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Development and Characterization of a Nano-Serum from Hylocereus undatus: Phytochemical Content, Antioxidant Activities, and Nanoparticle Properties

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Abstract: *Antioxidant activity and formulation study of Hylocereus undatus peel extract for cosmetic application. The yield of the extract was 5.47 ± 0.31% and had a weakly acidic pH (5.21 ± 0.35). The TPC and TFC were 172.49 ± 0.06 mg GAE/g and 134.66 ± 0.11 mg QE/g, respectively, and all were significantly higher than the extraction yield ($p < 0.0001$). Antioxidant activity was assessed as IC_{50} by DPPH (39.91 ± 0.5 mg/mL) and ABTS (85.95 ± 0.25 mg/mL), FRAP activity was observed to be 109.29 ± 0.22 μmol AEAC/100g. Nano formulated under ultrasonic treatment resulted in a 32% reduction in particle size (to 51.11 ± 1.83 nm) and an improved zeta potential of -9.30 ± 0.46 mV thereby improving colloidal stability and bioavailability. The optimized 0.2% w/w extract nano serum (C2) showed higher physical stability and cosmetic properties, thereby supporting its application as an advanced skincare product.*

Keywords: *Hylocereus undatus extract, Antioxidant activity, Nano-serum*

INTRODUCTION

Anthocyanins are water-soluble pigments of the flavonoid class of natural products. They comprise an aglycone (anthocyanidin), sugar applications and even acyl groups. There are over 30 unique anthocyanins, however only six, pelargonidin, cyanidin, delphinidin peonidin, petunidin, malvidin, exist majorly in nature. Different anthocyanin types have different color and physicochemical characteristics, and their color appearance and stability are dependent on many factors such as pH, molecular structure, temperature, ascorbic acid, sugar, etc [1]. Evidence of the multiple biological and pharmacological properties of anthocyanins, including its potent antioxidant activity, anti-inflammatory effect, cholesterol-lowering effect, anticancer and antiviral activities, has been well documented [2]. More importantly, anthocyanins are a type of antioxidant which has stronger antioxidant activity than vitamins C and E and offers double or even more inhibition of free radical and lipid peroxidation. This makes anthocyanins important red colorants for natural food and cosmetic industry [2]. Dragon fruit (Hylocereus spp.) (also called Dragon's fruit; pitaya) are a good source of betacyanins (phenolic glycosides responsible of the red colour in fruit). Like anthocyanins, betacyanins are water-soluble compounds and act as electron or hydrogen donors, efficiently neutralising reactive oxygen species (ROS) and acting as strong antioxidants [3-4]. The DPPH radical scavenging activity of the dragon fruit peel extract was found to be substantial, with an IC_{50} as low as 0.04 mg/mL, as reported from the literature [3]. The extract has a slightly acidic pH and the betacyanin concentration ranges between 0.6-2.78 mg/100 g dry peel, depending upon the extracting solvents and experimental conditions used [3-4]. These results support previous studies which have reported that dragon fruit peels are abundant in water soluble betacyanins that are red in color and known to possess high levels of antioxidants [3-4]. By virtue of these characteristics, this research was carried out in order to study the phytochemical content of peel extracts of dragon fruit, specifically determination of anthocyanin and betacyanin concentration, total phenolic and total flavonoid contents and antioxidant properties. In addition, the extracted material will be prepared to produce a serum

product with the help of nano emulsion technology, for better penetration into the skin. This new process not only increases the value of dragon fruit peels, a waste product that is commonly discarded, but also allows for its use in the cosmetic industry as a natural antioxidant and colorant [4].

MATERIALS AND METHODS

Materials

The plant sample that was tested in this study was the peel of H. undatus, which was collected from Chachoengsao Province. The chemicals used were ethanol, methanol, and ascorbic acid (all from Chem-supply); gallic acid, quercetin, 2,2-diphenyl-1-picrylhydrazyl hydrate and Folin–Ciocalteu reagent (all from SIGMA-ALDRICH); sodium carbonate, sodium nitrite, aluminum chloride, and sodium hydroxide (all from KEMAUS); and hydrochloric acid (KEMAUS). Other additives used were hydroxyethyl celluloses, glycerin, butylene glycol, pentanol, phenoxyethanol, chlorphenesin, and polysorbate 20 (all available from MySkinRecipes). The apparatus used in this work included a UV-Vis spectrophotometer (Shimadzu, UV-2700/UV-2700i Plus), rotary evaporator (BUCHI R-300), ultrasonicator (model GT-1860QTS, China), microscope (VH-S1, Keyence VH-Z450) and particle size and zeta potential analyzer (Malvern, Zetasizer Lab).

Methods

Preparation of Extract

The peels of Hylocereus undatus were trimmed into small pieces and dried in a hot air oven at 60 ° C for 8 h [5]. After drying, the dried peels were powdered. Isolation was performed by maceration method; weight of powdered Hylocereus undatus peel was taken in airtight container. Solvent: The solvent used was Ethanol with the ratio of 1:4 (w/w: dry powder to solvent) [6]. The combination was pressed into a mixture and macerated for 7 days [7]. After being extracted the mixture was filtered and the solvent was evaporated in vacuo with a rotary vacuum evaporator. The extracted was recovered and kept at 4°C, and the extraction yield was determined as a percentage with respect to the initial dry weight of the sample.

Quantification of Phenolic and Flavonoid Content

Determination of Total Phenolic Content

Total phenolic content (TPC) was determined by Folin-Ciocalteu reagent assay. An analytical reference solution using gallic acid at a concentration of 0.1 mg/mL was used to estimate the aliquot (0, 25, 50, 75, 100, 125, 150, 175, and 200 µL). To the aliquot was added 0.25 mL Folin-Ciocalteu reagent and mixed well. Thereafter, 1.5 mL of 7% Na_2CO_3 was added to the above solution and incubated in the darkness for 30 min. The absorbance was measured at 765 nm with a spectrophotometer [8]. A standard calibration curve was generated by using different concentrations of gallic acid, and then a linear regression equation (Y = mx + c) was calculated. This same approach was used for plant extracts, and the TPC was determined in mg GAE/g extract from the gallic acid standard curve using the following formula:

$$TPC = \frac{C \times V}{W} \quad (1)$$

where C was the concentration extracted from the standard curve (mg/mL), V was the volume of extracted solution (mL), and W was the weight of dry extract (g). All samples included triplicate analyses, and the values were averaged.

Determination of Total Flavonoid Content

The total flavonoid is calculated by the aluminium trichloride ($AlCl_3$) colorimetric method wherein a calibration curve of quercetin standard is prepared, and the law of Beer-Lambert is utilized for extrapolation. Quercetin standard solutions are mixed with 1.5 mL of 10%$AlCl_3$, 0.15 mL of 5% $NaNO_2$, and 1 mL of 4% NaOH at 25 mL reaction system [9]. The solution was then vortexed and allowed to stand at room temperature for 8 min. Spectrophotoscopic readings were taken at 415 nm [10]. A calibration curve (standard) was developed at different concentrations of quercetin and the equation of the linear regression (Y = mx + c) was established. The same process was performed with plant extracts, and total flavonoid content (TFC) was reported as milligrams of quercetin equivalent per gram of dry extract (mg QE/g extract) by the equation:

$$TFC = \frac{(C \times V)}{W} \quad (2)$$

where C = concentration from the standard curve (mg/mL), V = volume of extract (mL), and W = weight of the dry extract (g). Each experiment was performed in triplicate and results were averaged.

Antioxidant activity

The antioxidant capacity of compounds was quantitatively evaluated by DPPH, FRAP, ABTS, and NO scavenging assays, and each assay uses different mechanisms and calculations. These methods provide good information on capacity reduction, radical neutralization and nitric oxide modulation, with the main advantage of being very interesting evaluations of both natural and synthetic antioxidants.

Analysis of Antioxidant Activity Using the DPPH Assay Method

The radical scavenging assay of 2,2-diphenyl-1-picrylhydrazyl (DPPH) is a common method which is used to evaluate the antioxidant activity based on electron donation mechanism. For this experiment, ascorbic acid is used as a reference standard at different dilutions: 50-800 µg/mL [11]. Each of the test tubes receive 2000 µL of a 0.24 mg/mL of DPPH solution in ethanol, and the negative control contains 1000 µL of ethanol. After a vortex mixing, the samples are incubated at room temperature and in darkness for 30 min. The absorbance is determined at 517 nm [12] by UV-Vis spectrophotometry and the measurements are carried out in triplicate. It is expressed as a percentage of inhibition as follows:

$$\% \text{ Inhibition} = \frac{(A_{control} - A_{sample}) \times 100}{A_{control}} \quad (3)$$

where A control is the absorbance of the reagent, and A sample is the absorbance of the test sample. The IC_{50} is calculated by interpolation of the dose-response curve of inhibition versus sample concentration.

Analysis of Antioxidant Activity Using the FRAP Assay Method

Antioxidant capacity by the ferric reducing antioxidant power (FRAP) assay is based on the reduction of Fe^{3+} to Fe^{2+}. The FRAP (ferric reducing antioxidant power) reagent comprised of Fe3+-TPTZ (2,4,6-tripyridyl-s-triazine) in an acetate buffer (pH 3.6) [13] and becomes a blue Fe^{2+}-TPTZ complex when reduced. Evaluation of antioxidant activity is based on the absorbance measurement at 593 nm, after 30 min incubation. FRAP assay The FRAP is expressed as follows:

$$\text{FRAP (µmol AEAC/g)} = \frac{C \times V}{W} \quad (4)$$

where C is the concentration corresponding to the standard curve (µmol/L), V is the total volume of the extract (L) and W is the weight of the sample used (g).

Analysis of Antioxidant Activity Using the ABTS Assay Method

The ABTS assay evaluates the extent of radical scavenging by monitoring the discoloration of the $ABTS^{+}$ radical cation, and the absorbance is read at 734 nm [14]. The radical is generated by oxidation of ABTS with potassium persulfate. Inhibition percentage is calculated according to:

$$\% \text{ Inhibition} = \frac{(A_{control} - A_{sample}) \times 100}{A_{control}} \quad (5)$$

where A control is the absorbance of the blank (reagent) and A sample is the absorbance of the test sample. The IC_{50} (an amount of concentration which gives 50% inhibition) is calculated by interpolation of a curve representing an inhibition dose-response tested against the sample concentration.

Analysis of Antioxidant Activity Using the NO Assay Method

In the NO scavenging assay, the antioxidant retarded the conversion of sodium nitroprusside to nitrite in phosphate buffer (pH 7.4) containing NO donor (sodium nitroprusside) [15]. Residual nitrite is measured by using the Griess reagent at 546 nm. The percent of inhibition is calculated as follows:

$$\% \text{ Inhibition} = \frac{(A_{control} - A_{sample}) \times 100}{A_{control}} \quad (6)$$

where A control is the absorbance of the blank (reagent) and A sample is the absorbance of the test sample. The IC_{50} (an amount of concentration which gives 50% inhibition) is calculated by interpolation of a curve representing an inhibition dose-response tested against the sample concentration.

Development of Serum Product Formulation

Serum product formulation, the preparation of the serum product formulation comprised the formulation of three base serum formulations with different hydroxyethyl cellulose germinal agent concentrations [16]. The goal was to determine the best formulation for subsequent product development.

Preparation of Base Serum Formulations

Three different base serum formulations (F1, F2 and F3) were formulated, different in the amount of hydroxyethyl cellulose present. This polymer is the gelling agent and has a profound impact on the viscosity and texture of the ultimate product. The ingredients of each of those formulations are tabulated in Table 1 with their respective weight percents and functions in that table.

Table 1: Base serum formulations.

Ingredient	F 1 (%w/w)	F 2 (%w/w)	F 3 (%w/w)	Function
DI Water	88.75	88.55	88.35	Solvent
Hydroxyethyl Cellulose	0.2	0.4	0.6	Gelling agent
Glycerin	4	4	4	Humectant
Citric acid 50% w/v	0.05	0.05	0.05	Neutralizer
Butylene Glycol	4	4	4	Humectant
Pentanol	1	1	1	Humectant
Polysorbate 20	1	1	1	Emulsifier
Phenoxyethanol (and) Chlorphenesin (and) Glycerin	1	1	1	Preservative

Preparation of Base Serum

Formulation of serum, the serum was prepared according to the following formula, in the given order: the appropriate amount of deionized water (88.75, 88.55 or 88.35% w/w, respectively), was measured out in a recipient and gently mixed. Add hydroxyethyl cellulose slowly in stirring to form a homogeneous clear gel (make sure that the polymer is completely hydrated). Add glycerin (4% w/w), butylene glycol (4% w/w) and pentanol (1% w/w) in sequence to the wetted gel with stirring between the additions, until completely homogeneous. Finally, stabilize the composition by adding and thoroughly mixing 0.05% w/w of 50% w/v citric acid solution in a manner sufficient to adjust the pH. Then add polysorbate 20 (1% w/w) as emulsifier and the preservative combination of phenoxyethanol, chlorphenesin and glycerin (1% w/w) for antimicrobial protection. Lastly be sure to mix the entire preparation very well, the goal is to make sure all ingredients are dissolved and as well as spread evenly over the serum.

Preparation of Hylocereus undatus Serum

The serum formulation for containing Hylocereus undatus (dragon fruit) extract Therefore, the serum formulations of the serum formulation containing Hylocereus undatus (dragon fruit) peel extract according to the invention can be prepared by preparing a base serum of these ingredients: deionized water, hydroxyethyl cellulose (gelling agent), humectants such as glycerin, butylene glycol, pentanol (humectants), citric acid (neutralizer), polysorbate 20 (emulsifier), preservatives such as phenoxyethanol, chlorphenesin, and glycerin. This base is further divided into two separate formulations; one with incorporation of 0.1% w/w of Hylocereus undatus peel extract; and the other, 0.2% w/w of the extract. The extract is evenly mixed into bases and serums produced are recorded for further assessment and analysis. Another study conducted on the high doses of the extract of Hylocereus polyrhizus (a relative of Hylocereus undatus) peel extract showed that when the peel extract was administered orally to male and female rats at doses of 1250, 2500 and 5000 mg/kg per day for 14 days, its acute toxicity was studied. Results The results revealed no mortality in all test groups with a LD_{50} above 5,000 mg/kg. All animals gained weight, and activities were normal for the duration of the experiment. No significant differences were observed in the organ indexes for heart, lungs, liver, spleen and kidneys versus controls. The fact that tested doses are in great excess of typical formulation levels (0.1-0.2% w/w) reflects a confirmation of the high-local safety of dragon fruit peel extract for cosmetic formulations of the dermal type at these usage levels with respect of concerns of acute toxicity [17].

Particle Size Reduction by Ultrasonication Method

Nano reduction of Hylocereus undatus loaded serum base formulations was achieved by ultrasonication at 0.1% and 0.2% w/w. Ultrasonicator [18] (model GT-1860QTS, China) performed at frequency of 40

kHz and its ultrasonic power is 150 w by 30 min was used. This technique utilizes high-frequency ultrasonic waves to create cavitation forces that break down particle aggregates and decrease size of particles in the serum formulations [19].

Accelerated Stability Testing

Stability of the product samples was determined through the evaluation of their appearance, odor, and phase separation, both initially and after exposure to seven heating/cooling cycles [20]. The tests comprised only base gel formulations (F1, F2, F3) and gels enriched with Hylocereus undatus extract at concentrations of 0.1% (C1) and 0.2% (C2) w/w and appearance for clarity and color, odor for pleasantness and phase separation for any signs of separation or precipitation. In addition, with the help of statistical analysis, the physicochemical properties were determined before and after the heating/cooling cycles ($p < 0.05$).

Particle Size, Polydispersity, and Zeta Potential Analysis

Dynamic Light Scattering (DLS) is employed to determine hydrodynamic diameter, polydispersity index (PDI) and zeta potential (in mV). Three determinations for the same batch are made to give the statistical reliability and the data are averaged for final reporting [21]

Observation of Serum Nanoparticle Structure

Structural features, and the distribution of nanoparticles within a serum formulation, can be visually inspected for by light microscopy at 10x magnification. This method is advantageous to display the particle position and possible agglomerations in the nano-serum matrix, but it is constrained in the resolution for the fine nanostructures because optical microscopy is subject to the diffraction limit [22].

Statistical analysis

The results are expressed as mean ± SD from three independent experiments at least. Statistical comparison between groups were made by one-way ANOVA, and further testing to assess differences at $p < 0.05$ by Tukey post hoc test. Statistical analyses All statistical analyses were done in GraphPad Prism version 10.

RESULTS

Physical Characteristics of Extract

In general, the peel extract of Hylocereus costaricensis usually presents a bright red to deep magenta, as shown in Figure 1. This peculiar coloration is due to its abundant presence of betalain pigments, especially betacyanins [23-25]. The scent is particularly and identifiably mild-fruity with earthy background, a typical aroma for dragon fruit peels [26]. The extract is moderately viscous in terms of viscosity, which indicates presence of polysaccharides and soluble fiber [26-27]. The extraction yield was between 5.47 ± 0.31% [28]. The extract had a pH of 5.21 ± 0.35 [23,26], which is slightly acid. This pH is common of fruit-extractive solutions, which may be employed for several applications in foods and cosmetics because of their gentle nature and compatibility with skin and biological systems.

Figure 1: Appearance of the crude extract (Hylocereus undatus).

Total Phenolic Content (TPC)

The TPC of the Hylocereus undatus peel extract was very high with a value of 172.49 ± 0.06 mg GAE/g extract and if compared to the extraction yield, the difference was significant ($p < 0.0001$), as shown in Figure 2(a). This high phenolic content highlights the potential of this peel as an interesting source of compounds with antioxidant activity such as hydroxycinnamic acids, flavonoids, and other phenolic

derivatives. The high TPC values confirm that the peel is a good source of bioactive phenolics with possible augmentative effects on a variety of biological activities, such as antioxidant, anti-inflammatory, and antimicrobial activities. The statistically higher TPC above both yield percentage and flavonoid content further confirms the dominance of non-flavonoid polyphenolic compounds in the extract in the form of phenolic acids, tannins, phenolic derivatives that are responsible for the overall antioxidant potential [29].

Total flavonoid content (TFC)

Total flavonoid content (TFC) was 134.66 ± 0.11 mg QE/g, suggesting high concentration in flavonoid compounds. It was found that the TFC was significantly less than the total phenolic content ($p < 0.0001$) but higher than the extraction yield ($p < 0.0001$). It can therefore be concluded that, overall, flavonoids make up a significant, but not predominant proportion of total phenolic content in the peel extract. The higher level of flavonoids suggests multiple flavonoid groups such as flavonols, flavanols, anthocyanins, and flavones. These moiety divisions are known to have potent antioxidant activities and health benefits. Correlation analysis also shows that the flavonoid contents in the replicates are consistent, as shown in Figure 2(b)), suggesting the reliability of the isolation and analytical methods used. These flavonoids are expected to contribute to the extract's bioactivities such as free radical scavenging, enzyme inhibition, and catalytic applications in antiaging cosmeceutical products [29]. The bioactive elements of different Hylocereus species have been widely studied, especially their phenolic and flavonoid contents. The peels of dragon fruits are rich in betalains, phenolic acids, and flavonoids and when examined with other tropical fruit wastes have exhibited moderate to excellent antioxidant activities. Screening based studies were performed using DPPH, ABTS and FRAP assays which affirmed the potent free radical scavenging activities of Hylocereus extracts which is associated with the high phenolic and flavonoid content. Moreover, evaluation of enzyme inhibition of these extracts has shown promising results for inhibition of elastase, tyrosinase and collagenase which could make them leading new resources for future cosmetic products against aging. Hydrogel products formulated as delivery vectors containing Hylocereus extracts were created to improve the bioavailability and controlled release of bioactive compounds. All these data indicate that the peel of H. costaricensis may be a valuable source of natural antioxidants and bio-actives for pharmaceutical and cosmetic purposes.

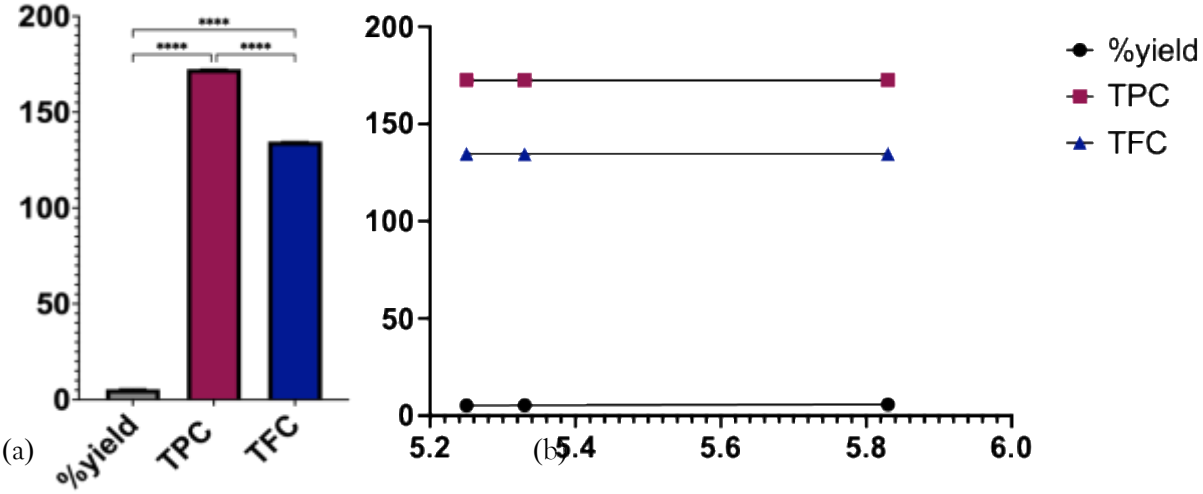


Figure 2: (a) Comparison of % yield, total phenolic content (TPC), and total flavonoid content (TFC). TPC and TFC were significantly higher than % yield (****$p < 0.0001$), and TPC was significantly higher than T (**$p < 0.0001$). (b) Correlation plot of replicate data for % yield, TPC, and TFC.

Antioxidant activities

DPPH Radical Scavenging Activity

Hylocerenus undatus showed substantial free radical scavenging activity indicated by its IC_{50} value (39.91 ± 0.5 mg/mL), as compared to standard ascorbic acid that showed IC_{50} value (2.44 ± 0.36 mg/mL) determined in DPPH assay. Treatments were highly significantly different (** $p < 0.0001$) and showed the great potential of the extracts to scavenge free radicals. DPPH assay permits to measure the antioxidant's hydrogen donating capacity by its reaction with DPPH radical. The DPPH scavenging activity of the dragon fruits peel 50.14-52.15% has been reported [3]. The higher IC_{50} value of the Hylocereus undatus

than ascorbic acid demonstrates less antioxidant activity. This result is in agreement with the IC_{50} values reported for different cultivars of Hylocereus undatus, varying from 13.50 to 74.92 mg/mL [29].

ABTS Radical Scavenging Activity

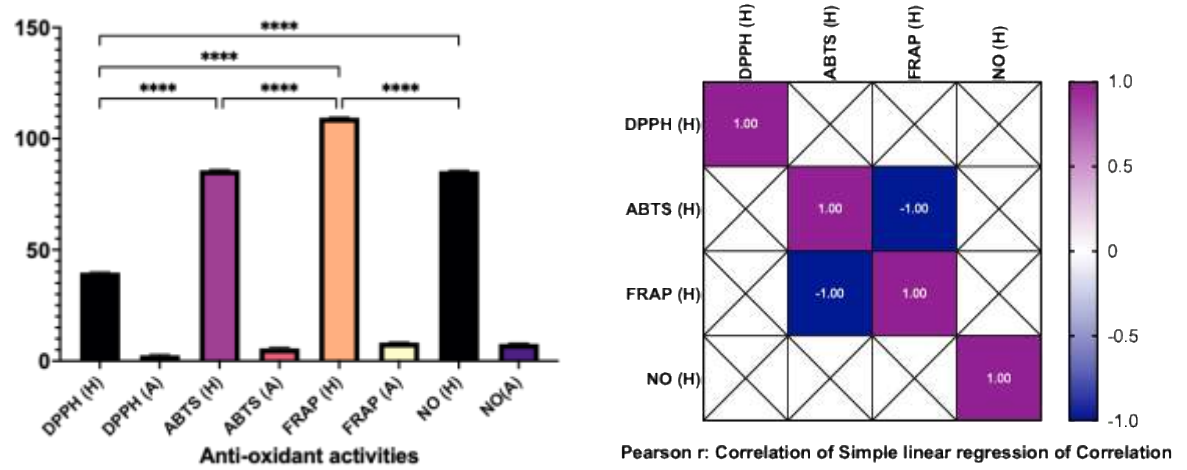
The IC_{50} value obtained from The ABTS radical cation decolorization assay of Hylocereus undatus was 85.95 ± 0.25 mg /mL, whereas ascorbic acid markedly possessed higher activity (IC_{50} of 5.23 ± 0.7 mg /mL). The highly significant difference (**p < 0.0001) confirms these results. The ABTS assay is also based on an electron-transfer reaction and the ability of the extracts to scavenge the ABTS radical produced was compared to that of a commercial antioxidant (positive control) [30], where red dragon fruit can effectively scavenge the ABTS radical cations albeit at higher concentrations relative to the positive control. This assay is especially useful as it quantifies both hydrophilic and lipophilic antioxidants and gives an overall profile of total antioxidant capacity of the plant extract.

FRAP (Ferric Reducing Antioxidant Power) Activity

The maximum antioxidant power was observed with FRAP assay of all studied parameters and was 109.29 ± 0.22 and 8.33 ± 0.2 µmol AEAC/100g in Hylocereus undatus and ascorbic acid respectively, whereas (**p < 0.0001) indicates maximum reducing ability of the dragon fruit extract. Ferric reducing activity in plasma (FRAP) measures the ability of antioxidants to reduce Fe^{3+} to Fe^{2+} and higher FRAP values suggest better antioxidant capability [30]. The high FRAP value of the Hylocereus undatus may be due to the presence of such reduction compounds as the total phenolic compounds and flavonoids, which improve its antioxidant. This result agrees with the previous findings that dragon fruit peel extracts have a remarkable reducing behavior in a dose-dependent manner [30].

Nitric Oxide (NO) Scavenging Activity

The assay showed Hylocereus undatus showed an inhibition of NO with an IC_{50} of 85.79 ± 0.3 µg/mL, ascorbic acid was observed to be more active, 7.35 ± 0.3 µg/mL. The treatments were statistically significantly (**p < 0.0001) different (Figure 1). The nitric oxide scavenging activity is particularly important because the nitric oxide is involved in several biological processes, and an excessive amount of it can lead to cellular damage. The ability of dragon fruit extract in scavenging nitric oxide may have protective effect on nitrosative stress. In addition, correlation analysis demonstrated a perfect positive correlation (r = 1.00) between DPPH and nitric oxide scavenging activities, indicating that DPPH radical scavenging compounds, which function via a similar hydrogen atom-donating pathway, may also participate in nitric oxide inhibition [30].



(a) **(b)**

Figure 3: (a) Antioxidant activities for DPPH, ABTS, FRAP, and NO assays in Hylocereus undatus (H) and ascorbic acid (A) at p < 0.05; *p < 0.01 and *p < 0.0001. (b) Pearson correlation coefficient (r) from simple linear regression analyses for antioxidant activities, strong positively and negatively correlated antioxidant assays tested.

Related research on antioxidant activities of Hylocereus undatus. Several studies have investigated the antioxidant properties of Hylocereus undatus using similar methodologies. Research has demonstrated that dragon fruit peel extracts show significant DPPH scavenging activity (50.14-52.15%) and good ferric reducing properties in FRAP assays, with antioxidant capacity being proportional to total phenolic content [3]. Comparative reports of different species of dragon fruit have shown that Hylocereus undatus has moderate antioxidant activity with IC_{50} values of 55.04 ± 2.15 mg/g FW for DPPH. This activity varies depending on extraction processes and fruit maturity. In addition, a study on flowers of Hylocereus

undatus has shown the efficient scavenging of DPPH and ABTS radicals via hydrogen-atom and electron-transfer modes directly associated with kaempferol as the main bioactive compound. In general, these results demonstrate the potential of Hylocereus undatus as natural antioxidant and valuable source for functional foods and drugs for therapies. Antioxidant activities were compared between H and A, measured by the DPPH, ABTS, and FRAP methods and NO scavenging (NO) method, as indicated in Figure 3(a). Moreover, the Pearson correlation coefficients (r) for simple linear regression among the antioxidant activities% show, strong positive and negative trend between the considered testing assays in Figure 3(b).

Basic Formulations

The three base systems showed different rheological behaviors which depended on their hydroxyethyl cellulose (HEC) concentration. Best results, with clear and thin gel appearance, with the lowest viscosity levels were obtained for formulation 1, with 0.2% w/w HEC. However, formulation F3 containing 0.6% w/w of HEC showed the highest viscosity which lead to the formation of the most viscous gel. F2 with a medium HEC concentration of 0.4% w/w showed a viscosity ranging between the highest and lowest values. The transparency and optical clarity of all the three formulations (suggests effective dissolution of the polymer and homogeneous gel formation and is depicted in Figure 4. The pH values were constant around 5.89 ± 0.25 throughout all formulated bases, indicating that the formulation chemistries for topically suitable formulations were stable. This concentration-dependent rheological comparison emphasizes the importance of HEC in the formulation as a gellant that dictates gelled product texture and application properties.

Hylocereus undatus Extract-Incorporated Formulations

The addition of Hylocereus undatus extract at concentrations of 0.1% w/w (C1) and 0.2% w/w (C2) presented with visual features quite different from the vehicle formulations. Both extracts loaded formulations showed the typical pale-yellow color, which reflects the successful incorporation of bioactive compounds of the plant extract. This change in color indicates the presence of phenolic compounds and other phytochemicals found in Hylocereus species known to have antioxidant properties. The remaining gel consistency in formulations C1 and C2 showed that there was no appreciable decrease in the gelling potential of the gel matrix due to the extract incorporation. Lighter color shade of C2 in comparison to C1 implies the difference in extract concentrations, where a shade of pale yellow for C2 indicates more intensity of yellow hue is opted due to increased concentration of chromogenic compounds as depicted in Figure 4. The main yellow pigment extracted from dragon fruit peel has been reported as betalain, a member of the betaxanthin family. The yellow pigments are water-soluble betaxanthins. Betalains are pigments that occur in abundance only in the order Caryophyllales, which is a member of the core eudicots and consists of three major groups of plants: the Cactaceae, Amaranthaceae, and Chenopodiaceae families. including the Hylocereus sp. desert plants. [31-32]. These results imply excellent formulation compatibility of the polymeric gel base with the natural plant extract, without compromising its appearance and function, and hence are conducive for cosmetic application.

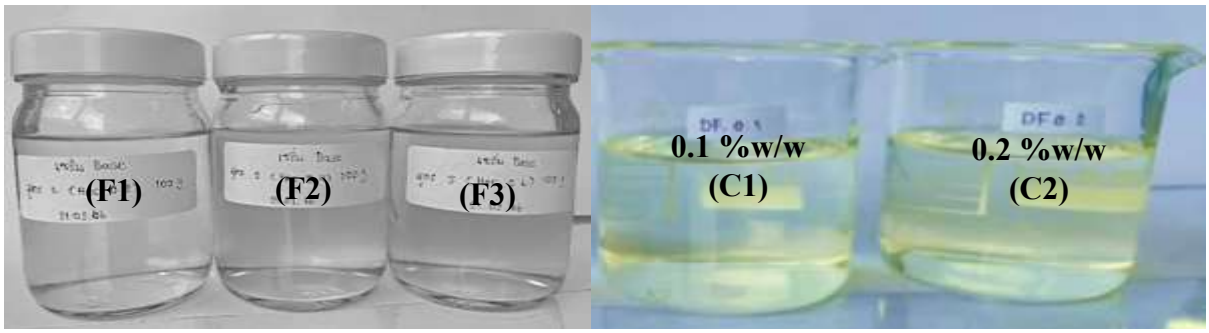


Figure 4: Visual appearance of base gel formulations (F1, F2, F3) and Hylocereus undatus extract-incorporated gels at 0.1% w/w (C1) and 0.2% w/w (C2).

Stabilities test

According from the stability studies, gel formulations showed excellent stability parameters at thermal stress condition. The base gel formulations (F1, F2 and F3) retained their clear, colorless characteristics, were odorless and possessed no phase separation or precipitation over the course of the test period. Similarly, the gels that contained Hylocereus undatus extract (C1 and C2) also had their light yellowish-

soft appearance with good fragrance preserved and also no touchable phase separation was seen up to seven heat-cool cycles. This physical stability implies that dragon fruit peel extract at both 0.1% and 0.2% did not contribute to any interruption of the gel matrix architecture, which is important for the development of cosmetics, as shown in Table 2.

Table 2: Stability Test Results of Product Samples

Condition/Property	F1	F2	F3	C1	C2
Initial					
Appearance	Clear/colorless	Clear/colorless	Clear/ colorless	Yellowish, soft	Yellowish, soft
Odor	Odorless	Odorless	Odorless	Fragrant	Fragrant
Phase separation	No separation/ precipitation	No separation/ precipitation	No separation/ precipitation	No separation/ precipitation	No separation/ precipitation
Heating/cooling 7 cycles					
Appearance	Clear/colorless	Clear/colorless	Clear/ colorless	Yellowish, soft	Yellowish, soft
Odor	Odorless	Odorless	Odorless	Fragrant	Fragrant
Phase separation	No separation/ precipitation	No separation/ precipitation	No separation/ precipitation	No separation/ precipitation	No separation/ precipitation

Notes: F1, F2, F3 are the base gel formulations C1 (0.1% w/w) and C2 (0.2% w/w) are the gel formulations containing Hylocereus undatus extract Clear/colorless means clear colorless while yellowish, soft means yellow color and soft. Fragrant describes a smell that is pleasing to the senses. "No Separation/Precipitation" signifies that no visually distinguishable phase separation or sedimentation was noticed under the condition applied.

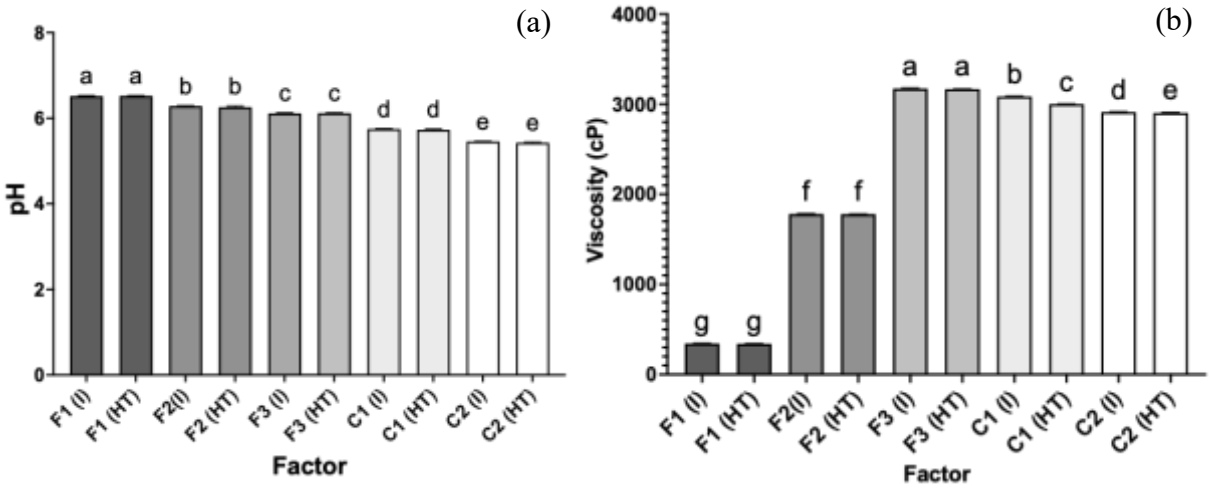


Figure 5: Stability of base gel formulations (F1, F2, F3) and Hylocereus undatus extract-incorporated gels at 0.1% (C1) and 0.2% (C2) w/w, comparing initial (I) and after 7 heating/cooling cycles (HT): (a) pH values and (b) viscosity (cP). Different letters indicate significant differences ($p < 0.05$).

The pH and viscosity results showed outstanding stability for all formulations during the thermal cycling. Statistical methods showed that the initial and post-thermal treatment values for all formulations, both pH and viscosities showed no significant differences ($p < 0.05$). Base gels F1, F2 and F3 slightly higher pH (6.5, 6.2, 6.1) was observed than the extract incorporated gels (c1, 5.8; c2, ~5.5) as depicted in Figure 5(a). Previous work has shown that the acidity of unprocessed Hylocereus undatus fruit varies slightly: 4.2-4.9. The best soil for growing dragon fruit plants is a soil which is slightly acidic to nearly neutral with

a pH range of 5.5 to 6.5; highly acidic soils will most likely not yield healthy plant growth and may even lead to the death of the plant. Essential bioactive compounds in dragon fruit including betalains are highly stable in weak acidic conditions (pH 3.0–7.0), thus, they can be formulated as active agents in cosmetic products at pH of approximately 5.0–6.0. This pH range provides the stability of betalains and matches the pH value of products cosmetics [33]. Viscosity results showed a similar trend; F3 had the highest viscosity (approximately 3200 cP) with C1 and C2 having an intermediate value (around 3000 and 2900 cP, respectively) (Figure 5(b). Finally, there was no statistically significant difference in the pH and viscosity values between T0 and T400 for all the formulations. The C1 formula (0.1% Hylocereus undatus extract) is the most preferred formula that was found to provide excellent viscosity properties yet with outstanding stability features. Previous studies have demonstrated that thermal cycling tests are a key to validation of the stability of cosmetics, which simulate the actual environmental conditions during storage and transportation processes.

Ultrasonic particle size reduction

As can be seen from the figures, the ultrasonic reduction process greatly improves the formulation properties of gels containing extract from Hylocereus undatus. Macroscopic view of the base gel (F3) and the drug-loaded formulations (0.1%, C1 and 0.2%, C2) are shown in Figure 6(a). Additionally, Figure 6(b) clearly demonstrates the influence of ultrasonic treatment on droplet size distribution at a microscopic level. In the "Before" image, droplets are predominantly large, non-uniform, but varying greatly in droplet size; however, in the "After" image, it is evidence that particle volume decrease, together with an increase in homogeneity and size uniformity within the gel matrix. Furthermore, this nanotexturing ultrasonic micronization technique ensures that the bioavailability and stability of the components are improved through increasing the specific surface area of the drugs and the surface-to-volume ratio of the particles and eventually prorogues the overall drug performance of the product. The ability to generate small, evenly distributed particles with this method represents an important step in pharmaceutical nanotechnology, having an impact on both the effectiveness and the costs of the delivery of the active ingredient.

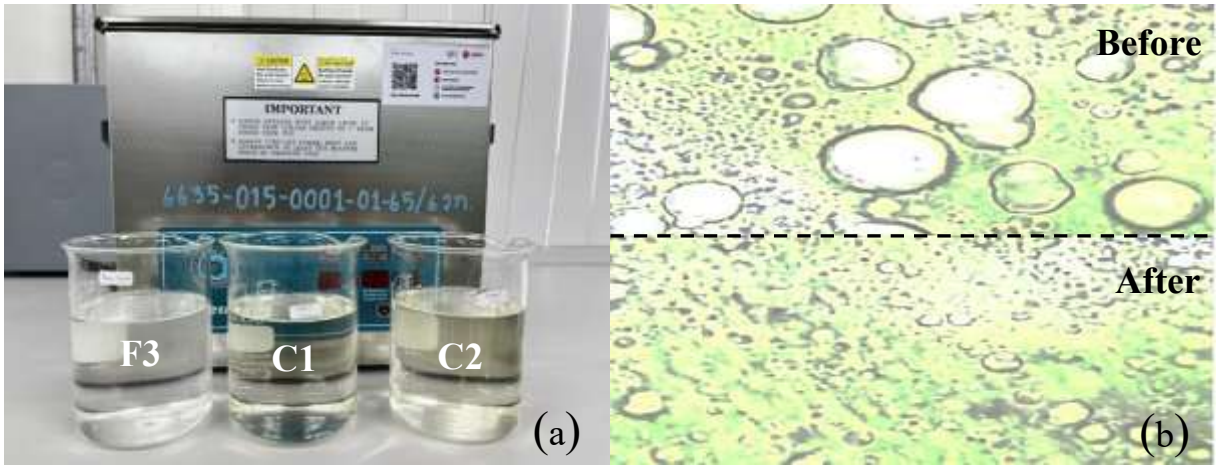


Figure 6: (a) Visual appearance of base gel (F3), and gels containing Hylocereus undatus extract at 0.1% (C1) and 0.2% (C2) w/w. (b) Comparison of droplet size in C2 gel before and after particle size reduction under a microscope at 10x magnification.

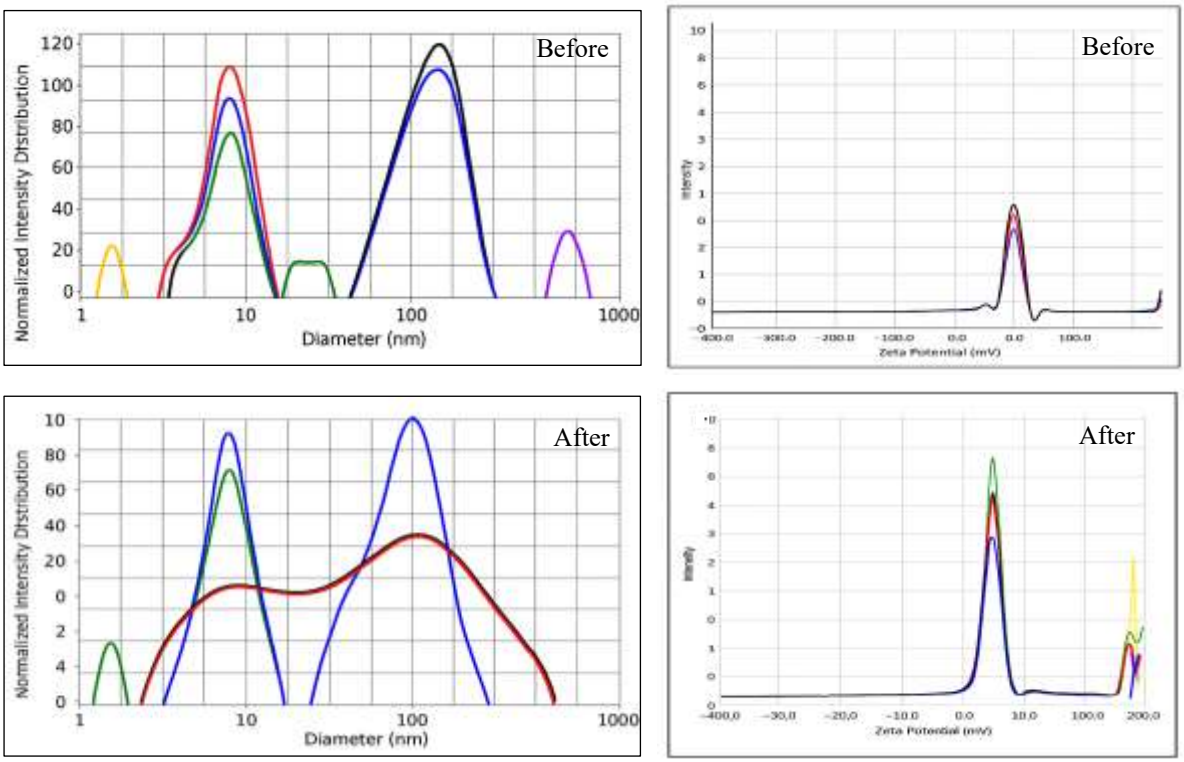
Particle Size Distribution Analysis

The ultrasonic treatment greatly enhanced the decrease of particle size, which gave rise to a significant 32% reduction of mean particle diameter. The broad initial size distribution of the coprecipitated fibers (110-120 nm and average diameter was 75.31 ± 1.26 nm) could then be efficiently narrowed down to 105-110 nm and average diameter of 51.11 ± 1.83 nm, as shown in Figure 7(a). The polydispersity index (P.I.) was then reduced to 0.15 ± 0.92, indicating improved particle uniformity, and size homogeneity. In cosmetic application, it is even more beneficial to reduce the size of the particles, as smaller nanoparticles have better skin penetration and bioavailability than larger nanoparticles.

Zeta Potential Characterization

Characterization The values of the zeta-potential of the samples, represented in Figure 7(b). This change in surface charge towards more negative direction indicates increased colloidal stability wherein particles

with zeta potentials from ±30 mV also shows better dispersion stability. While the final zeta potential of -9.30 ± 0.46 mV falls short of the values (31-40 mV) suggested in the literature to obtain the maximum stability, this observed value indeed stands as a significant enhancement over the near-neutral initial zeta potential, and the particles are less likely to aggregate or flocculate.



(a) (b)

Figure 7: Comparison of (a) normalized intensity distribution of particle diameter (nm) and (b) zeta potential intensity of Hylocereus undatus nanosereum concentrate 0.2% w/w (C2) before and after size reduction.

Optimal Formulation for Cosmetic Applications

The processed nano serum concentrate, 0.2% w/w C2 of Hylocereus undatus, is in fact the most suitable formulation for cosmetic purpose, based on the improved particle size and surface charge properties. More importantly, a decrease by 32% in particle diameter to 51.11 ± 1.83 nm and an enhanced zeta potential stability up to -9.30 ± 0.46 mV makes this nano serum as an extremely promising candidate for cosmetic applications. This composition has an improved uniformity and better penetrant characteristics, and acceptable colloidal stability for commercial cosmetic use, especially for serums and lip products, where a good skin absorbance and product stability are critical.

DISCUSSION

The present study reveals exciting antioxidant potentials of the peel extract of Hylocereus undatus thereby further suggesting that these peels may serve as a natural biologically active agent applicable in foods, pharmaceuticals, and cosmetics industry. Dragon fruit peel extracts are rich in phenolic compounds, flavonoids and betalain pigments, more significantly betacyanins and has important free radical scavenging and ferric reducing antioxidant activities. This is in accordance with the proposal that activity of phenolic antioxidants could occur through hydrogen atom transfer and electron transfer, as it has been demonstrated in a number of studies on plant phenolics and flavonoids where the combination of two different phenolics lead to a synergy increase in the total antioxidant capacity. The high TFC and TPC values obtained in this study are associated to a higher radical scavenging potential to DPPH, ABTS, FRAP and NO assays, which imbues to the extract a strong antioxidant profile as previously reported [25,29,34,35]. These results are based on the antioxidant hypothesis that phenolics, flavonoids and other antioxidants ameliorate oxidative stress, a mediating factor in multiple chronic diseases and aging. The

relationship between the structure and activity, especially the catechol group and the bond dissociation enthalpy in flavonoids, is behind its ability to act against the free radicals and network pharmacology activities. Betalains also contribute to antioxidant activity in Hylocereus peels and anti-inflammatory, anti-hyperglycemic, and detoxifying effects have been attributed to these compounds. Low viscosity and slightly acidic pH of the extracts also ensure the stability and compatibility for formulation in cosmeceuticals and nutraceuticals making compliance with the industry needs for bioactives [25,34,36,37,38]. Recent studies also demonstrated that the dragon fruit peel extract is more antioxidant than the tropical fruits' waste, especially by ABTS and FRAP methods. The unique color and slight aroma, in addition to resistance to oxidative stress, suggest the potential use of the extract as a functional food additive and in topicals. Furthermore, studies on enzyme inhibition also validate the potential elastase, tyrosinase and collagenase inhibitory activities, suggesting possible uses in anti-age products and treatments. TFC repeatability and the good relationship between antioxidant assays also do contribute to the reliability of analytical methods and the bio-efficacy of these peels as sustainable sources of health beneficial compounds [35-37]. The current study also showed that ultrasonic-assisted particle size reduction is an efficient tool for the development of stable and uniform nanocosmetic formulations containing natural plant-based extracts like dragon fruit (Hylocereus undatus) peel. The ultrasonic action contributes to an increased homogeneity and a decrease of the size of the particles in the gel matrices, guaranteeing better bioactivity and skin penetration of the loaded bioactive principles. This is also consistent with the rules of ultrasonic nanotechnology, in which cavitation microjets and shockwaves disperse larger agglomerates and interparticle collisions and surface erosion play a role in reducing the average dimensions and provide a uniform size. These mechanisms account for the observed droplet and particle size decrease, resulting in more aesthetically pleasing compositions with improved uniformity and sterility [39]. From a formulation point of view, particle size is an important factor in determining the occupational skin absorption efficiency. Nanoparticles can penetrate the stratum corneum and the deeper layers of the dermis much more efficiently than micron-sized particles. This attribute is important in providing for the topical application of actives like betalains and phenolics from dragon fruit skin, for which antioxidant activity and skin protecting capabilities are also enhanced by increased cellular penetration. The process of sonication is an energy-efficient, cost-effective process and offers a wide choice of surfactants and emulsions structures, thus these can be optimized in order to obtain the desired properties of the product and can be enhanced without affecting to the stability of the formulation. The enhanced zeta potential after ultrasonic treatment, although not ultra-negatively charged, will contribute to the improved stability, reducing the likelihood of aggregates or phase separation of the product during storage and use [39-40]. Moreover, there is prior art, and even patent literature, in support of Hylocereus undatus extract incorporation into nano cosmetics. The extract provides a luminous pale-yellow hue, due to its content of betalain compounds, that manifest skin radiance and fluorescent properties in cosmetic formulas. Properties such as of fluorescence and antioxidation are favorable for cosmetically applied products for visual improvement of the complexion of skin. Previous works have attested that dragon fruit extract used in diverse cosmetic forms such as serums, lotions and gels, imparts natural pigmentation, antioxidant activity as well as anti-imperfection properties to the skin. The ultrasonic nano emulsification of these ingredients enables them to achieve maximum efficacy and compatibility, providing a solid scientific basis to produce a number of commercial cosmetic serums with improved texture, stability, and performance (Anguraj et al. 2024).

CONCLUSION

From the peel extract of Hylocereus undatus, potential application for pharmaceutical and cosmetological agents has been continuous interest as a multifunctional bioactive material. This potential is due to its rich phenolic and flavonoid content, strongin vitro antioxidant activities, and good compatibility in products. The extract exhibits good physicochemical stability, and pH as well as viscosity of gels based upon the formulation constants are satisfactorily constant. Its thermal stability is also supported by stability studies demonstrating no phase separation or degradation. Furthermore, the decrease in particle size under sonication condition increases the homogeneity, bioavailability, and colloidal stability of the final nanoscale formulation with better penetration potential. Collectively, these data demonstrate a promising potential for the peel of dragon fruit in cosmetic applications and provide a renewable sustainable natural source of natural antioxidants that could be used in the innovation of cosmeceutical products, particularly for topical gel and nano-serum formulations.

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Conflicts of Interest
The authors declare that there is no conflict of interest regarding the publication of this article.

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