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Formulation and Antioxidant Activity Test of Gel from Fermented Red Pomegranate Peel Juice (*Punica Granatum* L)

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ABSTRACT: Red pomegranate (*Punica granatum* L.) peel has secondary metabolites such as phenolics, flavonoids, and tannins, which are known to have antioxidant potential. The purpose of this study was to evaluate the comparison of antioxidant activity of juice before and after fermentation and then formulate it into a gel preparation that is physically and chemically stable. Red pomegranate peel juice was dried by freeze drying method and then fermented with *Lactobacillus plantarum* ATCC 8014 bacteria and measured OD600, pH, and antioxidant activity using DPPH reagent. The results showed that pomegranate peel juice before fermentation had strong antioxidant activity with a value (of IC_{50} 35.64 ± 0.68 ppm) and after fermentation, it was in the very strong category (IC_{50} 8.00 ± 0.01 to 8.11 ± 0.06 ppm); pH before and after (3.96 ± 0.02 and 3.33 ± 0.01). Formula II with juice concentration of 300 x IC_{50} has the highest antioxidant activity with IC_{50} values (64.37 ± 1.13 ppm); pH (6.33); spreadability (6.20 ± 0.07); and viscosity (31333.3 ± 577.35 dPas). There was an increase in antioxidant activity of red pomegranate peel juice after fermentation, the resulting gel is physically and chemically stable based on the results of accelerated stability tests for 4 weeks.

Keywords: **antioxidant activity; fermentation; *Lactobacillus plantarum*; pomegranate peel.**

Introduction

Red pomegranate is a fruit from plant of the *Punicaceae* family that grows abundantly in tropical areas, especially in East Asian countries including Indonesia [1]. According to several studies that have been conducted, red pomegranate peel also has many benefits including anticancer, anti-inflammatory, antibacterial, and antioxidant [2]. 70% ethanolic extract of pomegranate peel shows high antioxidant activity in terms of DPPH and ABTS inhibition (79.5±6.5 and 94.6±6.10, respectively), while the highest phenolic compound was found in the aqueous extract of the peel [3]. Optimization to increase the utilization of red pomegranate peel as antioxidant can be done in several ways, one of which is by fermentation using lactic acid bacteria (LAB). Previous study showed fermentation of pomegranate juice using *Lactobacillus plantarum* PU1 increase antioxidant activity up to 40% compared to non-fermented [4]. Other results showed an increase of antioxidant activity (in terms of IC_{50} value) in unfermented compared to fermented pomegranate juice (119.05 µg/mL and 85.33 µg/mL, respectively), which was tested using the DPPH free radical scavenging method[5].

Free radicals found in the environment include air pollution from motor vehicles, cigarette smoke, waste, factories, food, and drugs [6]. Excessive exposure to free radicals can cause oxidative stress in cells, resulting in damage to lipids, proteins, and DNA that inhibits normal cell function [7]. Exposure to free radicals that is too frequent can cause various skin problems, including dull skin, wrinkles, dark spots, and various other signs of skin aging [8]. Phenolic compounds, especially the flavonoid group found in red pomegranate skin juice, have the potential as antioxidants and can be developed into topical gel preparations. In this study, the development of gel preparation formulation was carried out using variations in the concentration of red pomegranate peel juice after fermentation. Gel preparations have better potential as topical preparations because gels spread easily on the skin, are not sticky, are stable, and provide a moist but non-greasy feeling due to their high water content [9] Each concentration was tested for its physical and chemical stability for 1 month and its antioxidant activity was tested using the DPPH free radical scavenging method.

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Methods

Materials

Red pomegranate peel (*Punica granatum* L) from BALITRO, Bogor, *Lactobacillus plantarum* ATCC 8014 bacteria, De Man Rogosa Sharpe broth (MRS broth) from Oxoid, De Man Rogosa Sharpe agar (MRS Agar) from Oxoid, DPPH (1,1 Diphenyl-2-picrylhydrazil), ascorbic acid, Carbomer 940, propylene glycol, triethanolamine (TEA), phenoxyethanol, methanol, aquadest.

Microorganisms and Culture Conditions

Lactobacillus plantarum ATCC 8014 was inoculated on MRS Agar media and then incubated for 24 hours at 37°C. For activation 1-2 loops of *Lactobacillus plantarum* ATCC 8014 bacterial culture were inoculated on MRS broth media and incubated for 24 hours at 37°C.

Preparation of Pomegranate Peel Juice

Fresh red pomegranate peel was washed thoroughly using water and cut into smaller pieces. As much as 25% (w/v) of pomegranate peel and 75% distilled water were blended. The juice was filtered using a wringing cloth and then centrifuged at 4000 rpm, then the solvent was evaporated with a rotary evaporator and then dried using the freeze-drying method until dry powder of pomegranate peel juice was obtained.

Fermentation of Pomegranate Peel Juice

The culture of *Lactobacillus plantarum* ATCC 8014 bacteria in MRS broth media was then centrifuged at 3000 rpm for 20 minutes to obtain bacterial cell pellets. The cell pellets were resuspended with 0.9% NaCl and measured to obtain Optical Density$_{600}$=1,000±0.05. Dry powder of pomegranate peel juice as much as 1% was dissolved in distilled water and added to a suspension of bacterial cell pellets as much as 10% (v/v) and incubated at 37°C for 0, 24, 48, and 72 hours. The OD$_{600}$, pH, and antioxidant activity using the DPPH method were tested for each fermentation time unit.

Antioxidant Activity Test of Red Pomegranate (Punica granatum L.) Peel Juice with DPPH reagent

An amount of 1000 ppm ascorbic acid standard solution in methanol was prepared as the stock solution and then diluted to a concentration of 1, 2, 3, 4, and 5 ppm by adding 1.0 mL of DPPH to each tube and adding methanol to the limit mark then incubated at room temperature for 30 minutes protected from light. The test solution was prepared in four different ways, which are Cell-free supernatant (method I), Culture (Method II), Lysate supernatant (method III), and Culture Lysate (method IV) [10]. A 1% (w/v) solution of freeze-dried pomegranate peel powder in distilled water was made into 1000 ppm in methanol, then diluted to a concentration of 20, 25, 30, 35, and 40 ppm by adding 1.0 mL of DPPH solution and adding methanol until the limit mark was obtained. The sample concentration was then incubated for 30 minutes and protected from light. The prepared solution was measured for its absorbance using a UV-Vis spectrophotometer at the maximum wavelength of DPPH obtained [11]. The radical inhibition activity based on the absorbance data obtained can be calculated using the formula:

%Inhibition = (Blank Absorbance - Sample Absorbance) / (Blank Absorbance) x100%

Phytochemical Content Analysis

Identification of alkaloid, flavonoid, saponin, tannin, quinone, steroid, and triterpenoid content was carried out according to the appropriate method [12].

Table 1. Formulation of pomegranate peel juice gel preparations.

Ingredients	Formulation (%w/v)		
	Blanko	Formula I	Formula II
Red pomegranate peel juice after fermentation	-	0.16%	0.24%
Carbomer 940	0.75	0.75	0.75
Trietanolamin	0.5	0.5	0.5
Propilen glikol	10	10	10
Phenoxyetanol	0.5	0.5	0.5
Aquadest	Ad 100 mL	Ad 100 mL	Ad 100 mL

Table 2. Phytochemical screening of pomegranate peel juice.

No	Phytochemical Screening	Result
1	Alkaloid	+
2	Saponin	-
3	Tannin	+
4	Phenolic	+
5	Flavonoid	+
6	Triterpenoid	+
7	Steroid	-
8	Glycoside	+

Description:
(+) Contains secondary metabolite compounds
(-) Not contains secondary metabolite compounds

Formulation of Gel of Fermented Red Pomegranate Peel Juice

Prepare and weigh the ingredients used: Carbomer 940, triethanolamine, propylene glycol, phenoxyethanol, and distilled water. Carbomer 940 is added gradually into a beaker glass containing distilled water (20:1), then left for 24 hours until it expands, add TEA gradually until a gel base is formed (mixture A). Phenoxyethanol was dissolved in propylene glycol (mixture B), then fermented red pomegranate peel juice was added to mixtures A and B. The three mixtures are homogenized with a stirrer; the remaining distilled water is added and homogenized using a stirrer at a speed of 200 rpm and optimal stirring time until homogeneous, the formula shown in Table 1.

Result and Discussion

Plant Determination

This study used red pomegranate peel (*Punica granatum* L.) from Research Center for Spices and Medicinal Plants (BALITRO), Bogor. The determination results showed that the plant was red pomegranate peel (*Punica granatum* L.), with determination No.987/UN2.F3.11/PDP.02.00/2022.

Phytochemical Screening

Table 2 shows the results of phytochemical screening on pomegranate peel juice. Phytochemical screening was carried out to determine secondary metabolite compounds in red pomegranate. The study obtained positive results for alkaloids, flavonoids, tannins, phenolics, triterpenoids, and glycosides. Tannins, phenolics, and flavonoids have antioxidant activity.

Growth of *Lactobacillus plantarum* ATCC 8014 in Red Pomegranate (*Punica granatum* L.) Peel Juice

The growth of *Lactobacillus plantarum* ATCC 8014 in red pomegranate skin juice at zero hours is a slow phase (Lag phase). In this phase, it shows that the *Lactobacillus plantarum* ATCC 8014 population has not been able to reproduce or divide, but is still adapting to its new medium or environment. In the slow phase, it is possible for the cell size to increase, but not in the number of cells, while at 18 hours it shows the stationary phase. The stationary phase is when the number of bacteria grows the same as the rate of death, the growth rate slows down, and the number of dead cells balances the number of new cells [13]. The results of cell number measurements can be seen in Table 3 below.

Red pomegranate peel is a plant that has nutrients in the form of protein, carbohydrates, fats, and minerals[14]. These nutrients are utilized by the bacteria *Lactobacillus plantarum* ATCC 8014 to reproduce and carry out biochemical processes. Increased number of cells (OD600) *Lactobacillus plantarum* ATCC 8014 in red pomegranate peel juice compared to control (+). The control (+) was used

Table 3. Results of growth of *Lactobacillus plantarum* ATCC 8014 bacteria.

	Before Fermentation	After Fermentation
Optical Density (OD_{600})	0.2895 ± 0.01	0.1104 ± 0.02
	0.2925 ± 0.01	0.1105 ± 0.02
	0.2946 ± 0.01	0.1107 ± 0.02

Table 4. pH Parameters of red pomegranate peel juice fermentation.

	Before Fermentation	After Fermentation
pH	3.98 ± 0.01	3.35 ± 0.02
	3.95 ± 0.01	3.32 ± 0.02
	3.95 ± 0.01	3.30 ± 0.02

in bacteria grown in its selective media, MRSB (deMan Rogosa Sharpe Broth) media was use. The number of cells (OD600) at a substrate concentration of 1% has a variety of values from non-fermented and fermented treatments, (before and after = 0.1105 ± 1.5 and 0.2922 ± 0.02). Therefore, the higher the substrate concentration and the amount of inoculum, the greater the amount of *Lactobacillus plantarum* ATCC 8014 cell growth [15].

pH Parameters of Fermented and Unfermented Red Pomegranate Peel Juice

Lactobacillus plantarum ATCC 8014 can break down complex compounds into simpler compounds with the final result being lactic acid. Lactic acid has a low pH, thus creating an acidic atmosphere [16]. The metabolism of *Lactobacillus plantarum* ATCC 8014 bacteria will affect the pH, total acid content, total glucose content, total protein content, and total phenol content during the fermentation process. The results of measuring the pH value of the red pomegranate skin juice fermentation product (*Punica granatum* L.) as shown in Table 4 below.

The decrease in pH value can be caused by lactic acid contained in the sample in each treatment. Secondary metabolites can be produced when bacteria are in the stationary phase. The pH value with a substrate concentration of 1% in the fermented product of red pomegranate peel juice (before and after fermentation = 3.96 ± 0.02 and 3.33 ± 0.01). This condition occurs because the metabolism of *Lactobacillus plantarum* ATCC 8014 bacteria produces lactic acid so the longer the fermentation time, the more lactic acid is produced by the bacteria and the pH decreases.

Antioxidant Activity of Pomegranate Peel Juice Before and After Fermentation

In the antioxidant activity test of Ascorbic acid as a positive control, the average IC_{50} value was 3.27 ± 0.01 ppm, which means that this concentration can reduce 50% of free radicals and is included in the very strong category because it has an IC_{50} value of less than 50 ppm (<50 ppm). In red pomegranate peel juice before fermentation, the average IC_{50} value was 35.64 ± 0.68 ppm, which indicates a very strong category, because it has an IC_{50} value of less than 50 ppm (<50 ppm). In red pomegranate peel juice after fermentation, the average IC_{50} value was around 8.00 ± 0.00 and 8.11 ± 0.06 ppm, which indicates a very strong category [17]. The result is shown in Table 5.

Evaluation of Gel Preparation from Fermented Pomegranate Peel Juice

The evaluation of gel preparation containing fermented pomegranate peel juice includes the physical evaluation in terms of organoleptic, homogeneity, viscosity, rheology, and spreadability, and the chemical evaluation in term of pH.

Organoleptic and Homogeneity

The test results obtained as shown in Table 6 show that all formulas did not experience changes in color, or odor, and had a semisolid form. The gel preparation obtained was light yellow (FI) and brownish yellow (FII) because it contained red pomegranate skin juice that had been mixed with the base color of the gel preparation. The results of the homogeneity evaluation show that all formulas produced were homogeneous, so it can be seen that the active substances and additional substances can be mixed evenly.

Table 5. Antioxidant activity test of ascorbic acid juice comparison standard before and after fermentation.

IC_{50} Ascorbic acid (ppm)	IC_{50} Juice before fermentation	IC_{50} Juice after fermentation			
		Method I	Method II	Method III	Method IV
3.27 ± 0.01	35.64 ± 0.68	8.11±0.06	8.0 ± 0.02	8.00 ± 0.00	8.01 ± 0.01

Table 6. Evaluation test of red pomegranate peel juice gel preparation after fermentation.

Test Parameters	Formula I	Formula II
Color	Light yellow	Brownish yellow
Form	Semisolid	Semisolid
Odor	Odorless	Odorless
Homogeneity	Homogeneous	Homogeneous
Viscosity	36333.3 + 577.35	31333.3 + 577.35
Rheology	Thixotropic plastic	Thixotropic plastic
Spreadability	6.12 ± 0.05	6.20 ± 0.07
pH	6.55 ± 0.02	6.33 ± 0.01
Antioxidant activity	69.76 ± 1.09 ppm	64.38 1.13 ppm

Viscosity

Viscosity is a measure that states the thickness of a liquid or fluid. Factors that affect viscosity are temperature, pressure, cohesion, and rate of transfer. The viscosity of the gel will decrease if the temperature is increased and vice versa, this is because of the heat. The viscosity evaluation of gel preparation containing fermented red pomegranate peel juice using a Brookfield Viscometer type RV on spindle number 7 with RPM 20 demonstrates low viscosity in formula II, which is correlated with increase in the concentration of active substances used. The greater the amount of active substance used in the preparation, the lower the viscosity [14]. So it can be concluded that the addition of red pomegranate peel juice can affect the viscosity of the gel preparation. The result is shown in Table 6.

Rheology

Rheology is the science that studies the flow of liquids and the deformation of solids. The measurement results of all gel preparation formulas are included in the non-Newton system and have thixotropic plastic flow properties because they do not pass through the origin. In Figure 1 - Figure 3, the descending curve is visible to the left of the ascending curve. This shows that the preparation has high consistency at the beginning of the measurement, then the consistency decreases shortly after the measurement at the same shear rate. Thixotropic flow properties are ideal properties desired in a topical pharmaceutical preparation because they have a high concentration in the container, but can be poured or spread easily. This characteristic gives advantage to the application of the gel for topical application.

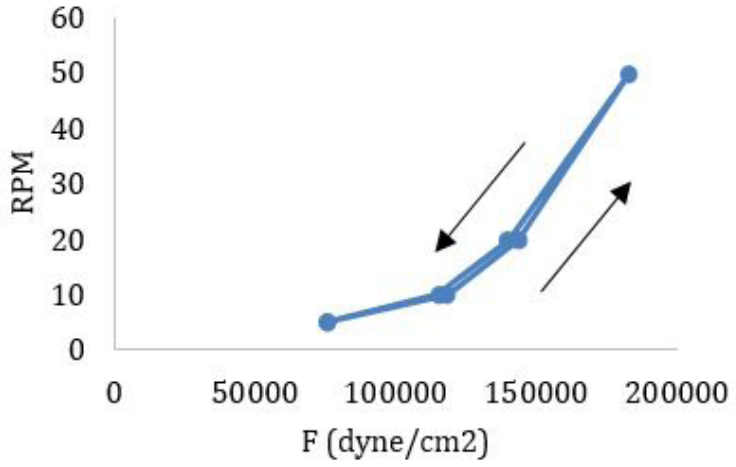

Figure 1. Flow properties graph of blank thixotropic plastic formula gel.

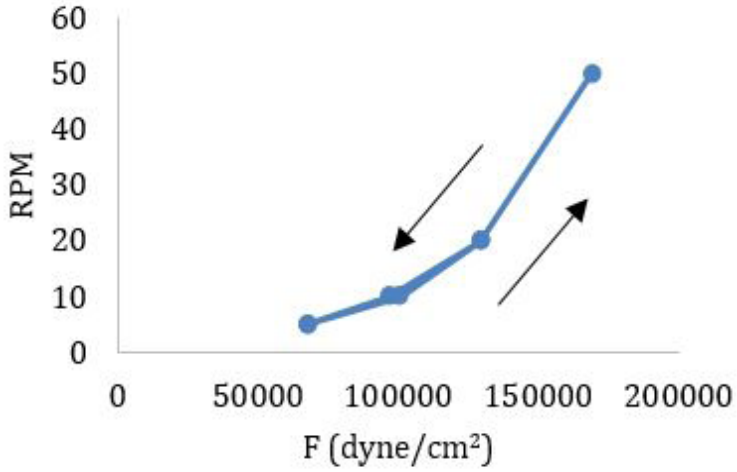

Figure 2. Flow properties graph of formula I thixotropic plastic gel.

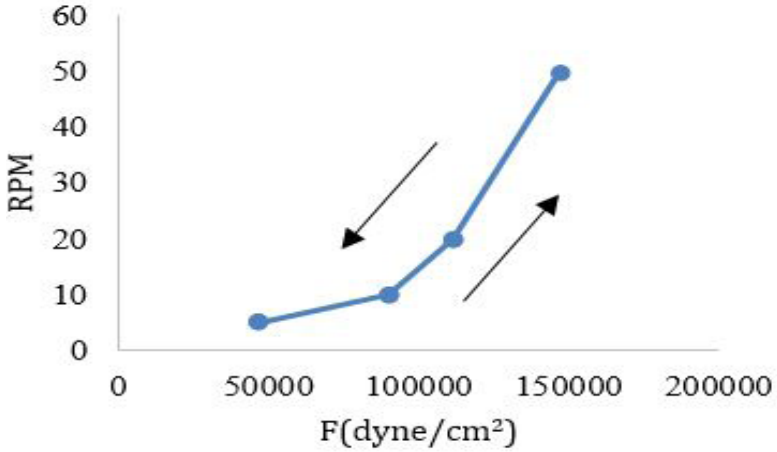

Figure 3. Flow properties graph of formula II thixotropic plastic gel.

Spreadability

The spreadability test aims to determine the ability of the gel to spread so that a gel preparation is obtained that is easy to apply to the skin. In addition, good spreadability can cause contact between the drug and the skin to be wider so that absorption into the skin takes place quickly. The addition of juice affects the value of the spreadability of the preparation, the higher the concentration of juice, the greater the spreadability. The results of the study obtained as shown in Table 8, an average diameter value of a good spreadability test of 6.20 cm in formula II producing a gel with the lowest viscosity so that it produces the greatest spreadability. the greater the spreadability given, the wider the ability of the active substance to spread on the skin. It can be concluded that the addition of pomegranate peel juice after fermentation can affect the spreadability of the gel preparation. In this study, the spreadability of the gel was obtained which met the requirements, which is in the diameter range of 5-7 cm [18].

Chemical Evaluation (pH)

The pH evaluation aims to see whether there is a change in pH during the storage period and whether the pH of the resulting preparation is following the skin pH or not so that irritation does not occur. The results of the pH evaluation of the blank formula, formula I, and formula II as shown in Table 6 have different pH. The blank has the highest pH value of all formulas, this is because the blank does not contain fermented juice so it has a pH close to neutral and the blank also contains Carbomer which has been neutralized with triethanolamine. In the formula containing fermented pomegranate peel juice, the higher the concentration of pomegranate peel juice, the more acidic the gel preparation will be. The pH of the preparation should not be too acidic because it can irritate the skin and also should not be too alkaline because it can make dry skin scaly, the optimum pH for skin preparations ranges from 4.0-6.0 is good for skin barrier [19]. This shows that the pH of the preparation produced by the

Table 7. Results of the viscosity stability evaluation of gel preparations.

Viscosity (cPs) at 20 rpm		
Formula	**Week of**	**Temperature 40°C**
Blanko	0	50000
	1	49500
	2	49000
	3	47300
	4	46600
FII	0	40200
	1	39000
	2	38500
	3	36000
	4	35100

blank, formula I, and formula II meets the requirements so that the preparation will not irritate the skin or make the skin dry.

Antioxidant Activity of Gel Preparation containing Fermented Red Pomegranate Peel Juice

The results obtained from the antioxidant activity test of gel preparations from formulas I and II as shown in Table 6 showed that they were classified as strong antioxidants with IC_{50} values of 69.76 ± 1.09 µg/mL; 64.38 ± 1.13 µg/mL respectively. The IC_{50} value of the preparation decreased compared to the IC_{50} value of red pomegranate peel juice (before fermentation = 35.64 µg/mL) and (after fermentation ranging from = 8.00 ± 0.01 to 8.11 ± 0.06 µg/mL). This can occur due to the addition of additional ingredients to the gel preparation, which affects the antioxidant activity obtained. Formula II has greater antioxidants 64.38 ± 1.13 µg/mL compared to formula I, although not too significant. This can be caused by formula II have an active substance concentration of 300 x IC_{50} [20].

Selection of the Best Formula for Stability Test

Based on the results of the physical and chemical evaluation of the red pomegranate peel juice gel preparation after fermentation, as shown in Table 6, it was found that all formulas met the requirements of each evaluation and all formulas had a strong antioxidant activity category. The results of the viscosity evaluation showed that formula I had a curve that was far apart, while formula II had a curve that overlapped. Therefore, formula II was chosen as the formula to be used in the stability test.

Stability Test of Gel Preparation containing Fermented Red Pomegranate Peel Juice

Organoleptic and Homogeneity

The data from the organoleptic stability and homogeneity evaluation test of red pomegranate peel juice gel preparation after fermentation for 4 weeks of storage from week 0 to week 4 in Formula II had a good physical condition, did not experience any physical changes, which are color, odor, and shape. The results show that the mixture of ingredients in each formula that has been made is good and stable for 4 weeks of storage at a temperature of 40°C [21].

Viscosity

The results of the viscosity test of the red

Table 8. Evaluation of the spreadability and pH of gel preparations.

Formula	Spreadability (cm) Week of					pH Week of				
	0	1	2	3	4	0	1	2	3	4
Blanko	6.20 ± 0.07	6.33 ± 0.02	6.68 ± 0.02	6.80 ± 0.02	6.97 ± 0.02	6.71	6.69	6.65	6.65	6.71
II	5.70 ± 0.02	5.82 ± 0.03	5.87 ± 0.04	5.87 ± 0.01	5.96 ± 0.01	6.33	6.31	6.28	6.26	6.23

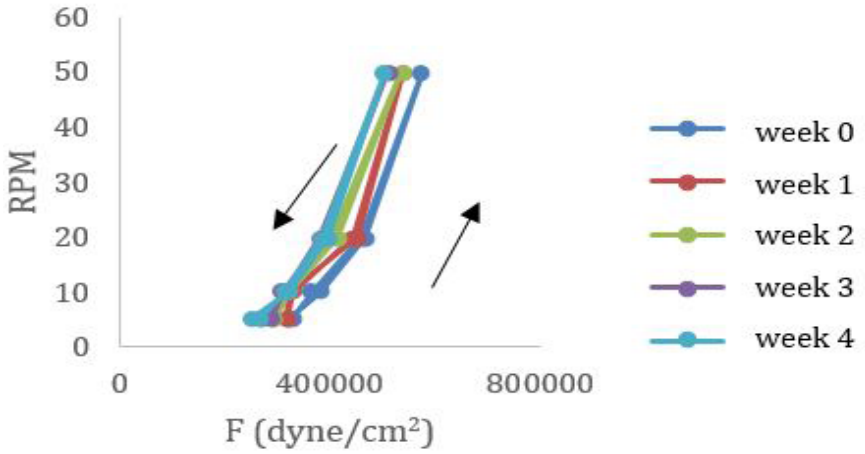

Figure 4. Flow properties of blank formula at 40°C.

pomegranate skin juice gel preparation after fermentation using a Brookfield Viscometer type RV on spindle number 7 with RPM 20 obtained low viscosity in formula II, this is known in the formula has an increase in the concentration of the amount of active substances used. The greater the amount of active substances used in the preparation, the lower the viscosity will be [14]. The result is shown in Table 7.

Flow Properties

Based on Figure 4 and Figure 5, the preparation of red pomegranate peel juice gel after being fermented in storage at a temperature of 40°C for 4 weeks did not experience any changes.

Spreadability

Based on Table 8 result of the stability evaluation, the average diameter value of formula II was 5.70 - 5.96 which increased. This is because the storage period at a temperature of 40°C for 4 weeks affects the viscosity of the preparation. From these results, the spreadability still meets the requirements of semisolid preparations, which is 5-7 cm.

pH stability

The pH stability evaluation aims to see whether there is a change in pH during storage at 40°C for 4 weeks. Based on Table 8, result of the stability evaluation on the gel preparation decreased. This can occur because the chemical reaction takes place faster under high temperatures (40°C). From the measurement results, the pH of Formula II ranges from 6.33-6.23. These results are within the range of pH requirements for topical preparations according to SNI 16-4399-1996, which has a pH range of 4.5-6.0 and is good for the skin barrier [22].

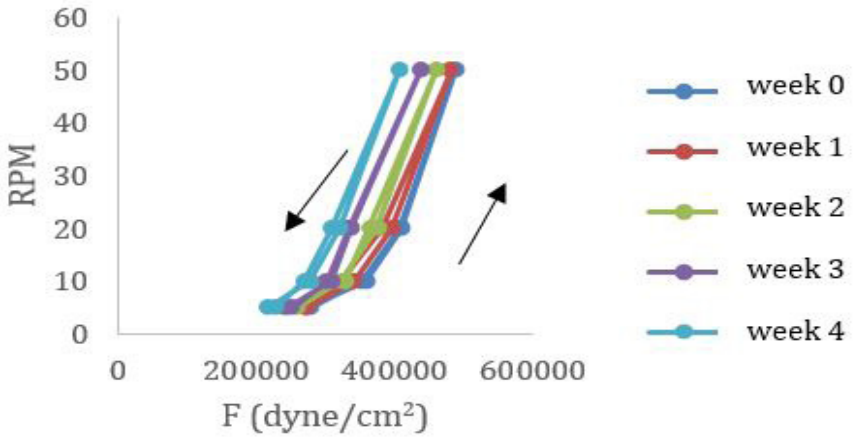

Figure 5. Flow properties of formula II at 40°C.

Conclusion

Red pomegranate (*Punica granatum* L.) peel juice was fermented by *Lactobacillus plantarum* ATCC 8014 bacteria with pH values (before and after = 3.96 ± 0.02 and 3.33 ± 0.01); and an increase in OD_{600} values (before and after = 0.1105 ± 1.5 and 0.2922 ± 0.02). There was an increase antioxidant activity of red pomegranate rind juice after fermentation by *Lactobacillus plantarum* bacteria (IC_{50} = 8.00 ± 0.01 to 8.11 ± 0.06 ppm) compared to the juice before fermentation (IC_{50} = 35.64 ± 0.68 ppm). Red pomegranate (*Punica granatum* L.) peel juice after fermentation can be formulated into a gel preparation that meets the physical and chemical quality requirements, which is producing a homogeneous gel, yellow-brown in color, pH = 0.33-0.23, viscosity = 36333.3-31333.3 cPs, and spreadability = 5.70-6.20. The resulting gel is physically and chemically stable based on the results of accelerated stability tests for 4 weeks.

Conflict of Interest

The author declares that there is no potential conflict of interest.

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