NOVEL PHYTOSOMAL CREAM CONTAINING SPINY AMARANTH (*Amaranthus spinosus L.*) EXTRACT: PREPARATION USING CHLOROFORM AND DISTILLED WATER

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Abstract

Spiny amaranth (**Amaranthus spinosus** L.) contains phenolic compounds known as a potential source of antioxidants. In this study, a cream preparation was formulated using the active ingredient in the form of phytosome delivery of spiny amaranth extract. The aim of this research was to obtain the best cream formulation with spiny amaranth extract phytosomes. Before the cream preparation formulation, several procedures were carried out, including phytochemical screening, phytosome formulation, and physical characterization of the phytosomes.The results showed that the spiny amaranth extract tested positive for phenolic content and that the physical characteristics of the phytosomes met the expected criteria. The cream formulation was based on concentrations of spiny amaranth extract phytosomes ranging from 0.05–0.1% and soybean lecithin from 0.4–0.8% in 100 grams of preparation. Physical and chemical evaluations were performed using several tests, including organoleptic, homogeneity, pH, spreadability, and adhesiveness tests.The results showed that both formulas had a semi-solid form, yellowish-green color, and no odor. The homogeneity test results indicated that both F1 and F2 were homogeneous. In the pH test, F1 showed a score of 6.08, while F2 had a score of 5.74. The spreadability test results for F1 and F2 were 6.16 cm and 5.9 cm, respectively. In the adhesiveness test, F1 and F2 achieved values of 8.41 seconds and 5.29 seconds, respectively.

Keywords: *Spiny amaranth, soybean lecithin, phytosome, cream preparation*

Introduction

Amaranthus spinosus L. (spiny amaranth) is a medicinal plant that has attracted considerable attention due to its rich phytochemical composition and potent antioxidant activity. Previous studies have reported that spiny amaranth contains a high total phenolic content of approximately 194.21 mg/g and exhibits very strong antioxidant activity, with an IC_{50} value of 24.38 ppm. Antioxidant activity with an IC_{50} value below 50 ppm is generally classified as very strong, indicating the plant's significant potential as a natural source of antioxidants (House *et al*., 2022; Widiantari & Sari, 2022).

Among the phenolic compounds present in spiny amaranth, caffeic acid has been identified as the predominant constituent, accounting for approximately 65.23% of the total

phenolic content (Rjeibi *et al*., 2018). Phenolic compounds, including caffeic acid, play an important role in preventing oxidative stress by scavenging reactive oxygen species (ROS). Excessive ROS production is associated with cellular damage, premature aging, and the development of various chronic diseases. Therefore, antioxidant compounds are widely recognized for their protective effects against oxidative damage and their contribution to maintaining overall health (Haerani *et al*., 2018).

Despite its promising antioxidant potential, the application of spiny amaranth extract is limited by the physicochemical properties of its phenolic constituents. Most phenolic compounds are highly polar, resulting in poor bioavailability and limited permeability across biological membranes, particularly the lipid-rich layers of the skin. Consequently, an appropriate balance between hydrophilic and lipophilic characteristics is required to enhance the absorption and bioavailability of these bioactive compounds. One promising strategy to overcome this limitation is the utilization of phospholipid-based delivery systems, particularly phytosomes (Afrin *et al*., 2018; Aulia & Sriwidodo, 2022).

Phytosomes represent an advanced drug delivery technology in which phytoconstituents form stable molecular complexes with phospholipids through hydrogen bonding interactions. This complexation enhances the physicochemical stability, solubility, and membrane permeability of bioactive compounds. Unlike conventional liposomes and ethosomes, phytosomes involve the formation of stronger chemical interactions between the active compounds and phospholipid molecules, resulting in improved stability and bioavailability (Aulia & Sriwidodo, 2022). Several methods have been employed for phytosome preparation, including solvent evaporation, antisolvent precipitation, and thin-layer hydration techniques. Among these methods, thin-layer hydration has demonstrated high entrapment efficiency, reaching up to 96.98%, while requiring relatively small amounts of solvents such as ethanol and distilled water (Indalifiany *et al*., 2021).

Soy lecithin has been widely utilized as a phospholipid source in phytosome formulations due to its biocompatibility, safety, and natural origin. In addition to supporting the concept of plant-based pharmaceutical products, soy lecithin may contribute to antioxidant activity through its major phospholipid components, phosphatidylcholine and phosphatidylethanolamine. These compounds possess metal-chelating and free-radical-scavenging properties that can synergistically enhance the antioxidant effects of plant extracts while improving the physical and chemical stability of the formulation (Astuti *et al*., 2022).

The integration of spiny amaranth phenolic compounds with soy lecithin-based phytosome technology represents a promising approach for enhancing the bioavailability and therapeutic efficacy of natural antioxidants. This strategy is particularly relevant for topical drug delivery systems, where adequate penetration through the skin barrier is essential for achieving optimal biological activity. Topical formulations offer several advantages, including localized action, minimal systemic toxicity, and improved patient compliance. Among various topical dosage forms, cream formulations are widely preferred because of their ease of application and favorable cosmetic properties. Water-in-oil (W/O) cream systems, in particular, provide prolonged skin residence time and facilitate deeper penetration of active compounds into the epidermal layers, thereby enhancing therapeutic effectiveness (Tsabitah *et al*., 2020).

The stability and performance of cream formulations are strongly influenced by the selection of suitable emulsifying agents. Emulsifiers function by reducing interfacial tension between aqueous and oil phases, thereby promoting homogeneity and physical stability. Nonionic surfactants such as Tween and Span are commonly employed in topical formulations due to their low toxicity, good compatibility, and excellent emulsification properties (Baskara *et al*., 2020).

Based on these considerations, the present study aims to develop a phytosome-based cream containing *Amaranthus spinosus* extract using soy lecithin as the phospholipid carrier. The study focuses on evaluating the physical characteristics and stability of the formulated cream to determine its suitability as a topical antioxidant preparation. Through the application of phytosome technology, this formulation is expected to enhance the solubility, penetration, and effectiveness of spiny amaranth phenolic compounds, thereby contributing to the development of stable and effective plant-based topical pharmaceutical products.

Materials and Method

Instruments

The instruments used in this study included a magnetic stirrer, sonicator, desiccator, rotary evaporator, particle size analyzer, centrifuge, optical microscope, Fourier-transform infrared (FTIR) spectroscope, pH meter, oven, refrigerator, dropper pipettes, Bunsen burner set, analytical balance, spatula, glass stirring rods, Buchner funnel, porcelain dish, cream containers, stopwatch, mortar and pestle, adhesion tester, and spreadability tester.

Materials

The materials used were spiny amaranth (*Amaranthus spinosus* L.) extract, distilled water, chloroform, stearic acid, cetyl alcohol, liquid paraffin, Span 60, Tween 60, glycerin, propylene glycol, propyl paraben, and methyl paraben.

Phytochemical Screening

Phytochemical screening of *Amaranthus spinosus* L. extract was conducted to identify the presence of polyphenolic compounds. The extract sample was treated with five drops of ferric chloride ($FeCl_3$) solution. A positive result was indicated by the formation of a dark bluish-green coloration, confirming the presence of phenolic compounds (Kusumo *et al*., 2022).

Phytosome Formulation

This study employed several ratios of *Amaranthus spinosus* extract to soy lecithin based on the formulation reported by Indalifiany *et al*. (2022). Soy lecithin possesses a hydrophilic-lipophilic balance (HLB) value ranging from 9 to 12, indicating its relatively polar nature. Higher HLB values reflect a greater proportion of polar phosphate groups compared to nonpolar lipid components, which contributes to the efficient encapsulation of bioactive compounds (Isabella *et al*., 2022). All formulations utilized the same solvent composition consisting of 20 mL chloroform and 20 mL distilled water.

Table 1. Composition of materials in phytosome formulations

No	Material	Function	F1	F2	F3
1	*Amaranthus spinosus L*. Extract	Active ingredient	0,05	0,05	0,1
2	Soy lecithin	Phospolipid	0,4	0,8	0,8
3	Chloroform	Solvent	20 ml	20 ml	20 ml
4	Distilled water	Solvent	20 ml	20 ml	20 ml

Phytosomes were prepared using the thin-layer hydration method. Initially, *Amaranthus spinosus* ethyl acetate extract was dissolved in 10 mL chloroform according to the formulation ratio, while soy lecithin was separately dissolved in another 10 mL chloroform. The solutions were combined and stirred using a magnetic stirrer at 700 rpm for 5 min, followed by sonication for 30 min to achieve homogenization. The solvent was subsequently removed using a rotary evaporator at 45 rpm and 40°C until a thin lipid film was formed. The resulting film was stored in a desiccator for 24 h.

The dried thin film was then hydrated with 20 mL distilled water using a rotary evaporator at 90 rpm and 45°C for 20 min. Finally, the phytosome suspension was homogenized again by sonication to obtain a stable phytosome system (Indalifiany *et al*., 2022).

Physical Characterization of Phytosomes

Particle Size and Polydispersity Index (PDI)

One milliliter of phytosome suspension was diluted with 10 mL distilled water. Subsequently, 5 mL of the diluted sample was transferred into a cuvette and analyzed using a particle size analyzer at 25°C. Particle size and polydispersity index (PDI) values were recorded (Indalifiany *et al*., 2021).

Zeta Potential Measurement

One milliliter sample was diluted with 10 mL distilled water, and 5 mL of the resulting solution was transferred into a cuvette. The sample was then analyzed using a particle size analyzer equipped with zeta potential measurement capabilities (Putri, 2023).

Entrapment Efficiency

The prepared phytosome suspension was centrifuged at 6,000 rpm for 60 min (Akib *et al*., 2021). The resulting supernatant was collected and analyzed using UV–Visible spectrophotometry. The supernatant represented the amount of unentrapped bioactive compounds. Entrapment efficiency (EE) was calculated using the following equation (Indalifiany *et al*., 2022):

$$\mathbf{EE\ (\%) = ((Qt - Qs) / Qt) \times 100}$$

where:

- EE = Entrapment efficiency (%)
- Qt = Total amount of bioactive compounds
- Qs = Amount of bioactive compounds in the supernatant

Total phenolic content was determined quantitatively using the Folin–Ciocalteu method. Standard gallic acid solutions (5, 10, 25, 50, 75, and 100 ppm) were prepared, and 0.1 mL of each standard was mixed with 0.8 mL of 7.5% Na_2CO_3 solution and allowed to stand for 5 min. Subsequently, 0.1 mL of 10% Folin–Ciocalteu reagent was added under dark conditions, and the mixture was incubated for 30 min. Absorbance was measured using a UV–Visible spectrophotometer within a wavelength range of 400–800 nm to determine the optimum wavelength. A calibration curve was generated from the absorbance values of gallic acid standards. The absorbance of phytosome samples and supernatants was then measured, and total phenolic content was calculated using the regression equation obtained from the calibration curve (Siddiq *et al*., 2017).

Phytosome Complex Analysis

The complexity of phytosome formation was evaluated using FTIR spectroscopy. Potassium bromide (KBr) powder was first dried prior to use. The sample was mixed with dry KBr at a ratio of 1:100 and homogenized thoroughly. The mixture was analyzed using FTIR spectroscopy within the wavelength range of 400–4000 cm^{-1} (Sasongko *et al*., 2019).

pH Measurement

The pH of the phytosome suspension was determined using a calibrated pH meter. Prior to analysis, the instrument was calibrated using standard acidic and basic buffer solutions. Approximately 0.5 g of sample was dissolved in 5 mL distilled water. The electrode was immersed in the solution, and the pH value was recorded after stabilization (Handayani *et al*., 2023).

Cream Formulation

The phytosome-based cream containing *Amaranthus spinosus* extract was prepared by accurately weighing all ingredients according to the formulation design. The oil phase, consisting of stearic acid, cetyl alcohol, liquid paraffin, BHT, Span 60, and propyl paraben, was heated in a water bath at 70°C with continuous stirring. Simultaneously, the aqueous phase containing glycerin, methyl paraben, Tween 60, propylene glycol, and distilled water was heated to the same temperature.

The cream emulsion was formed by gradually adding the aqueous phase into the oil phase while continuously stirring until a homogeneous cream base was obtained. The phytosome preparation was gently ground using a mortar and incorporated gradually into the cream base with continuous mixing to ensure uniform distribution. The finished cream was transferred into tightly closed cream containers and stored in a cool place protected from direct sunlight (Riski *et al*., 2017).

Evaluation of Cream Formulations

Organoleptic Evaluation

Organoleptic evaluation was performed to assess the physical appearance of the cream, including color, odor, and consistency. This test ensured that the formulation met the required quality standards and was suitable for topical application (Pratasik *et al*., 2019).

Homogeneity Test

The homogeneity test was conducted to ensure uniform distribution of ingredients throughout the formulation. One gram of cream was spread thinly onto a glass slide and visually examined for the presence of coarse particles or aggregates. A homogeneous cream should exhibit a smooth texture without visible particles (Pratasik *et al*., 2019).

pH Evaluation

One gram of cream was dispersed in 10 mL distilled water. The pH meter electrode was immersed into the sample dispersion until completely submerged. The pH value was recorded after stabilization. An acceptable pH range for topical cream formulations is between 4.5 and 6.5, corresponding to the physiological pH of human skin (Pratasik *et al*., 2019).

Spreadability Test

Spreadability was evaluated to determine the ability of the cream to spread uniformly on the skin surface. One gram of cream was placed on a glass plate, and another glass plate was positioned on top. Additional weights of 50 g were applied every minute until a total load of 250 g was reached. The diameter of spread was measured in both horizontal and vertical directions. Cream formulations with spreadability values ranging from 5 to 7 cm were considered acceptable (Zam & Musdalifah, 2022).

Adhesion Test

The adhesion test was conducted to evaluate the ability of the cream to remain attached to the skin surface. One gram of cream was placed between two glass plates and compressed with a 250 g weight for 5 min. After removing the load, the time required for the plates to separate was recorded. A satisfactory adhesion time for cream formulations is greater than 4 s. Longer adhesion times indicate improved residence time on the skin and enhanced potential for active compound absorption (Pratasik *et al*., 2019).

Result and Discussion

The analysis of Formulas 1, 2, and 3 demonstrated that all formulations successfully met the expected nanoparticle size criteria, ranging from 100 to 2500 nm, as described by Mishra and Tiwari (2013). Nanoparticles within this size range are particularly important because particle size directly influences the penetration and distribution of active compounds within biological systems. The successful attainment of the desired nanoparticle size also

reflects the effectiveness of the thin-layer hydration method employed for phytosome preparation, which is recognized for its ability to produce particles with suitable dimensions. Consequently, the resulting phytosomes are expected to exhibit enhanced bioavailability and improved therapeutic efficiency.

Table 2. Physicochemical characteristics of *Amaranthus spinosus* phytosome formulations

Formula	Ratio	Particle Size (nm)	Polydispersity Index	Zeta Potential (mV)
1	0.05 : 0.4	238.6	0.552	-22.1
2	0.05 : 0.8	1704	0.586	-15.4
3	0.1: 0.4	181.1	0.516	-9.1

In addition to particle size, the polydispersity index (PDI) is another critical parameter used to evaluate the uniformity of particle size distribution within a phytosome system. An optimal PDI value ranges from 0.08 to 0.7, indicating a relatively homogeneous particle size distribution and good system stability. Conversely, PDI values exceeding 0.7 suggest a broad and heterogeneous particle size distribution, which may increase the risk of sedimentation and reduce formulation stability (Cita, 2017). The PDI values obtained for all three formulations fell within the acceptable range, indicating a uniform particle distribution and supporting the successful development of stable phytosome formulations.

Zeta potential represents another important parameter for evaluating phytosome stability. It reflects the electrostatic repulsive forces between particles that prevent aggregation and flocculation, thereby maintaining colloidal stability. According to McNeil (2011), nanoparticles with zeta potential values between −10 mV and +10 mV are generally considered neutral, while values greater than +30 mV indicate cationic characteristics and values lower than −30 mV indicate anionic characteristics. Based on the obtained results, Formula 3 exhibited a zeta potential value close to neutrality, which is generally associated with optimal system stability. In contrast, Formulas 1 and 2 displayed predominantly anionic characteristics, which may also contribute to system stability through electrostatic repulsion, although through different interaction mechanisms compared with neutral systems.

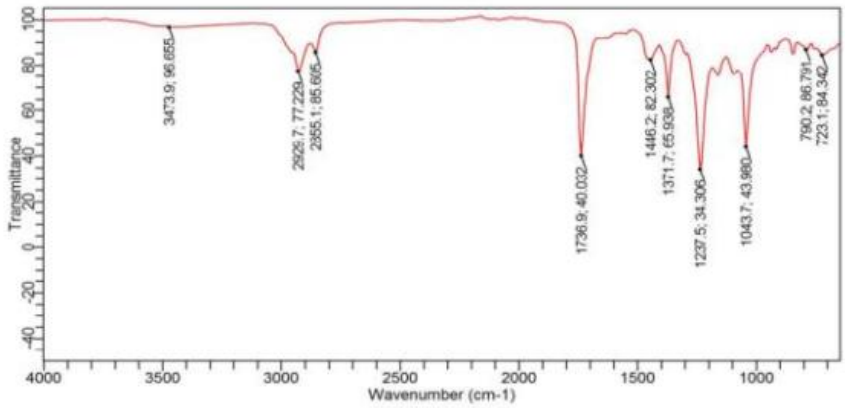

Figure 1. FTIR spectrum of Amaranthus spinosus extract

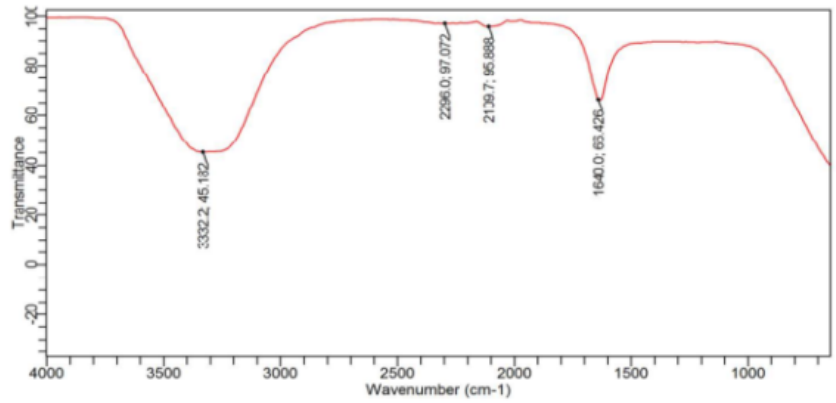

Figure 2. FTIR analysis of phytosome complex in Formula 1

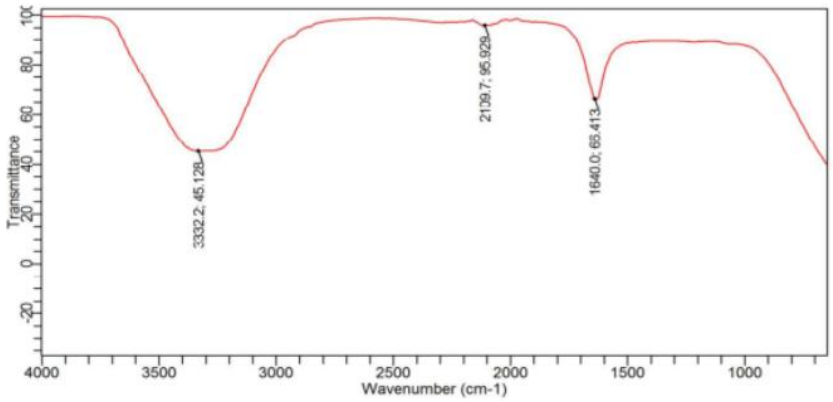

Figure 3. FTIR analysis of phytosome complex in Formula 2

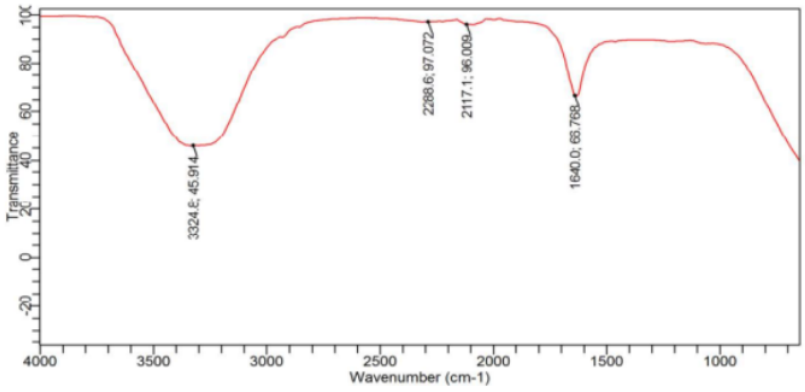

Figure 4. FTIR analysis of phytosome complex in Formula 3

One of the key aspects of the characterization process was the evaluation of hydroxyl (O–H) functional group peaks, which serve as important indicators of hydrogen bond formation. According to Daz and Kalita (2014), hydroxyl groups are typically observed within the wavenumber range of 3743–3228 cm^{-1}. The FTIR spectrum of *Amaranthus spinosus* extract showed the presence of hydroxyl groups at 3473.9 cm^{-1}. Furthermore, phytosome Formulas 1 and 2 exhibited hydroxyl absorption bands at 3332.2 cm^{-1}, whereas Formula 3 showed an absorption band at 3324.8 cm^{-1}. The shift toward lower wavenumbers indicates an increase in hydrogen-bonding interactions within the system. This spectral shift suggests the successful

formation of phytosome complexes through hydrogen bonding interactions between phytoconstituents and soy lecithin or other components present in the phytosome matrix. Such interactions are essential because they provide evidence of complex formation and may contribute to enhanced stability and improved bioavailability of the encapsulated phytoconstituents. By strengthening the interaction between the active compounds and the phospholipid carrier, phytosomes can facilitate more efficient delivery of bioactive compounds to target cells, thereby improving their therapeutic potential.

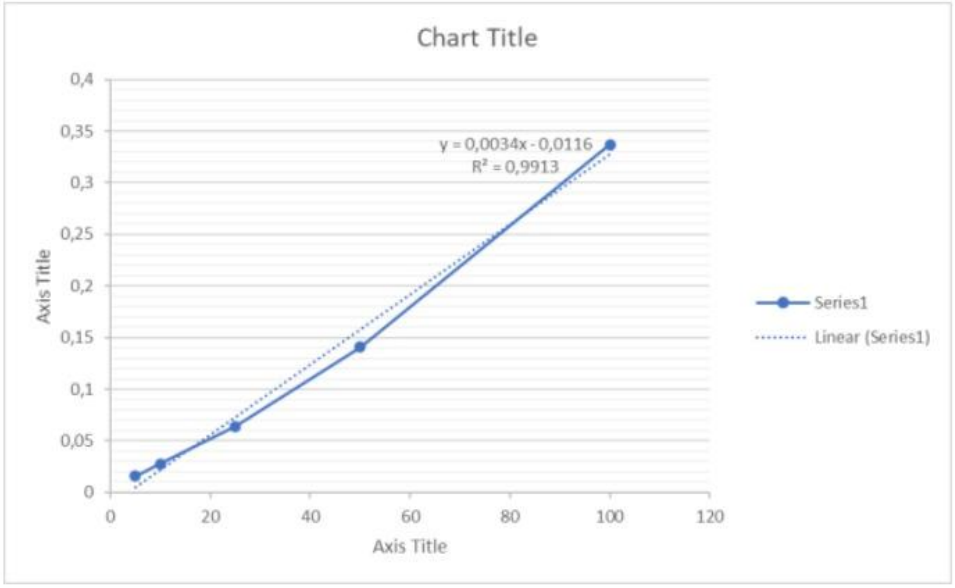

Figure 5. Standard calibration curve for quantification of entrapment efficiency

The entrapment efficiency analysis of the phytosome formulations was initiated by determining the maximum absorption wavelength of gallic acid. The maximum wavelength was identified at 750 nm using a 100 ppm gallic acid solution. The determination of this wavelength is essential because it serves as the reference wavelength for measuring sample absorbance in subsequent analyses. Accurate wavelength selection ensures reliable quantification of phenolic compounds and provides a robust basis for evaluating the entrapment efficiency of the phytosome formulations.

The determination of total phenolic content in the phytosome samples began with the construction of a calibration curve using a linear regression equation obtained from absorbance measurements of gallic acid standard solutions at concentrations of 5, 10, 25, 50, and 100 ppm. The analysis showed a correlation coefficient of r = 0.9913, indicating a strong linear relationship between absorbance and gallic acid concentration. This high correlation coefficient demonstrates that the calibration curve was reliable and suitable for determining the phenolic content of the samples.

Following the determination of the maximum wavelength and establishment of the regression equation, absorbance measurements were conducted for the three phytosome formulations and their corresponding supernatants. The obtained absorbance values were subsequently used to calculate the phenolic content of each sample based on the established linear regression equation.

Table 3. Entrapment efficiency of phytosome formulations

Formula	entrapment efficiency (%)
1	16,56
2	61,01
3	47,23

The results indicated that the phytosome systems were capable of entrapping phenolic compounds with varying efficiencies. This variation may be influenced by several factors, including the composition and physicochemical characteristics of the phytosomes, such as particle size, particle distribution, and polarity, which affect the interaction between phenolic compounds and the phytosome matrix.

The entrapment efficiency values were calculated and are presented in Table 3. Based on the obtained data, Formula 2 exhibited the highest entrapment efficiency among the three formulations, with a value of 61.01%. This finding suggests that Formula 2 possessed a greater capacity to incorporate phenolic compounds, which is an important indicator of phytosome performance as a delivery system for bioactive substances. The optimal entrapment efficiency achieved by Formula 2 provides a promising basis for further development of phenolic compounds as antioxidant agents for the prevention of skin aging.

The pH evaluation of the phytosome formulations revealed that all formulations exhibited acidic characteristics, with pH values ranging from 4.5 to 6.5. This acidity can be attributed to the primary components of the phytosome system, namely *Amaranthus spinosus* L. extract and soy lecithin. Both materials are known to contribute to the formation of an acidic environment, thereby influencing the final pH of the phytosome formulations.

It is important to note that the concentration of soy lecithin played a significant role in determining the pH of the system. An increase in the amount of lecithin resulted in lower pH values, indicating possible interactions between lecithin and other phytosome components that may modulate the chemical properties of the formulation.

Table 4. pH measurement of phytosome formulations

Formula	pH
1	5,28
2	5,14
3	5,06

The presence of pH values within the range of 4.5–6.5 is not only desirable from a formulation perspective but also highly relevant for topical applications. Phytosome systems with pH values compatible with human skin, which typically ranges from 4.5 to 5.5, may minimize the risk of irritation and adverse skin reactions often associated with topical products containing active ingredients (Azkiya *et al*., 2017).

Referring to the findings reported by Azkiya *et al*. (2017), maintaining an appropriate pH is essential in the development of cosmetic and pharmaceutical formulations. Products intended for topical application should ensure both user comfort and safety while maintaining their ability to deliver active compounds effectively. Therefore, the pH results obtained in this study indicate that the developed phytosome system possesses considerable potential for topical applications involving bioactive compounds.

Organoleptic evaluation of the spiny amaranth phytosome cream was performed using human sensory observation. The results demonstrated consistency among all formulations in terms of appearance, color, and odor. The creams exhibited a semi-solid form with a soft, non-sticky texture, a yellowish-green color, and no detectable odor. Homogeneity testing was subsequently conducted to ensure uniform distribution of ingredients and the absence of coarse

particles within the cream formulations. The creams were spread on glass slides and visually inspected. Based on the obtained data, all three formulations demonstrated good homogeneity, with no visible coarse particles observed on the glass slides. Homogeneous creams possess a smooth texture without lumps or aggregates, providing greater comfort during application. Furthermore, non-homogeneous formulations may negatively affect product stability, efficacy, and uniform distribution of active compounds on the skin (Pratasik *et al*., 2019).

The pH of the cream formulations was measured using a pH meter to ensure compatibility with the physiological pH of human skin, which ranges from 4.5 to 6.5. Maintaining an appropriate pH is essential to ensure product safety, user comfort, and the prevention of skin irritation (Pratasik *et al*., 2019).

Based on the results, all phytosome cream formulations exhibited pH values within the acceptable range of 4.5–6.5. This finding is important for maintaining both product safety and effectiveness, as formulations that are excessively acidic or alkaline may damage the skin's protective barrier and compromise skin health (Pratasik *et al*., 2019).

Spreadability testing was conducted to evaluate the ability of the cream formulations to spread uniformly over the skin surface. A desirable spreadability value for cream formulations ranges from 5 to 7 cm, indicating suitable consistency and ease of application. Adequate spreadability also facilitates optimal absorption of active compounds through the skin (Pratasik *et al*., 2019).

The spreadability values obtained for all three formulations fell within the acceptable range of 5–7 cm, indicating favorable spreading characteristics. Several factors may influence cream spreadability, particularly mixing temperature and stirring duration. Lower mixing temperatures may increase the water content of the cream, resulting in a less viscous formulation and greater spreadability. In addition, stirring duration affects particle size distribution within the cream. Extended stirring generally produces smaller particles, resulting in reduced spreadability but potentially enhanced skin absorption. Conversely, shorter stirring times tend to generate larger particles, increasing spreadability and facilitating application. Therefore, careful control of mixing temperature and stirring time is necessary to obtain a cream formulation with desirable application properties (Baskara *et al*., 2020).

Adhesion testing was performed to assess the ability of the cream to remain attached to the skin after application. According to Pratasik *et al*. (2019), a satisfactory adhesion time for cream formulations should exceed 4 seconds. Based on the obtained data, all phytosome cream formulations demonstrated acceptable adhesion properties, with adhesion times greater than 4 seconds. Formula 1 exhibited the highest adhesion time of 8.41 seconds, whereas another formulation showed a lower adhesion time of 5.29 seconds. Prolonged adhesion on the skin is advantageous because it allows a longer contact time between the active compounds and the skin surface, thereby enhancing the release and absorption of bioactive substances and potentially improving therapeutic effectiveness (Pratasik *et al*., 2019).

Conclusion

Based on the results of this study, it can be concluded that the phytosomes containing spiny amaranth (*Amaranthus spinosus* L.) extract prepared using the thin-layer hydration method successfully met the required characterization parameters, including particle size, polydispersity index (PDI), phytosome complex formation, and pH. Among the formulations evaluated, Formula 2, consisting of an extract-to-lecithin ratio of 0.05:0.8, demonstrated the highest entrapment efficiency and was therefore identified as the optimal formulation. These findings indicate that the selected ratio of extract and lecithin plays a significant role in enhancing phytosome formation and encapsulation performance, making Formula 2 the most promising candidate for further development into topical delivery systems such as cream formulations.

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