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Formulation and Evaluation of Lozenges From Durian Peel Extract (*Durio zibethinus* Murr) as an Antioxidant

Lia Intan Humairoh[1] , Dante Alighiri[2]

ABSTRACT

Background: The durian peel is known to possess antioxidant activity due to the presence of flavonoid compounds in it. However, the potential of durian peel as an antioxidant is yet to be fully utilized, necessitating innovative approaches.

Aim: This research aimed to formulate durian peel extract into antioxidant lozenge tablets.

Method: The durian peel was extracted using the reflux method with 96% ethanol as the solvent. The lozenge tablets were prepared in three formulations with varying fillers, Formula 1 with mannitol, Formula 2 with combination of mannitol-lactose, and Formula 3 with lactose.

Result: Evaluation of granule quality and physical properties of the lozenge tablets showed that Formula 2, with 50% mannitol and 50% lactose concentration, had exhibited better granule quality and physical properties compared to the other formulations. It had a flow rate of 0.88 seconds, an angle of repose of 19.85°, a compressibility index of 10%, tablet friability of 0.33%, tablet hardness of 11.67 kg, and a disintegration time of 16 minutes. The antioxidant activity of the durian peel extract lozenge tablets was identified using the DPPH method, with vitamin C tablets and imboost lozenge tablets as positive controls.

Conclusion: The sample of durian peel extract lozenge tablet demonstrated higher antioxidant activity (IC_{50} value = 197.25 µg/mL) compared to the Imboost© lozenge tablet (IC_{50} value = 268.09 µg/mL). However, the antioxidant activity was still inferior to that of the vitamin C tablet, which had an IC50 value of 86.81 µg/mL.

Keywords: durian peel, lozenge tablet, antioxidant

BACKGROUND

Durian (*Durio zibethinus* Murr) belongs to the Bombaceae family, and is one of the most popular tropical fruits in Southeast Asian countries. In Indonesia, durian is one of the most popular fruits producing around 700,000 tons annually (Pratiwi *et al.*, 2021). High consumption of durian unknowingly contributes to plenty of durian peel waste. Based on research by Masturi *et al.* (2020), durian skin contains compounds belonging to the class of flavonoids, phenolics, alkaloids, steroids, saponins and terpenoids. Flavonoids are active compounds that determine the antioxidant content of a plant. Antioxidants have a crucial role in the health of the human body because they are inhibit oxidation by reacting with reactive free radicals to form unstable unreactive free radicals (Setyowati & Damayanti, 2014) .

*Correspondence: citrapramesti60@students.unnes.ac.id
[1]Pharmacy Department, Universitas Negeri Semarang, Indonesia
Full list of author information is available at the end of the article

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The use of traditional ingredients by the Indonesian people as medicine has been widely used for a long time but still in a simple form, such as boiled water. Along with the development of pharmaceutical science, many traditional ingredients have been formulated in dosage forms, such as tablets, capsules and instant powders. One of the reasons for using natural ingredients is that they have relatively minor side effects when compared to synthetic ingredients (Wulandari *et al* ., 2017; Pane *et al* ., 2021)

Tablets are medicinal ingredients in solid dosage forms, usually made with appropriate pharmaceutical additives (Allen et al., 2011)Tablets have the advantage of being low in production costs, the lightest and most compact oral dosage form, easy and cheap to pack and ship, and easy to produce on a large scale (Rubinstein, 2000 in Harbir, 2012). However tablets usually cannot mask a drug bitter taste. There is a type of tablet that can mask the bitter taste, namely lozenges. Lozenges are a type of tablet preparation that is easy to consume, especially for patients who have difficulty swallowing drugs, because the tablet directly contacts saliva in the mouth so that the tablet will dissolve gradually (Widayanti et al. (Widayanti et al., 2013)

This study aims to formulate lozenges of durian peel extract and test its antioxidant activity. Durian peel was extracted using the reflux method with ethanol solvent, then prepared into lozenges with various combinations of mannitol-lactose fillers using the wet granulation method, and the antioxidant activity was measured using the DPPH (2,2-diphenyl-1-picrylhidrazyl) method.

MATERIAL AND METHODS

Durian peels were collected from Gunungpati, Central Java, Indonesia. The chemicals used in the analysis of the raw material include aquadest, ethanol, methanol (Merck), quercetin (Merck), potassium acetate, $AlCl_3$, DPPH (2,2-diphenyl-1 picrylhydrazyl) (Sigma-Aldrich), rotary vacuum evaporator (basic RV 10 IKA), UV-Vis spectrophotometer (Shimadzu), oven, flow tester, hardness tester, friability tester, disintegration tester, and some glasswares.

Durian Peel Extraction

One hundred grams of durian peel powder sample was put into the reflux flask, and added with 1500 mL of ethanol solvent. Reflux was assembled and run at 85°C for 3 hours. The extract was thickened using a rotary evaporator at a temperature of 50°C, a pressure of 20 Psi and a rotation of 120 rpm.

Phytochemicals Screening

Phytochemical testing includes alkaloids, terpenoids, flavonoids, and phenolics. Testing for alkaloid compounds was performed by adding two drops of concentrated HCl and five drops of Dragendorff reagent to 2 ml of extract durian skin. Test for terpenoid compounds was performed by adding 0.5 mL of chloroform to 2 mL of sample, then adding 0.5 mL of acetic anhydrous acid and 2 mL of concentrated H_2SO_4. Phenolic compounds were tested using 2 mL of extract plus 2-3 drops of 1% $FeCl_3$ solution. The flavonoid compounds were tested with durian peel extract with 0.5 g of magnesium powder and 1 mL of concentrated HCl.

Formulation

The antioxidant tablet formula of durian skin extract was prepared by wet granulation with a weight of 1000 mg. The extract contained in each tablet is 8% or 80 mg.

Table 1. Formula of Lozenge from Durian Peel Extract

Material	F1	F2	F3
Durian peel extract	8%	8%	8%
PVP	5%	5%	5%
Talk	2%	2%	2%
Mg stearate	2%	2%	2%
Citrii oil	qs	qs	qs
Mannitol	83%	42.5%	-
Lactose	-	42.5%	83%

The thick extract of durian peel was first mixed with the mannitol lactose filler until homogeneous. The mixture was then added with PVP binder and then dripped with ethanol to form a lumpy mass, then sieved using a No. 12 mesh sieve to obtain granules. The granule was dried using oven at a temperature of 40-50°C. The dried granules were sieved again using a 12-mesh sieve.

Evaluation of Granule

Flowability test was conducted by putting as much as 10 g of granules into the funnel of *the flow tester,* which had previously been closed at the bottom. After that, the open button was pressed, and the time it took for all the granules to pass through the funnel was recorded. The height and diameter of the granules that came out from the funnel were measured to determine the angle of repose. Compressibility test is done by pouring granules into a 30 ml measuring cup, and recording the initial volume. The measuring cup is attached to the volumenometer and shaken to a constant volume, then terminal volume was recorded to measure % compressibility.

Tablet Evaluation

The organoleptic test was carried out by observing the shape, color, smell, and taste of the tablets of each formula. The weight variation test was carried out by weighing 20 tablets and calculating the average weight of each tablet. If weighed one by one, there may not be more than two tablets whose respective weights deviate from the average weight by more than the price set in column A6 and not one tablet whose weight deviates from the average weight by more than the price set by column B, as shown in Table 2.

Table 2. Acceptance Criteria of Weight Variation Test

Average tablet weight	deviation average weight in %	
	A	B
< 25 mg	15%	30%
26 - 150 mg	10%	20%
151 - 300 mg	7.5%	15%
> 300 mg	5%	10%

(Kementrian Kesehatan RI, 2020)

The tablet hardness test was carried out by placing the tablet into the hardness tester until it is precise, given pressure until the tablet cracks or crumbles. Tablet hardness is indicated on the scale when the tablet is broken with units of kg. The friability of the tablets was tested by taking 20 tablets, weighing them, and putting them into the friability tester, rotating them 100 times. All tablets were weighed, and the % of tablet weight loss was calculated. Disintegration time was tested by placing six tablets in the basket, then, the basket was raised and lowered 30 times per minute. The water used for soaking is around 37° C.

Test TFC (*Total Flavonoid Content*)

Determination of TFC (*Total Flavonoid Content*) was carried out using *the Aluminum Chloride Colorimetry method*. Before determining the TFC value, the maximum wavelength of 50 µg/ml quercetin was determined. After obtaining the maximum wavelength, the quercetin standard's calibration curve was made from a series concentration of 0-50 µg/ml dissolved in methanol pa. Solution test extract and 2 mL of lozenges were pipetted and then added with 0.1 mL of aluminum chloride solution (10% w/v) and 0.1 mL of potassium acetate solution with a concentration of 0.1 mM. The mixed solution was then incubated at room temperature for 30 minutes. Absorbance was calculated at a predetermined wavelength using UV-Vis spectrophotometer.

Test of Antioxidant Activity

Before testing of antioxidants activity, maximum wavelength of DPPH 60 µg/ml on wave range of 400-800 nm was determined. Test solution was made into five concentrations, namely 100, 125, 150, 175, and 200 µg/mL dissolved with methanol pa. Each solution was pipetted 100 µL, injected into microplate, added 100 µL of DPPH 60 µg/mL solution, incubated for 30 minutes, and measured the absorbance of the solution using a UV-Vis spectrophotometer at the maximum λ that had been determined previously.

RESULTS AND DISCUSSION

Phytochemicals Testing

Table 3. Results Of Phytochemicals Screening of Durian Peel Extract

Compound	Results	Interpretation
Alkaloids	Orange	+
Terpenoids	Red	+
Flavonoids	Orange	+
Phenolic	Blackish green color	+

The results of the phytochemical screening in this study showed that durian peel extract contains alkaloids, flavonoids, phenolics, and saponins.

TFC Test

Table 10. TFC extracts and lozenges Extract Durian skin

Sample	absorbance	TFC value (mg QCE/g DFLA)
Extract durian skin	0.705	34,11

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TFC test is a quantitative test for knowing the amount of flavonoids in a sample. Based on the table above, durian peel extract contains 34.11 flavonoids mg QCE/ g extract.

Evaluation of Granule

In the flow time test, angle of repose, and compressibility test of three formula, the result obtained in table 4.

Table 4. Results of Evaluation of Granule

Formulas	Flow time (second)	Angle of repose	Compressibility
1	0.92	20.38°	8.96%
2	0.88	19.85°	10%
3	0.89	20.11°	11.45%

Granule evaluation aims to determine the quality of the granules before they are pressed into tablets. The granule tests carried out include flow time, angle of repose and compressibility tests. Flow time must meet the requirements to produce tablets with uniform weight. The requirement for a good granule flow time is no more than 1 second for 10 grams of granules (Shehzad *et al*., 2019). Based on the flow time test result on granule 3 of the durian peel extract lozenge formula, all granules met the requirements of good flow time because the flow time <1 second.

The results of the test angles of repose of the three formulas is the three lozenges have an angle of repose that is in the very good category, less than 25° (Shehzad *et al*., 2019). The results of the test angles of repose of the three formulas are in accordance with the theory that the smaller the angle of repose of the granules, the better the flow properties of the granules. Based on the Carr's index criteria of compressibility, formulas one and two have a very good index, namely $\leq$ 10%, while formula three has a good index, 11-15% (Shehzad *et al*., 2019). A good granule compressibility will produce compact granules, resulting in tablets that do not break easily.

Tablet Evaluation

Durian peel extract is made in a lozenge preparation because it has the advantage that it can be easily consumed by pediatric and geriatric patients, increases drug retention time in the oral cavity, reduces gastric irritation and easy to use (Widayanti *et al*., 2013). In the formulation, a combination of mannitol and lactose is used as a filler. Fillers are made with variations combination of mannitol-lactose to be three formulas, there are: FI (mannitol 100%), FII (mannitol-lactose 50%:50%), FIII (lactose 100%). Variations combination was made with the aim of knowing the difference in evaluation of granule and tablets.

Test of Organoleptic

The result of organoleptic test of three formulas can be seen in table 5 and figure 1.

Table 5. Results test organoleptic

Observation	Formula 1	Formula 2	Formula 3
Form	Flat round	Flat round	Flat round
Color	Brownish-yellow	Brownish-yellow	Brownish-yellow

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Smell Flavor	Typical like herbs Sweet and cool	Typical like herbs Sweet and quite cool	Typical like herbs Sweet

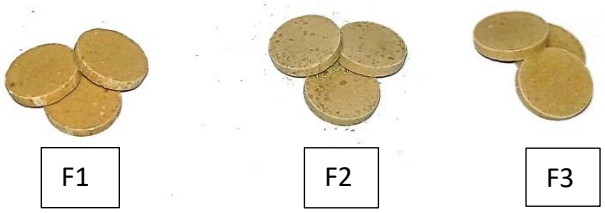

Figure 1. three of formulas lozenges

The shapes for tablets of the three formulas are flat and round, the color is brownish yellow, and smell similar to those of herbs from durian peel extract. Formula 1 had sweet and cool flavor, formula 2 sweet and quite cool, and formula 3 had sweet flavor.

Test of uniformity weight

Table 6. Results of the Weigh Variation Test

Formulas	Average weight	5%	10%	Result
1	991.03	941.5 <X> 1040.6	892.0 <X> 1090.1	Pass
2	994.9	945.1 <X> 1044.6	895.4 <X> 1094.4	Pass
3	1000.76	950.8 < X > 1050.8	900.7 < X > 1100.9	Pass

The measurement results of 20 tablets from each formula were weighed individually, and none of the tablet's weight deviated from the average weight in each formula.

Test of friability

Table 7. Friability of Lozenges Extract Durian Peel

Formulas	Friability	Requirement
1	0.36%	<1%
2	0.33%	
3	0.34%	

Based on the test results of the three formulas for lozenges of durian peel extract, each formula met the requirements for good tablet friability, which was less than 1% (Najihudin et al., 2021). The friability test aims to determine the resistance of the tablet surface to friction that occurs during packaging and shipping. The results of friability test were carried out by the One-way ANOVA test, the p value was 0.12, which means that there is no significant difference in each formula.

Hardness Test

Table 8. Results of Hardness Test of Lozenges Extract Durian Peel

Tablet	Tablet hardness (kg)		
	Formula 1	Formula 2	Formula 3
1	11 kg	11 kg	10.5 kg
2	10 kg	12 kg	11 kg
3	11.5 kg	12 kg	12 kg

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Average	10.83 kg	11.67 kg	11.17 kg

Based on the hardness test result, formula 2 had the highest tablet hardness value of 11.67 kg, followed by the third formula, 11.17 kg, and formula 1, 10.83 kg. The hardness test is carried out to determine the resistance of the tablet to the pressure applied. The three formulas for lozenges of durian peel extract have met the requirements for good tablet hardness, which is between 7-14 kg (Saputri *et al*., 2022). There is an interaction between mannitol and lactose which can increase the hardness of the tablet. Mannitol is a filler binder which produces tablets that are fracture resistant and abrasion resistant, and lactose has good compressibility properties so that the mixture of the two is able to produce tablets with high hardness. Hardness is influenced by the friability of tablet. The higher the friability, the lower the hardness of the tablet. The result of hardness test were tested for significancy using One-way ANOVA test. The p value was 0.73, which means that there is no significant difference in each formula.

Disintegration Time

Table 9. Results of disintegration time of Lozenges Extract Durian Peel

Formulas	Disintegration Time	Requirement
1	15 minutes	< 30 minutes
2	16 minutes	
3	16 minutes	

The disintegration time test aims to find out how long it takes for the tablet to disintegrate when exposed to a solution or liquid. The disintegration time requirement for lozenges is less than 30 minutes (Saputri *et al*., 2022). The test results of the three formulas for lozenges of durian peel extract showed that all formulas met the requirements for good disintegration time. In the statistical test with One-way ANOVA, the p value was 0.14, which means that there is no significant difference in each formula.

Based on the results of evaluating the physical properties of the lozenges, all formulas meet the requirements for a good lozenges. Formula 2 was chosen as the optimum formula because in terms of price, formula 2 with a combination of mannitol-lactose has a more affordable price compared to formula 1 which only uses mannitol. Formula 2 also produces tablets with a sweet taste and a slight cooling sensation in the mouth which comes from mannitol compared to formula 3 which only has a sweet taste because the filler used is 100% lactose.

Test of Antioxidant

The antioxidant activity test of the lozenges aims to see how much the lozenges can counteract free radicals. From the test results obtained results like the table 10.

Table 10. Sample IC_{50} Value and comparison

Sample	Linear equation	R^2	IC_{50} value (µg/mL)	Antioxidant category
Durian peel extract	y = 0.1217x + 36.152	0.9873	113.79	Moderate
Pure Vitamin C	y = 0.0953x + 46.098	0.976	40.94	Very strong

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Positive control	y = 0.0423x + 46.328	0.9383	86,81	Strong
F2 lozenges	y = 0.1127x + 27.77	0.9686	197.25	Weak
Imboost lozenges	y = 0.1499x + 9.814	0.9804	268.09	Very weak
Negative control	y = 0.0159x + 0.842	0.1723	3091.7	-

From the results of IC_{50} calculations in this study, pure vitamin C had the strongest IC_{50} value (below 50 µg/mL), followed by durian peel extract with moderate IC_{50} (100-150 µg/mL). Lozenges with a concentration of 8% durian peel extract have an IC_{50} value which is in the weak category, which is in the range of 150-200 µg/mL.

IC_{50} is defined as the sample concentration required to reduce the color intensity of the DPPH free radical by 50%. The lower the IC_{50} value, the better the sample's ability to scavenge free radicals. The IC value of$_{50}$ durian peel extract was 197.25 µg/mL, which means still much higher than the IC_{50} tablet of vitamin C because pure vitamin C has powerful antioxidant, while pure durian peel extract is in the moderate category. Another comparison used in this study is the Imboost lozenge® because is a famous lozenges containing natural ingredients which have benefits as antioxidants. The tablet had the weakest IC_{50} value of 268.09 µg/mL.

CONCLUSION

Based on the research that has been done, it can be concluded that durian peel extract can be formulated into lozenges with a combination of mannitol-lactose as fillers. The optimum formulation of durian peel extract lozenges is a formula with a combination of 50%:50% mannitol-lactose. The antioxidant activity of durian peel extract lozenges is 197.25 µg/mL.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

AUTHOR DETAILS

[1]*Department of Pharmacy, Universitas Negeri Semarang, Indonesia*
[2]*Department of Chemistry, Universitas Negeri Semarang, Indonesia*

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