = 0.02681x + 0.01191, the R value obtained was 0.9999. And obtained the sum of the cumulative value and the total flux value. It can be seen in **Figure 2** penetration testing for 360 minutes with time intervals of 0, 10, 30, 60, 90, 120, 180, 240, 300, 360 minutes. That the highest cumulative amount of antioxidant cream was obtained in F2 (10% oleic acid) at 341.983 ± 1.511 µg/cm2, followed by F1 (10% propylene glycol) at 261.815 ± 0.986 µg/cm2, F3 (5% propylene glycol and 5% oleic acid) at 256.205 ± 0.823 µg/cm2, and the lowest cumulative value was obtained in F0 (without the addition of enhancer) at 168.852 ± 0.320 µg/cm2. This is consistent with studies (Kurniawan et al., 2018) that preparations containing oleic acid enhancers with a concentration of 10% have the largest cumulative amount. In this study, all formulas with a replication process of 3x minutes 0 to minutes 360 are assumed to have permeability or penetration in this study has not yet reached a stable state (Safitri & Yuwono, 2014). That the steady state is characterized by a time lag, after a certain time the flux value obtained is relatively constant. Based on the research results that there is no lag time, the method used to evaluate uses the flux value.

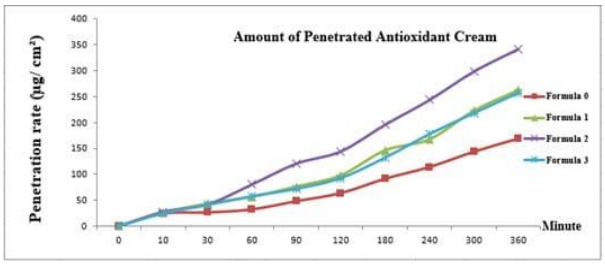
Flux is the rate of penetration of active ingredients into the membrane in a given time interval. The higher the flux value, the speed at which a medication enters the skin. Table 6 shows that F0 (without enhancer) has the lowest total flux value. F2 (10% oleic acid) has the highest flux value followed by F1 (10% propylene glycol) and F3 (5% propylene glycol and 5% oleic acid). The results of statistical analysis with SPSS there is a significant difference using the Mann-Whitneyy test shows that each formula has a significant difference with Sig. value <0.05. It has been proven that propylene glycol and oleic acid enhancers have the same effect as enhancers, which is to strengthen the product's ability to penetrate the stratum corneum.

However, for the comparison of propylene glycol and oleic acid enhancers in this study, the flux results were greater in F2, namely with the addition of a single 10% oleic acid enhancer. This research is in accordance with (Kurniawan et al., 2018). That preparations containing oleic acid enhancers with a concentration of 10% have the greatest amount of flux. The total penetration flux can be seen in **Table 7.** The graph of the cumulative amount of penetration cream preparations can be seen in **Figure 2.**

Table 7. Total penetration flux

Formula	Flux(µg /cm²/min)	Mean± SD
F0		
Replication 1	0.442	
Replication 2	0.445	0.443 ±
Replication 3	0.442	0.002
F1		
Replication 1	0.686	
Replication 2	0.686	0.686 ±
Replication 3	0.685	0.001
F2		
Replication 1	0.923	
Replication 2	0.932	0.928 ±
Replication 3	0.930	0.005
F3		
Replication 1	0.679	
Replication 2	0.680	0.679 ±
Replication 3	0.679	0.001

Figure 2. Graph of number of penetrated cream preparations



CONCLUSIONS

The antioxidant activity of vitamins based on the inhibition percentage value is greater when compared to antioxidant cream, namely 41.604. KLPE contains levels of the compound naringin 1.94 mg/g and hesperidin 25.34 mg/g. Antioxidant cream preparation of KLPE with the addition of 10% oleic acid enhancer has good penetration power so it easily penetrates the skin at the stratum corneum.

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AUTHORS' CONTRIBUTIONS

Meta Safitri, Mohammad Zaky contributed as research supervisors, Syifa Afiatun Nisa, Firdanu Nupus contributed to data collection, data analysis guidance and script writing, Nuriyatul Fathonah contributed to proofreading.

CONFLICT OF INTERESTS

The authors have no conflict of interests related to this publication

ETHICAL CONSIDERATION

Assessment In This Research Has Been Obtained Ethical Clearance From Research And Health Ethics Committee, Ahmad Dahlan University, Yogyakarta. Number:022310124.

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