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Spray-gel formulations of Cantigi extract and Cantigi extract-loaded gelatin nanoparticles as antioxidant

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ABSTRACT: Spray-gel formulations may contain natural antioxidants like plant extracts. They can reduce free radicals and prevent premature aging. This research aims to develope a formulation of spray-gel formulations using Cantigi extracts and Cantigi extract-loaded gelatin nanoparticles as antioxidants. Extract preparation used the maceration method concentrated by a rotavapor and characterized for specific and nonspecific parameters. Antioxidant activity analysis of extract, nanoparticles, and formulations used the DPPH assay. Gelatin nanoparticle synthesis was done using the nanoprecipitation method and then characterized for particle size, polydispersity index, zeta potential, entrapment efficiency, aldimine linkage formation, and morphology. Two spray-gel formulations were manufactured (F1 contained the extract, and F2 contained the nanoparticles) and evaluated for one month for organoleptic, homogeneity, viscosity, flow properties, spray pattern, pH, and antioxidant activity tests. The extract and nanoparticles meet all parameters. The antioxidant activities (IC_{50}) are Cantigi extract of 17.4 ppm, gelatin nanoparticles of 33.6 ppm, F1 of 60.6 ppm, and F2 of 99.5 ppm. After the stability study, the spray-gel formulation characteristics were: Organoleptics, homogeneity, homogeneity, and viscosity complied (F1 and F2); flow property showed plastic thixotropy properties (F1 and F2); spray pattern showed best at 20 cm distance (F1 and F2); pH complied (F1 and F2); and IC_{50} of F1 was 63.0 ppm while F2 was 103.3 ppm. Conclusions were that the spray-gel formulations (F1 and F2) complied with the standards and were stable during the storage time. However, F1 has more potent antioxidant activity than F2.

KEYWORDS: Antioxidants; cantigi extract-loaded gelatin nanoparticles; cantigi extract; spray-gel formulations.

INTRODUCTION

A spray formulation is a topical dosage form used by spraying on skin surfaces. Topical formulation may provide systemic or local effects and several advantages, like avoiding first-pass metabolism, effects of acid pH and enzymes in the stomach, and a large available surface area. Compared to other topical dosages, spray formulation provides some benefits, like ease of use, low irritation incidence, excellent coverage of the skin or wound, equal distribution of active ingredients when applied, adjustable dosage, ease of cleaning from clothing, and no cross-infection of wounds caused by finger contact [1]. The spray formulations may contain natural, semisynthetic, or synthetic polymers. They are later well-known as a spray-gel formulation. This preparation may use synthetic chemicals, natural extracts, or biologics as active ingredients [2]-[8].

Nanotechnology has prospects to produce advancements and innovations in formulations and delivery systems. This fast-developing technology has been exploited widely in diagnosis and therapeutic uses. Nowadays, cosmetic formulations integrating nanotechnology are a relatively current but promising and important researched area. Nanotechnology can improve cosmetic performance in several ways, such as improving the entrapment efficiency and dermal penetration of the active ingredient, controlling drug release, improving physical stability and moisturizing power, and offering better UV protection. Also, the nanotechnology application in cosmetics can solve the limitations associated with traditional cosmetics and add better features to a formulation. nano cosmetic and nano cosmeceutical uses are to study skin, hair, nails, lips, and teeth, and the incorporation of nanomaterials can improve product efficacy and consumer satisfaction. These are leading to the replacement of many traditional cosmeceuticals with nano cosmeceuticals [9],[10]. Voriconazole (VCR) is a broad-spectrum antifungal that has serious side effects systemically. However, by topical drug delivery, they decrease. Mumtaz et al. enhance the topical delivery of VCR in the film-forming spray (FFS) by developing novel VRC-loaded polymeric nanoparticles [11].

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Spray-gel formulations may contain natural antioxidants like plant extracts such as Cantigi extracts. The extracts have potent antioxidant activity [12]. They can reduce free radicals and prevent premature aging. This research aims to study spray-gel formulations using Cantigi extracts and Cantigi extract-loaded gelatin nanoparticles as antioxidants. Both formulations have different characteristics. Nanoparticles may entrap extract to protect it from its unfriendly environment and release extract slowly to achieve its target.

MATERIALS AND METHODS

Material

Cantigi leaves (*Vaccinium varingiaefolium* (Blume) Miq.) were from White Crater, Mount Patuha, Ciwidey, Bandung; gelatin from Nitta Gelatin India Ltd (India), ethanol (Mallinckrodt, USA), and poloxamer 188 (Croda, France). Other materials, like glutaraldehyde, carbopol 940, propylene glycol, phenoxyethanol, triethanolamine, and purified water, were pharmaceutical grades.

Method

Preparation of plant extract

The determination of Cantigi plants was in the Biota Collection Room at the University of Indonesia, Depok. Fresh Cantigi leaves were washed, dried, and blended to provide dry powders. They then were screened using a screen mesh of number 4 and number 18. To make Cantigi leaf extract, 1 part dry powder was macerated with ten parts of ethanol 70% for 48 hours. The macerate was filtered and concentrated using a rotavapor at 45^{o}C until a thick extract resulted [13],[14]. Extract characterization included phytochemical screening, organoleptic, pH, determination of water content, and antioxidant activity [13]-[16].

Synthesis of gelatin nanoparticles containing cantigi extracts

The gelatin nanoparticle synthesis used the nanoprecipitation method, with gelatin as the polymer and glutaraldehyde as the cross-linker. Then, the characterization of the nanoparticles included particle size, polydispersity index, zeta potential, functional groups, morphology, entrapment efficiency, and antioxidant activity [17]-[19]. Poloxamer 188 was dissolved in ethanol 96% and then stirred until dissolved. Gelatin was dissolved in hot water and mixed with Cantigi extract dissolved in DMSO and ethanol 96%. The mixture of gelatin and extract was added into the poloxamer solution drop by drop while stirring with a stirrer. After mixing, wait for 15 minutes and then add glutaraldehyde drop by drop. Next, the nanoparticle solution was left overnight while stirring with a stirrer. After the process completion, the nanoparticle solution was centrifuged for 20 minutes. The precipitate was washed three times with purified water. The purified nanoparticles were spray-dried and stored in a refrigerator. Then, nanoparticle deposits were freeze-dried, homogenized, and weighed. Characterization was carried out by examining particle morphology using a Scanning Electron Microscope (SEM), examining particle size and distribution using a Particle Size Analyzer, determining zeta potential value using a zetasizer, determining entrapment efficiency using a UV-vis spectrophotometer, and determining antioxidant activity using the DPPH assay.

Formulations of spray gel containing cantigi extracts (F1), gelatin nanoparticles containing cantigi extracts (F2), and a Blank (F0)

Carbopol 940 (1 part) was developed in purified water (20 parts) for 24 hrs, neutralized with TEA, stirred into transparent mass gel form, and diluted by adding 10 mL of purified water (S1). Then, to dissolve phenoxyethanol and Cantigi extract (or gelatin nanoparticles), propylene glycol was used (S2). Next, S1 and S2 were mixed, made the volume 100% with purified water, and homogenized. The spray gels were filled into bottles with a manual sprayer and evaluated for organoleptic, viscosity, flow properties (rheology), spraying pattern, pH, antioxidant activity, and short-term stability [20],[22]. A blank is a formulation without Cantigi extract or gelatin nanoparticles.

RESULTS & DISCUSSION

Preparation of plant extract

Table 1. Characteristics of simplicia and extract of Cantigi leaves.

No	Paramaters	Results
1	Report of plant determination	No. 112/UN2.F3.11/PDP.02.00/2023.
2	Fineness degree of dry simplicia powder (%)	100% passes through sieve number 4 26.52% passes through sieve number 18
3	Yield of extract (%)	15.69±0.05
4	DER-Native	6.37±0.02
5	Organoleptic of extract	Thick shape, reddish brown color, and a distinctive smell.
6	Water content of extract (%)	8.20±0.03
7	pH of extract	4.33±0.02
8	Phytochemical screening of extract	Positives for flavonoids, alkaloids, saponins, tannins, phenolics, and triterpenoids.
9	Antioxidant activity of extract and control (ppm)	17.40±0.12 (extract) 2.75±0.01 (control)

Table 1. shows the characteristics of simplicia and extract of Cantigi leaves consisting the report of plant determination, fineness degree of dry simplicia powder, yield of extract, DER-Native, organo;eptic of extract, water content of extract, pH of extract, phytochemical screening of extract, and antioxidant activity of extract and control.

Based on the plant determination at the Depokensis Herbarium, Faculty of Mathematics and Natural Sciences, Universitas Indonesia, the plant samples are *Vaccinium varingiaefolium* (Blume) Miq. of the Ericaceae family as seen on the report of No. 112/UN2.F3.11/PDP.02.00/2023.

The degree of fineness of the dry simplicia powder is 100% passing through sieve of number 4 and 26.52% through sieve of number 18. This measurement is to provide the optimal size of simplicia powder [13]. The extraction process yielded 15.69% extract and a DER-Native of 6.37. Yield calculation is to know the amount of extract obtained from simplicia used, and DER-Native to determine the weight of simplicia used to make 1 gram of extract [13]-[23]. The characteristics of the Cantigi extract are as follows: Thick shape, reddish brown color, and a distinctive smell. An organoleptic examination is carried out by visually observing the thick extract. The extract has an average water content of 8.20, meeting the standard. If the water content is more than 10%, it will facilitate fungal and microbial growth [13]. Examination of the pH of the extract using a pH meter provides a result of 4.33. This result may be caused by acid biometabolites, as reported by a previous study [24].

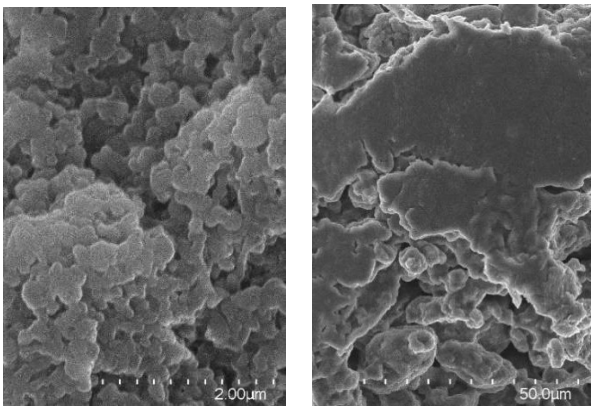
The phytochemical screening of the extract was positive for flavonoids, alkaloids, saponins, tannins, phenolics, and triterpenoids. Flavonoids, alkaloids, saponins, tannins, phenolics, and triterpenoids can be sources of antioxidants, depending on the structures. The IC_{50} value of vitamin C as standard was 2.75 ppm. Meanwhile, the Cantigi extract has 17.40 ppm, which is in the potent category and close to a previous report [12].

Synthesis of gelatin nanoparticles containing cantigi extracts

The synthesis of gelatin nanoparticles is by the nanoprecipitation method first developed and patented by Fessi et al. in 1989 and 1992. This method has many advantages, like straightforward, fast, and easy to perform. The formation of nanoparticles is instantaneous. The whole process is in only one step. Briefly, it requires two miscible solvents. Ideally, the polymer and the active component dissolve in the first solvent, not the non-solvent. The method takes place through a fast desolvation of the polymer when its solution is added to the non-solvent. The polymer-containing solvent diffuses into the dispersing medium. Then, the polymer will precipitate, involving prompt drug entrapment. That is because interfacial turbulence occurs at the interface of solvent and non-solvent and from combinations like flow, diffusion, and various surface tensions. Nanoprecipitation can synthesize small nanoparticles (100–300 nm), narrow distributions, and various polymers. It does not require extended mixing rates, sonication, or high temperatures. This method is a non-oily-aqueous interface that can destroy a protein structure [17],[18],[19],[25].

In this study, the solvent is gelatin and extract in a mix of DMSO and ethanol (96%), while the non-solvent contains poloxamer and ethanol 96%. The nanoparticle formation occurs by adding a cross-linker glutaraldehyde. Characterizations are by examining particle morphology using a scanning electron microscope (SEM), particle size and distribution using a particle size analyzer, zeta potential value using a zetasizer, entrapment efficiency using a UV-vis spectrophotometer, and antioxidant activity using the DPPH assay. The results show a particle size of 238.5 nm with a polydispersity index of 0.227. Examination of the particle size and polydispersity index aims to determine the size of the nanoparticles formed and the particle size distribution. The zeta potential was -8.54 mV, meaning the charge properties of the particles were negative.

The nanoparticle purification used centrifugation and then freeze-dried for 24 hours to provide light brown dry powder nanoparticles with a distinct odor. The entrapment efficiency is measured with a UV-vis spectrophotometer with the results of 52.69%. This measurement was to determine how much active substances are encapsulated in the nanoparticles. Using the SEM, particle morphology was spherical (Figure 1), consistent with a previous study [26]. The aspect ratio and surface chemistry of nanoparticles will affect their performance, like cell uptake, drug release, and diffusion, with high aspect ratio shapes showing enhanced properties relating to their spherical counterparts [27]. The antioxidant activity of the nanoparticles was 33.40 ppm, as the potent category. The measurement used the DPPH assay.



Left figure 1 scale of 200 nm & right figure 1 scale of 5 µm.

Figure 1. The morphology of gelatin nanoparticles containing cantigi extract.

Formulations of Spray Gel Containing Cantigi Extracts (F1), Gelatin Nanoparticles containing Cantigi Extracts (F2), and a Blank (F0)

Tables 2 and 3 present the summary data of the spray gel formulations (F0, F1, and F2) and stability data for a short term (one month). Generally, the formulations are stable during the storage time, as seen in the parameters (color, odor, shape, homogeneity, viscosity, rheology, and spray patterns). The formulation pHs meet a standard of 4.5-6.5. The viscosities meet a requirement as a spray gel formulation as they are thin, have plastic thixotropic rheology, and are easy to spray. Meanwhile, the antioxidant activities (IC_{50}) slightly change caused by increased temperature.

Table 2. The characteristics of the F0, F1, and F2 spray gel formulations at 25-30^{o}C for one month.

Parameters	Room temperature (25-30^{o}C)								
	F0			F1			F2		
	Day-1	Day-14	Day-30	Day-1	Day-14	Day-30	Day-1	Day-14	Day-30
Color	CWSC	CWSC	CWSC	CB	CB	CB	CB	CB	CB
Odor	No odor	No odor	No odor	Specific	Specific	Specific	Specific	Specific	Specific
Shape	Thin gel	Thin gel	Thin gel	Thin gel	Thin gel	Thin gel	Thin gel	Thin gel	Thin gel
Homogeneity	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous

Viscosity (cP)	111.3± 0.2	107.7± 0.2	103.6± 0.1	109.2± 0.2	104.6± 0.1	99.5± 0.1	110.3± 0.2	105.4± 0.1	101.3± 0.1
Rheology	Thixotr	Thixotr	Thixotr	Thixotr	Thixotr	Thixotr	Thixotr	Thixotr	Thixotr
Spray patterns [Dist (Ø), cm]	10 (4.18) 15 (6.50) 20 (9.72)	(4.30) (6.32) (8.60)	(4.18) (6.63) (9.67)	(4.22) (6.60) (9.78)	(4.12) (6.42) (9.58)	(4.23) (6.70) (9.72)	(4.27) (6.72) (9.75)	(4.27) (6.42) (9.67)	(4.35) (6.75) (972)
pH	6.27± 0.05	6.26± 0.03	6.23± 0.01	5.90± 0.03	5.89± 0.01	5.85± 0.02	6.34± 0.01	6.28± 0.02	6.27± 0.02
Antioxidant activity (µg/mL)	201.12± 0.07	-	203.22± 0.02	60.55± 0.74	-	62.98± 0.37	99.51± 1.14	-	103.27± 3.17

CWSC : Clear With Slightly Cloudy; CB : Clear Brown; Dist (Ø) : Distance (Diameter); F0 : Blank; F : Formulation; Thixotr : Thixotropic.

Table 3. The characteristics of the F0, F1, and F2 spray gel formulations at 40°C for one month.

Parameters	Accelerated temperature (40°C)								
	F0			F1			F2		
	Day-1	Day-14	Day-30	Day-1	Day-14	Day-30	Day-1	Day-14	Day-30
Color	CWSC	CWSC	CWSC	CB	CB	CB	CB	CB	CB
Odor	No odor	No odor	No odor	Specific	Specific	Specific	Specific	Specific	Specific
Shape	Thin gel	Thin gel	Thin gel	Thin gel	Thin gel	Thin gel	Thin gel	Thin gel	Thin gel
Homogeneity	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous
Viscosity (cP)	111± 0.3	105.7± 0.2	100.1± 0.1	108.6± 0.3	102.6± 0.1	96.5± 0.1	107.5± 0.2	104.7± 0.1	98.8± 0.1
Rheology	Thixotr	Thixotr	Thixotr	Thixotr	Thixotr	Thixotr	Thixotr	Thixotr	Thixotr
Spray patterns [Dist (Ø), cm]	10 (4.18) 15 (6.47) 20 (9.72)	4.22 6.57 9.75	4.22 6.63 9.82	4.32 6.35 9.47	4.22 6.37 9.63	4.22 6.35 9.67	4.25 6.62 9.60	4.23 6.67 9.87	4.33 6.77 9.87
pH	6.28± 0.03	6.14± 0.03	6.17± 0.03	5.98± 0.01	5.87± 0.02	5.81± 0.02	6.28± 0.02	6.22± 0.02	6.18± 0.02
Antioxidant activity (µg/mL)	201.26± 0.04	-	204.67± 0.05	61.22± 0.17	-	66.15± 0.15	100.94± 0.76	-	106.62± 0.62

CWSC : Clear With Slightly Cloudy; CB : Clear Brown; Dist (Ø) : Distance (Diameter); F0 : Blank; F : Formulation; Thixotr : Thixotropic

▪ CONCLUSION

Based on this study, we conclude that the spray-gel formulations (F1 and F2) complied with the standards and were stable during the storage time. F1 has more potent antioxidant activity than F2. While F0 formulation as the blank has negligible antioxidant activity. It happens because the active ingredient (extract) of F1 is available faster in solution, while the active ingredient of F2 needs more time to release from the nanoparticles.

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