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Formulation of Instant Granules from Ethanolic Extract of Melinjo Peel (*Gnetum gnemon* L) Extract as Anti-Hyperuricemia

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ABSTRACT

Melinjo (*Gnetum gnemon* L) is extensively found in Indonesia, and all of its components are highly employed, with the fruit being the most commonly used. However, melinjo fruit can induce hyperuricemia if ingested excessively since it contains purines, which can raise uric acid levels. Several investigations have found that melinjo peel can lower uric acid levels in experimental rats in vivo. As a result, the goal of this study is to create and evaluate immediate granule formulations of melinjo peel extract. Plant determination, standardization of specified parameters, standardization of non-specific parameters, formulation, and physical and chemical assessment of instant granules of melinjo peel extract are all steps of the technique. This study employed two instant granule formulations of melinjo peel extract FI and FII with varying PVP concentrations (1g FI and 3g FII). Flow time testing, angle of repose testing, compressibility index testing, water content testing, and dissolving time testing were all part of the physical examination of instant granules. The chemical evaluation took the form of a UV-Vis spectrophotometer study of total flavonoid levels in instant extracts and granules. The FI and FII instant granule formulas had a yellow color, the flow time test results were in a good category (44 g/s and 81 g/s), the angle of repose test results was in the very good flow properties category (19° and 16°), the compressibility test results, the water content test, and the dissolving time test were performed in triple, in 0, 7th, and 14th day, and the results were in a good category. In conclusion, the physical features of instant granules of FI and FII melinjo peel extracts fulfilled the requirements for all test parameters and had a high possibility to be produced as anti-hyperuricemia preparations.

Keywords: Instant granule; Hyperuricemia; *Gnetum gnemon* peel; Formulation; Evaluation

INTRODUCTION

Gout is the most prevalent inflammatory joint condition caused by hyperuricemia. The global prevalence of uric acid is <1-6.8%; however, the prevalence of uric acid varies by nation as well. Regional variances might be due to environmental, nutritional, or genetic factors.[1] As reported by Riskesdas (2018), the prevalence of gout in Indonesia was 11.9% based on diagnosis and 24.7% based on symptoms, with the highest prevalence occurring at the age of 75 years (54.8).[2]

Gout also known as hyperuricemia, is caused by excessive amounts of purines in the blood; if not treated promptly, it can lead to gout arthritis. The occurrence of hyperuricemia can be caused by several factors, namely age, alcohol, obesity, and other non-communicable diseases.[3] Many individuals do not consistently do health checks, particularly uric acid tests, in the current period of the Covid-19 pandemic. As a result, people are unaware that they have hyperuricemia until it is too late.

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Gnetum gnemon L, often known as melinjo, is a tree-like plant with open seeds native to tropical Asia and the West Pacific.[4] Melinjo may be found in both rural and urban regions in Indonesia. Almost every component of this plant is edible. Young leaves are known as kroto, blooms are known as kroto, old seed coats may be utilized as culinary components, and fruit seeds can be used to make chips (emping). There are several melinjo trees and Banten chip-producing hubs in the Banten area.[5]

According to Siswoyo et al. (2017), the antioxidant activity of the melinjo plant may be found in practically all sections of the plant, beginning with extracts of the plant's roots, leaves, seeds, and stems, which can combat free radicals.[6] Melinjo extract contains a protein level of 9-10% and can serve as an antioxidant to combat free radicals, which are the primary cause of cancer. According to these findings, the melinjo plant has significant potential as a nutraceutical product that is useful to public health, including illness prevention and treatment.[7]

Melinjo seeds are the most commonly utilized parts. However, excessive consumption will result in hyperuricemia since it contains purines, which can raise uric acid levels in the blood.[8] Several studies have found that melinjo peel can lower uric acid levels. According to Hasan et al. (2020), in vivo in experimental rats, 70% ethanol extract from melinjo bark (doses of 450 mg/kg and 900 mg/kg) was more efficient as an anti-hyperuricemia treatment than allopurinol 90 mg/kg, lowering uric acid levels by 50% and 54%, respectively.[9] Sari et al. (2019) discovered, the ethanol extract of melinjo peel at a dose of 13 mg/kgBW can reduce uric acid levels by up to 31.25%.[10]

Regardless of the fact that the effects of medicinal plants have been scientifically proven through numerous studies conducted in the modern world, there has been not much work put into processing these natural ingredients into formulas that are more practical and easier to apply, such as instant granules. An instant granule is a dosage form of spheres or aggregates that are regular in shape and served by brewing.[11] There has been no study on instant granules utilizing melinjo peel extract until now, despite in vivo testing as an anti-hyperuricemia based on investigations of the melinjo peel plant's pharmacological action. As a result, research was conducted on the formulation creation and assessment of immediate granules of melinjo peel extract.

Based on this information, the researchers were interested in incorporating the peel extract into two anti-hyperuricemia formulae in the form of instant granules.

METHODS

This was an experimental study. The stages of this research began with plant identification, followed by the production of melinjo peel extract, standardization of the extract, the formulation of instant melinjo peel extract granules in two formulas, and the physical evaluation and calculation of total flavonoid levels in melinjo peel instant granule preparations.

Tools and materials

The tools used in this study were laboratory glassware (Pyrex®), analytical balance (Mettler Toledo), vacuum rotary evaporator (Buchi), oven (Memmert), evaporating cups, filter paper, hot plates, silicate crucibles, sieve numbers. mesh 30, 20, 16 and 12 (B-One), spatula, mortar and stamper, stopwatch, granule flow tester, tap density, UV-Vis spectrophotometer (Rigol Ultra-3660), moisture balance (Radwag MA 50 R).

The materials used were melinjo peel extract, Polyvinylpyrrolidone (PVP) (Pharma Preneur), Mannitol (Palapa Muda Perkasa Inc.), Aspartame (Palapa Muda Perkasa Inc.), Sodium benzoate (Pharma Preneur), green tea flavoring (Palapa Muda Perkasa Inc.), 95% ethanol, 70% ethanol, lactose (Pharma Preneur), AlCl3 (Palapa Muda Perkasa Inc.), 1 M Sodium Acetate, Aquadest, Quersetin (Palapa Muda Perkasa Inc.).

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Collection of plant materials

Melinjo was discovered in the Serang region of Banten Province, Indonesia. Melinjo peel was employed in this study as a component of the melinjo plant. The selected melinjo peel is old or the color is red.

Plant determination

Determination of melinjo plant was conducted at the Biology Research Laboratory, Faculty of Applied Science and Technology, Ahmad Dahlan University, Special Region of Yogyakarta. The results of identified and authenticated the plant with the determination of the melinjo plant with ID. 325/Lab.Bio/B/VII/2022, species *Gnetum gnemon* L.

Standardization of specific parameters

Melinjo peel extraction

The slicing method was used on the melinjo peel sample that had been removed from the fruit. Furthermore, weighing was performed before drying for three times in a row for 24 hours in a 40°C oven. To get melinjo husk powder, the dried simplicia was crushed with a pollinator (grinder) and sieved with a mesh no. 60, then extraction was carried out using the 96% ethanol solvent maceration technique with a powder to solvent ratio of 1: 6. Maceration lasted two days, with stirring every six hours during the first six hours. It was then left for two days before being filtered through filter paper and evaporated for six hours in a rotary evaporator at 40°C to yield a thick extract.[9]

Phytochemical screening of melinjo peel extract

Identification of phytochemical compounds was carried out by identifying flavonoids, alkaloids, flavonoids, saponins and tannins.[9]

Levels of soluble and dissolved compounds in certain colvents

Each 1 g of condensed extract was macerated for 24 hours in an 18 volumetric flask with 20 mL of water:chloroform (1:1) and shaken for the first 6 hours in 20 mL of 96% ethanol. The mixture was then allowed to stand for 18 hours before being filtered. At 105oC, 5 mL of filtrate was boiled. Then the percentages of chemicals that were soluble in water and ethanol were calculated.[12]

Standardization of non-specific parameters

Non-specific parameters were determined by calculating ash content, acid soluble ash content, acid insoluble ash content, water content, specific gravity, and drying shrinkage. The approach employed was consistent with the procedure outlined in the Indonesian Herbal Pharmacopoeia.[12]

Melinjo peel instant granule formulation

This study employed two instant granule formulations of melinjo peel extract FI and FII with varying PVP concentrations of 1 g FI and 3 g FII (Table 1). The wet granulation process was used to produce immediate granules of melinjo peel extract. The components were filtered through mesh no. 20 and weighed according to the recipe. Mannitol, aspartame, and sodium benzoate were gradually combined in a container before adding lactose and stirring until homogenous. Green tea flavor and PVP were added to the mixture, and then 70% ethanol was poured gradually or until a clenched mass was formed.[13]

The resultant mass was sieved with a mesh size of 12. The granules were then dried in a 50°C oven for 24 hours. The dry granules that resulted were filtered again with mesh no. 16. The prepared instant granules were then submitted for a physical examination.[13]

Physical and chemical evaluation of instant granule formula

Physical Evaluation

A stability test was used to evaluate the physical characteristics of the instant granule formula of melinjo peel extract. The physical stability of the instant

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granule was tested for two weeks while it was kept at room temperature. Every 7 days, tests were performed with time intervals ranging from 0 to 7 days. Each test was performed in triplicate. The five test parameters used to determine stability were the flow time, angle of repose, compressibility index, moisture content, and dissolving time.[13]

Flow time

Flow characteristics were utilized to evaluate lubricant efficacy. A total of 100 g of instant granules were weighed and flow time was measured. The granule flow rate was indicated in grams per second, and the granules flow for no more than 10 seconds.[14]

Angle of Repose

The measurement of the angle of repose was stated to be between 25-40°. The angle of repose was determined by the equation: [15]

$$\text{Tan } \alpha = \frac{h}{r}.$$

Compressibility index

A total of 25 grams of melinjo peel extract instant granule sample was placed in a 100 ml measuring cup, and the volume (V bulk) was measured. The compressed volume was produced by tapping the measuring cup and holding the grains 300 times. The compressibility index value was computed using the following equation: [13]

$$\text{Compressibility Index} = \frac{\rho \text{ tapped} - \rho \text{ bulk}}{\rho \text{ tapped}}$$

Moisture content

A moisture balance was used to determine the moisture content. 1 gram of instant granules was weighed in aluminum foil and the moisture content was determined. A healthy moisture level was between 1 and 5%.[13]

Dissolving Time

Weighing 20 g of granules was used to perform the dissolving time test. The weighted grains were then dissolved in 100 mL of cold water and constantly agitated. The speed of dissolution was then determined using a stopwatch. It took less than 5 minutes for the granule to dissolve.[13]

Chemical Evaluation

The chemical evaluation of the instant granule formula of melinjo peel extract included an analysis of total flavonoid levels based on research with the following stages:

Quercetin standard preparation

A 1000 ppm quercetin mother liquor was made by weighing 25 mg of quercetin and dissolving it in 95% ethanol to 25 mL. Then, the concentration was diluted to 100 ppm.[16]

Maximum wavelength determination

The maximum wavelength was determined using a reference concentration of 100 ppm quercetin. The wavelength with the greatest absorption value was utilized as the maximum wavelength for analysis.[17]

Quercetin standard curves

Furthermore, variations in the concentration of quercetin solution were managed to make standard curves, namely 2, 4, 6, 8, and 10 ppm by dilution of 100 ppm quercetin mother liquor. Each of these concentrations was taken as much as 0.5 mL; 1 mL; 1.5 mL; 2 mL; and 2.5 mL into a 25 mL volumetric flask. Each flask was added 7.5 mL of 95% ethanol; AlCl3 as much as 0.5 mL; 0.5 mL of 1 M sodium acetate and added distilled water up to the mark, incubated for 25 minutes, and then measured the absorbance using a UV-Vis spectrophotometer. The absorbance results of the five concentration variations were made into linear regression equations.[17]

Determination of total flavonoid levels from melinjo peel extract

A total of 25 mg of melinjo peel extract was measured and then dissolved in 25 mL of 95% ethanol. Subsequently, 2.5 mL of the solution was pipetted into a 25 mL

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volumetric flask and added with 7.5 mL of 95% ethanol, 0.5 mL of 10% AlCl3, 0.5 mL of 1 M sodium acetate, and distilled water. Next, it was shaken until homogenous, incubated for 25 minutes, and absorbance was measured using a UV-Vis spectrophotometer at the previously acquired maximum wavelength.[17]

Determination of total flavonoid levels of melinjo peel extract granules

Melinjo peel extract was evaluated using UV-Vis spectrophotometry, which measured the absorbance of the standard flavonoid quercetin at a maximum wavelength of 424 nm in methanol.

RESULT AND DISCUSSION

One kilogram of melinjo peel simplicia powder (Gnetum gnemon L) was collected from the simplicia results in order to extract the active ingredients and chemical components included in the simplicia. The melinjo peel was extracted using the maceration process, which involved soaking the simplicia in 96% ethanol to produce a viscous extract weighing 110.5 g and yielding 11.05%. The phytochemical screening results were based on secondary metabolites of alkaloids, flavonoids, saponins, and tannins (Table 2).

When the amounts of specific solvent-soluble components were tested, it was shown that melinjo peel extract was more soluble in ethanol (70.31%) than in water (40.35%). Because the solvent utilized in the extraction procedure was ethanol, it may be assumed that it possesses nearly semi-polar characteristics.[18]

Non-specific parameter test findings included ash content, acid-soluble ash content, and acid-insoluble ash content. The inorganic (mineral) content in the extract was defined as the ash content, while the acid-soluble ash content was the acid-soluble inorganic content, and the acid-insoluble ash content was the acid-insoluble inorganic (Table 3).

According to the Second Edition of the 2017 Indonesian Herbal Pharmacopoeia, the limit for ash content, acid soluble ash content, and acid insoluble ash content is commonly set at 10%. The acid soluble ash level was 10%, with a 0.3% acid insoluble ash content. The high ash percentage showed that the maceration extract included a high concentration of minerals. This showed that the extract did not match the acceptable extract ash content criteria. While the acid-soluble ash and acid-insoluble ash contents matched the standards. The water content of the extract was used to determine its stability. High water concentration can function as a medium for microbial development, reducing the extract's stability. The results of the duplo test produced an average value of 24.22%, indicating that the necessary water content, namely the Indonesian Herbal Pharmacopoeia, was less than 10%.[18]

The specific gravity test achieved using the duplo test yielded the same result, 1.2535 g. The specific gravity data cannot be compared to the melinjo peel extract specific gravity standards since no reference to the melinjo peel extract standard specific gravity values had been discovered. The drying shrinkage value achieved from this drying shrinkage study was 24.265%. The drying shrinkage parameter had no requirements or permitted limits.[18]

The granulation formulations yielded instant granules weighing 104.945 g for FI and 107.420 g for FII (Figure 1). Although there were noticeable variances in hue in the preparations, the resultant granules exhibited no significant distinctions visually. Whereas FI was greenish in color, FII was yellowish.

(a) (b)

Figure 1. Instan granules (a) FI (PVP 1%); (b) FII (PVP 3%)

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Table 1. Formulation of instant granule melinjo peel extract

Materials	Total (g)		Usage
	FI	FII	
Melinjo Peel Extract	0.45	0.45	Active substance
Polyvinyl Pyrrolidone (PVP)	1	3	Binder
Mannitol	20	20	Diluent
Aspartame	1.5	1.5	Sweetener
Sodium Benzoate	0.5	0.5	Preservative
Green tea flavor	5	5	Taste
Ethanol 70%	q.s	q.s	Solvent
Lactose	70	70	Filler

Table 2. Phytochemical screening of melinjo peel extract

Reagen	Test Result	Description
Alkaloid Mayer	-	No white precipitate formed
Alkaloid Dragendroff	+	A brick-red precipitate formed
Flavonoid	+	Orange color formed
Saponin	+	Stable foam is formed
Tanin	+	The blackish blue color formed

Table 3. Standardization of non-specific parameters

Testing	Test Result
Ash content	10.485%
Acid-soluble ash content	9.91%
Acid insoluble ash content	0.575%
Water content	24.22%
Specific gravity	1.2535 gr
Drying shrinkage	24.265%

Table 4. Physical evaluation of instant granules

Sample	Flow Time (g/s) (mean ± SD)	Angle of Repose (°) (x ± SD)	Compressibility Index		
			H-0	H-7	H-14
FI	44.62 g/s ± 0.046	19° ± 0.189	21.81 %	19.64%	19.64%
FII	81.18 g/s ± 0.118	16° ± 0.082	16.94%	16.94%	16.94%

Table 5. Evaluation of moisture content of instant granules

Sample	Moisture Content of Instant Granules (%)		
	H-0	H-7	H-14
FI	1.18 %	1.21%	1.29%
FII	1.32 %	1.52 %	1.56 %

Table 6. Evaluation of physical dissolution time of instant granules

Sample	Dissolving Time of Instant Granules (Minute)		
	H-0	H-7	H-14
FI	1 minute 30 seconds	1 minute 21 seconds	1 minute 20 seconds
FII	1 minute 37 seconds	1 minute 34 seconds	1 minute 30 seconds

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The flow time, angle of repose, and compressibility index test results (Table 4) revealed that FI and FII had good flow rates. It is possible to deduce that the granules were non-cohesive.[13] The angle of repose test revealed that FI had a larger repose angle than FII. The findings of the repose angle may be classified as very good. The compressibility index test results acquired an evaluation of the compressibility index on days 0, 7, and 14 when the two formulas had different percentages, the compressibility index values in FI and FII surpassed 10% and less than 38%, respectively. A material with a low compressibility index value had superior flow qualities than one with a high compressibility index value. A compressibility index value of less than 10% indicated extremely good flow, while more than 38% indicated very poor flow. However, the ensuing flow qualities of instant granules remained within the required range, specifically the compressibility index was reported to be good, allowing for free flowing.[14]

The moisture content test results of instant melinjo peel granules (Table 5). The water content of the two formulations was fairly good because it did not exceed 10% as required by the granules. According to the results in Table 5, both formulations fulfilled the standards as excellent instant granules where the percentage of moisture content was between 2-4%.[13]

The granule dissolving time test was performed by dissolving a number of granules in the solvent (Table 6). Based on the dissolution time test findings, it is possible to deduce that the time in both formulations was less than 5 minutes. The PVP content in the formulation affected dissolving time; nevertheless, there was no substantial variation in dissolving time; both were still eligible. However, the results showed that FI had a faster disintegration time due to the lower PVP concentration of 1%.[13]

The standard curve was determined using a UV-Vis spectrophotometer, yielding a value of y = 0.1133x - 0.1231, and a correlation value (R) of 0.9905, or near to 1 (Figure 2). A linear calibration curve was shown by an R-value close to 1, and there was a link between the concentration of the quercetin solution and the absorbance value.[20] According to the Lambert-Beer rule, concentration is exactly proportional to absorbance, and the higher the absorbance value, the higher the concentration of the drug present in a sample. The maximum wavelength obtained from the test was 431 nm.

The total flavonoid levels in melinjo peel extract were calculated and evaluated in triplo using a UV-Vis spectrophotometer with a maximum wavelength of 431 nm. Flavonoids' polar nature allows them to absorb UV-Vis radiation rays obtaining total flavonoid levels of 1.158% (Table 7). While utilizing a UV-Vis spectrophotometer with a wavelength of 431 nm to calculate the amounts of melinjo peel extract tested in triplo, the total flavonoid levels obtained were 0.0061% for FI and 0.0058% for FII. The findings of FII levels were lower than those of FI levels. Variations in the concentration of the binder, notably PVP, induced this. PVP is commonly employed as a binder in both dry and wet granulation processes. PVP is utilized at a concentration of 2.0-5.0% w/w, according to Rowe et al.[21] The use of PVP in the wet granulation process resulted in a superior physical granule but a longer disintegration period. The usage of PVP concentrations in FI that were lower than the range might be the source of high levels in FI when compared to levels in FII utilizing a PVP concentration of 3%. The use of 3% PVP in FII enabled the granules to be more compressed, which strengthened the connections between the granule particles.[22] PVP owns a C-N bond known as a covalent bond. Covalent bond tends to dissolve, and this makes a distinct content in FI and FII.

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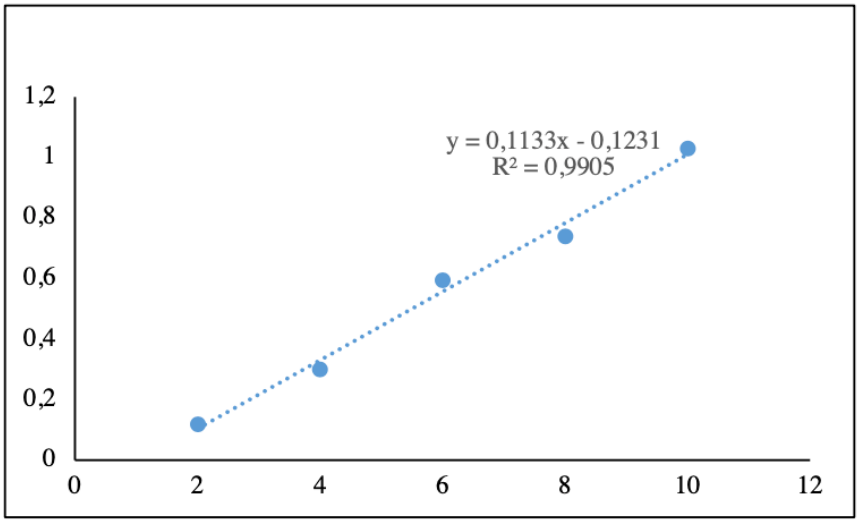

Figure 2. Quercetin standard curve

Table 7. Total flavonoid levels of extract and instant granules of melinjo peel extract

Replication	Ekstract	Instant Granule	
		FI	FII
1	0.2051	0.6436	0.6132
2	0.2048	0.6526	0.6186
3	0.2055	0.6525	0.6184
Total Flavonoid Content (%)	1.158	0.0061	0.0058
Mean ± SD	0.205 ± 0,00035	0.655± 0,0051	0.616± 0,0030

CONCLUSION

Melinjo peel extract can be made into instant granules, and the formulation had passed physical and chemical testing. Melinjo peel extract has an active component that can be used to treat hyperuricemia. Based on the physical examination results, both FI and FII met the standards as instant granules in the good category. According to the chemical assessment results (total flavonoid content determination), FI outperformed FII with a concentration value of 0.0061% vs 0.0058% for FII.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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