Optimization formulation and efficacy examination of cream combination of fig extracts (*Ficus carica* L.) and pomegranate extracts (*Punica granatum* L.) as antioxidants

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Abstract. A cream formulation incorporating fig extract (*Ficus carica* L.) and pomegranate peel extract (*Punica granatum* L.) serves as an effective antioxidant. This study seeks to develop and assess the efficacy of antioxidants in a cream formulation that integrates fig extract and pomegranate peel extract, and to compare it with commercially available cream products. This study employed an experimental laboratory method. The cream preparation commences with the amalgamation of the cream base, followed by the incorporation of 0.5 grams of fig extract (F1), 1 gram of fig extract (F2), 0.5 grams of pomegranate peel extract (F3), 1 gram of pomegranate peel extract (F4), 0.25 grams of fig extract and 0.25 grams of pomegranate peel extract (F5), 0.5 grams of fig extract and 0.5 grams of pomegranate peel extract (F6), and a formulation devoid of any extract (F7). The evaluations conducted on the formulations included organoleptic assessments, homogeneity analysis, pH measurement, adhesion evaluation, spreadability assessment, viscosity testing, irritant testing, and antioxidant activity analysis utilizing the ABTS method. The test results indicated that all creams were brown, possessed a distinctive odor, exhibited homogeneity, and demonstrated stability. The mean pH test result was 6.73 ± 0.078. The mean adhesion test result was 1.27 seconds ± 0.189. The mean spreadability test result was 6.09 cm ± 0.14. The viscosity test indicated that the cream exhibited plastic and pseudoplastic flow characteristics. The irritation test indicated that the cream was non-irritating to the skin. The antioxidant activity test findings for the cream indicated great efficacy for F1, F2, F5, and F6, while F3 and F4, along with comparisons to commercial cream products, demonstrated moderate efficacy. This study concludes that F6 is the formula exhibiting optimal stability and demonstrating robust antioxidant activity in its category.

1 Introduction

The skin is an important organ that protects against external environmental conditions. However, excessive exposure to sunlight can affect the skin, including hyperpigmentation. Hyperpigmentation is a skin problem that causes the skin colour to darken [1]. This problem is contrary to the current societal perspective on skin. The perspective of a bright face seems to be a benchmark for beauty and is beneficial, so a way is needed to improve hyperpigmentation on the skin [2]. This method is done by using cosmetic products such as skin lightening cream [3]. Cream is a semi-solid preparation used for external use. It is applied to the skin with a content of not less than 60% water. There are two types of cream: oil and oil in water [4]. Natural ingredients that have antioxidant effects are figs (*Ficus carica* L.) and pomegranate skin (*Punica granatum* L.). Parts of the fig plant that have the potential to have antioxidant activity are the leaves, fruit flesh, and fruit skin, with compounds such as alkaloids, flavonoids, phenolics, terpenoids, steroids, and saponins [5]. Pomegranate skin (*Punica granatum* L.) is a part of the pomegranate plant that is rich in flavonoid compounds, phenolic acids, tannins, anthocyanidins, ellagic acid, quercetin, gallic acid, catechins, and vitamin C which are effective as antioxidants [6]. Antioxidants play a role in inhibiting and preventing damage to the skin, such as the appearance of brown pigment spots on the skin [7]. Previous research has been conducted on the formulation of anti-hyperpigmentation cream, but in that study only used pomegranate skin. Based on the research results, the formulation of anti-hyperpigmentation cream from pomegranate peel extract is good, effective, and safe. Cream with 1% pomegranate peel extract concentration is unstable. Anti-hyperpigmentation cream with 0.5% and 1% pomegranate peel extract has IC50 values of 363 ppm and 290 ppm, respectively, classified as having activity against tyrosinase [8]. Previous research has been carried out on the formulation of cream preparations using fig leaf extract with the DPPH method, which showed that the cream has strong antioxidants with an IC50 value of 23.23 ppm [9]. Previous research has also conducted a cream formulation containing fig extract using the DPPH method, but the preparation did not use a combination of extracts. The formulation dramatically reduced skin pigmentation, trans-epidermal water loss, and skin sebum levels. The formulation greatly enhanced skin hydration while having little effects on

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skin erythema. A stable topical cream (water/oil emulsion) containing *Ficus carica* fruit extract influences skin melanin levels, trans-epidermal water loss, hydration metrics, and sebum production, and may potentially be utilized for hyperpigmentation, acne, freckles, and wrinkles [10]. Based on this, the innovation in this study is to design a cream formulation of a combination of fig fruit extract and pomegranate peel extract as an antioxidant. Another innovation in the study that will be carried out is using the ABTS method. This method was chosen because the reaction time of ABTS with antioxidants is faster than the DPPH method.

2 Methods

2.1 Materials

The tools used in this study were analytical balance (Mettler Tolledo®), oven (Memmert®), pH meter (Mettler Toledo®), glassware (Iwaki Pyrex®), ultraturrax (IKA), centrifuge (Hettich®), viscometer (Brookfield ametek®), LC-MS, UV-Vis spectrophotometer,
The materials used in this study were fresh figs, pomegranate peel, 96% ethanol, cetyl alcohol, stearic acid, liquid paraffin, propylene glycol, isopropyl myristate, triethanolamine, methyl paraben, propyl paraben, glycerin, distilled water, ABTS (sigma®), potassium persulfate (sigma®), quercetin (sigma®), ethanol pa (sigma®), market cream. The materials used were cosmetic grade and pro analysis grade materials.

2.2 Extraction

Figs were cleaned, then sliced, and dried using an oven. Pomegranates were cleaned, peeled, skin dried, and sliced. After that, each sample was crushed using a blender and then weighed. Figs and pomegranate skin were extracted using the maceration method or soaked with 96% ethanol 1:10 for three days, then maceration with 96% ethanol 1:5 and stirred daily. After that, filtering was carried out. All macerates were evaporated with a rotary evaporator until a thick extract was obtained [11].

2.3 Liquid Chromatography-Mass Spectrometry (LC-MS) assessment

The mobile phase used in LC-MS phytochemical screening is 0.1% formic acid in water and 0.1% in acetonitrile (CH3CN). The sample used in solid form is taken sufficiently and dissolved using ethanol, then vortexed. Filtered using 0.22 µm miles, then injected into five µL LC-MS, which will then be detected by the detector and produce a chromatogram [12].

2.4 Antioxidant cream formulation

Table 1 shows the formulation of fig cream and pomegranate peel.

Table 1. Formulation of Cream Preparation Combination of Fig Fruit Extract and Pomegranate Peel Extract.

Materials	Weight						
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
Fig fruit	0.5	1	-	-	0.25	0.5	-
Pomegranate Peel	-	-	0.5	1	0.25	0.5	-
Stearic acid	1	1	1	1	1	1	1
Cetyl alcohol	1	1	1	1	1	1	1
Triethanolamine	1	1	1	1	1	1	1
Propylene Glycol	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Liquid paraffin	1	1	1	1	1	1	1
Isopropyl myristate	1	1	1	1	1	1	1
Glycerin	1	1	1	1	1	1	1
Methyl paraben	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Propyl paraben	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Aquadest	19.5	19	19.5	19	19.5	19	20

2.5 Organoleptic test

Organoleptic test by visually observing the odour, colour preparation, and texture. Testing is done with three replications. The preparation is said to be stable if, after storage, there is no change in shape, odour and colour [13].

2.6 Homogeneity test

As much as 1 gram of cream is applied to transparent glass. After that, the preparation is observed to be homogeneous, and no coarse grains are visible. The test is carried out with three replications. The preparation is considered homogeneous if there are no particles or coarse grains [13].

2.7 pH test

As much as 1 gram of cream preparation was diluted with 10 ml of distilled water. The test was carried out with three replications. The pH test standard ranges between pH 4.5-8.0 [14]

2.8 Viscosity test

The viscosity of the preparation was assessed using a Brookfield viscometer, with the cream placed in a glass beaker. The spindle was thereafter immersed in the viscometer at a designated speed of 10 rpm. The viscosity of the preparation was seen on the scale in the tool after stability was achieved. The viscosity test standard ranges between 2000-50.000 cps [14].

2.9 Adhesion test

Weigh 0.25 grams of cream to the centre of the glass, and then a load weighing 1 kilogram is given for 5 minutes. The load is lifted, and then the two attached glass plates are released; the time until the two plates are released is recorded. The standard for the adhesive power of the cream is more than 1 second. The test is carried out with three replications [15].

2.10 Spreadability test

Weigh 0.5 grams of cream, then place it in the middle of the petri dish in an inverted position, leaving it with a load of 50 grams, 100 grams, and 200 grams every 1 minute. The standard cream spreadability is 5 cm - 7 cm. Testing is carried out with three replications [16].

2.11 Physical stability test

The stability test uses a centrifuge, which puts enough cream preparation into the test tube. Then, it is put into the centrifuge at a speed of 2000 rpm for 5 minutes. Observed to see the physical changes that occur in the preparation, which is marked by phase separation [17].

2.12 Antioxidant Test ABTS Method

The initial step of the ABTS technique involves the preparation of the ABTS stock solution. 7.5 mg of ABTS is dissolved in 5 ml of distilled water. Subsequently, 3.5 milligrams of potassium persulfate is measured and diluted in 5 ml of distilled water. The two solutions are combined, and ethanol p.a. is added to a total volume of 25 ml, followed by incubation for 12 to 16 hours. The absorbance of the ABTS blank solution is determined by pipetting 1 ml of ABTS solution into a 5 ml volumetric flask and adding ethanol p.a. to the calibration mark. The solution was thereafter incubated for 15 minutes, after which its absorbance was measured at a certain wavelength. The sample was measured by preparing a solution with a concentration of 1000 ppm and pipetting 50 µl, 100 µl, 200 µl, 400 µl, and 800 µl to achieve concentrations of 10 ppm, 20 ppm, 40 ppm, 80 ppm, and 160 ppm, respectively. Subsequently, the ABTS solution was introduced to the border mark. Subsequently, it was homogenized, and the absorbance was quantified utilizing UV-Vis spectrophotometry. The amount of antioxidant activity (AA) was calculated using the formula [18].

$$AA=\frac{absorbance\ of\ blank\ solution-\text{sample absorbance}}{absorbance\ of\ blank\ solution}\text{x}100\% \quad (1)$$

2.13 Irritation test

This irritation test refers to the 2014 BPOM RI Nonclinical In Vivo Toxicity Test Guidelines, which state that irritation tests are conducted on test animals, namely rabbits. This test aims to determine whether the formulated cream preparation causes irritation or not when applied to the skin. The rabbits used were two male albino New Zealand white rabbits aged approximately three months. The test animals were acclimatized before the irritation test for one week with food and drinking water ad libitum. After that, the test animal's fur was shaved. The rabbit's hair was shaved on its back carefully to avoid abrasions using a shaver and Veet® hair removal cream. The rabbit's skin was cleaned using cotton moistened with distilled water. The rabbit's back was divided into 6 square sections to apply the cream preparation. 0.5 grams of cream was applied, and the rabbit's back was covered with gauze and plaster for 24 hours. Observations were made after application for 24 hours, 48 hours, and 72 hours, followed by observations until the 14th day to see the reversibility of the rabbits. The test results for each treatment were analyzed and evaluated. The category of irritation response on rabbit skin was assessed using the primary irritation index. The primary irritation test was observed from oedema and erythema on rabbit skin. The calculation of the primary irritation index can be calculated using the formula [17]:

$$\frac{\text{£ erythema score}+\text{£ edema score}}{2} \quad (2)$$

Description:
Erythema score = sum of erythema scores (24 hours + 48 hours + 72 hours)
Edema score = sum of edema scores (24 hours + 48 hours + 72 hours)

Table 2. Assessment of skin reactions

Formation of Erythema	**Score**
No erythema	0
Very small (almost indistinguishable) erythema	1
Erythema is clearly visible	2
Moderate to severe erythema	3
Severe erythema (flesh red) to eschar formation that hinders assessment of erythema	4
Edema Formation	
No edema	0
Edema is very small (almost indistinguishable)	1
Small edema (area boundaries are clearly visible)	2
Moderate edema (area increases by about 1 mm)	3
Severe edema (area increases by more than 1 mm and extends beyond the area exposed to the test preparation)	4

Table 3. Irritation index assessment

Irritation Index	Score
Non-irritating	0.00
Slightly irritating	0.04-0.99
Mild irritation	1.00-2.99
Moderate irritation	3.00-5.99
Severe irritation	6.00-8.00

3 Results and discussion

3.1 Extraction

Fig powder as much as 313.6 grams, and pomegranate peel powder, as much as 305 grams, each soaked in 96% ethanol for five days with a ratio of 1:10 and macerated for two days with a ratio of 1:5. After that, it was filtered using filter paper and heated on a water bath using a pan at a temperature of 65 ° C. From the heating process, the weight of the fig extract was obtained as much as 64.8 grams, so the extract yield was obtained as much as 20.66%. The weight of the pomegranate peel extract was obtained as much as 126.3 grams, so the extract yield was obtained as much as 41.41%.

3.2 Liquid Chromatography-Mass Spectrometry (LC-MS) assessment

Phytochemical screening conducted in this study used the LC-MS method. The column or stationary phase used was a non-polar C-18 column; the mobile phase used was solution A, 0.1% aqua dest-formic acid, and solution B, 0.1% acetonitrile-formic acid. The results of identifying compounds in figs can be seen in Figure 1.

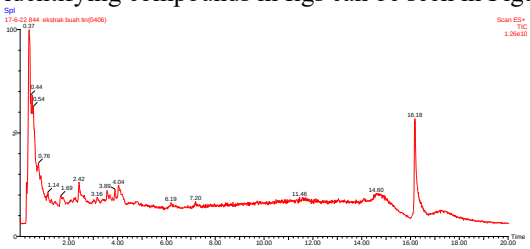

Figure 1. LC-MS Chromatography of Fig Fruit

The results of phytochemical screening of figs using LC-MS showed 11 sequential peaks. Several namely (9E,12E)-9,12-octadecadienoate which is linoleic acid, C16H32O2 which is palmitic acid, and docosenamide which has antioxidant activity. Linoleic acid and palmitic acid are fatty acids that have antioxidant activity. The docosenamide compound also has benefits as an antioxidant. In addition, a hexadecane compound is a non-organic compound that makes up surfactants. Surfactants are compounds that can be used to reduce the interfacial tension between oil and water so that they can be combined into a cream. From the results of the phytochemical screening, compounds were obtained in figs that have benefits as antioxidants. The presence of these compounds in the extract means that fig extract can be used as the active ingredient in this cream preparation due to its benefits as an antioxidant [19].

The next phytochemical screening is pomegranate peel. The results of identifying compounds in pomegranate peel can be seen in Figure 2.

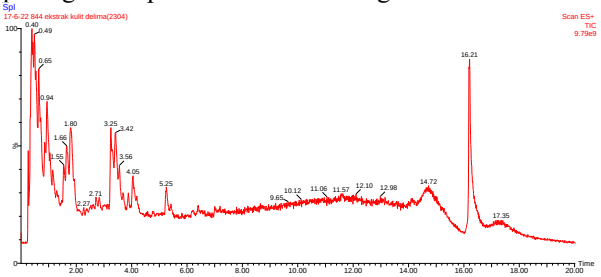

Figure 2. LC-MS Chromatography of Pomegranate Peel

The results of phytochemical screening of figs using LC-MS showed eight consecutive peaks, namely 1,5-diphenylcarbohydrazide, soyasapogenol a, 3,4',5-trimethoxystilbene, dihydrobenzoic acid pentose, methyl octadecanoate, and desaminotyrosine. Pomegranate peel contains xanthoangelol which is a flavonoid compound. In addition, there are compounds such as dihydrobenzoic acid pentose and desaminotyrosine, which are also flavonoid compounds. These compounds have potential antioxidant activity. The compound in pomegranate peel 3,4', 5-trimethoxystilbene is useful as an antioxidant. Pomegranate peel also contains the compound methyl octadecanoate, which is stearic acid. Stearic acid is a fatty acid that has antioxidant activity. From the results of the phytochemical screening, compounds were obtained in pomegranate peels with antioxidant activity. The presence of these compounds in the extract allows pomegranate peel extract to be used as an active substance in this cream preparation because of its benefits as an antioxidant [6].

3.3 Antioxidant cream formulation

The preparation is made in seven formulas. The difference in the cream formula lies in the weight of fig extract (BT) and pomegranate peel extract (KD). Formula 1 (0.5 grams of BT), formula 2 (1 gram of BT), formula 3 (0.5 grams of KD), formula 4 (1 gram of KD), formula 5 (combination of 0.25 grams of BT and 0.25 grams of KD), formula 6 (combination of 0.5 grams of BT and 0.5 grams of KD), formula 7 (0 grams of BT, 0 grams of KD) which is a placebo or negative control. The cream preparation is divided into 2 phases: the water and oil phases. The oil phase consists of stearic acid, cetyl alcohol, liquid paraffin, propylene glycol, isopropyl myristate, and propylparaben (Magdalena et al., 2016). Stearic acid functions as an emulsifier in cosmetic preparations, cetyl alcohol functions as a thickener that is safe for the skin because its content is taken from plants, liquid paraffin functions as a softener, propylene glycol functions as a moisturizer or humectant that can prevent and treat dry, rough, itchy, and irritated skin, isopropyl myristate functions as a skin penetration.

In contrast, propylparaben functions as an effective preservative for antifungals. At the same time, the water phase consists of triethanolamine, glycerin,

methylparaben, and distilled water. Triethanolamine is a thickener to produce homogeneous and stable preparations; glycerin is a moisturizer; methylparaben is an effective preservative for antimicrobials; and distilled water is a solvent in cream preparations.

3.4 Organoleptic test

Organoleptic is a test to see the quality of the cream preparation that will be related to comfort in use. Organoleptic tests are carried out by observing the physical form, texture, smell, and color of the cream directly. This test is a subjective test. The cream preparation can be seen in Figure 3 until 6.

Figure 3. F1 and F2 cream preparations

Figure 4. F3 and F4 cream preparations

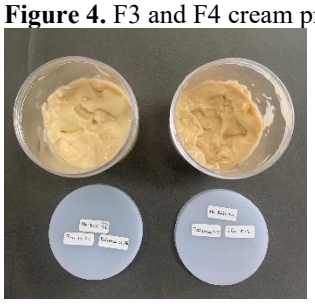

Figure 5. F5 and F6 cream preparations

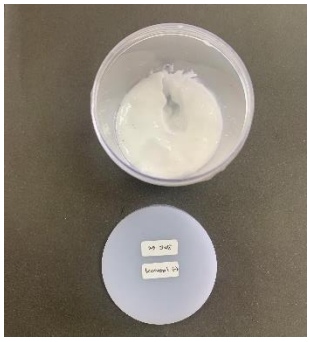

Figure 6. F7 cream preparations

The observation results showed that the cream preparation formulation that had been made starting from formula 1-7 was a semisolid preparation. The cream preparation formula 1-6 odor had a distinctive odor for each active substance or extract, namely figs and pomegranate peel. In contrast, formula seven did not have a distinctive odor because there was no addition of active substances in the formula. Furthermore, the color of Formula 3 was light yellowish brown. Formula 4 was dark yellowish brown, which was darker than Formula 3. Formulas 1 and 5 were yellowish brown, slightly darker than formula 3. Formulas 2 and 6 were light brown, darker than formulas 1 and 5. Each formula's color difference was the color concentration based on the amount of active extract added: the more active substances, the more concentrated the color of the preparation. The color of Formula 7 was milky white because there were no active extract substances in the formula. The brown color of the cream preparation was obtained from figs and pomegranate peel that had gone through the extraction process. The attractive appearance of the cream preparation affected the comfort of use.

3.5 Homogeneity test

The homogeneity test results conducted on the combination cream preparation of fig fruit extract and pomegranate peel extract show that no particles or coarse grains were present in any of the preparations. This shows that the cream preparation is homogeneous because there are no particles or coarse grains. The homogeneity of this cream preparation can be assumed that each application of the preparation to the skin releases the active substance in the same amount.

3.6 pH test

The pH test findings for the cream formulation indicate a range of 6.57 to 7.02. The cream formulation complies with the specified pH range of 4.5-8.0, indicating its safety for dermal application. The cream's pH value is close to the skin's physiological pH, making it suitable for topical application. An excessively alkaline pH can lead to scaly skin, whilst an overly acidic pH can influence skin irritation levels. The pH value of F7 or the placebo is elevated compared to other formulations due to the absence of active components from fig extract and pomegranate peel extract.

3.7 Viscosity test

A viscosity test is also conducted to determine the type of non-Newton flow, which can be seen from the relationship between Shearing Stress and Shearing Rate, which is then formed into a rheogram curve. The curve will show the flow properties of the preparation. The determination of flow properties is seen from the magnitude of the correlation coefficient (r). The preparation can be said to have pseudoplastic flow if the correlation coefficient value (r) of the relationship between log SS vs. log SR is greater than the correlation

coefficient value (r) of the relationship between SS vs. SR and the slope value (B) is more than 1. The preparation exhibits plastic flow if the correlation coefficient (r) of the relationship between log SS and log SR is less than that of the relationship between SS and SR, along with the slope value (B). The calculation results and graphs depicting the relationship between SS and SR indicate that the flow properties of the cream preparations in F3, F5, and F6 exhibit plastic flow, as the correlation coefficient (r) between log SS and log SR is less than that between SS and SR. The flow characteristics of F1, F2, F4, and F7 exhibit pseudoplastic behavior, since the correlation coefficient (r) between log SS and log SR exceeds the correlation coefficient (r) between SS and SR. Preparations with pseudoplastic flow properties show that the greater the force or shearing stress given, the lower the viscosity of the preparation. Pseudoplastic flow has an effect when applied to the face; the viscosity of the preparation will decrease, resulting in increased spreadability and making it easier to use the preparation [17].

3.8 Adhesion test

The results of the adhesion test of the cream preparation show that the preparation has good adhesion, as indicated by a value of more than 1 second. This shows that the cream preparation can provide effective contact time with the skin so that the purpose of its use is achieved.

3.9 Spreadability test

A spreadability test is conducted to determine the ability of a cream preparation to be easy to use and spread when applied to the skin. This test is conducted by weighing the cream preparation as much as 0.5 grams and then giving it a load of 50 grams, 100 grams, and 250 grams every 1 minute. A good spreadability test is a spreadability value with a range limit between 5-7 cm. The greater the spreadability of the cream preparation, the wider the surface of the skin that comes into contact with the preparation, and the active substance will be distributed well. Based on the results of the spreadability test, the cream preparation shows that the preparation meets good spreadability. This shows that the cream preparation can be used widely, and the active substance can be distributed well on the skin.

3.10 Physical stability test

Physical stability testing was carried out using a centrifuge. This test was carried out at a speed of 2000 rpm for 5 minutes to see the physical changes in the preparation marked by phase separation. The occurrence of phase separation indicates the stability of the cream preparation. The results obtained in the formulated cream preparation did not show a separation between the oil and water phases, indicating that the preparation was stable [20].

3.11 Antioxidant Test ABTS Method

The antioxidant activity test in this study used the ABTS method. The ABTS method was chosen because the reaction time of ABTS with antioxidants is faster. Determination of antioxidant activity was measured using a UV-Vis spectrophotometer. The test's principle is removing ABTS color to measure the antioxidant capacity that reacts directly. The antioxidant activity test was carried out on 11 samples, namely F1 (0.5 gram fig cream), F2 (1 gram fig cream), F3 (0.5 gram pomegranate cream), F4 (1 gram pomegranate cream), F5 (combination cream 0.5 grams), F6 (combination cream 1 gram), F7 (negative control), fig extract, pomegranate peel extract, quercetin as a positive control, and market cream is a cream preparation containing pomegranate extract as a comparison. The samples were prepared and then placed in a dark place; operating time was carried out for 30 minutes. Operating time is the time when the solution reacts optimally and perfectly. After 30 minutes, the absorbance of the samples was measured with a UV-vis spectrophotometer at a wavelength of 752 nm. The extent of antioxidant activity in samples is assessed according to the IC50 value. The IC50 figure denotes the concentration required to diminish 50% of the total ABTS. A lower IC50 value indicates enhanced antioxidant action. The IC50 values for each sample are presented in Table 4.

Table 4. Antioxidant profile of each formula

Formula	IC_{50}	Antioxidant profile
F1	74.20	Strong
F2	66.91	Strong
F3	114.46	Moderate
F4	105.83	Moderate
F5	76.50	Strong
F6	71.97	Strong
F7	434.98	Very weak
Fig Fruit Extract	37.86	Very strong
Pomegranate Peel Extract	41.01	Very strong
Quercetin	1.45	Sangat Kuat
Commercial cream	142.93	Moderate

Several excipients in the formula affect the effectiveness of the preparation. Stearic acid is a fatty acid that has antioxidant activity. Stearic acid in the formula causes negative control even though it is not added with extract, but there is an antioxidant with very weak properties. In addition, the presence of propylene glycol in the formula can act as an enhancer in topical preparations so that it helps the cream preparation to penetrate the skin [21]. Data processing was carried out to obtain the IC_{50} value from the results of absorbance measurements on all formulas. The IC_{50} value is

calculated from the results of the linear regression equation, which is the relationship between the concentration of the formula solution used and the percentage of inhibition or free radical capture. Based on Table 4 in fig extract, pomegranate peel extract, and quercetin with IC_{50} values of 37.86, 41.01, and 1.45, strong antioxidant properties were obtained. This shows that fig extract and pomegranate peel extract are used as antioxidants in the preparation because they have very strong antioxidant properties [11].

Also, the antioxidant properties of quercetin are very strong, so they can be used as positive controls. Measurement of F1, F2, F5, and F6 with IC_{50} values of 74.20; 66.91; 76.50; 71.97 obtained strong antioxidant properties. The formula produces strong antioxidant properties due to the presence of active substances, namely fig extract, which has very strong antioxidant properties, so it affects cream preparation with strong antioxidant properties [22]. In addition, some excipients affect the effectiveness of the preparation. Measurement of F3 and F4 with IC_{50} values of 114.46 and 105.83 obtained moderate antioxidant properties. The formula has moderate antioxidant properties because the strength of the active substance from the pomegranate peel extract is not stronger than that of the active substance from the fig extract [23]. The difference in IC_{50} values is due to differences in the concentration of active substances used in each formula. F7, with an IC50 value of 434.98, obtained very weak antioxidant properties. This is because F7 is a negative control in which active substances are not added in the preparation, so it does not have an antioxidant effect. In the commercial cream used for comparison, the IC_{50} value of 142.93 has moderate antioxidant properties that are not stronger than the F1-F6 cream preparations. This is probably because this commercial cream preparation does not add other synthetic antioxidants that support the antioxidant strength of the cream. In addition, the concentration of pomegranate used in the preparation is also unknown; the claim of this commercial preparation also only focuses on moisturizing the skin at night.

3.12 Irritation test

This irritation test was carried out after obtaining an ethical statement from the Faculty of Medicine and Health Sciences health research ethics committee, Muhammadiyah University of Yogyakarta number 172/EC-KEPK FKIK UMY/VIII/2022 and refers to the 2014 BPOM RI In Vivo Nonclinical Toxicity Test Guidelines; the irritation test was conducted on test animals, namely rabbits. The rabbits used were two male albino New Zealand white rabbits aged approximately three months. The test results for each treatment were analyzed and evaluated with observation parameters for erythema (redness) and edema (swelling) on a scale of 0-4. The category of irritation response on rabbit skin was assessed using the primary irritation index on a scale of 0-8. The results of the primary irritation index in the irritation test can be seen in Table 5.

Table 5. Irritation test results

Formula	Index irritation	
F1	0.33	slightly irritating
F2	0.5	slightly irritating
F3	0.5	slightly irritating
F4	0.83	slightly irritating
F5	0.00	not irritating
F6	0.00	not irritating
F7	0.00	not irritating

Based on the primary irritation index in F1, F2, F3, and F4, it is slightly irritating, while in F5, F6, and F7, there is no irritation. This is likely due to the varying levels of hypersensitivity of the rabbit's skin. In addition, scratches can occur during shaving of the rabbit's skin, which disrupts the first barrier of the skin. In general, the results of the irritation test in F1, F2, F3, and F4 are slightly irritating to the skin, while in F5, F6, and F7, they do not irritate the skin as seen from the presence of erythema and edema. The results of this irritation test indicate that the cream preparation is safe and non-irritating for use on the skin.

4 Conclusion

The combination cream preparation of fig fruit extract (*Ficus carica* L.) and pomegranate peel extract (*Punica granatum* L.) has a physical preparation evaluation result that meets the requirements and good physical stability.The effectiveness of the combination cream preparation of fig fruit extract and pomegranate peel extract when compared with commercial cream preparations is seen from the antioxidant activity, namely the IC_{50} value. F1 (74.20) and F2 (66.91) obtained a strong category, F3 (114.46) and F4 (105.83) obtained a moderate category, F5 (76.50) and F6 (71.97) obtained a strong category, and the commercial cream (142.93) obtained a moderate category. The combination cream preparation of fig fruit extract and pomegranate peel extract, which was seen from the results of the primary irritation index at F1-F4, was slightly irritating, and at F5-F7, there was no irritation to the skin.

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