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Developments and antioxidant evaluation of *Sesbania sesban*-leaf-extract loaded carboxymethyl cellulose hydrogel as a potential skin cosmetic

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ABSTRACT

Natural antioxidant products are receiving great attention as a safe alternative to chemically synthesized ones. For this, the phenolic compounds in the Sesbania sesban L. leaves possess potential antioxidant activities. Therefore, in this study, the Sesbania sesban L. leaf extract (SSE) was prepared and incorporated in the carboxymethyl cellulose (CMC) hydrogel as a natural antioxidant product. Firstly, the SSE was produced by the sonication-assisted extraction method, which demonstrated a total phenolic content of 61.44 ± 7.23 mg gallic acid equivalent/g dry powder weight, and a high antioxidant activity (IC_{50} = 15.381 ± 1.270 µg/mL). Then, the SSE was loaded into the CMC hydrogel and physicochemically evaluated in terms of physical observation, viscosity, gelation time, and drug release profiles. The hydrogel showed acceptable properties with a gradual release of polyphenol content over two stages for at least 180 min. Finally, utilizing the 2,2-diphenyl-1-picrylhydrazyl (DPPH) test, the antioxidant action of the SSE was well-maintained in the SSE loaded CMC hydrogel. In summary, the SSE loaded CMC hydrogel could be further investigated to become a potential cosmetic in the market.

1. INTRODUCTION

Reactive oxygen species (ROS), namely nitric oxide, superoxide anions, peroxynitrite radicals, and hydrogen peroxide, are the main factor driving skin oxidative stress associated to the pathology of numerous vital diseases (Jurkiewicz & Buettner, 1996; Liebel et al., 2012; Marrot, 2018; Masakil et al., 1995). Oxidative stress, ROS, together with their resulting oxidative damages could significantly alter the skin properties, including aging, wrinkling, dryness, and pigmentation. Therefore, the development of antioxidant products, often in the cosmetic form, for use on the skin is of much interest.

Plants, a great source of non-toxic antioxidants, have been increasingly investigated for the last few decades (Halliwell, 2008). Amongst numerous plants, *Sesbania sesban* L., Fabaceae family (SS) has showed potential antioxidant activity and has a long history of use in India (Kathiravan & Kalava, 2021; Pham et al., 2022). The SS leaves ethanolic extract (SSE) is a rich source of polyphenols content that could be classified as very strong antioxidants (Fitriansyah et al., 2017). Thus, SSE is an interesting candidate to be a skin antioxidant product.

One of the dosage forms of interest to the cosmetic industry is hydrogel, which is widely used in hair care, makeup, and skin care products (Pham et al., 2021, 2022; Thi et al., 2022; Tien et al., 2023). The

hydrogel preparations are often non-sticky, skin-friendly, and possess an effective drug delivery environment in the skin (Pelen et al., 2016). Moreover, compared with creams and ointments, hydrogels have a high water content, allowing for more drug dissolution and better control of the active drug release profiles (Rehman & Zulfakar, 2014). Amongst various hydrogel materials, carboxymethyl cellulose (CMC) is a commonly used agent. CMC, a polyelectrolyte cellulose derivative that contains carboxyl and hydroxyl groups, is hydrophilic, non-toxic, non-irritate, easy to form hydrogel, and could interact with the encapsulated compounds (Rajendraprasad et al., 2021). These properties are ideal for formulating hydrogel in skin applications (Benhalima et al., 2017).

Therefore, this study developed a novel SSE loaded CMC hydrogel as a potential antioxidant product for skin application. To this end, the SSE was first extracted by sonication-assisted extraction, determined the extract total phenolic content, and evaluate its antioxidant action in *in vitro* setting. Then, SSE loaded CMC hydrogels were formulated and evaluated their physicochemical properties. Finally, the hydrogel antioxidant actions were evaluated.

2. MATERIALS AND METHODS

2.1. Materials

The SS leaves were sourced from Can Tho, Viet Nam, in 11/2021. Folin-Ciocalteu reagent and powdered CMC were imported from China. 2,2-diphenyl-1-picrylhydrazyl (DPPH) was purchased from Merck, Germany. Ascorbic acid (99%), Na_2CO_3 (99.8%), gallic acid (98%), methanol (MeOH) (96%), and ethanol (EtOH) (96%) were purchased from Xilong, China.

2.2. SS leaves extraction

Initially, the SS leaves were dried under the room temperature, for approximately 3 - 4 days, until a humidity of < 10% (measured by the moisture analyser (Kern DAB 100-3)), and ground to powder. Then, the SS leaf powder (1 g) was extracted, with sonication, using 15 mL of EtOH at different temperatures of 30ºC or 60ºC for different extraction times of 60 min or 120 min. After the extractions, the total phenolic content in the SSE was determined utilizing the Folin-Ciocalteu chemical, following the published method (Cuong et al., 2022; Singleton et al., 1999). Briefly, 0.1 mL SSE was combined with 0.5 mL of Folin-Ciocalteu reagent (10% *v/v*) and 0.4 mL Na_2CO_3 (7.5% *w/v*). After 1-h incubation at room temperature, the mixture optical density was determined by UV-Vis spectroscopy at 765 nm. The total polyphenol contents were then calculated using the gallic acid standard curve (range: 0 - 60 µg/mL, y = 0.0108x + 0.0302, R^2 = 0.9984) and equation (1), and denoted in terms of mg gallic acid equivalent/g dry powder weight (mg GAE/g DPW).

$$C' = \frac{C \times V \times k \times 1000}{m} \times 100 \qquad (1)$$

where C', C are the concentrations of total phenolic content in the SEE with the unit mg GAE/g DPW and the unit µg GAE/mL, V is the sample volume (mL), k is the dilution factor, and m is the dry powder weight (mg).

2.3. CMC hydrogel formulations

The blank CMC hydrogel (hydrogel without the SSE) was prepared by dissolving 1.07 g CMC in 50 mL of a mixture of EtOH and water at various volume ratios of 20:30, 25:25, and 30:20, followed by continuous stirring at 1500 rpm until the hydrogel was formed.

Regarding the SSE-loaded CMC hydrogel, 1 mL SSE, containing 40 µg/mL of the total phenolic content, was added to the EtOH and water mixture, and the hydrogel was prepared similarly to the blank hydrogel process.

2.4. Evaluations of hydrogel formulations

Physical evaluation: The hydrogel color, appearance, application feel, consistency, and texture were personally observed and determined.

Gelation time: The vial inversion method was used to determine the hydrogel gelation time (sol-gel transition time). Briefly, 1 mL of each formulation, immediately after the CMC dissolving step, was placed in a vial at room temperature and inverted on a regular basis to track the gel conditions. The gel/sol status was the non-flowing solid and the flowing liquid, respectively. The time point at which the transformation occurred was used to calculate the sol-gel transition time.

Viscosity: The viscosity of the hydrogel was measured at 25 ± 0.5ºC using a viscometer (Brookfield, DV-E) with a 40-mm plate and a rotational speed of 15 rpm. One mL of the hydrogels was gently positioned on the plate, followed by the viscosity test performance, according to the manufacturer's instruction.

2.5. Drug release study

The *in vitro* cumulative polyphenol release rate of the SSE loaded CMC hydrogel was evaluated by the shaker technique at 37 ± 0.5°C in a phosphate buffer at pH 5.5, simulating the skin environment (Pham et al., 2018). For this, 10 mg hydrogel was gently placed in 5 mL medium and orbitally shaken at 200 rpm for 3 h. Every 30 min, 0.5 mL medium was taken and the same amount of buffer was replenished. The sample was then centrifuged at 15000 rpm for 5 min, and the total polyphenol content in the supernatant reacted with the Folin-Ciocalteu and UV-Vis spectroscopic measured at 765 nm. The total polyphenol released (µg/mL) at time t (C_t) was determined using gallic acid standard curve, and the total polyphenol release rate was calculated following equation (2).

$$\%\ \text{Cumulative release} = \frac{C_t V_0 + V\sum_1^{t-1} C_i}{M_0} \times 100\% \quad (2)$$

where C_t and C_i are the released total phenolic at time t and i, V_0 is the release buffer volume (5 mL), V is the taken sample volume (0.5 mL), and M_0 is the original amount of total phenolic content.

2.6. *In vitro* antioxidant DPPH assay

The DPPH radical scavenging actions of the free SSE, the blank CMC hydrogel, and the SSE loaded CMC hydrogel were determined following the previous approach (Cuong et al., 2022; Shekhar & Anju, 2014).

For the free SSE, 40 µL DPPH in MeOH (0.1 mM) was combined with 960 µL SSE at different concentrations ranging from 0 to 20 µg/mL. The mixture was reacted for 30 min, light-absence, at room temperature, and the scavenging activities of the samples were measured by UV-Vis spectroscopy at 517 nm. The SSE scavenging activity was calculated by equation (3), and the sample IC50 was derived using the corresponding calibration curves.

$$DPPH\ scavenging\ (\%) = \frac{Abs_1 - Abs_2}{Abs_1} \times 100\% \quad (3)$$

where Abs_1 and Abs_2 are the optical densities of the control (DPPH solution without extracts) and the samples.

Regarding the hydrogel samples, the hydrogels (960 µL) were combined with 40 µL DPPH in MeOH (0.1 mM). The scavenging activity of the hydrogel was tested at various incubation times of 60 min, 120 min, and 180 min. After the reaction, the samples were then centrifuged (2000 rpm, 2 min), and the supernatant was measured for absorbance at 517 nm. The hydrogel scavenging action was then determined using equation (3).

2.7. Statistical analysis

All quantitative results were demonstrated as mean ± standard deviation (SD). To compare the experimental values, the Student's t-test and ANOVA were used for the statistical differences, with $p < 0.05$ for significant comparisons.

3. RESULTS AND DISCUSSION

The present work formulated and characterized the SSE loaded CMC hydrogel as the antioxidant product for skin application. For this, the SSE was first extracted, followed by the formulations and characterizations of SSE loaded CMC hydrogel and the determinations of the product antioxidant activity in *in vitro* DPPH assay.

3.1. SS leaves extraction

The SSE was subjected to a series of extraction procedures to determine the optimal condition that yielded the highest total phenolic content (Figure 1). Obviously, the phenolic content of SS leaf extracted at 60°C was greater than that at 30°C ($p < 0.05$), and a 120-min extraction time did not enhance the overall phenolic content compared to that at 60 min. Therefore, in our case, the optimal extraction setting was with a temperature of 60°C for 60 min, which resulted in a total phenolic content of 61.44 ± 7.23 mg GAE/g DPW. Our data was greater than that of the SS leaves from Indonesia (51.8 mg GAE/g DPW) (Fitriansyah et al., 2017), suggesting the impact of nutrition and geography on SS chemical contents.

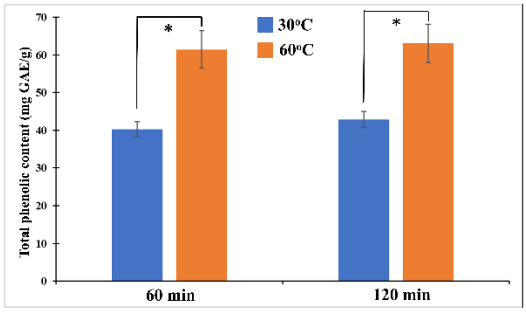

Figure 1. The total phenolic content (mg GAE/g DPW) of the *Sesbania sesban* L. leaves extracts at extraction time of 60 or 120 min and at a temperature of 30°C or 60°C (n = 3). * denotes significant differences ($p < 0.05$)

3.2. CMC hydrogel formulations

Physically, the blank CMC hydrogels were white, translucent, and turned green with the addition of SSE. All hydrogels possessed a good consistency, a smooth texture, and were soft when applied to the skin.

Regarding the gelation time and viscosity (Table 1), the blank and SSE loaded CMC hydrogels were formulated with the EtOH:water ratios of 20:30, 25:25, and 30:20 *v/v*. In general, the gelation time undergoes two main stages of (1) CMC dissolution in the solvent and (2) CMC solution gelation. These two phases depend mainly on the solubility of CMC. Since CMC is more soluble in water than in EtOH, increasing the amount of EtOH decreased the time of phase 2, leading to a decrease in the total gelation time. Moreover, an increase in EtOH also reduced the CMC aqueous solubility, resulting in a more viscous hydrogel (Pham et al., 2022; Tien et al., 2023). Conclusively, the hydrogel properties could be controlled by varying the EtOH amount.

The addition of SSE in the hydrogel did not significantly affect the gelation time, but statistically reduced the viscosity. This result could be explained by the fact that SSE contained compounds soluble in EtOH, which led to space competition between these compounds and CMC, consequently hindered the swelling of CMC, thereby decreasing the viscosity of CMC hydrogels. In summary, the gel viscosity was suitable to be used as skin cosmetic.

Table 1. The blank and *Sesbania sesban* L. extract loaded CMC hydrogel properties at different EtOH:water ratios of 20:30, 25:25, and 30:20 (n = 3).

Formulation	Gelation time (min)	Viscosity (cPs)
Blank hydrogel		
EtOH:H_2O 20:30	51.7 ± 1.5^{a}	1725 ± 14^{a}
EtOH:H_2O 25:25	49.0 ± 1.0^{a}	1853 ± 22^{b}
EtOH:H_2O 30:20	46.5 ± 0.9^{b}	2110 ± 36^{c}
SSE loaded hydrogel		
EtOH:H_2O 20:30	$48.0 \pm 2.0^{*}$	$1250 \pm 18^{*}$
EtOH:H_2O 25:25	$47.2 \pm 1.2^{*}$	$1567 \pm 10^{\#}$
EtOH:H_2O 30:20	$45.7 \pm 1.3^{\#}$	$1699 \pm 28^{\$}$

Note: Different letters (a, b, c)/symbols(, #, $) denote significant differences ($p < 0.05$) between the blank hydrogels/SSE loaded hydrogels.*

3.3. Drug release study

Regarding the total polyphenol release pattern of SSE loaded CMC hydrogel (Figure 2), the release behavior could be separated into two main phases of (1) rapid release for the first 60 min and (2) gradual release and degradation for the remaining time. Since the SSE contains various phenolic compounds, some of them located on the surface of the hydrogel and some located in the interior. Thus, the surface compounds were rapidly exposed to the dissolution medium and rapidly released in the first phase. In contrast, the others took more time for the solvent to penetrate the hydrogel structure and dissolve the active substances. Additionally, the total polyphenol release remained constant due to the balance between the release compounds and the polyphenol degradations. The body tends to excrete the active substances, especially on the skin; this release feature ensures both the release of a sufficient amount of medicine for the initial effect and the maintenance of drug content over time, thereby shortening the number of times that cosmetics are used on the skin (Pham et al., 2023).

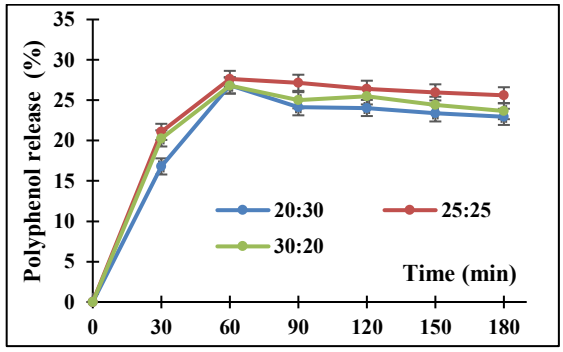

Figure 2. *In vitro* cumulative total phenolic release profile of the *Sesbania sesban* L. extract loaded CMC hydrogel at different EtOH:water ratios of 20:30, 25:25, and 30:20, in the simulated skin condition (pH 5.5) (n = 3)

3.4. *In vitro* antioxidant DPPH assay

DPPH scavenging capability is essential for skin cosmetic because an overabundance of free radicals affecting the skin (Wang et al., 2010). For this reason, the product antioxidant activity was investigated and the data are shown in Table 2. Firstly, the extract had an IC_{50} of 15.381 ± 1.270 µg/mL, which was considered a strong antioxidant according to Blois (IC_{50} < 50 µg/mL) (Blois, 1958; Zongo et al., 2023).

Secondly, all blank CMC hydrogels, at different ratios of EtOH:water, demonstrated a low radical scavenging activity of < 3%, indicating that the CMC did not affect the SSE antioxidant activity (Pham et al., 2023).

Finally, the SSE loaded CMC hydrogel could effectively maintain the antioxidant efficacy of the encapsulated SSE. Moreover, the DPPH scavenging activity of SSE hydrogel significantly increased with time, from 30% in 30 min to 50% in 180 min (Table 2). This fact was consistent with the total-polyphenol release profile of the hydrogels (Figure 2), which showed the gradual release over time. Thus, the findings suggest that the antioxidant activity of SSE loaded CMC hydrogel depends on the release of phenolic chemicals from the gel.

Table 2. The DPPH scavenging action (%) of the blank CMC hydrogel and the SSE loaded CMC hydrogel at different EtOH:water ratios of 20:30, 25:25, and 30:20, and at various time point (30, 90, and 180 min) (n = 3)

	Ratio of EtOH:water	Testing time		
		30 min	90 min	180 min
Blank CMC hydrogel	20:30	2.774 ± 0.424%	2.791 ± 0.376%	3.121 ± 0.432%
	25:25	2.132 ± 0.158%	2.445 ± 0.158%	2.584 ± 0.453%
	30:20	2.762 ± 0.105%	3.036 ± 0.218%	2.674 ± 0.214%
SSE loaded CMC hydrogel	20:30	36.301 ± 0.275%	46.098 ± 0.766%	54.604 ± 0.216%
	25:25	36.077 ± 0.476%	45.348 ± 0.374%	52.372 ± 0.169%
	30:20	37.529 ± 0.728%	47.388 ± 0.199%	57.863 ± 0.183%

4. CONCLUSIONS

The present study has successfully prepared and characterized CMC hydrogels containing *Sesbania sesban* L. leaf extract with different EtOH:water ratios. The products satisfied all physicochemical properties of a skin cosmetic, such as green color, translucency, good consistency, soft and smooth texture, suitable gelation time of < 60 min, and acceptable viscosity of 1500 - 2000 cPs. Moreover, in the skin-simulated medium, the hydrogels showed two-phase release profiles of total phenolic contents, a burst release phase followed by a sustain release phase, which was beneficial for skin products. Additionally, the hydrogels could preserve and exhibit the extract antioxidant activity in a time-dependent manner. These results, as well as the inherent high antioxidant activity of the SSE (IC_{50} of 15.381 ± 1.270 µg/mL), suggest that the SSE loaded CMC hydrogel could be further investigated to become a potential skin cosmetic.

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