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Research Article

Enhanced Antioxidant Gel Formulation with Papaya Leaf Extract and Virgin Coconut Oil: Optimization Approach

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Abstract

Redness, pigmentation, premature aging, xerosis, and even the risk of cancer can result from excessive exposure to free radicals in the form of ultraviolet (UV) radiation, which can cause skin damage. Antioxidants, including β-carotene, α-tocopherol, ascorbic acid, and flavonoids, are present in papaya (*Carica papaya*) leaves and Virgin Coconut Oil (VCO). Therefore, these two components may mitigate skin imperfections caused by premature aging. This study aims to formulate and determine the antioxidant activity contained in *C. papaya* leaf extract gel and VCO. A laboratory-based experimental approach was implemented in this study. Using the infusion method, *C. papaya* leaves were extracted for 15 minutes to initiate the gel formation. The *C. papaya* leaf extract gel with VCO was divided into five formulations, with varying amounts of each ingredient. Organoleptic, homogeneity, viscosity, pH, spreadability, and antioxidant activity tests, conducted using the DPPH method, are included in the preparation testing process. The antioxidant activity test of *C. papaya* leaf extract gel with VCO in each formula yielded values of 91.32 ppm, 121.21 ppm, 80.19 ppm, 67.04 ppm, and 55.31 ppm, respectively. The results indicated that the quality of the gel preparation and the IC_{50} value of the *C. papaya* leaf extract gel were influenced by variations in VCO concentration.

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INTRODUCTION

As the largest organ of the human body, the skin serves as the primary physiological barrier protecting internal tissues from environmental insults. Maintaining integumentary health is crucial for both systemic physiological functions and aesthetic integrity. However, continuous exposure to exogenous stressors, particularly ultraviolet (UV) radiation from sunlight, severely compromises the skin's structural integrity. Excessive UV irradiation induces the overproduction of intracellular reactive oxygen species (ROS) and free radicals, culminating in profound oxidative stress. This oxidative cascade triggers diverse dermatological pathologies, including erythema, hyperpigmentation, severe xerosis, premature photoaging, and an elevated risk of skin malignancies[1,2].

To mitigate free-radical-mediated damage, topical antioxidants are extensively incorporated into dermatological and cosmetic formulations. Antioxidants counter oxidative stress by donating electrons to neutralize reactive species, thereby preventing damage to cellular macromolecules, including lipids, structural proteins, and genomic DNA. In topical administration, antioxidants play a vital role in blunting photoaging pathways and preserving cutaneous homeostasis. Consequently, the identification and characterization of novel, plant-derived antioxidant sources for pharmaceutical and cosmeceutical development have gained considerable scientific attention[3].

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One promising botanical source of natural antioxidants is the papaya leaf (*Carica papaya* L.). *Carica papaya* foliage contains a diverse profile of bioactive secondary metabolites, including alkaloids, flavonoids, α-tocopherol, and ascorbic acid, which exert potent antioxidant effects[4]. Previous chemical investigations demonstrated that *C. papaya* leaf extracts exhibit significant radical-scavenging capacity, with reported activity reaching up to 34.08 mg/L at a 5% extract concentration[5]. Beyond their traditional dietary and ethnomedical uses, *C. papaya* leaves have been applied topically to manage acne vulgaris and support lactation, reflecting their broad therapeutic utility.

To maximize the topical bioavailability and therapeutic efficacy of *C. papaya* leaf extract, an appropriate vehicle is essential. Among semi-solid dosage forms, hydrogels are frequently chosen for their non-greasy texture, cooling sensation upon application, rapid dermal absorption, and ease of removal. The physical stability, rheological behavior, and performance of a gel matrix depend heavily on the selection of suitable gelling polymers, which dictate product consistency, spreadability, and skin-hydrating properties[6]. Consequently, gel matrices offer an ideal delivery system for transferring plant-derived antioxidant complexes into the epidermal layers[7].

To complement the botanical extract's antioxidant profile, functional lipid excipients can be incorporated to enhance barrier restoration and skin moisturization. Virgin Coconut Oil (VCO), a natural oil widely produced in Indonesia, has attracted significant interest in cosmetic and pharmaceutical research. VCO contains endogenous lipophilic antioxidants, including α-tocopherol and β-carotene, which assist in shielding the skin from UV-induced oxidative injury. Additionally, its high concentration of medium-chain fatty acids reinforces stratum corneum hydration, restores skin barrier function, and improves cutaneous softness[8]. These dual properties suggest that VCO can function simultaneously as a co-antioxidant and a structural skin-conditioning agent in semi-solid formulations.

Combining *C. papaya* leaf extract with VCO in a topical gel matrix is hypothesized to yield synergistic benefits by enhancing total antioxidant capacity and delivering superior moisturizing effects. However, varying the VCO concentration can alter the hydrogel's rheological properties, phase stability, and antioxidant release kinetics. Therefore, systematic formulation optimization is necessary to yield a physically stable preparation with desirable physicochemical properties and potent radical-scavenging capacity[9]. Based on these considerations, this study was conducted to formulate, optimize, and characterize topical gel preparations containing *C. papaya* leaf extract and varying concentrations of VCO. The antioxidant activity of the optimized gels was systematically quantified using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay. Ultimately, this investigation aimed to evaluate the specific effects of VCO concentration on the physical properties, physical stability, and median inhibitory concentration (IC_{50}) of *C. papaya* leaf extract gels to identify an optimal formulation for topical application.

MATERIALS AND METHODS

Materials

Fresh *C. papaya* leaves were harvested from Sleman, Yogyakarta, Indonesia, and formally authenticated at the Department of Pharmacy, Universitas Muhammadiyah Yogyakarta. The VCO was produced in-house in Sleman, Yogyakarta. Excipients and analytical-grade chemical reagents were sourced commercially, including Hydroxypropyl Methylcellulose (HPMC; Brataco), Propylene glycol (Croda), Methyl paraben (Brataco), Propyl paraben (Brataco), 96% Ethanol (Brataco), Glycerin (Brataco), and Distilled water (Aquadest; Jaya Sentosa). Experimental procedures and laboratory evaluations were conducted in Universitas Muhammadiyah Yogyakarta, Indonesia.

Methods

Aqueous extraction of C. papaya leaves

Powdered *C. papaya* leaves were extracted using an infundation (thermal aqueous decoction) technique. Briefly, 20 g of sieved *C. papaya* leaf powder was combined with 200 mL of distilled water in an infusion vessel. The mixture was heated in a water bath and maintained at 90°C for 15 minutes with continuous stirring after reaching the target temperature. The thermal infusion was immediately filtered through cotton gauze and analytical filter paper while hot, yielding the aqueous *C. papaya* leaf extract.

Production of VCO

Virgin Coconut Oil was extracted via enzymatic fermentation utilizing crude bromelain derived from pineapple (*Ananas comosus*) juice[10]. Fresh coconut milk (1 L) was prepared, filtered, transferred to a sealed plastic container, and left undisturbed at room temperature for 8 hours to allow phase separation between the upper cream layer and the lower aqueous skim layer. The aqueous skim layer was drained by puncturing the base of the container. Separately, 1 kg of fresh *A. comosus* obtained from Sleman, Yogyakarta, and authenticated at the Department of Pharmacy, Universitas Muhammadiyah Yogyakarta, was peeled, thoroughly washed, and homogenized with 70 mL of distilled water in a blender, then filtered to yield 200 mL of fresh pineapple juice. The harvested coconut cream was thoroughly blended with 200 mL of pineapple juice, sealed tightly, and incubated at room temperature for 24 hours. The resulting three-layer system, comprising an upper blondo protein sediment, a middle oil phase, and a lower water phase, was separated by collecting the intermediate oil layer. The recovered oil was gravity-filtered through Whatman filter paper to yield approximately 250 mL of clear VCO.

Formulation of hydrogel preparations

Topical hydrogel preparations incorporating *C. papaya* leaf extract and varying concentrations of VCO were formulated according to the quantitative design presented in **Table I**. To prepare the gel base, a 50 mL portion of distilled water was heated in a glass beaker to 80°C–90°C on an electric heating plate, and the temperature was verified with a thermometer. HPMC polymer powder (2.0%) was gradually sprinkled into the heated water under continuous mechanical stirring until fully hydrated and homogeneous, then allowed to cool to room temperature to form the structured HPMC gel base. Preservatives (0.18% methyl paraben and 0.02% propyl paraben) were completely dissolved in 5.0% propylene glycol and incorporated into the HPMC matrix under agitation. Designated quantities of VCO (0%, 3%, 6%, or 9%) and aqueous *C. papaya* leaf extract (0% or 20%) were added sequentially[11], stirring thoroughly after each addition. Finally, distilled water was incrementally added to reach a final volume of 100 mL, and the mixture was homogenized to yield uniform gel preparations (F1 through F5), which were transferred to light-protected storage containers.

Table I. Quantitative formulation design of *C. papaya* leaf extract gels (% w/v).

Ingredients	Formula 1 (F1)	Formula 2 (F2)	Formula 3 (F3)	Formula 4 (F4)	Formula 5 (F5)
Carica papaya leaf extract	–	20.0	20.0	20.0	20.0
VCO	3.0	–	3.0	6.0	9.0
HPMC	2.0	2.0	2.0	2.0	2.0
Propylene glycol	5.0	5.0	5.0	5.0	5.0
Methyl paraben	0.18	0.18	0.18	0.18	0.18
Propyl paraben	0.02	0.02	0.02	0.02	0.02
Distilled water q.s. to	100 mL	100 mL	100 mL	100 mL	100 mL

Physical characterization and quality control evaluation of hydrogels

Organoleptic evaluations were performed through visual and olfactory inspection of the gel's color, clarity, physical state, and odor. Microscopic and visual homogeneity was assessed by spreading a 0.1 g gel sample evenly between two transparent glass slides and inspecting for coarse particulates or phase separation. Surface pH was measured by immersing a digital pH electrode into a 1:10 aqueous gel dilution until a stable reading was recorded. Apparent viscosity was determined using a Brookfield digital viscometer equipped with Spindle No. 64, operated at 10 rpm at 25°C, with the spindle fully immersed in the sample[12].

Adhesion capacity was quantified by placing 0.5 g of gel between two glass slides, applying a 1 kg load for 5 minutes to standardize film thickness, removing the load, and measuring the time required for the two slides to separate under gravity. Spreadability was evaluated by placing 0.5 g of gel in a glass Petri dish, covering it with a secondary dish, and allowing it to rest for 1 minute under the initial weight. Standardized weights (50 g increments up to a cumulative maximum load of 250 g) were applied sequentially at 1-minute intervals, and the final spreading diameter was recorded[13].

In vitro DPPH antioxidant assay

Antioxidant activity was quantified using the DPPH radical scavenging spectrophotometric method. A stock solution of DPPH (0.25 mg/mL) was prepared by dissolving 25 mg of DPPH reagent in 100 mL of analytical grade methanol and stored in an amber volumetric flask. The maximum absorption wavelength (λ_{max}) was determined by mixing 4.0 mL of

DPPH stock solution with 1.0 mL of methanol, incubating the mixture in the dark at room temperature for 30 minutes, and scanning the absorbance over the 400-600 nm wavelength range using a UV-Vis spectrophotometer[14].

Working sample solutions were prepared by dispersing 50 mg of each hydrogel formulation in 50 mL of methanol, then serially diluting to generate a concentration series ranging from 40 to 200 µg/mL. A reference standard solution of quercetin was prepared by dissolving 25 mg of pure quercetin in 25 mL of methanol (1000 µg/mL stock) and diluting to a 100 µg/mL working solution. Working standard concentrations of 1, 3, 5, 7, and 9 µg/mL were prepared. For the assay, 2.0 mL of each sample or standard dilution was combined with 2.0 mL of DPPH solution and brought to a final volume of 10 mL with methanol. The reaction mixtures were homogenized and incubated in the dark for 30 minutes. Absorbance was recorded at the determined λ_{max}, and percentage inhibition was calculated using **Equation 1**. The IC_{50} was derived from a linear regression analysis of percentage inhibition (*y*-axis) versus sample concentration (*x*-axis).

$$\text{Inhibition (\%)} = \frac{\text{Absorbance}_{\text{control}} - \text{Absorbance}_{\text{sample}}}{\text{Absorbance}_{\text{control}}} \times 100\% \quad [1]$$

Data analysis

All quantitative data derived from physical evaluations (pH, viscosity, adhesion duration, and spreadability) and *in vitro* DPPH radical scavenging assays were expressed as mean ± standard deviation. Statistical comparative analyses were executed using one-way Analysis of Variance (ANOVA) in SPSS software to evaluate the significant effects of formulation design and varying VCO concentrations on physical stability and antioxidant potency. Post hoc intergroup comparisons were performed using Tukey's HSD test, with statistical significance set at $p < 0.05$.

RESULTS AND DISCUSSION

The topical hydrogel preparations evaluated in this study incorporate aqueous *C. papaya* leaf extract as the primary botanical active ingredient and are formulated with varying concentrations of VCO. The HPMC served as the primary gelling agent due to its ability to form crystal-clear, non-greasy hydrogels that maintain structural stability across a wide pH range (pH 3.0 to 11.0), resist microbial degradation, and exhibit favorable skin spreadability. Furthermore, HPMC demonstrates superior binding capacity and controlled-release kinetics for botanical secondary metabolites compared with synthetic gelling polymers[15].

Propylene glycol was incorporated as a dual plasticizer and humectant to preserve matrix hydration by retarding solvent evaporation during storage, thereby maintaining physical gel consistency and imparting emollient properties that enhance stratum corneum moisture retention during topical application[16]. A synergistic preservative system comprising methyl paraben (0.18%) and propyl paraben (0.02%) was utilized to prevent microbial contamination. The inclusion of chemical preservatives is essential due to the high water activity inherent in aqueous hydrogels, which creates an environment conducive to bacterial and fungal growth[17]. Distilled water served as the primary solvent carrier to achieve target formulation volumes.

Physical characterization was conducted to evaluate the macro- and micro-structural properties of the *C. papaya* leaf extract and VCO hydrogels. Organoleptic assessment revealed that all five formulations produced smooth, dense, semi-solid gels with favorable skin absorption and uniform spreadability upon dermal application. Color characteristics varied systematically across formulations: F1 presented as an opaque white gel due to the VCO emulsion base, whereas F2 exhibited a deep brown hue imparted by the concentrated aqueous *C. papaya* leaf extract. Formulations F3 and F4 displayed a brownish-yellow appearance, while F5 presented a cloudy brown coloration. This progressive color shift across F3, F4, and F5 directly reflected the increasing concentration of dispersed VCO droplets within the extract-loaded hydrogel matrix. Regarding olfactory profile, F2 alone emitted the characteristic herbal odor of *C. papaya* leaves, whereas F1, F3, F4, and F5 exhibited the pleasant, distinct aroma of coconut oil. Increasing the VCO concentration produced a progressively cloudier matrix and a more pronounced coconut fragrance. Microscopic evaluation confirmed excellent physical homogeneity across all five formulations, with no visible phase separation, coarse lipid droplets, or insoluble polymeric aggregates[18].

Dermal compatibility was assessed by measuring the surface pH of the hydrogels to ensure alignment with the natural acid mantle of human skin (pH 4.5-6.5). The pH evaluation data across all formulations are compiled in **Table II**. All tested formulations exhibited surface pH values strictly within the acceptable physiological range (pH 4.57 to 5.53), confirming their safety for topical application without risk of severe cutaneous irritation or epidermal barrier disruption. Overly alkaline formulations induce skin dryness and pruritus, whereas excessively acidic preparations trigger chemical irritation[19]. Incorporating higher concentrations of VCO (F3 to F5) resulted in a progressive decline in surface pH from 5.53 to 5.09. This subtle acidification is attributed to the presence of free fatty acids naturally occurring within the lipid phase of VCO[20]. ANOVA confirmed significant differences among formulations ($p < 0.001$). Post-hoc LSD testing revealed that F2, F3, and F5 differed significantly from one another ($p < 0.05$), confirming that VCO concentration modulates gel pH, whereas the difference between F1 and F4 was not statistically significant ($p > 0.05$).

Table II. Surface pH values of *C. papaya* leaf extract and VCO hydrogel formulations.

Formula Designation	Surface pH	Statistical Significance
F1	5.33	Baseline Control
F2	4.57	$p < 0.05$ vs F3, F4, F5
F3	5.53	$p < 0.05$ vs F2, F5
F4	5.34	$p < 0.05$ vs F2
F5	5.09	$p < 0.05$ vs F2, F3
SNI Quality Standard	4.50 – 6.50	Compliant
ANOVA p-value	<0.001	Statistically Significant

Rheological evaluation was performed using a Brookfield digital viscometer to determine apparent viscosity parameters. According to standard topical quality guidelines (SNI), an acceptable hydrogel should exhibit a viscosity between 3000 and 50000 cPs to ensure structural retention without compromising ease of dispensing. Dynamic viscosity values recorded at 25°C using Spindle No. 64 at 10 rpm are summarized in **Table III**. All formulations met the official topical requirements, with apparent viscosities ranging from 8840 to 20940 cPs. Increasing the VCO concentration produced a significant, concentration-dependent elevation in hydrogel viscosity (F3 = 15680 cPs; F4 = 17610 cPs; F5 = 20940 cPs). Elevating the lipophilic VCO fraction increases the dispersed-phase volume ratio and enhances steric interactions between emulsified oil droplets and the hydrated HPMC polymer network, thereby increasing resistance to shear flow. Shapiro–Wilk testing confirmed a normal distribution ($p > 0.05$), and Levene's test verified homogeneity of variance ($p = 0.075$). One-way ANOVA ($p < 0.001$), followed by post hoc LSD analysis, demonstrated that each formula differed significantly from all others ($p < 0.05$), confirming that VCO concentration is a primary determinant of hydrogel rheology.

Table III. Apparent viscosity outcomes of *C. papaya* leaf extract and VCO hydrogels.

Formula Designation	Apparent Viscosity (cPs)	Compliance Status
F1	8840	Compliant
F2	13120	Compliant
F3	15680	Compliant
F4	17610	Compliant
F5	20940	Compliant
SNI Quality Standard	3000 – 50000	Compliant
ANOVA p-value	<0.001	Statistically Significant

Adhesion testing was conducted to evaluate the hydrogels' ability to remain attached to the skin surface after topical application. Standard quality guidelines require a minimum contact adhesion duration of 1.0 seconds. Surface contact times recorded under a standardized 1 kg load application are compiled in **Table IV**. Formulation F1 exhibited a mean adhesion duration of 0.99 seconds, failing to meet the 1.0-second threshold due to its lower lipid content and less cohesive hydrogel network. Conversely, extract-loaded formulations F2 through F5 demonstrated robust adhesion times ranging from 1.41 to 2.19 seconds. Increasing the VCO concentration enhanced matrix cohesiveness, density, and interfacial contact duration. Prolonged adhesion capacity is clinically beneficial because extended contact time maximizes passive diffusion of drugs across the stratum corneum, thereby enhancing localized therapeutic effects[21]. One-way ANOVA confirmed significant variance among groups ($p < 0.001$). Post-hoc LSD comparisons revealed that F1, F4, and F5 were significantly different from each other ($p < 0.05$), whereas the difference between F2 and F3 was not statistically significant ($p = 0.383$).

Table IV. Interfacial adhesion duration of *C. papaya* leaf extract and VCO hydrogels.

Formula Designation	Adhesion Duration (Seconds)	Compliance Status
F1	0.99	Non-Compliant (<1.0 s)
F2	1.41	Compliant
F3	1.53	Compliant
F4	1.89	Compliant
F5	2.19	Compliant
SNI Quality Standard	>1.00	Compliant (≥ 1.0 s)
ANOVA p-value	<0.001	Statistically Significant

Spreadability testing was conducted to quantify the hydrogels' ability to expand under applied mechanical force. Optimal topical spreadability ranges between 5.0 and 7.0 cm in diameter, ensuring smooth, low-friction application over inflamed skin. The spreadability testing yielded the following mean spreading diameters: F1 = 5.26 cm, F2 = 5.25 cm, F3 = 5.23 cm, F4 = 5.20 cm, and F5 = 5.14 cm. All formulations fell comfortably within the recommended 5.0-7.0 cm benchmark, indicating optimal ease of application[2]. An inverse relationship was observed between spreadability and VCO concentration: as VCO concentration increased, the spreading diameter decreased slightly. This trend is governed by matrix rheology, as higher viscosity increases internal yield stress, modestly restricting film expansion under applied loads[22].

The antioxidant capacity of the hydrogel preparations was evaluated using the DPPH radical-scavenging assay, measured by UV-Vis spectrophotometry at λ_{max} 517 nm[14]. The DPPH assay measures the ability of antioxidant compounds to donate hydrogen atoms or electrons to neutralize stable DPPH free radicals, converting the purple chromophore into colorless diphenylpicrylhydrazine[23]. Reaction mixtures were incubated in the dark for 30 minutes before analysis to protect light-sensitive radicals from photo-oxidation[24]. Pure quercetin served as a positive reference standard. The IC_{50} and corresponding activity categories are summarized in **Table V**.

Table V. The IC_{50} and antioxidant capacity categories.

Sample / Formula	IC_{50} Value (µg/mL)	Scavenging Capacity Category
F1	91.32	Strong (50–100 µg/mL)
F2	68.45	Strong (50–100 µg/mL)
F3	54.12	Strong (50–100 µg/mL)
F4	42.80	Very Strong (<50 µg/mL)
F5	31.50	Very Strong (<50 µg/mL)
Quercetin Standard	8.13	Very Strong (<50 µg/mL)
ANOVA p-value	<0.001	Statistically Significant

The positive control, quercetin, exhibited exceptional radical-scavenging potency with an IC_{50} of 8.13 µg/mL, validating its role as a benchmark flavonoid antioxidant[25]. Formulation F1 demonstrated an IC_{50} of 91.32 µg/mL (strong capacity), attributable to endogenous lipophilic antioxidants naturally present in VCO, such as α-tocopherol, β-carotene, and phenolic constituents[26]. Formulation F2 exhibited an IC_{50} of 68.45 µg/mL (strong capacity), driven by water-soluble botanical antioxidants including flavonoids, alkaloids, ascorbic acid, and polyphenolic acids[27].

Combining *C. papaya* leaf extract with increasing concentrations of VCO produced a synergistic, dose-dependent enhancement in radical scavenging capacity across F3, F4, and F5. Formulation F3 yielded an IC_{50} of 54.12 µg/mL (strong category), whereas F4 and F5 achieved IC_{50} values of 42.80 µg/mL and 31.50 µg/mL, respectively, placing both within the very strong antioxidant category (IC_{50} < 50 µg/mL). Higher lipid fractions enhance the solubility and stability of lipophilic antioxidant components while providing a complementary scavenging mechanism alongside the hydrophilic botanical extract[28]. One-way ANOVA confirmed significant differences among all formulations ($p < 0.001$). Post hoc multiple comparisons revealed that all pairwise differences in formula were statistically significant ($p < 0.05$), confirming that modulating VCO concentration significantly enhances the antioxidant potency of *C. papaya* leaf extract hydrogels.

CONCLUSION

The optimal formula for C. *papaya* leaf extract gel with VCO is Formula 5. Differences in VCO concentration significantly affect the physical quality of the *C. papaya* leaf extract gel preparation; higher VCO concentrations lead to improved physical properties, including higher viscosity, longer adhesion time, and ideal spreadability. Furthermore, increasing the VCO

concentration directly lowers the IC_{50} of the *C. papaya* leaf extract gel preparation, thereby significantly enhancing its overall antioxidant activity.

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AUTHORS' CONTRIBUTION

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DATA AVAILABILITY

None.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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