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Formulation and Characterization of Antioxidant Capsules Containing Cantigi Extract-loaded Nanoparticles Synthesized Via Nanoprecipitation Method

Kosasih Kosasih[1*], Deny Susanti[2], Immanuel Puji Hosanna Asianski[1], Dede Irving Maryanto[1]

[1]*Faculty of Pharmacy, Universitas Pancasila, South Jakarta, DKI Jakarta, Indonesia.*
[2]*Department of Chemistry, Kulliyyah of Science, International Islamic University Malaysia, Bandar Indera Mahkota, Kuantan, Pahang, Malaysia.*
*Corresponding Author : kosasih@univpancasila.ac.id

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ABSTRACT: Cantigi extract exhibit numerous activities, including antioxidants. Various dosage forms have been developed, except a capsule formulation. Capsule formulation offers numerous advantages. Objectives: To prepare and characterize the cantigi extract, extract-loaded nanoparticles, capsules containing extract, and capsules containing nanoparticles as antioxidants. Methods: The Cantigi extract was prepared using the maceration method and characterized for both specific and non-specific parameters. The preparation of extract-loaded nanoparticles utilized the nanoprecipitation method with gelatin, poloxamer, and glutaraldehyde as the polymer, stabilizer, and crosslinker, respectively. Characterization of the nanoparticle included particle size, polydispersity index, zeta potential, and entrapment efficiency. Capsule formulation (F): F1 contained the extract, while F2 contained the nanoparticles. Capsule characterization involved assessment of content uniformity, weight variation, disintegration, and release profile. Antioxidant activity was measured using the DPPH method for extract, nanoparticles and capsules. Results: The cantigi extract met specific and non-specific parameters. Nanoparticle size was found to be 235.8±12.62 nm with a polydispersity index of 0.226±0.050, a zeta potential of -8.53±0.27 mV, and an entrapment efficiency of 52.69±1.06%. Characteristics of F1 and F2 included content uniformity of 97.24±4.23 and 89.86±1.48%, weight variation of 185.5±1.31 and 127.22±1.86%, disintegration time of 3.67-4.08 and 5.35-5.97 minutes, extract content of 97.24±4.23 and 89.86±1.48%, and release rate of 86.78±3.98 and 61.79±3.48%, respectively. Antioxidant activities of the extract, extract-loaded nanoparticles, and capsules (F1 dan F2) were determined to be 17.40±0.94, 33.60±1.85, 66.81±1.46, and 106.61±3.32 ppm, respectively. Conclusion: Cantigi extract and nanoparticles exhibited potent antioxidant activities while meeting quality parameters. The capsule formulation displayed varying antioxidant activities and release profiles, with capsules containing nanoparticles demonstrating a sustained release profile.

KEYWORDS: antioxidants; cantigi extract; nanoprecipitation; release profile

1. INTRODUCTION

Antioxidants are substances that can prevent or delay several types of cell damage. Some foods, including fruits and vegetables, naturally produce antioxidants, such as vitamins C and E, beta-carotene, and selenium. Additionally, our bodies create antioxidant molecules, which include alpha-lipoic acid, glutathione, and coenzyme Q10 [1]. A new study describes the world's most and least biodiverse countries. To draw conclusions, researchers compiled available data on mammals, amphibians, fish, reptiles, and plant species in each country to create a comprehensive index ranking the countries with the highest biodiversity worldwide. Brazil ranks first, followed by Indonesia [2]. One plant species thriving in Indonesia, Cantigi (*Vaccinium varingiaefolium* Blume Miq.), exhibit potent antioxidant activity (with an IC_{50} of 18.87 ppm) [3].

For the time being, the use of nanotechnology in drug development has been progressing. For example, gelatin has been studied in nanotechnology as a carrier. This material is biocompatible, biodegradable, inexpensive, and non-toxic. It has been used for pharmaceutical applications for a long time. Moreover, gelatin nanoparticles (GNPs) are a promising delivery system for hydrophilic and macromolecular drugs [4]. GNPs loaded with plant extracts have become attractive. Some researchers have produced plant extract-loaded GNPs for their antiaging [3,5], antioxidant [5,6], antimicrobial [7], and anticancer [8,9] activities.

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Today, the capsule come as the second choice after tablet among solid preparations used frequently for drug delivery, and its utilization is increasing. In 2014, capsule formulation comprised roughly 10–15% of FDA-approved drugs, doubling the rate from in 2007. Initially designed to mask the unpleasant taste of certain drugs, capsules are now favoured for nanoparticle-based drug delivery due to numerous advantageous factors and incentives [10,11]. Till now, there has been no study on the formulation and characterization of antioxidant capsules containing Cantigi extract and extract-loaded nanoparticles. The study aimed to prepare and characterize the Cantigi extract, extract-loaded nanoparticles, capsules containing extract, and capsules containing nanoparticles as antioxidants.

2. MATERIALS AND METHODS

2.1. Material

The Cantigi leaves were obtained from Kawah Putih (White Crater) of Mount Patuha, Ciwidey, Bandung, and identified by botanist at Universitas Indonesia, Jakarta. All chemicals and reagents used were analytical grades.

2.2. Procedure

2.2.1. Extract preparations

The maceration method involved using 70% ethanol on dry powder simplicia of Cantigi leaves to prepare the Cantigi extract, followed by drying by using a vacuum rotavapor. Subsequently, the dried extract was tested for specific and non-specific parameters [12,13].

2.2.2. Gelatin nanoparticle preparations

The nanoparticles were prepared using the nanoprecipitation method, employed gelatin as the polymer and glutaraldehyde as a cross-linker. Subsequently, they were characterized for particle size, polydispersity index, zeta potential, functional groups, morphology, and efficiency entrapment percentage [14,15].

2.2.3. Antioxidant activity tests by DPPH method

The antioxidant properties of the Cantigi extract, the extract-loaded nanoparticles, and the capsules containing the extract and the extract-loaded nanoparticles were evaluated using the DPPH radical assay with slight modifications [16]. Initially, 100 µL of test samples were added to a 96-well plate, followed by the addition of 100 µL of 4 mM methanolic DPPH solution, and the mixture was thoroughly stirred. Ascorbic acid used as the positive control, while purified water was used as the negative control. Subsequently, the absorbance of the test samples was measured at a wavelength of 517 nm using a UV-VIS spectrophotometer. The analyses were conducted in triplicate for each test sample. The antioxidant capacity was expressed as an IC_{50} value, representing the extract concentration that cause a 50% decrease in the initial absorption of the DPPH radical.

$$\% \text{ DPPH scavenging} = (\text{Abs control} - \text{Abs sample}) / \text{Abs control} \times 100$$

Where: Abs sample was the absorbance of the sample, and Abs control was the absorbance of the control sample.

2.2.4. Preparation of capsules containing dry extract/dry extract nanoparticles

The capsule mass was prepared by manually blending various materials, such as the active ingredients (dry extract/dry extract nanoparticles), fillers, and glidan. Subsequently, the capsule mass was manually filled into empty hard gelatin capsules of number 2. Before filling, several tests were conducted, including moisture content [17], particle distribution [18], bulk density [19], tapping density [19], Carr's index, Hausner ratio, and flowability [20]. Following the filling process, the resulting capsule dosage forms required examinations including mass uniformity, in vitro disintegration time, and in vitro dissolution rate [21].

3. RESULTS

Table 1. Parameters of specific and non-specific of the Cantigi extract

Test paramaters		Results
Organoleptic	Color	Dark brown
	Odor	Typical Cantigi
	Appearance	Viscose
pH		4.33±1.56
Solubility	in methanol	Soluble
	in ethanol 96%	Soluble
	in DMSO	Freely soluble
	in purified water	Soluble
Specific gravity (g/mL)		1.2479±0.0010
Moisture content (%)		8.200±0.05
Metal contamination:	Pb	Not detected
	Cd	Not detected

Table 2. Formulation and characteristics of gelatin nanoparticles containing the Cantigi extract

No	Materials	Quantity	Parameters	
1	Extract Cantigi	3 mg	Particle size (nm)	235.8±12.62
2	DMSO	0.2 ml	Index polydispersity	0.226±0.050
3	Ethanol 96 %	0.2 ml	Zeta potential (mV)	-8.53±0.27
4	Gelatin	5 mg	Entrapment efficiency (%)	52.69±0.53
5	Purified water	1 ml	Shapes of nanoparticles	Spherical
6	Poloxamer	700 mg	Moisture content (%)	7.00±1.20
7	Glutaraldehyde 2%	0.5 ml	Solubility: in purified water	Soluble
8	-	-	in methanol	Soluble
9	-	-	in DMSO	Soluble
10	-	-	Specific gravity (g/mL)	0.3536±0.0097

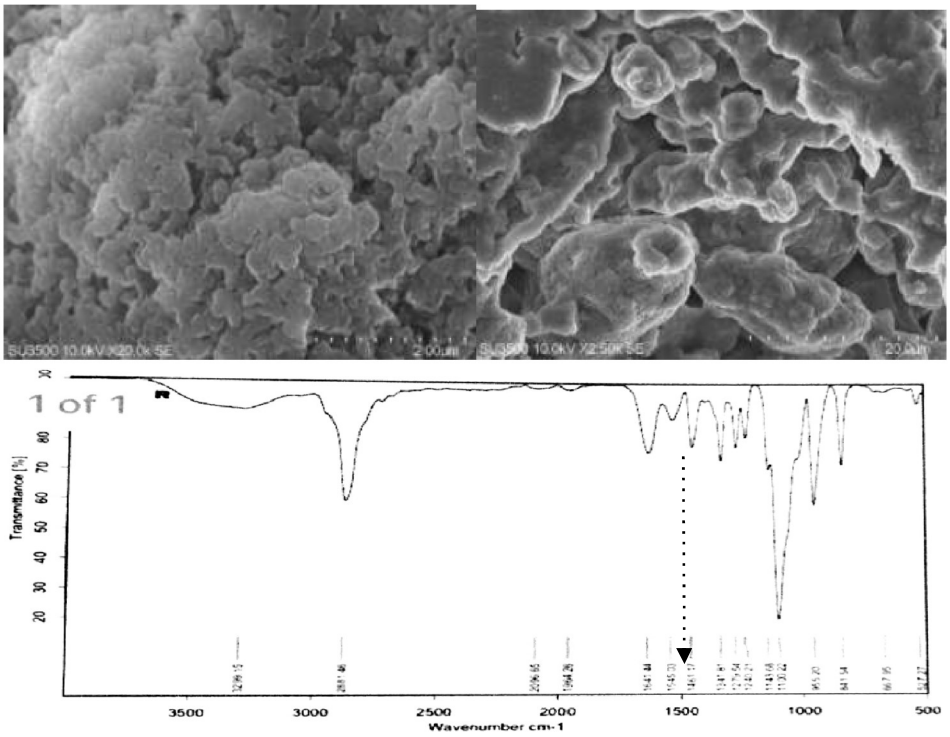


Figure 1. Spheric shapes of gelatin nanoparticles containing the Cantigi extract by SEM and the FTIR profile.

Table 3. Formulations of the capsules containing the Cantigi extract (F1) and the gelatin nanoparticles (F2) and their characteristics.

	Formula I	Formula II
Capsule formulations		
Cantigi extract	54.1 mg	-
Gelatin nanoparticles	-	101.5 mg
Aerosil	0.5%	0.5%
Avicel PH 102	up to 100%	up to 100%
Hard gelatin capsule	No. 2	No. 2
Capsule mass characteristics		
Moisture content (%)	3.69±0.07	3.32±0.03
Flowability: mass/time (g/min)	4.23±0.13	5.45±0.12
angle of repose (°)	27.92±1.1	26.56±1.92
Average particle size (µm)	188; nonnormal distribution	218; nonnormal distribution
Compressibility (%)	7.7-17.3 (fair)	8.3-16.6 (fair)
Capsule dosage form characteristics		
Weight variation (mg)	185.5±1.31	127.22±1.46
Disintegration time (min.)	3.67-4.08	5.35-5.97
Extract content (%)	97.24±4.23	89.86±1.48

Table 4. Results of antioxidant activity tests of the Cantigi extract, the gelatin nanoparticles, the capsules, and the control.

Samples	Linearity equation, R^2	IC_{50} (µg/mL)
Cantigi extract	y = 2.8404x + 0.6401; R^2 = 0.9839	17.40 ± 0.94
Gelatin nanoparticles	y = 1.197x + 9.8208; R^2 = 0.9980	33.60±1.85
Capsules F1	y = 0.0072x + 0.0676; R^2 = 0.9926	66.81±1.46
Capsules F2	y = 0.3312x + 14.904; R^2 = 0.9995	106.61±3.32
Vitamin C (control)	y = 6.4113x + 32.388; R^2 = 0.9989	2.75 ± 0.04

Table 5. Formulations of the capsules F1 and F2 and release model analysis

Capsule materials	Formula I	Formula II
Cantigi extract	54.1 mg	-
Gelatin nanoparticles	-	101.5 mg
Aerosil	0.5%	0.5%
Avicel PH 102	up to 100%	up to 100%
Hard gelatin capsule	No. 2	No. 2
Release model analysis		
Zero order	Y = 0.7217 X – 1.0853; R^2 = 0.9962	Y = 0.5358 X – 1.3373; R^2 = 0.9975
First order	Y = 0.0074 X + 1.1083; R^2 = 0.9591	Y = 0.079 X + 0.9282; R^2 = 0.9289
Higuchi	Y = 11.076 X – 39.99; R^2 = 0.9689	Y = 8.2897 X – 30.761; R^2 = 0.9860
Kosmeyer-Peppas	Y = 89.642 X – 109.88; R^2 = 0.9091	Y = 67.624 X – 84.019; R^2 = 0.9400

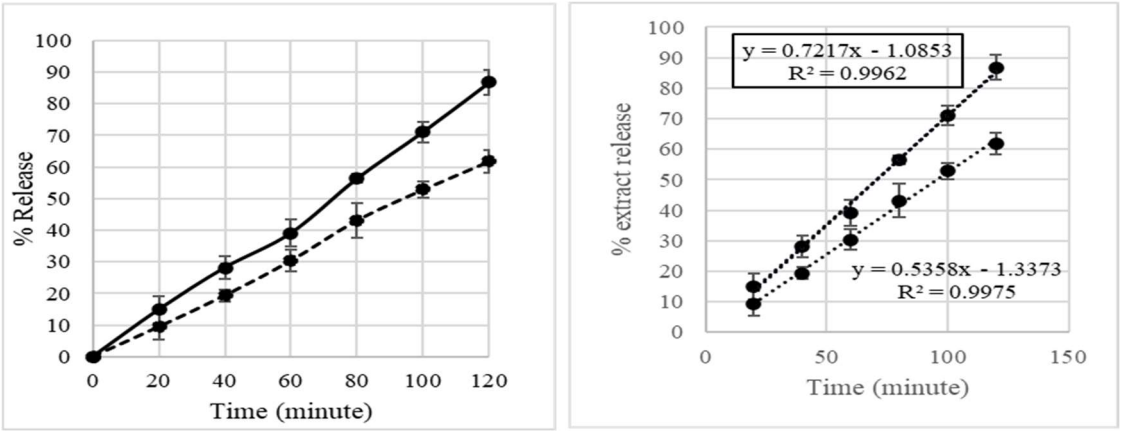


Figure 2. Release profile of capsules F1 and F2

4. DISCUSSION

4.1 Extract preparations

In this study, green Cantigi leaves were utilized, whereas the previous study employed red ones. Table 1 shows the parameters of specific and nonspecific of the Cantigi extracts. The results of all test parameters met the established standards [13,22,23]. Typically, standardization extract generally relies on analogous data.

4.2 Gelatin nanoparticle preparations

Table 2 displays the formulation and characteristics of gelatin nanoparticles containing the Cantigi extract [14,15]. Previous studies utilized the desolvation method nanoparticles production, whereas the current studies employed the precipitation method, which is known for its simplicity, fast, cost-effectiveness and ease of purification. The particle size fell within the defined range of 1-1000 nm [24], and the polydispersity index remained within the 0-1.00 range. Additionally, nanoparticles stability can be attributed to their zeta potential, with the desired zeta potential for nanoparticle typically being +30 mV for optimal stability. In this study, the zeta potential measured -8.53 mV at pH 7. However, nanoparticle stability can be enhanced through various way, including the addition of poloxamer [25]. The entrapment efficiency of the extract in this study was found to be 52.69%, signifying that 1 g of nanoparticles contain 52.69 mg of extract. Thus, future optimization of formulas and processes is essential to improve this entrapment efficiency. The observed zeta potential and entrapment efficiency were consistent with previous studies [26]. Furthermore, the moisture content was maintained within the acceptable range (less than 10%) to prevent microbial growth [27]. The solubility of nanoparticles in various solvents provides crucial information for subsequent processes such as analysis and formulation. Figure 1 depicts the spherical shape of the nanoparticle and the FTIR profile, indicating the formation of an aldimine linkage (CH=N) at 1461 cm^{-1}, consistent with the finding from previous study [9]. This linkage arises from the reaction between the aldehyde group of glutaraldehyde (crosslinker) and the amino acid group of gelatins. Another characteristic of the nanoparticles is their specific gravity, which was measured at 0.3536 g/mL, significantly lower than that of gelatin due to the freeze-drying process.

4.3 Antioxidant activity tests by DPPH method

Table 4 presents the results of antioxidant activity tests conducted on the control (vitamin C), the Cantigi extract, the gelatin nanoparticles, and the capsules (F1 and F2). The IC_{50} value obtained for the control demonstrates the suitability of the DPPH method for assessing antioxidant activity. The lower antioxidant activity observed for gelatin nanoparticles compared to the Cantigi extract can be attributed to the lesser availability of free extract within nanoparticles at the time of testing. The dissolution process differs between capsules F1 and F2: while the dissolution of extract from capsule F1 requires the breaking of the hard capsule before dissolving, capsule 2 necessitates the breaking of the hard capsule, subsequent release of the nanoparticles, and then dissolution media. Consequently, the antioxidant activity of capsule F2 is lower than that of capsule F1. The antioxidant classification reveals that the control, the Cantigi extract, and the nanoparticles exhibit potent antioxidant activity (less than 50 µg/mL), whereas capsule F1 demonstrates strong antioxidant activity and capsule F2 exhibits weak antioxidant activity.

4.4 Preparation of capsules containing dry extract/dry extract nanoparticles

Hard gelatin capsules no 2 were utilized in this study, with details of the capsule formulations provided in Table 5. The preparation of capsule mass involved blending the Cantigi extract (F1) or the freeze-dried gelatin nanoparticles (F2) with excipients, such as aerosil and Avicel pH 102. The capsule mass for F1 and F2 exhibited different characteristics in terms of moisture content, flowability, average particle size, and compressibility. However, both formulations met the specified criteria, except for the particle-size distribution. The filling process of empty capsules was performed using a manual capsule filling machine. Subsequently, the filled capsules underwent evaluation for weight variation, disintegration time, and extract content. While the standard parameters of weight variation and disintegration were fullfiled, the extract content of F2 found to be less than 90%. This issue may be attributed to the limited volume of the capsule number 2, which could not accommodate the voluminous nanoparticles, as indicated by the specific gravity of 0.3536±0.0097. The characteristics of capsule dosage forms (F1 and F2) differed, notably in terms of weight variation with F2 less than F1. This finding aligns with the specific gravity of the nanoparticle, which is less than that of the extract.

The release profiles of capsules F1 and F2 are detailed in Table 4 and Figure 2. The analysis data were fitted using the 4-release model, such as the zero order, first order, Higuchi, and Kosmeyer-Peppas. The best fit was observed with the zero order. In our previous study, the release profile of Cantigi extract from gelatin nanoparticles conformed to the Higuchi model [28]. However, in this study, gelatin nanoparticles were formulated as capsule preparation with a pH of 6.8, whereas the previous study utilized nanoparticles with a pH of 7.4. The second-best fit was observed with the Higuchi model, indicating that the change in release profile from the Higuchi to the zero-order model may be attributed to the hard capsule used in this study.

5. CONCLUSION

The Cantigi extract and nanoparticles exhibited significant antioxidant efficacy and met the required quality standard. The capsule formulations exhibited distinct antioxidant activities and release profiles, with those containing nanoparticles demonstrating a sustained release profile.

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