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Formulation and Evaluation of instant granules from Ketapang Badak fruit (*Ficus lyrata* Warb) using wet granulation method as an antioxidant supplement

Norisca Aliza Putriana*.[1], Efri Mardawati[2], Yoga Windu Wardhana[1], Nurul Afifah[1], Anting Wulandari[2], Dwi Wahyudha Wira[3], Nanang Masruchin[4]

[1]Department of Pharmaceutical and Formulation Technology, Faculty of Pharmacy, Universitas Padjadjaran, Jalan Raya Bandung-Sumedang KM 21, Jatinangor 45363, Indonesia
[2]Faculty of Agricultural Industrial Technology, Universitas Padjadjaran, Jalan Raya Bandung-Sumedang KM 21, Jatinangor 45363, Indonesia
[3]Faculty of Veterinary, Universitas Padjadjaran, Jalan Raya Bandung-Sumedang KM 21, Jatinangor 45363, Indonesia
[4]Biomaterial Research Center, Indonesian Science Institutions, Jalan Raya Bogor Km 46, Cibinong Bogor, 16319, Indonesia
e-mail: norisca@unpad.ac.id

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Abstract

Free radicals are naturally produced from the body's metabolic processes, but the excessive amount of free radicals can interfere with human health because they cause oxidative stress. Therefore, our bodies need antioxidants that can protect against free radicals. *Ficus lyrata* W. is one of the antioxidant sources. This study aim to formulate instant granules from the Ethanol extract of *Ficus lyrata* W. using the wet granulation method. The formula was optimized using the Design Expert with the two-level factorial method. The optimized factors were xanthan gum 0.8-1.5% and polyvinylpyrrolidone (PVP) 0.5-5%. Granules were evaluated and analyzed using the Design Expert. As a result, all the four formulas obtained showed that Formula 4 with a combination of xanthan gum 0.8% and PVP 5% is the best formula, which the evaluation result is Loss On Drying (LOD) 3.28%, Flowability 16.043 ± 0.221 (g/s), Angle of Repose 21.77 ± 0.862; no precipitate for 15 minutes, pH = 4.7, dispersed in 31 seconds and sedimentation time is 52.213 ± 1.7878 minutes, the results of the antioxidant activity test of the ethanol extract of *Ficus lyrata* W. is 38.27 µg/ml, and instant granules is 145.02 µg/ml.

Keywords: Antioxidant, *Ficus lyrata* W., Instant granules, Design expert

1. Introduction

Free radicals naturally are produced by the cellular metabolism process. It plays an important role in our body's physiology which the excessive amount of free radicals will cause health problems (1). Free radicals are defined as a molecule that contains one or more unpair electrons in the outside orbital, which is relatively unstable and reactive, so it can protect against another molecule to reach the stable state (2).

Oxidative stress is a condition where there's unbalance condition between the production and accumulation of Reactive Oxidant Species (ROS) and its ability to balance it back (3). Free radicals that induced oxidative stress have been reported to be involved in the development of several degenerative diseases such as cancer, diabetes

*Corresponding author,
e-mail : norisca@unpad.ac.id (N. A. Putriana)

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mellitus, rheumatoid arthritis, respiratory diseases, cardiovascular and neurodegenerative diseases (2).

Ketapang Badak (Ficus lyrata W.) is an annual plant that is usually used as an ornamental and shade plant because of its long stems and thick leaves (4). Ketapang Badak (Ficus lyrata W.) is one of the plants of the Ficus genus whose utilization is still lacking. According to the research, from the six types of Ficus genus plants, Ficus lyrata w. has the highest antioxidant activity with an IC50 value is 38,37 ppm (5). The antioxidant activity of Ketapang Badak (Ficus lyrata W.) is because there are phenolic compounds, which according to research (6).

Ketapang Badak (Ficus lyrata W.) has the potential to be developed as an antioxidant source. So far, there have been no reports that have developed the fruit of Ketapang Badak (Ficus lyrata W.) to be formulated into a dosage form as an antioxidant supplement, including instant granules. Granules preparations have better stability, flowability, more practical, and suitable for preparations.

So, this study aim to formulate the Ketapang Badak (Ficus lyrata W.) extract to become instant granules as an antioxidant supplement.

2. Methods

2.1 Materials

Spectrophotometer UV-Vis (TECAN M200 pro), analytical measurement (Mettler Toledo). Granulator, powder density tester, flowability and angle of repose tester (ERWEKA GT), oven (Memmert), macerator, rotary evaporator (BUCHI Rotavapor R-300), water bath (Memmert), ethanolic extract of *Ficus lyrata* W, DPPH (1,1-diphenyl-2-picyhydrazyl) (Sigma Aldrich), Vitamin C (Bratachem), ethanol 70%, ethanol 95%, n-hexane, ethyl acetate, Citric acid (Quadrant), Sodium Citrate (Quadrant)l, Xanthan Gum (Fufeng), Sucrose (ROFA), and Lactose (Dwilab Mandiri).

2.2 Material collection and plant determination

Plant material used was collected from Padjadjaran university surroundings. The plant was determined at the Taxonomy Laboratory, Biology Department, Faculty of Mathematics and Natural Sciences, Padjadjaran University.

2.3 The Extraction of Ketapang Badak (*Ficus lyrata* W.)

Every 100 grams of simplicia powder were extracted using three different solvents (ethanol, methanol, and ethyl acetate) with maceration method for 3x24 hours, which every 24 hours, the filtrate was collected and changed with a new solvent. It is concentrated using the rotary evaporator with the maximum temperature is 40℃ (7)

Rendement (%) =

$$\frac{Total\ weigh\ of\ extract}{Total\ weigh\ of\ simplicia}\ x\ 100\% \ldots \text{(Eq. 1)}$$

2.4 Antioxidant Activity Test

2.4.1 Sample preparation

Ethanol extracts were prepared with a stock solution of 100 ppm. 100 ppm stock solution was diluted to concentrations 10, 20, 30, 40, and 50 ppm.

2.4.2 Preparations of Comparative solutions

Ascorbic acid was prepared with a solution of 100 ppm and diluted the stock solution standard to concentrations 0, 1, 2, 3, and 4 ppm.

2.4.3 Preparation of DPPH solution

DPPH was weighed and dissolved in ethanol p.a at a concentration of 0.1 M for immediate use and maintained in low temperatures, and protected from light exposure.

2.4.4 Maximum Wavelength Determination

DPPH 8 mg was dissolved with 50 mL ethanol. 0.6 mL of DPPH solution was put to the cuvette and added methanol until its volume was 3 mL. The solution was incubated for 30 minutes. It was measured at a wavelength from 400-800 nm (8)

2.4.5 Determination of percent inhibition

The sample solutions of each concentration were put to the cuvette and then added 0.6 mL of DPPH solution. It was added methanol until the volume is 3 mL. The mixture solution was incubated for 30 minutes, protected from light exposure, and measured at its maximum wavelength (517 nm)

Inhibition (%) = $\frac{Blank\ absorbance - Sample\ absorbance}{Blank\ absorbance} x\ 100\%$ … (Eq.

2.4.6 Determination of IC_{50} with DPPH method

Substitute the sample concentration and percent inhibition on the x and y axes in the linear regression equation, respectively. The equation was used to determine the IC_{50} value of each sample, their value is 50, and the x values will be obtained as IC_{50} (8)

2.5 Determination of Total Phenolic Content of Extract

2.5.1 Determination of standard curve using Gallic Acid

Gallic acid was prepared with a solution of 400 ppm. Diluted the stock solution standard to concentrations 30, 40, 60, and 80 ppm with methanol p.a. 1 mL of each solution was added 5 mL of Folin-Ciocalteau reagent and incubated for 8 minutes. After that, 4 mL of NaOH 1% was added and incubated for an hour. The solutions were measured at 765 wavelengths (9)

2.5.2. Determination of Total Phenolic Content

200 mg extract was dissolved at 25 mL methanol. 1 mL of extract solution was pipetted to 10 mL of a volumetric flask with methanol. 1 mL sample solution was added to the test tube with 5 mL of Folin-Ciocalteau and incubated for 8 minutes. The solution was added with 4 mL of NaOH 1% and incubated for an hour (9). The total phenolic content can be calculated by the equation:

Total Phenolic Content (TPC) $\frac{c\ x\ v\ x\ fp}{g}$

Notes:

c = Phenolic concentration (x value)

v = volume used (mL)

fp = dilution factor

g = sample weigh (g)

2.6 The Formulation of Instant Granules

The formulating was optimized by a Design Expert, where there are four formulas that contain two factors that have been varied: Suspending agent and the binder

Tabel 1. Instant granules formulas

	F1 (%)	F2 (%)	F3 (%)	F4 (%)	Function
Ficus lyrata extract	3.6	3.6	3.6	3.6	Active substance
PVP	5	0.5	5	0.5	Binder
Xanthan Gum	1.5	0.8	1.5	0.8	Suspending agent
Citric acid	0.3	0.3	0.3	0.3	Acid flavoring

Sodium citrate	0.3	0.3	0.3	0.3	pH balancing
Sucrose	40	40	40	40	Sweetening agent
Lactose	Ad 100	Ad 100	Ad 100	Ad 100	Filler

2.7 Formula Optimization using ANOVA Design Expert

Determination of the best formula is done using Design-Expert software by entering the results of the Evaluation as a response and determining the optimum value of each response used. Furthermore, the Design Expert will perform an analysis of variance (ANOVA) on the responses used. The results of the analysis of the response can be seen from several results, including the value of the contribution of factors to the response, the P-Value to see the significance of each response, the mathematical equation of the response used, the interaction graph of each formula design on the response and the desirability value (10).

2.8 Evaluation of Granules

2.8.1 Loss on Drying (LOD)

The granules were weighed at 10 grams and placed on a moisture content analyzer. Then click start and after 10 minutes, the instrument showed the LOD results in percentage (11).

2.8.2 Flowability and The Angle of Repose

The granules were weighed at 20 g and put into the funnel with a closed bottom hole. When measuring, the bottom hole was opened and the time needed by the granules to flow down was calculated using a stopwatch. Flow rate was determined by the following equation.

Flowability = $\frac{w}{t}$ … (Eq. 3)

Description:
w = granul weight (g)
t = the time needed by the granules to flow (s)

The granules that were formed like cones on a flat plane and measured for their angle of repose, with the following equation:

$\alpha = \arctan \frac{h}{r}$ … (Eq. 4)

Description:
α = angle of repose(°)
h = heap height (cm)
r = heap radius(cm)

2.8.3 Dispersion Time

5 grams of granules were dispersed into 100 mL of aquadest in a beaker. The dispersion time was recorded by measuring the time from the start until all the granules were homogeneously dispersed in aquadest (Husni et al., 2020).

2.8.4 pH Solution

5 grams of instant granules were dissolved into 100 mL aquadest. pH solution was measured by pH meter that was previously calibrated using pH 4 and 7 buffers. The pH meter was inserted into the instant granule solution and the measured pH was recorded.

2.8.5 Sedimentation Volume

5 grams of instant granules were dissolved into 100 mL aquadest. The solution was stirred until it was dispersed. The amount of sediment that occurs was observed in a period of 1-15 minutes (12).

2.8.6 Dispersibility

5 grams of instant granules were dissolved into 100 mL aquadest. The solution was stirred until it was dispersed. The time until the formation of a precipitate is observed and recorded.

2.8.7 Redispersibility

The redispersion test was carried out after the evaluation of the sedimentation volume was completed. The test tube containing the dispersed preparation was rotated 180^o and inverted to its original position. Good

redispersibility if the sediment in the solution can be completely dispersed (13).

2.8.8 Homogeneity Test

Homogeneity test was done by measuring the total phenolic content of instant granule preparations. A number of granules were weighed equivalent to 0.2 grams of extract (5 times) and then dissolved in 25 ml of methanol. The absorbance of the sample solution was measured and the polyphenol content was calculated.

1. Result

3.1 Determination

The result of plant determination show *Ficus lyrata* W. fruit belongs to the Family Moraceae, Genus: *Ficus*, Species: *Ficus lyrata* W., which Indonesian name is Ketapang or Biola cantik.

3.2 Extraction

Extraction using three kinds of solvents with the maceration method shows the result as in the Table 2.

Tabel 2. Rendement result of *Ficus lyrata* extract

Solvent	Rendement
Methanol	8.39%
Ethanol	11.49%
Ethyl acetate	1.39%

3.3 Antioxidant activity

Antioxidant activity of the ethanol extract of Ketapang Badak fruit (*Ficus lyrata* W.) decreased after being made in the form of instant granules. It can be caused by the influence of pH on the granule preparation. In a study conducted by (14), pH significantly affected the ability of polyphenols to reduce lipid oxidation where the caffeic acid content increased at pH 6 compared to pH 2 and 4.

Tabel 3. IC_{50} values

	Concentration	Absorbance average	Inhibition (%)	IC_{50} (ppm)
Ascorbic acid	1	0.629	29.2463	1.7
	2	0.222	75.0281	
	3	0.088	90.1012	
	4	0.082	90.7762	
Ethanol extract	10	0.7743	14.0902	38.1575
	20	0.6240	30.7692	
	30	0.5150	42.8624	
	40	0.3967	55.9911	
	50	0.3710	58.8388	
Methanol extract	10	0.763	17.5432	37.056
	20	0.622	32.7810	

	30	0.50767	45.1369	
	40	0.40567	56.1599	
	50	0.37067	59.9424	
Ethyl acetate extract	50	0.730	17.8853	116.62
	100	0.524	41.0574	
	150	0.246	72.3285	
	200	0.157	82.3397	
Instant granules	25	0.732	9.1346	145.020
	50	0.662	17.8329	
	75	0.588	27.0170	
	100	0.55867	30.6578	
	125	0.48733	39.5118	
	150	0.375	53.4547	
	175	0.29867	62.9293	
	200	0.251	68.8457	

3.4 Total phenolic content

Tabel 4. Total phenolic content results

Sample	**Average of absorbance**	**Test solution volume (mL)**	**Weight (g)**	**Linear equation**	**R^2**	**Total polyphenol content (µg GAE/g)**
Extract	0.5513	25	0.2053	Y = 0.0126x + 0.0064	0.9966	52665.218
Instant granules	0.4367	25	0.2	y = 0.0085x + 0.1841	0.9957	37066.46

3.5 Evaluation of Instant Granules

Several evaluations were completed, including LOD, flowability and the angle of repose, dispersion time, the pH solution, sedimentation volume, dispersibility, redispersibility, and homogeneity test.

LOD (Loss on Drying) test is to measure the moisture balance in the granules that can affect the stability of the granules, which is the lower the water content is, the higher the stability of the granules. The requirement of the good LOD value is in the range of 2-4% (12).

Flowability and the angle of repose

Flow rate is defined as the time it takes for a number of grams of granules to flow through a funnel. Good granules are granules that can flow easily. Flow properties can be influenced by particle shape, particle size and cohesiveness between particles, while he angle of repose is the maximum angle that the granule surface can form in the horizontal plane. The size of the angle of repose is influenced by the size of the particles, the magnitude of the attractive force and the friction between the pa rticles (12).

Dispersion time aims to determine the time required for the granules to be dispersed in water. The dispersed time of granules is influenced by the size distribution of the granules, where smaller granules are dispersed faster than larger granules. The uniform particle size also causes the water medium to more easily penetrate into the granule particles thereby increasing the granule dispersal time. The dispersed time requirement is less th an 5 minutes (15).

pH solution was evaluated to know the exact pH of the granules after being dispersed in water, which all the four formulas of the gra nules showed the range pH is about 4.

Sedimentation volume test was carried out to determine the deposition ratio (F) that occurred during a certain time storage. A good F value is close to 1, meaning that the particles in the suspension are evenly dispersed in the carrier liquid (16). Meanwhile the sedimentation evaluation was carried out to measure the time needed to form a sedimentation of the granules after being dispersed.

The homogeneity test was carried out to determine the uniformity of the extract content in the granule preparation. This test was carried out by measuring the total polyphenol content several times in instant granule preparations.

Tabel 5. Evaluation of instant granules

Evaluation		**Formula**			
		1 (n=3)	**2** (n=3)	**3** (n=3)	**4** (n=3)
LOD (%)		2.85 ± 0.00	2.30 ± 0.00	4.08 ± 0.00	3.28 ± 0.00
Flowability (s)		15.593 ± 2.114	16.053 ± 0.488	15.063 ± 0.685	16.043 ± 0.221
Angle of repose (º)		21.204±1.355	19.057±1.363	21.933±0.368	21.770±0.862
Dispersion time		3’ 23”	2’ 21”	1’ 26”	31”
pH		4.645	4.535	4.845	4.735
Sedimentation volume (mL)	**15 min**	0.91	0.92	-	-
	60 min	0.9	0.87	0.6	0.87
Sedimentation time (s)		7.590 ± 0.829	6.227 ± 0.935	26.890 ± 1.64	52.213 ± 1.788
Redispersibility		+	+	+	+

Homogeneity	Tested by looking at the total phenolic content of granules for five times replication

+: Dispersed granules can be redisperse

-: Dispersed granules cannot be redisperse

4. Discussion

Simplicia was extracted using three different solvents to obtain which one is the best solvent to get the better rendement and IC_{50} value. As presented in the Table 3., the ethanol extract is the one that has the highest rendement and the IC_{50} value categorized as the strong antioxidant. As it mention in the research conducted by Do, Ethanol has been known as a good solvent for polyphenol extraction and is safe for human consumption(17). So, for the formulation of instant granules, the chosen solvent is ethanol.

The antioxidant activity test was carried out using a UV-Vis spectrophotometer with DPPH-method. The DPPH method has advantages such as being simple, easy, fast and requiring a small number of samples. The working principle of the DPPH method is that the hydrogen atom (H+) in the antioxidant compound will bind to free electrons in the DPPH radical compound so that it causes a change from free radicals to non-radical compounds (diphenylpicrylhydrazine). This is indicated by a change in color from purple to yellow (free radical compounds are reduced by the presence of antioxidants) (Setiawan et al., 2018). The ability of a sample to capture DPPH radicals is an indication that the sample has antioxidant activity. The parameter used for the DPPH radical scavenging test is the IC_{50} value, which is the concentration of a test sample required to reduce DPPH radicals by 50%. The IC_{50} value is obtained from a linear regression equation which states the relationship between the concentration of the test sample and the percent inhibition of the DPPH radical.

A compound is said to have very strong antioxidant activity if the IC_{50} value is less than 50 ppm, strong if the IC_{50} value is 50-100 ppm, moderate if it is 100-150 ppm, and weak if the IC_{50} value is 150-200 ppm (18). Based on the results of the study of IC_{50} ethanol extract *Ficus lyrata* W. is 38.27 ppm categorized as a very strong antioxidant, and the IC_{50} of instant granules is 145.02 ppm is categorized as a moderate antioxidant.

Determination of total polyphenol content was carried out on extracts and granules using Folin-Ciocalteau reagent. Folin-Ciocalteau reagent is used because this reagent can react with phenolic compounds to form a colored solution which can then be measured absorbance (9).

The principle of this method is the formation of a complex blue compound. When phenolic compounds are reacted with the Folin-Ciocalteau reagent, a change from yellow to blue will occur (19). Phenolic compounds will only react with Folin-Ciocalteau in an alkaline environment so that proton dissociation occurs in phenolic compounds into phenolic ions, so the addition of a base is required (9). The intensity of the blue color is determined by the amount of phenol content in the test compound. The greater the concentration of phenolic compounds in the sample, the darker the blue color seen (19).

From the results of testing the total polyphenol content, it can be seen that the instant granule compound decreased the total polyphenol content. This is in line with the decrease in antioxidant activity (IC_{50}), which may be due to the influence of pH on the granule preparation. In a study conducted by (Kim and Choe, 2018), pH significantly affected the ability of polyphenols to reduce lipid oxidation where the caffeic acid content increased at pH six compared to pH 2 and 4.

4.1 Formula optimization using Design Expert

The response data for the optimization of the formula entered into the Design Expert is the Evaluation of the flowability and sedimentation time by determining the category criteria for the response of flowability and sedimentation time, namely "maximize"

because the higher the flowability value, the better the flow properties of the granules. The longer the sedimentation time, the better the quality of the granule preparation. The effect of using Xanthan Gum and PVP on the flowability and sedimentation time is shown in Table 6**.**

Tabel 6. Contribution percentage of excipients

No	Excipient	% Contribution to Flowability	% Contribution to Sedimentation time
1	Xanthan Gum	9.22257	10.2091
2	PVP	0.118008	76.5825
3	Xanthan Gum - PVP	0.106408	12.6747

Tabel 7. Desirability values

Formula	Xanthan Gum	PVP	Desirability value
1	1.5	5	0.467
2	0.8	0.5	0.210
3	1.5	0.5	0.229
4	0.8	5	0.723

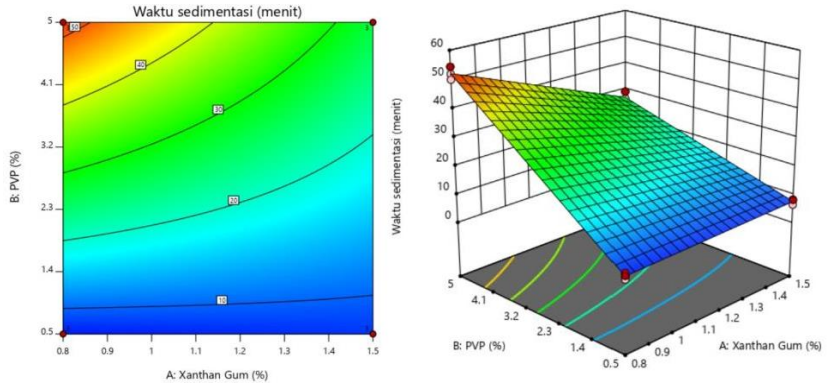

Figure 1. Contour plot dan 3D *surface* formula to sedimentation time

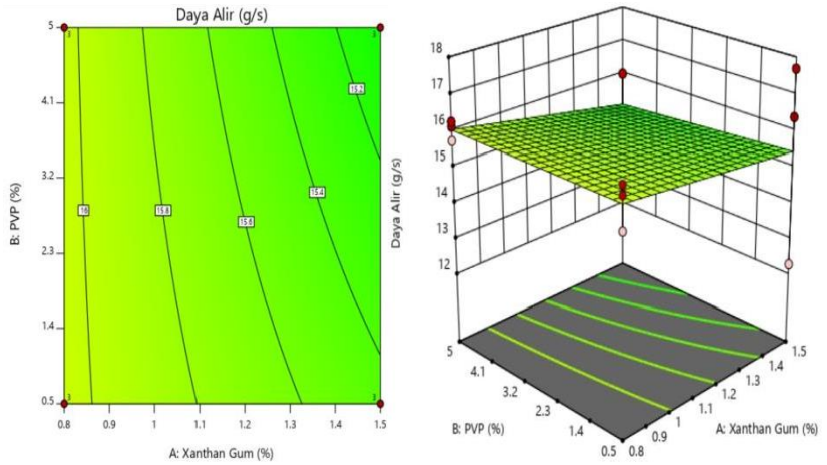

Figure 2. Contour plot dan 3D *surface* formula to flowability

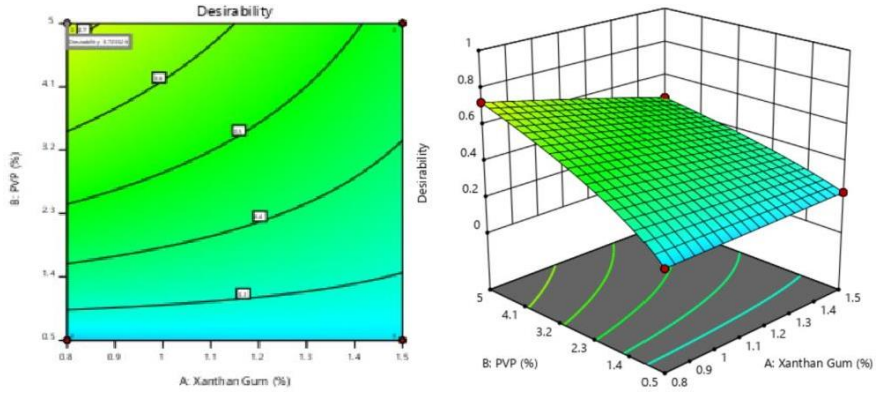

Figure 3. Contour plot dan 3D *surface* formula to desirability value

5. Conclusion

The best formula for instant granule ethanol extract of the Ketapang Badak fruit (*Ficus lyrata* W.) was Formula 4 with a concentration of 0.8% xanthan gum and 5% PVP, which met the requirements for good granule quality. The results of the Evaluation of Formula 4 showed a LOD value of 3.28%, flowability 16.043 ± 0.221 (g/s), angle of repose 21.77 ± 0.862, did not form a precipitate for 15 minutes, pH = 4.7, dispersed within 31 seconds and a sedimentation time of 52.213 ± 1.7878 (minute).

The antioxidant activity of extracts and instant granules was obtained, where the IC_{50} value of the ethanol extract was 38.27 g/ml, which was a very good antioxidant group, while the IC_{50} value of the granule preparations was 145.02 g/ml, which was included in the moderate antioxidant group.

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