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Formulation of Effervescent Tablet from Extract of Durian (*Durio zibethinus* Murr.) Peels and its Antioxidant Activity

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ABSTRACT

Background: Durian (*Durio zibethinus* Murr.) is a seasonal fruit that is abundant in Indonesia, leaving durian peel waste, which is usually thrown away after the durian fruit is consumed. Meanwhile, durian peel contains flavonoids, phenolics, alkaloids, steroids, saponins and several terpenoids. Based on the the literatures, durian peel has various pharmacological activities, one of which is as a source of antioxidants.

Aim: The study aims to formulate durian peel extract into effervescent tablets and evaluate their physical characteristic and antioxidant activity.

Method: This study used a quantitative descriptive method with test parameters including organoleptic, moisture content, ash content, polyphenol qualitative, polyphenol content and antioxidant activity

Result: The formula of effervescent tablets of durian peel extract was made with variations of the dry extract concentration of Formula 1 of 0%, Formula 2 of 16%, Formula 3 of 20%, and Formula 4 of 30%. Durian peel was extracted using reflux method with 96% ethanol solvent. Effervescent tablets of durian peel extract were then tested for physical properties and their antioxidant activity using the DPPH method.

Conclusion: The evaluation results show that all formulas meet the required standards. Formula 4 showed higher antioxidant activity compared to the other three formulas. Its IC_{50} value was 117.73 µg/mL, in the category of moderate antioxidant activity.

Keywords: Effervescent Tablets, Durian Peels, Antioxidants

INTRODUCTION

Infectious agents will easily penetrate the body's defenses and cause disease when the body's immune system is weak. Therefore, the human body needs an immune system to fight dangerous foreign substances or antigens such as fungi, bacteria, viruses and parasites as the body's defense mechanisms (Abbas *et al.*, 2018). One way to boost the immune system is to consume antioxidant-rich fruits or vegetables. The antioxidant mechanism in boosting the immune system occurs through antibodies, a specific protein that binds to an antigen so it becomes neutral and cannot infect the host cell (Kim *et al.*, 2021). Natural sources of antioxidants can come from a variety of plants, such as fruits, vegetables, spices, teas, or enzymes and proteins. Consuming sufficient amounts of antioxidants has been able to reduce the incidence of degenerative diseases, improve immunological status and inhibit the onset of aging-related degenerative diseases (Rahmi, 2017).

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Durian (*Durio zibethinus* Murr.) is a seasonal fruit whose presence is abundant in Indonesia, with a production of about 700,000 tons per year (Pratiwi *et al.*, 2021). According to data from the Central Agency of Statistics (2021), the production of durian (*Durio zibethinus* Murr.) in Indonesia by 2021 will reach 1.35 tons/year. As the production of durian increases, the amount of waste produced also increases. Durian peel is usually thrown away after being consumed. Meanwhile, durian peel contains flavonoid, phenolic, alkaloid, steroid, saponin, and several terpenoid compounds that underlie the durian peel having various pharmacological activities, one of which is as a natural source of antioxidants (Courtney *et al.*, 2014).

One form of preparation that available for development of pharmaceutical preparations is an effervescent tablet. An effervescent tablet is a form of preparation that produces a gas bubble as a result of a chemical reaction in a solution (Nariswara & Hidayat, 2013). This type of tablet will be dissolved in water and taken orally in the form of a solution (Greene *et al.*, 2016; Tanjung & Puspitasari, 2019). The effervescent tablets have many advantages compared to other preparations, including being easy to consume, quickly dissolving in water without having to be stirred, giving a refreshing effect like soda, and rapid absorption in the body because there is no need to wait for time to disintegrate (Pribadi & Sari, 2014). These advantages make effervescent tablets a great alternative for those who may have difficulty swallowing due to illness or age (Patel & Siddaiah, 2018).

The study aims to formulate durian peel extract in an effervescent tablet preparation. This type of dosage form is expected to be an alternative method to consume natural antioxidants. The effervescent tablet formula of durian peel extract was made with several variations of extract concentrations and then tested for antioxidant activity using the DPPH method and measured the IC_{50} value.

MATERIAL AND METHODS

The materials used include durian peel, 96% ethanol, Dragendorff's reagent, HCl, chloroform, anhydrous acetic acid, H_2SO_4, $FeCl_3$, magnesium powder, 10% Aluminium chloride, potassium acetate, quercetin, methanol, aquadest, citric acid, tartrate acid, aspartame, sodium bicarbonate, PEG6000, PVP K-30, mannitol, DPPH (1,1-diphenyl-2-picrylhydrazil), vitamin C, and Imboost® Effervescent tablets.

The tools used in the study are reflux, beaker glass, volumetric flask, blender, oven, rotary evaporator, analytical balancer, test tube, porcelain dish, water bath, dryer, aluminum foil, dripping pipette, volume pipette, spatula, measuring flask, mortar and stamper, mesh sieve 16 and 40, granulator machine, flow tester, tapped density tester, single punch tablet printer, friability tester, pH meter, and UV-Vis spectroscopic photometry.

Extraction of Durian Peel and Phytochemical Screening

The durian peel was cleaned with running water and then dried in the oven at 40-50°C. It was dried and then ground using a blender until it became powder. The powder was standardized for water and ash content. Durian peel was extracted using the reflux method. Ethanol was used as a solvent with a ratio of 1:10. The reflux was run at 85°C for 3 hours. The resulting extract was then thickened using a rotary evaporator.

The identification of flavonoid was done by adding 10 mL of hot water to 1 g of durian peel extract, boiling it for 5 minutes, and filtering it while hot. As much as 5 mL of the filtered product was added with 0.1 g of Mg powder and 5 drops of concentrated HCl. Positive result is indicated by color formation on the amyl alcohol layer. Alkaloid testing was carried out using Dragendorff's reagents. A total of 2 mL of extracted durian peel sample was poured into the test tube, then 2 drops of HCl and 5 drops of Dragendorff's reagent were added. The positive result is shown with the presence of a change color to orange (Wijaya *et al.*, 2013). Testing for phenolic compounds was carried out by adding 2-3 drops of $FeCl_3$ into 2 mL of sample extract. Positive results are indicated by the presence of blackish-blue or green. Testing for the saponin compound was carried out by putting 1 mL of the extract into the test tube, then adding 10 mL of aquadest and heating it over the water bath. The filtrate was shaken and waited for 15 minutes until stable foam was formed. A positive result was shown by the formation of foam on the sample.

Dried extract was produced by adding a filler to the thick extract of durian peel. The addition of filling material can maintain the stability of the bioactive components by avoiding excessive heat use. The mannitol filling material is added to the thick extract in a 1:3 ratio.

Formulation of Effervescent Tablet and Evaluation

The effervescent tablets were manufactured using wet granulation method, with formula presented in Table 1. The thick durian peel extract was diluted using mannitol in a 1:1 ratio. The homogenized mass was then sieved using a mesh No. 16 and dried at 50°C for ± 24 hours. The production of acid and base granules was done separately to avoid acid-base reactions. Acid granules were made by mixing citric acid, tartrate acid, and PVP, whereas the base granule was made by blending dry extract, sodium bicarbonate, aspartame, mannitol, and PVP. The mixture of acidic granules was poured gradually into the base granules and then sieved with mesh No. 16 and dried at 50°C for ± 30 minutes. After the granules were dried, the granules were sieved with mesh No. 40 and blended with PEG 6000.

Table 1. Formula *of Effervescent* Tablet from Durian Peel Extract

Material	F1 (%)	F2 (%)	F3 (%)	F4 (%)
Durian peel extract	-	16	20	30
Citrate acid	9.6	9.6	9.6	9.6
Tartrate acid	19.16	19.16	19.16	19.16
Na. Bicarbonate	32.43	32.43	32.43	32.43
PVP K30	0.5	0.5	0.5	0.5
PEG 6000	1	1	1	1
Aspartame	1	1	1	1
Orange essence	1	1	1	1
Mannitol	Ad 100%	Ad 100%	Ad 100%	Ad 100%

The granules were evaluated for flowability and compressibility. As much as 100 g of granules were weighed. The samples were poured through a funnel. The time required by the granule to pass was recorded (Hadisoewignyo dan Fudholi, 2013). The diameter (D) and height of the granule (H)

were measured in cm to calculate angle of repose. To calculate compressibility, 50 g of granules were poured into the measuring cylinder and recorded as the initial volume (V1), then it was tapped 20 times, and recorded for the final volume (V2). The effervescent granules that have been evaluated were subsequently printed into tablet shapes using a single punch device with a diameter of 18 mm.

The effervescent tablets were tested for organoleptic, weight variance, friability, dissolving time, and pH. Organoleptic testing was carried out by directly observing the shape, color, smell, and taste of the effervescent tablet (BPOM RI, 2014). Weight variance of tablets were tested by weighing twenty tablets individually. The average (W_0) and percentage of deviation of each tested tablet to average (W_1) were calculated. The acceptance criteria is that there are no more than two tablets whose weight deviation is greater than the value specified in column A (5%), and no tablet whose weight deviation is greater than the value specified by column B (10%) (Depkes RI, 1979).

Friability test was conducted using friability tester. Twenty tablets were cleansed from dust and then weighed (A). The tablets were put into the friability tester and rotated for 4 minutes at a speed of 25 rpm (100 rounds). Tablets were cleaned from dust and then weighed (B). The acceptance criteria is weight loss ≤ 1% (Noorjannah dan Noval, 2020).

Dissolving time of the effervescent tablet was conducted by calculating the time required for effervescent to dissolve completely in 200 mL of water (Pribadi & Sari, 2014). The solubility time of effervescent tablets containing herbal extracts is less than 5 minutes (BPOM RI, 2014). The pH of the solution of effervescent tablets was measured as well. The tests are performed in 3 repetitions. The acceptance criteria for pH was 5-7 (Herlina *et al.*, 2020).

Antioxidant Test of Effervescent Tablet from Durian Peel Extract

Antioxidant activity was tested using UV-Vis spectrophotometry. DPPH standard solution was made by dissolving 1 mg of DPPH in 10 mL of methanol (100 ppm). A blank DPPH solution was made by diluting 6 ml of 100 ppm of a standard solution of DPPH in 10 mL of methanol (60 ppm). It was used for maximum wavelength determination. Vitamin C solution was prepared by dissolving 10 mg in 10 mL of methanol (1000 ppm). As a positive control, three Imboost Effervescent tablets were crushed. As much as 10 mg of powder was dissolved in 10 mL of methanol (1000 ppm concentration). The sample solution was prepared using the same method using 3 effervescent tablets of durian peel extract. The solutions were made with concentrations of 100 ppm, 125 ppm, 150 ppm, 175 ppm, and 200 ppm. The test solutions were incubated at room temperature for 30 minutes. The absorption is measured at the maximum wavelength obtained.

RESULTS AND DISCUSSION

Extraction of Durian Peel and Phytochemical Screening

Durian peel was dried before to reduce water content so that microbes do not easily contaminate it. Then, dried durian skin was ground using a blender into powder to increase the surface area, hence facilitating the penetration of solvents into it so that the extraction runs efficiently. The powder was then standardized for water content and ash content to ensure the quality of raw material. The water content of durian peel powder was 6.53%. It met the requirement, which stated no more than 10% (Departemen Kesehatan RI, 2017). The ash content obtained from durian peel powder was 17.11%. The ash content was an indication of the total mineral content of durian peel powder.

Durian peel powder was extracted by the reflux method using an ethanol solvent (ratio 1:10). The reflux method is more effective for extracting durian peels because it involves heating and soaking in the process of separating the active compound. The use of heat in the reflux method causes the cells in the durian peels to open so that more extract is produced compared to the maceration method, which does not use heat.

The solvent used in the extraction process must be chosen based on the target compound. Flavonoids are polar compounds, so ethanol is a suitable solvent for extracting them. Ethanol has the same polarity as the durian peel when compared to a more polar solvent such as methanol. In addition, the selection of ethanol as a solvent in the extraction process is also based on its more affordable price as well as its relatively non-toxic properties when compared to other organic solvents such as methanol and acetone. The yield of durian peel extract was 3.86%.

Phytochemical tests were carried out to identify the content of the active compound contained in the durian peel extract. In this study, the phytochemical tests carried out were flavonoid, alkaloid, phenolic, saponin, and terpenoid tests. In phytochemical tests, it was found that durian peel ethanol extract contains flavonoid, alkaloid, phenolic, and saponin compounds.

Table 2. Phytochemical Test Results of Ethanol Extract of Durian Peel

Compounds	Reagent	Result	Indicator
Flavonoids	+ 0.1 grams of Mg powder + 5 drops of concentrated HCl	+	Orange color
Alkaloid	+ 2 drops of concentrated HCl + 5 drops of Dragendorff's reagent	+	Orange color
Phenolic	+ 2-3 drops of $FeCl_3$	+	Greenish-black color
Saponins	+ 10 mL aquadest	+	Stable foam formed

Formulation of Effervescent Tablet and Evaluation

Granules were made previously before the tablet pressing to increase the size of the particles of the effervescent powder into larger particles, hence improving the flowability of the powder. Evaluations were carried out on granules, including flow time testing, angle of repose, and % compressibility. The appearance of granules is presented in Figure 1.

Figure 1. The appearance of granules of durian peel extract before pressing into tablets (from left to right: F1, F2, F3, and F4).

Flow properties of granules can be assessed by testing flow time and angle of repose. Granules with a good flow time will flow more easily from the hopper to the die hole in the tablet printer machine so that the weight consistency and dosage accuracy are higher (Noval *et al.*, 2021). Based on the flow time test results (Table 3), the four formulas have flow time rates ranging from 6-9 seconds/100 grams of granules. The results show that all formulas passed. The size and shape of particles can influence the properties of granules. Granules with increasing size and increasing round shape show better flow properties (Kusuma *et al.*, 2014). Besides meeting the requirement of flow time, all formulas also met the angle of repose test, with 'good' to 'fairly good' granule flow properties. The value of the angle of repose will affect the quality of the tablet after the tablet pressing. The smaller the angle of repose, the better the characteristics of the granule.

Table 3. Results of Granule Evaluation

Formula	Flow Time	Angle of Repose	% Compressibility
F1	6.62	33.34°	17.4
F2	6.18	28.23°	16.4
F3	6.85	31.67°	17
F4	8.7	36.6°	18.6
Requirement	100 grams ≤ 10 seconds (Hadisoewignyo and Fudholi, 2013)	20° - 40° (Noval *et al*, 2021)	< 20% (Noval *et al*, 2021)
Conclusion	Pass	Pass	Pass

Percent of compressibility was performed to determine the capacity of a granule to be compressed. Low values indicate good flow properties of a granule. All formulas have % compressibility values with ranges between 16 - 18% (good compressibility), hence meeting the requirement (Hadisoewignyo and Fudholi, 2013). Compressibility may affect the uniformity of the tablet pressing.

Organoleptic evaluation was performed on all tablet formulas. Results in Table 4 show that all formulas have the same shape. Formula 2,3 and 4 have the same color, smell, and taste. While formula 1, which does not contain extract, produces different organoleptic results from other formulas. The addition of the active ingredients of durian peel extract produced the brownish yellow color of formula 2,3, and 4 tablets. All formulas produce tablets with the same smell of orange due to the addition of orange essence in the same amount. Formula 1 produces a stronger orange smell than any other formula since there is no interference from durian peel extract. The flavors produced in formulas 2, 3, and 4 were the same: slightly bitter acid. These were due to the use of two different types of acids, citric acid and tartrate acid, while the bitter taste is derived from the addition of the active substance, durian peel extract. The acid that reacts with the base produces the final product of salt, which causes a salty taste. The addition of sweeteners, such as aspartame, to all formulas improved the flavor of the effervescent tablet.

Table 4. Effervescent Tablets Organoleptic Test Results

Formula	Shape	Color	Odor	Flavor
F1	Flat tube	White	Orange	Salty
F2	Flat tube	Yellow-brown	Orange (smell faint)	Slightly bitter acid
F3	Flat tube	Yellow-brown	Orange (smell faint)	Slightly bitter acid
F4	Flat tube	Yellow-brown	Orange (smell faint)	Slightly bitter acid

Tablet weight uniformity may affect the dose. According to the Farmakope Indonesia Edition III (1979), of 20 tablets that have been weighed individually, there must not be more than two tablets whose weight deviates 5% from the average weight and none of the tablets which deviate 10% from the average weight (Table 5). The results showed that all tested tablets from all formulas met the specified weight deviation from the average.

Table 5. Weight Uniformity of Effervescent Tablet Test Result

		Weight (mg)			
		F1	**F2**	**F3**	**F4**
Average		1005.35	990.3	995.6	999.3
A Column (5%)	min	955.05	940.8	945.8	949.4
	max	1055.65	1039.8	1045.4	1049.2
B Column (10%)	min	904.85	891.27	896.1	899.4
	max	1105.85	1089.3	1095.1	1099.2
Conclusion		+	+	+	+

The friability test aims to determine the resistance of tablets to friction that may occur during packaging and delivery. From the results of the tests, it can be concluded that all formulas have met the requirements, which is less than 1% (Siregar dan Wikarsa, 2010).

Table 6. Effervescent Tablets Friability Test Result

	Friability				
	F1	**F2**	**F3**	**F4**	**Requirements**
Weight A (g)	20.10	19.80	19.91	19.98	< 1% (Siregar dan Wikarsa,
Weight B (g)	18.59	17.05	17.65	17.45	2010)
%Friability	0.08	0.16	0.12	0.14	
Conclusion	+	+	+	+	

The effervescence dissolving time aims to find out how much time the tablet takes to solve perfectly in water with a certain volume. From the test results (Table 7), all formulas have met the requirements for an effervescent tablet because it is solved in less than 5 minutes. The addition of binders in small concentrations caused quick dissolution time.

Table 7. Dissolving Time of Effervescent Tablet

Formula	Average of Dissolving Time (seconds)	Requirements	Conclusion
F1	91.6	< 5 minutes or 300 seconds (BPOM RI,2014)	Pass
F2	177		
F3	149		
F4	132.6		

The pH test on the solution of effervescent tablets of durian peel extract aims to determine the level of acidity of the produced tablet. The pH of the efferfescent solution will affect the acceptance from consumers. pH value for each formula is presented in Table 8.

Table 8. pH Value of Effervescent Tablet

Formula	Average of pH	Requirements	Conclusion
F1	6	5-7 (Herlina *et al*., 2020)	Pass
F2	6.34		
F3	6.17		
F4	5.3		

Antioxidant Test of Effervescent Tablet from Durian Peel Extract

The antioxidant test method used in this study is the DPPH method. DPPH (2,2-diphenyl-1-picrihydrazyl) is a stable free radical replacement compound that is often used in antioxidant testing. The antioxidant activity of a compound can be evaluated by reduced absorption using UV-Vis spectroscopic photometry and changing the color of the solution from purple to yellow. Vitamin C was chosen as a comparator because of its high antioxidant capacity, feasibility to obtain, and high polarity compared to other vitamins. The absorption of each sample and positive control was then calculated for their % inhibition value and IC_{50} value. The IC_{50} values of each sample and comparator are shown in Table 8.

Table 8. The IC_{50} Value of Sample and Control

Sample	Linear Equation	IC_{50} (µg/mL)	Antioxidant Category
Vitamin C	y = 0.0954x + 46.093	40.95	Very Strong
Extract	y = 0.1328x + 36.428	110.14	Medium
Imboost	y = 0.1199x + 42.363	63.69	Strong
Base + Vit.C	y = 0.1139x + 39.205	94.78	Strong
F1	y = 0.1926x + 10.722	203.94	Very Weak
F2	y = 0.1751x + 17.243	187.08	Weak
F3	y = 0.1759x + 19.212	175.03	Weak
F4	y = 0.4009x + 2.8009	117.73	Medium

The IC_{50} value indicates the amount of concentration of the sample that can inhibit free radical activity by 50%. The smaller the IC_{50}, the stronger the antioxidant activity. Based on the results of the test (Table 9), the lowest IC_{50} value was shown by pure vitamin C (IC_{50} value 40.95 μg/mL, followed by Imboost with a value of 63.69 μg/mL. The effervescent tablet of durian peel extract F2, F3, and F4 showed IC_{50} values of 187.08 μg/mL, 175.03 μg/mL, and 117.73 μg/mL, respectively (Table 8). The IC_{50} value of the extract before formulated was 110.14 μg/mL. There were IC_{50} decline of the extract before and after formulation. This is due to the addition of lower amounts of extracts as well as the use of organic acids such as citric acid and tartrate acid in the effervescent tablet formulation of durian peel extract, thus affecting the content of active substances and antioxidant activity found in each formulation.

Antioxidant activity was carried out on the base also to ensure whether the excipients affect the antioxidant activities of the effervescent tablet of durian peel extract. Ideally, the excipients should be inert so that they do not affect the activity of the active substance (Rosch *et al.*, 2021). The results showed that F1 (effervescent base) had weak antioxidant activity. This might be due to citric acid. These findings are supported by a study conducted by Putri *et al*. (2022), which stated that the concentration of citric acid affects antioxidant activity. Of all formulas, F4, which contained most extracts (30%), showed the strongest antioxidant activity.

In this study, Imboost effervescent tablets were chosen as a positive control. It showed stronger antioxidant activity compared to the durian peel extract. The antioxidant activity of Imboost effervescent tablets were caused by their active ingredients, *Echinacea purpurea* and Vitamin C.

CONCLUSION

In this study, durian peel extract was formulated into 1000 mg effervescent with varying extract concentrations of 0%, 16%, 20%, and 30%. The excipients used in the formulation are citric acid (9.16%), tartrate acid (19.16%), sodium bicarbonate (33.43%), PVP (0.5%), aspartame (1%), PEG 6000 (1%), orange essence, and mannitol. All formulas showed good physical properties and meet the requirements. Formula 4, with the highest concentration of extract, showed the highest antioxidant activity compared to the other formulas.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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