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INSTANT GRANULE FORMULATION COMBINING WHITE SWEET POTATO LEAVES EXTRACT (*Ipomoea batatas* (L.) Lam.) AND JAVANESE CHILI (*Piper retrofractum* Vahl)

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ABSTRACT

Dengue haemorrhagic fever is a viral infection transmitted by the Aedes aegypti mosquito, which is one of the symptoms is thrombocytopenia. The extract from white sweet potato leaves is recognized for its potential to increase the number of platelet count. This research aimed to develop a formula for an instant granule combining white sweet potato leaves extract with Javanese chili extract meeting taste preferences and societal acceptability. The preparation of the extract was performed by maseration using 70% ethanol and then concentrated with a rotary evaporator. The result was a thick extract which was then dried in an oven at 50℃. The manufacture of instant granule formulations was conducted using wet granulation method. Various formulations were obtained by differentiated concentration of Javanese chili used in the formula (FI 1%, FII 2%, and FIII 3%). The instant granule formulation was evaluated by organoleptic assay and other essential parameters for instant granule, such as moisture content, flow rate, angle of repose, and particle size distribution. The FII 2% formulation emerged as the most acceptable with an average score of 2.17. Non-parametric analysis indicated no significant difference among the three formulas, as the obtained significant value (α) was ≥ 0.05, leading to the acceptance of the null hypothesis H_0.

ABSTRAK

Formulasi Granul Instan Kombinasi Ekstrak Daun Ubi Jalar Putih (*Ipomoea batatas* (L.) Lam.) dan Ekstrak Cabe Jawa (*Piper retrofractum* Vahl)

Demam berdarah dengue adalah infeksi virus dengue yang ditularkan melalui nyamuk *Aedes aegypti* yang salah satu gejalanya yaitu trombositopenia. Ekstrak daun ubi jalar putih diketahui berpotensi dapat meningkatkan jumlah trombosit terhadap demam berdarah dengue. Tujuan penelitian ini untuk memperoleh formula dari ekstrak daun ubi jalar putih yang dikombinasikan dengan ekstrak cabe jawa, dalam bentuk sediaan granul instan yang memenuhi persyaratan dan rasanya dapat diterima. Ekstraksi daun ubi jalar putih dan cabe jawa dilakukan menggunakan metode maserasi menggunakan pelarut etanol 70% dan dipekatkan menggunakan *rotary evaporator*, hingga diperoleh ekstrak pekat. Ekstrak ini kemudian dikeringkan pada suhu 50 ºC. Metode pembuatan formula granul instan dilakukan dengan cara granulasi basah. Penggunaan ekstrak cabe jawa divariasikan sebanyak 1-3%, yaitu FI 1%, FII 2% dan FIII 3%. Sediaan granul instan ekstrak daun ubi jalar putih kombinasi cabe jawa dievaluasi secara kualitatif meliputi uji organoleptis, uji kadar air, uji waktu alir dan sudut diam, uji distribusi ukuran partikel, uji waktu melarut dan uji hedonik (tingkat kesukaan). Hasil uji menunjukkan bahwa formula granul instan yang paling disukai adalah FII. Namun secara statistik, penerimaan terhadap ketiga formula tidak memiliki perbedaan yang nyata, karena didapatkan nilai *(α) ≥ 0,05* yang menunjukkan bahwa Ho diterima.

Kata kunci: Demam Berdarah; Ekstrak Daun Ubi Jalar Putih; Ekstrak Cabe Jawa; Granulasi Basah; Granul Instan.

INTRODUCTION

Dengue fever (DF)/*dengue haemorrhagic fever* (DHF) is an infectious disease caused by the dengue virus which could be transmitted by the *Aedes aegypti* mosquito with clinical manifestations of fever, muscle aches and/or joint pain accompanied by leukopenia, rash, lymphadenopathy, thrombocytopenia, and haemorrhagic diathesis. Dengue fever poses a of the significant health challenge in Indonesia with 95,893 reported cases of DHF and 661 deaths in 2020. The majority of those affected were aged 15 - 44 years (37.45%), followed by ages 5-14 years (33.97%), and ages 1–4 years (14.88%). The disease tends to spread more widely in line with increasing mobility and population density (Kementerian Kesehatan RI, 2020) . The primary cause of death in DHF patients is associated with a reduced number of platelets, leading to blood escaping into the tissues (bleeding) and ultimately causing blood vessels to lack of fluid and oxygen (Hoffbrand *et al*., 2005).

Treatment of DHF generally involves supportive treatment, focusing on alleviating symptoms like pain, nausea, fever, while addressing various medical parameters. This includes giving Ringer's lactate infusion to prevent dehydration. Many kinds of alternative medicine have been traditionally applied by the community for generations. The use of natural medicines is believed to be able to offer protection and improve of community health. One plant that has been proven efficacious in helping to increase platelet is white sweet potato leaves. Based on the results of Damayanti's research, the ethanol extract of white sweet potato leaves (*Ipomoea batatas* (L.) Lam) could provide platelet-increasing activity at a dose of 100 mg/kg body weight (BW) in male rats, equivalent to the positive control used, namely quercetin (Damayanti, 2011). The administration of aqueous extract to sweet potato at a dose of 80 mg/kg BW showed no toxic effects on liver histopathology. Similarly, the administration of a dose of 1000 mg/kg BW did not result in any changes in the haemoglobin levels of white rats (Regina *et al*., 2020). The active compounds contained in purple sweet potato leaves, extracted with 70% ethanol, exhibited a total phenol content of 4.786 (mgGAE/g) and a total flavonoid content of 4.634 (mgOE/g) (Irawan *et al*., 2020).

Based on this research study, an instant granular preparation was made of white sweet potato leaves extract (*Ipomoea batatas* (L.) Lam) which is combined with Javanese chili extract (*Piper retrofractum* Vahl) to covered unpleasant taste of sweet potato leaves. Javanese chili has immunomodulatory activity as an immunostimulant at a dose of 5.6 mg/20 g body weight (Roseno *et al*., 2019). Javanese chili extracted by using 80% ethanol solvent has a strong anti-bacterial, which has inhibition zones on the growth of *E. coli* and *S. aureus* of 17.12 mm and 15.76 mm (Sari *et al*., 2020). According to research finding of Klawikkan *et al* (2011), Javanese chili contains piperine alkaloids, pipernonalin, and dehydropipernonalin which possess anti-dengue properties (Klawikkan *et al*., 2011).

Instant granule is a product in the form of spheres or aggregates that are regular in shape and served by brewing, so that their application is more practical and attractive. Formulation of instant granules was carried out by using the wet granulation method, which expected to improve flow properties and longer storage time (Parikh, 2021). In this study, a health drink formulation was carried out using the basic ingredients of Javanese chili extract and extract of sweet potato leaves. Three variations of the formulations with differences in the amount of Javanese chili extract were evaluated, according to the parameters and requirements for traditional medicinal product in the form of instant granules as specified by National Agency Drug and Food Control (BPOM).

MATERIALS AND METHODS

Materials

The plant and chemical materials used in this study included white sweet potato leaves were obtained from Ngasuh Village, Jasinga District, Bogor Regency, West Javanese, while Javanese chili (*Piper retrofractum* Vahl) was provided by the Bogor Medicinal Plant Research Institute (BALITRO), 70% ethanol, aquadestilata, anhydrous lactose, stevia sweetener, polyvinyl pyrrolidone (PVP), chloroform ($CHCl_3$), Dragendorff reaction (potassium iodide, acetic acid), Mayer's reagent (10% hydrochloric acid, 10% ammonia and chloroform).

The equipment used in this study included a grinder, analytical balance, mesh sieves (No. 12, 16, and 60), drying cabinet, oven (Memmert), rotary evaporator RE300 (vacuum pump RE3022C (Stuart)), digital waterbath RE300D

(Stuart), stopwatch, flowmeter, mortar and pestle, desiccator, and glassware for laboratory use.

Methods

Extraction (Irawan et al., 2020)

Extraction is carried out through maceration method. 500 g of white sweet potato leaves simplicia powder and 600 g of Javanese chili were put into a 5 litres bottle then macerated using 70% ethanol solvent with a ratio of 1:3 (v/v) for 1 x 24 hours, then filtered. The filtrate was then concentrated using a vacuum rotary evaporator and dried in a drying cabinet (temperature 50 °C) until a thick extract was obtained.

Extract yield is calculated by the formula:

$$\text{Yield (\%)} = \frac{weight\ of\ extract}{weight\ of\ extracted\ simplicia}\ x\ 100\%$$

Phytochemical screening (Harborne, 1998; Marjoni, 2016)

Phytochemical screening was carried out to determine the content of secondary metabolites (alkaloids, flavonoids, tannins, phenols and saponins) from Javanese chili and white sweet potatoes.

Instant Granule Formulation

The health drink formulation, which is combination of extract of white sweet potato leaves and Javanese chili is made in the form of instant granules through wet granulation method. The formula used in this study were shown in Table 1.

Instant Granule Evaluation

Organoleptic Test

Organoleptic tests were carried out to see the physical appearance of the obtained granule by observing the shape, colour and flavor of the formulas that had been made (BPOM RI, 2019).

Determination of Water Content (Depkes RI, 2020)

The water content determination was determined following gravimetric method. The samples were heated in the oven at a temperature of 105 °C for 3 hours and reheated for 1 hour, then repeated every 30 minutes until the weight is constant. The determination of the water level was calculated based on the difference in weight of the samples before and after heating.

Flow Time and Angle of Repose (Voight, 1995).

Granule Flow Test Meter was used to determine the flow time and angle of repose of the formula. The flow time of the granules is tested by weighing ± 25 grams of the granule mixture, inserting it into the flow test meter in the form of a funnel, and calculating the flow time for the granule mixture. Flow properties are good if ± 25 grams of the granule mixture flows for no more than 10 seconds. The angle of repose (Θ) was calculated using the formula below.

$$\text{Tan}\ \theta = \frac{h}{r}$$

h = height of the cone

r = diameter of the radius

If the angle of repose is less 25° it indicates that the powder can flow freely if the angle is greater than or equal to 40° usually the flowing ability is categorized poor (Lachman *et al*., 1994).*Particle Size Distribution*

Sieves of different mesh sizes were consecutively arranged from top to bottom, with the largest sieve number at the top. The weighed granules were placed on the top sieve and vibrated for 5 minutes. Then, the granules trapped in each sieve and the pan were weighed. The objective of this test was to obtain a good grain distribution and % fines of <10 % (Lachman *et al*.,1994).

Table 1. Granule instant formulas per 10 g (Hertati *et al.*, 2016)

Ingredients	Function	Formula I	Formula II	Formula III
		(% Weight/weight)		
White sweet potato leaves extract	Active substance	11.2	11.2	11.2
Javanese chili extract	Active substance	1	2	3
PVP	Binder	5	5	5
Stevia	Sweetener	1	1	1
Lactose	Filler	Add 100	Add 100	Add 100

Table 2. Weight and Yield of Extract

Ethanol (%)	Javanese chili	White sweet potato leaves
70	94.25 g; 15.70%	139.78 g; 27.96%

Notes: Simplicia of Javanese chili 600 g and white sweet potato leaves 500 g were extracted using 70% ethanol solvent with a ratio of 1:3

Table 3. Result of Phytochemical Screening

No	Phytochemical parameter	Result of phytochemical test	
		Javanese chili	White sweet potato leaves
1.	Alkaloid	+	+
2.	Flavonoid	+	+
3.	Saponin	+	+
4.	Tanin	+	+
5.	Phenol	+	+

Solubility

Each instant granule of formulas I, II and III were weighed to the equivalent of 10 grams and then dissolved in 200 mL of water at 37°C then observed by the naked eye in the light until it seems homogeneous. The time required for the granules to dissolve was then recorded. The standard time required for the granules to dissolve is less than 5 minutes (Siregar & Wikarsa, 2010) .

Hedonic Test

The test was conducted by involving 30 adult respondents. Respondents were firstly asked to be evaluated undissolved granules that is to evaluate the color, flavor, and texture. Secondly, the respondents were asked to evaluate the granules which are dissolved in water. Then the respondents were asked about their responses and acceptance of the taste, flavor, solubility, and colour of the instant granules. Instant granules are declared to meet the requirements or be considered acceptable if more than 50% of respondents confirm their acceptance of the instant granules (Kharis & Alifah, 1996; Zaddana *et al*., 2022).

RESULT AND DISCUSSION

Simplicia Extraction Results

It is well established that the type of extracting solvents greatly impacts to obtaining maximum yields of the substances. Our previous study found that ethanol are efficient solvents for extraction process (Irawan *et al*., 2020). In this study, extraction results with 70% ethanol produced more sweet potato leaves extract than Javanese chili, this indicates that the volatile compound content of sweet potato leaves is more soluble in water or in polar solvents compared to Javanese chili (Table 2). In line with our result, previous study indicated that sweet potato leaves possess a number of water-soluble components (Zhang *et al*., 2019).

Phytochemical Screening

Phytochemical screening is aimed to qualitatively analyse compounds from secondary metabolites, including alkaloids, flavonoids, phenols, tannins and saponins, in Javanese chili and white sweet potato leaves. A summary of the results of the phytochemical screening can be seen in Table 3.

Based on the test results for the alkaloid content, it was confirmed that the extract contained alkaloids as evidenced by the formation of a white precipitate upon the addition of Bouchardat reagent. In line with this, positive results for Javanese chili and white sweet potato leaves extract were also demonstrated in the Dragendorff test, revealing the formation of a brick red precipitate. Examination of alkaloids by adding Mayer, Bouchardat and Dragendorf reagents previously added HCl because alkaloids are alkaline, so they must be extracted with a solvent containing acid (Harborne, 1998). In the flavonoid test, filtrate which was added with metal Mg gives a red color after adding of HCl, this shows a positive result for the presence of flavonoids, this occurs because of the interaction between flavonoid compounds and metal Mg to form flavilium salts which cause color changes (Sangi *et al*., 2012).

The results of the phenol identification test showed positive results, as evidenced by the formation of a blackish brown color after the addition of $FeCl_3$. This colour changes occur due to the reaction between $FeCl_3$ compound and the hydroxyl groups present in phenol compounds (Marliana, 2007). The tannin identification test obtained a white precipitate formed from the addition of gelatin, this is because tannins interact with gelatin to form water-insoluble copolymers (Simaremare, 2014).

The extract gave positive results in the saponin test. The foam produced was about 5 cm after being allowed to stand for 10 minutes and the foam was not lost by the addition of 2N HCl, the foam produced was due to the hydrophilic groups

that bind to water and the hydrophobic groups which bind to air. After the foam is formed, HCl is added which increases the polarity so that the hydrophilic group will bind to the foam (Hayati & Halimah, 2010).

The secondary metabolites from natural sources, particularly Javanese chili and white sweet potato leaves, are known to have potential bioactivity in treating several diseases, including dengue fever. Previous studies reported an antiviral activity of the natural alkaloid and flavonoid against dengue virus through the inhibition of its replication (de Castro Barbosa *et al*., 2022; Quintana *et al., 2020)*. Furthermore, (Figueiredo *et al*., 2021) revealed that ethanolic extracted saponin from medicinal plants exert a high virucidal activity against DENV-2 without cytotoxic effect in in vitro study. The effects of instant granule from this study and its underlying mechanisms on dengue fever, however, remained to be elucidated. Further studies are necessary to be attempted to determine it.

Instant Granule Formulation

Instant granule from white sweet potato leaves extract and Javanese chili extract was made into 3 various formulas which is shown in Table 4 (Hertati *et al*., 2016). Formula variations were aimed to find out which formula is preferred by the public or consumers, which will be studied through a hedonic test.

Instant Granule Evaluation

Organoleptic Test

From the results of organoleptic examination of instant granules of the three formulas, namely formulas I, II and III, can be concluded that there are no significant differences in color, but the taste and flavor are significantly different, this is might due to differences in the concentration of Javanese chili extract added in the formulations.

Determination of Water Content

Determination of water content is carried out since the moisture content is closely related to the flow properties, angle of repose, particle size and storage process. This test was conducted to ensure that water content in the granules is less than 10%. If the water content is higher than 10%, it might affect the flow time, angle of repose, storage time, and shelf life, since high water content might allow bacteria to growth, as well as mold and yeast, which might lead to produce a different taste. The results of the water content measurement indicated that the water content of the three formulas were as follow: FI 1.15%, FII 1.75%, and FIII 2.28%. These numbers signified that these formulas meet the requirements for granule, as the required limit falls between 3-5% (Hadisoewignyo & Fudholi, 2013).

Flow Time and Angle of Repose

One of the most important things in the production of solid dosage forms is the flow properties of the granules. The mass flow will affect the weight uniformity in the product.

The angle of repose is the fixed angle that occurs between the heap of conical particles and the horizontal plane. If a few granules or powders are poured into the measuring device, the size of the angle of repose is affected by the shape, size, and humidity of the powder.

The granule flow time test was carried out to determine the flow time of the granules flowing in the funnel, with the amount of powder flowing per unit of time (Parikh, 2021). The results of determining the average granule flow time of FI, FII and FIII were 3.43, 3.86, and 4.17 seconds respectively, which were categorized as good flow time requirements criteria, since the flow times were less than 10 g/sec as defined in the requirement (Siregar & Wikarsa, 2010).

Table 4. Granule Evaluation Results

Formula	Water content (%)	Flow time (g/sec)	Angle of Repose (°)	Granule size (μm)	Solubility at 37 ºC (min)
F1	1.15 ± 0.02	3.43 ± 0.64	12.09 ± 0.59	790.4	2.92 ± 0.04
F2	1.75 ± 0.12	3.86 ± 0.41	12.02 ± 0.69	783.9	3.12 ± 0.02
F3	2.28 ± 0.15	4.17 ± 0.30	11.73 ± 0.61	805.3	3.17 ± 0.03
Requirements (Siregar & Wikarsa, 2010)	3 - 5	Not more than 10 second	25 - 45	250 - 2000	Less than 5 minutes

Table 5. Average Results of Hedonic Test on Undissolved Instant Granules

Test Parameters	Undissolved Instant Granules					
	Formula I		Formula II		Formula III	
	Total score	Average	Total score	Average	Total score	Average
Color	104	3.47 ± 0.57	102	3.40 ± 0.50	99	3.30 ± 0.60
Flavour	103	3.34 ± 0.57	105	3.50 ± 0.51	95	3.17 ± 0.70
Texture	97	3.23 ± 0.57	105	3.50 ± 0.57	102	3.40 ± 0.56

Table 6. Average Results of Hedonic Test on Dissolved Instant Granules

Test Parameters	Dissolved Instant Granules					
	Formula I		Formula II		Formula III	
	Total score	Average	Total score	Average	Total score	Average
Solubility	105	3.50 ± 0.68	113	3.77 ± 1.07	110	3.67 ± 0.55
Color	93	3.10 ± 0.80	102	3.40 ± 0.86	104	3.47 ± 0.63
Flavor	99	3.30 ± 0.84	97	3.23 ± 0.82	91	3.03 ± 0.61
Taste	96	3.20 ± 0.55	111	3.70 ± 1.15	101	3.37 ± 0.49

The difference in the angle of repose serves as indirect method for assessing the ability of flow properties, determined through the funnel method. The angle of repose test identified the maximum angle formed on the surface of horizontal stack. The size of the repose angle is strongly impacted by the frictional and tensile forces between the granule particles. The criteria for a good and acceptable angle of repose are less than 25º - 40º, if more than 40º it is very difficult to flow and has a bad angle of repose (Hadisoewignyo & Fudholi, 2013). From the evaluation results of instant granules with an average value of FI, namely 12.09º, FII 12.02º, and FIII 11.73º, it shows that all three formulas are meet the requirements for a good angle of repose and are accepted because they are less than 25º (Siregar & Wikarsa, 2010).

Particle Size Distribution

The particle size of solid drug ingredients has an important role in the manufacture of drug preparations and in their physiological effects (Moechtar, 1990). Making granules is very important to achieve the required flow properties and obtain weight uniformity (Martin *et al*., 2008). The instant granule size distribution test results shows that the three formulas FI, FII and FIII are still meet the requirements, as the required limit is between 250 – 2000 µm (Goeswin, 2012). The largest granule size is FIII of 805.3 µm and the smallest granule size is FII of 783.9 µm.

Solubility

One of the physical and chemical properties of a drug is its solubility, especially in water. The solubility of a drug greatly affects the therapeutic effect. If a drug is poorly soluble it will show imperfect absorption. The conditions for good dissolution of granules are not more than 5 minutes (Siregar & Wikarsa, 2010). Solubility test results FI I 2.92 minutes, FII 3.12 minutes, and FIII 3.17 minutes fulfilled the requirements of not more than 5 minutes. The test results for dissolving granules showed that the granules are easily dispersed homogeneously and can be accepted by respondents due to the comfort level consumption. The speed at which a drug product dissolves is strongly influenced by particle size, the smaller the particle size, the faster the granule dissolves completely.

Hedonic Test

In this test, respondents were firstly given instant granules that had not been dissolved and asked to give a score for the parameters of granule color, granule texture, and flavor, then given granules that had been dissolved and asked to rate them with similar parameters plus taste, but not included texture. In the results of the average value of the granules before dissolving which is more preferred is FI for color, FII for flavor and texture. The hedonic test on instant granule before dissolving with observations on the colour of the granules showed the highest average score of respondents 3.47 was given for color from FI and the lowest average score of respondents was 3.30, was obtained by FIII. In the granular flavor test, the highest average value of the respondents was 3.50, indicating that respondents liked FII, and the lowest average value was 3.17, indicating that respondents quite liked FIII. In the granule texture test, the highest average value was 3.50,

indicating that the average respondent liked the FII texture, and the lowest average value was 3.23, indicating that the average respondent quite liked the FI texture. The results of the assessment of all respondents obtained a conclusion for the colour parameter the highest score was 104 for FI, in flavor the highest score was 105 for FII and in texture the highest score was 105 for FII (Table 5).

The granular flavor test has the highest average value of 3.30 indicating that the average respondent likes the FI texture, and the lowest average value is 3.03 indicating that the average respondent quite likes the FIII texture. In the taste test, the highest average value was 3.70, indicating that the respondent particularly enjoyed the FII texture. On the other hand, the lowest average value was 3.20, indicating that the respondent moderately liked FI. Notably, on the taste parameter test, there were variations in preferences based on different concentrations of Javanese chili, with the FI, FII and FIII at 1%, 2%, and 3%, respectively. From the results of the assessment of all respondents who obtained the most accepted on the solubility of instant granules or obtained the highest score is FII of 113, while the highest score on colour is FIII that is 104. The highest score for flavour was 99, which was achieved by FI, and for taste the highest score was 111 for FII (Table 6).

CONCLUSION

Based on the research results that has been conducted, from the three instant granule formulations of combination of sweet potato leaves and Javanese chili in the form of instant granulated drinks, it is proven that all three formulas are meet the requirements specified by BPOM as traditional medicine powders (water content is less than 10%, flow time is less than 10 g/sec, angle of repose is less than 25º - 40º, particle size distribution is between 250 – 2000 µm and standard time required for the granules to dissolve is less than 5 minutes). The results of the hedonic test showed that formulation II with a 2% amount of Javanese chili extract was the most preferred by respondents. The present study revealed that formula II comparatively better than other formulas. Further research is needed to verify the lead compound of the formula, as well as its effects on dengue fever through *in vitro* and *in vivo* studies.

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