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Electrospray-Mangiferin Nanoparticles Gel: A Promising Agent for Sun and Age Defense

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Abstract: UV irradiation causes skin damage and aging. This study aimed to develop and evaluate a gel formulation loaded with electrospray mangiferin nanoparticles (MNPs) as a double-action product with photoprotective and anti-aging properties. The MNPs were prepared using the electrospraying technique and loaded in a gel formulation. The MNP formulation was evaluated regarding its physical appearance, viscosity, in vitro sun protection factor (SPF), and in vitro anti-oxidant activity and compared with a formulation containing purified mangiferin (PM) at the same concentration of 0.2% (*w*/*v*). Moreover, both formulations were analyzed for their in vitro release and ex vivo skin permeation. The MNP formulation had a considerably higher SPF value than the PM formulation at the same concentration (20.43 ± 0.13 and 12.19 ± 0.27, respectively). The in vitro anti-oxidant activities of the formulations with MNPs and PM were 74.47 ± 2.19% and 80.52 ± 1.05%, respectively. The MNP formulation showed potent photoprotective and anti-oxidation activities with acceptable stability in all parameters under accelerated conditions (4 ± 2 °C 48 h/45 ± 2 °C 48 h for 6 cycles) and after 30 days of storage under various conditions. The release profile data of the MNPs showed a controlled release pattern at 76.97 ± 0.06% at 480 min. Furthermore, after using a Franz diffusion cell for 8 h, the MNP formulation showed the release of 37.01 ± 2.61% and 22.39 ± 1.59% of mangiferin content in the skin layer as stratum corneum and viable epidermis, respectively. Therefore, the overall results demonstrate that electrospray MNPs in a gel formulation are suitable for skin and constitute a promising delivery system for mangiferin in developing cosmetics and cosmeceutical products with good potential.

Keywords: mangiferin; electrospray; nanoparticles; photoprotective; anti-aging

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1. Introduction

Excessive exposure to UV light can cause skin redness, pigmentation, and accelerated aging of the skin. Skin redness or sunburn is caused by UV-B, which has a wavelength of 290 to 320 nm, while skin darkening and aging are caused by UV-A radiation, which has a wavelength of 320 to 400 nm [1]. The frequency and length of UV radiation influencing the skin determine how much damage is created; prolonged exposure weakens the skin's natural defenses, necessitating the use of sunscreen preparations among other measures [2]. Sunscreen acts as a photoprotective agent, shielding the skin from the damaging effects of direct UV light. Current research focuses on producing broad-spectrum sunscreens that gradually reduce the harmful effects of direct UV radiation. Phytoconstituents are becoming increasingly popular as important components in cosmetic formulations because they are

natural; they have anticarcinogenic, antimutagenic, and nontoxic properties; and they can greatly impede the intricate process of carcinogenesis [3]. Synthetic photoprotective agents possess the potential to be toxic and carcinogenic. Natural herbal-based cosmetics are less irritating, especially for hypoallergic skin [4]. They also contain native ingredients that can rejuvenate the skin and provide sufficient protection against UV-A and UV-B radiation, atmospheric temperature fluctuations, pollution, hyperpigmentation, and aging. Because bioactive components are harmless, do not show negative effects, do not include any harmful synthetic compounds that could endanger human health, and are environmentally sustainable, their use in cosmetic formulations has recently grown [3,5]. Furthermore, bioactive substances exhibit a wide range of pharmacologic characteristics. These include naturally occurring preservatives and anti-oxidants, hypo-allergenic properties compared with synthetic products, and environmentally friendly features [6]. According to published research, water-in-oil or oil-in-water systems are the most widely used for sunscreen formulations [7]. However, the greasy nature of these emulsion systems can make skin oily, and they are considered unsuitable for skin that is prone to acne [8]. Gels are a great choice for topical medications because they are easy to apply and stay effective for a long time. Unlike creams and ointments, gels also release the medication in a controlled way [9].

Scientists are increasingly looking for natural substances that are safe and effective for treating various conditions. Plant molecules are especially promising because many have targeted effects within the body. Mangiferin, a plant-based xanthone glycoside, stands out for its wide range of potential benefits, including reducing inflammation, regulating the immune system, controlling blood sugar, fighting cancer, killing microbes, and protecting cells from damage [10,11]. Mangiferin, a naturally occurring compound found in plants like mangoes (*Mangifera indica* L.), is particularly abundant in their leaves. Tayana et al. showed varying levels of mangiferin in different parts of dried plants. Young leaves contain the highest average concentration at 6.78% (*w*/*w*). The content decreases in older leaves (5.89% *w*/*w*) and twigs (2.75% *w*/*w*). However, mangiferin was undetectable in both ripe and unripe fruit samples [12]. This anti-oxidant powerhouse offers potential protection for skin, hair, and lips from the damaging effects of UV rays. It may also help improve overall skin quality and fight signs of aging [13,14].

Mangiferin itself could penetrate the skin barrier but exhibits poor solubility in aqueous media and a low lipophilicity [15]. Mangiferin dissolves poorly in water and is not very attracted to oily compositions of skin. As a result, creams and gels containing mangiferin may not deliver enough of the compound to deeper skin layers for optimal effectiveness [16]. The ability of a substance to penetrate the skin barrier is related to its log *p* value (the octanol–water partition coefficient) and molecular weight. Substances with log *p* values between 1 and 3 and molecular weights <500 Da (1 Da = 1 g/mol) are more likely to penetrate the skin barrier [17]. Mangiferin has a log *p* value of 2.73 and a molecular weight of 422.33 g/mol, suggesting that it possesses the potential to penetrate the stratum corneum [18]. Developing an aqueous formulation containing the 0.5% *w*/*v* ratio of mangiferin isolated from *Mangiferin indica* L. variety Nam Dok Mai leaves, using a co-solvent system, could increase the solubility of mangiferin. Chanikanda et al. found that adding certain ingredients called co-solvents, like polyethylene glycol 600 or dipropylene glycol, can improve mangiferin absorption compared to using water alone [19]. This approach makes it more available for the body to use. In fact, researchers in Indonesia successfully incorporated mangiferin, extracted from *Phaleria macrocarpa* fruits, into a sunscreen using a gel formulation. The SPF values of the formulation were 11.2, 38.6, and 88.53 loading on mangiferin concentrations of 1.25, 2.5, and 5%, respectively [13]. However, no research has been conducted to develop formulations containing mangiferin in an electrospray nanoparticle platform that could improve its solubility and bioactivity. One promising approach is to use electrospraying technology, which constitutes a potential technique for preparing nanoparticles that help dissolve poorly soluble drugs. It may be effective in improving the loading of poorly soluble active ingredients in the formulation [20].

Electrospraying or electro-hydrodynamics is one technique of electrospinning that involves breaking up a liquid into fine droplets using an electric field. Electrospraying is a technique that uses electricity to create tiny droplets from a liquid solution. A high voltage is applied to a thin tube, forcing the liquid into a cone shape. This cone then breaks up into droplets, whose size can be controlled by adjusting the voltage, how fast the liquid flows, and the distance between the tip and the collector [21]. Electrospraying offers several advantages for creating tiny particles for various uses. It excels at efficiently trapping materials (high encapsulation efficacy), allowing for large-scale production (increased bulk production) and consistently producing particles of the same size (reproducibility characteristics). This technique is especially helpful for poorly water-soluble ingredients, making them more usable. Recently, advancements in electrospraying have been adapted to create micro and nanoparticles, opening doors for exciting applications in pharmaceuticals, biomedicine, and cosmetics [20,22]. Our previous study showed that fabricating mangiferin nanoparticles (MNPs) using an electrospraying technique exhibited an efficient delivery system for anti-aging agents in cosmetic formulations [23].

In summary, we investigated an electrospray MNP formulation with double action including photoprotective and anti-aging properties. The findings underscore the potential for increased mangiferin loading, augmented stability within the formulation, and enhanced dissolution and permeability, all of which substantiate its applicability in the realm of cosmeceuticals.

2. Materials and Methods

2.1. Chemicals

PM and MNPs were prepared following the study by Chomchoei et al., 2023 [23]. Mangiferin standard (MS) with a purity of 99% and 2,2-diphenyl-1-picrylhydrazyl were purchased from Sigma-Aldrich (St. Louis, MO, USA). Dialysis tubing (molecular weight cut-off of 10 kDa, 35 mm dry I.D.) was secured from Thermo Fisher Scientific (Rockford, IL, USA). Acrylates/C10-30 Alkyl Acrylate Crosspolymer (Carbopol® ultraz 21), polysorbate 80, butylene glycol, triethanolamine, and spectrastat BHL were bought from Namsiang, Co., Ltd. (Bangkok, Thailand). Absolute ethanol, isopropanol (IPN), glacial acetic acid, methanol (HPLC grade), acetonitrile (HPLC grade), dimethyl sulfoxide (DMSO), sodium metabisulfite, di-sodium EDTA, di-sodium hydrogen orthophosphate, sodium dihydrogen phosphate, and sodium chloride were acquired from RCL Labscan (Pathumwan, Bangkok, Thailand). L-ascorbic acid 99.5% was purchased from Loba Chemie PVT., Ltd. (Colaba, Mumbai, India).

2.2. Preparation of Electrosprayed MNPs

MNPs were prepared based on the study by Chomchoei et al. (2023) [23]. Cellulose acetate (CA) was used to fabricate the nanoparticles. CA is a safe and biodegradable material. Then, 2% CA was mixed with a mixture in a 4:3:3 ratio of dimethylacetamide, isopropanol, and acetone. PM was added to the polymer solution of 2% (*w*/*v*). To make the nanoparticles, the solution was sprayed through a needle at a high voltage of 15 ± 0.5 kV. The flow rate of the polymer solution was 0.3 mL/h, the distance between the needle tip and the collector was 10 cm, and the humidity was at 55–60%. The particle size of the MNPs was 295.47± nm, the polydispersity index (PDI) was 0.29 ± 0.01, and the zeta potential was 21.25 ± 1.20 mV.

2.3. Development of Gel Formulation

2.3.1. Preparation

The composition of a gel formulation containing the PM or formulation 1 (F1) and MNPs or formulation 2 (F2) was prepared following the study by Eff, A.R.Y. et al. with some modifications [13], and the results are shown in Table 1. Carbopol® ultraz 21 was dispersed in ultrapure water and stirred until a gel formed. The remaining compositions were then dissolved in ultrapure water and stirred to obtain a uniform solution. Finally,

the carbopol® ultraz 21 gel was combined with the solution of compositions to create the gel base. The formulation was supplemented with PM and MNPs (0.2% w/v) due to their significant in vitro anti-oxidant activity. Hence, PM and MNPs were mixed into the gel base at an amount of 0.2% (w/v) by stirring, and the pH was adjusted to 5.5 using triethanolamine.

Table 1. Compositions of PM and MNP gel formulation.

No.	Composition	Quantity (%w/w)		Function
		F1	F2	
1	Butylene glycol	5.00	5.00	Humectant
2	Carbopol® ultraz 21	1.50	1.50	Gelling agent
3	Spectrastat BHL	1.00	1.00	Preservative
4	Triethanolamine	0.35	0.35	pH adjuster
5	PM	0.20	-	Active ingredient
6	MNPs	-	0.20	Active ingredient
7	Sodium metabisulfite	0.10	0.10	Preservative
8	di-Sodium EDTA	0.10	0.10	Chelating agent
9	Purified water	91.75	91.75	Solvent

The formulations containing PM and MNPs were prepared for the in vitro activity test. For the in vitro activity test, one gram of the formulation was combined with 2 mL of 20% (v/v) polysorbate 20 and centrifuged at 10,000 rpm for 45 min at 25 °C. The supernatant was then collected. Polysorbate 20 at a concentration of 20% (v/v) was chosen as the vehicle. This non-ionic surfactant dissolved mangiferin, making it suitable for the biological activity test. Additionally, it did not show an interaction with the enzymes and reagents.

2.3.2. Viscosity and Spreadability

Rheology is a measurement of the viscosity of a formulation comprising PM and MNPs, which indicates the fluid's resistance to flow. The gel's viscosity was measured using a Brookfield viscometer with spindle No. P25 (AMETEK Brookfield, Middleboro, MA, USA) for three minutes at room temperature [23]. The formulation's spreadability was assessed using Bhatla and Salnl [24]. The gel's spreadability was measured by placing a weighed sample between two glass slides and applying a weight of 500 g for 5 min. After that, no further spreading was envisaged. The initial and ultimate diameters of spread circles were measured and used to compare spreadability.

2.3.3. In Vitro Anti-Oxidant Activity of Gel Formulation

The anti-oxidant activities of the formulation containing PM and MNPs were measured according to their radical scavenging activity. The DPPH scavenging activity occurred in the manner described by Nanjo F. et al. [25]. An amount of 20 µg of each sample was mixed with 180 µL of a solution containing 166 µM of DPPH dissolved in absolute ethanol and incubated in the dark for 30 min at room temperature. The absorbance was measured at 520 nm using a microplate reader (BMG Labtech, Ortenberg, Germany, SPECTRO star nano). The percentage of inhibition was estimated using the following equation:

$$\% \text{ inhibition} = \frac{(\text{Absorbance of control}) - (\text{Absorbance of sample})}{(\text{Absorbance of control})} \times 100 \quad (1)$$

2.3.4. In Vitro SPF Determination of Gel Formulation

A sunscreen agent's efficacy is often measured by its sun protection factor (SPF). The higher the SPF, the more efficient the product at avoiding sunburn. Firstly, the UV spectra

of MS and PM were studied using a UV–visible spectrophotometer (Shimadzu UV-1800, Shimadzu Corporation, Tokyo, Japan). Mangiferin standard and purified mangiferin were prepared at 0.00001% (10 µg/mL). A 10 µg/mL sample solution was prepared in 50% (*v*/*v*) isopropanol (IPN), and the UV absorption spectra were recorded in the 200 to 500 nm wavelength range. Secondly, the SPF of the PM, MNPs, and the formulation containing PM and MNPs was determined according to Vinood et al. [26] with some modifications using an SPF UV-spectrophotometer (Labshere 2000s Ultraviolet Transmittance Analyzer, Labsphere, Inc., North Sutton, NH, USA) [27]. The PM and MNPs were dissolved in 50% of IPN at the same concentration. The samples were loaded and spread evenly on the PMMA substrate to set the samples on a PMMA plate at 1.3 mg/cm^3. Prior to measurement, the sample-loaded PMMA plate was placed in the dark at room temperature for 30 min. The samples put onto the PMMA plate were tested for their SPF. The samples' scanning spectra were acquired using a UV–visible spectrophotometer at wavelengths ranging from 290 to 400 nm at 5 nm intervals. The in vitro SPF value was calculated from the UV-2000s program according to the equation below:

$$\text{In vitro SPF} = \frac{\int_{290}^{400}[\text{E}(\lambda) \times \text{S}(\lambda) \times \text{d}\lambda]}{\int_{290}^{400}[\text{E}(\lambda) \times \text{S}(\lambda) \times \text{d}\lambda]/\text{MPF}_\lambda} \quad (2)$$

where E(λ) = solar intensity spectrum;
S(λ) = erythemal effect spectrum;
dλ = wavelength step (5 nm);
MPF_λ = monochromatic protection factor;
Rλ = reference scan in voltage at wavelength λ;
Sλ = scan reading in voltage at wavelength λ.

2.3.5. Stability Test

The stability study of the formulations containing PM and MNPs was conducted by storing the samples at different temperatures (4 ± 2 °C, 40 ± 2 °C), at room temperature (30 ± 5 °C) for 30 days, and by using accelerated tests (heating/cooling cycling method for six cycles (24 days), 4 ± 2 °C 48 h/45 ± 2 °C 48 h). The samples were observed at 0 and 90 days, using accelerated tests. Thereafter, the samples were evaluated for their physical appearances (color, pH, and viscosity), in vitro anti-oxidant activity, and in vitro SPF. This study was conducted in accordance with Bhattacharya et al. [8].

2.4. Ex Vivo Permeation Study

The skin permeability of the formulation including PM and MNPs was measured using a Franz diffusion cell. This study was carried out in accordance with the study by Ochocka et al. [18], with minor revisions, and that by Chomchoei et al. [23]. First, fat was extracted from dorsal pig skin and deposited in the receiving chamber. The donor chamber was filled with one milliliter of the samples. The medium was stirred at a temperature of 32 ± 0.5 °C. One milliliter of media was collected every hour until 8 h, and then it was substituted with a new medium. After 8 h, the penetrants were removed from the skin, and the stratum corneum layer was separated using a tape-stripping method and sticky tape for 20 fragments. The mangiferin levels in the receiving compartment were measured. Following separation, the sticky tapes and all skin layers were removed separately with methanol, and the mangiferin content was measured by HPLC. Schieber et al. [28] reported the HPLC method with a few adjustments. The HPLC system applied an analytical column (C 18, 5 µm, 4.6 × 250 mm) with a detection wavelength of 258 nm (Hewlett Packard, Milpitas, CA, USA; Agilent HP1100, Agilent, Santa Clara, CA, USA). The flow rate was set to 0.8 mL/min, the injection volume was 20 µL, and the column temperature at 25 °C. The HPLC mobile phase contained (A) 2% acetic acid in ultrapure water and (B) 0.5% acetic acid/acetonitrile in a ratio of 1:1 (*v*/*v*). The gradient elution was performed in the following

order: 5% of B at 0 to 2 min; 5 to 25% of B at 2 to 10 min; 25 to 55% of B at 10 to 40 min; 55 to 90% of B at 40 to 45 min; and 90 to 55% of B at 45 to 50 min.

2.5. In Vitro Release Study

The release of mangiferin from the formulation comprising PM and MNPs was conducted using dialysis bag diffusion as described by Kim et al. [29], with minor changes, as well as Chomchoei et al. [23]. Briefly, 2 mL of the formulation containing PM and MNPs was dissolved in 5 mL of pH 7.4 PBS buffer and deposited in dialysis bags. The dialysis bag was kept at 32 ± 0.5 °C through the rotation of the medium and collected every 0, 15, 30, 45, 60, 120, 180, 240, 360, and 480 min. Every hour, until 8 h was reached, one milliliter of the medium was collected and replaced with new medium. The mangiferin content was measured using HPLC at 258 nm. Schieber et al. [28] described the HPLC method, which was modified as mentioned in 2.4.

2.6. Statistical Analysis

Statistical analysis was conducted using the SPSS Program, version 17.0, with a significance level of $p < 0.05$ in all cases. The findings are shown as mean ± SD. The parametric variables were analyzed by applying the *t*-test. A *p*-value of <0.05 indicates significance.

3. Results

3.1. Preparation of Electrospray MNPs

PM and MNPs were applied from our previous study [24] in the form of a pale yellow powder. Mangiferin was obtained from the Guangxi University of Chinese Medicine, Nanning, China (purity 88.46%, lot number 20110530) and purified using the recrystallization method with 50% (*v*/*v*) IPN in ultrapure water. Using the electrospraying technique, it was shown that both PM (purity 95.71%) and MNPs displayed in vitro anti-oxidant and anti-aging activities. The applied voltage and distance between the needle tip and collector had a significant impact on the particle size. The particles had an average size of 295.47 ± 5.58 nm, a PDI of 0.29 ± 0.01, and a zeta potential of 21.25 ± 1.20 mV, and they were produced at an applied voltage of 15 kV and 10 cm between the needle tip and collector.

3.2. Gel Formulation

3.2.1. Physical Characterization

All formulations were homogenous and smooth in texture with pale yellow gels. The pH of formulations F1 and F2 were observed to be 5.57 ± 0.03 and 5.52 ± 0.03, respectively (Table 2). Viscosity is an important feature since it influences the spreadability and consistency of the formulation. The viscosity of formulations F1 and F2 were found to be 14.68 ± 0.40 mPas and 13.80 ± 0.56 mPas, respectively. The spreadability showed the diameter of formulations F1 and F2 to be 2.55 ± 0.03 and 2.71 ± 0.02 cm, respectively, indicating that they were effectively distributed on the skin when applied. With these values, both formulations exhibited suitable viscosity and spreadability.

3.2.2. UV-VIS Spectroscopic Study

The UV-VIS spectrum of PM at a concentration of 0.00001% in 50% (*v*/*v*) isopropanol gave absorption peaks at 240, 258.5, 318.5, and 369.5 nm, similar to the spectrum of MS presented at 240.5, 258.5, 318.5, and 369.5 nm, as shown in Figure 1, corresponding to the absorption peaks at 240, 258, 318, and 366 nm presented in the related study [30].

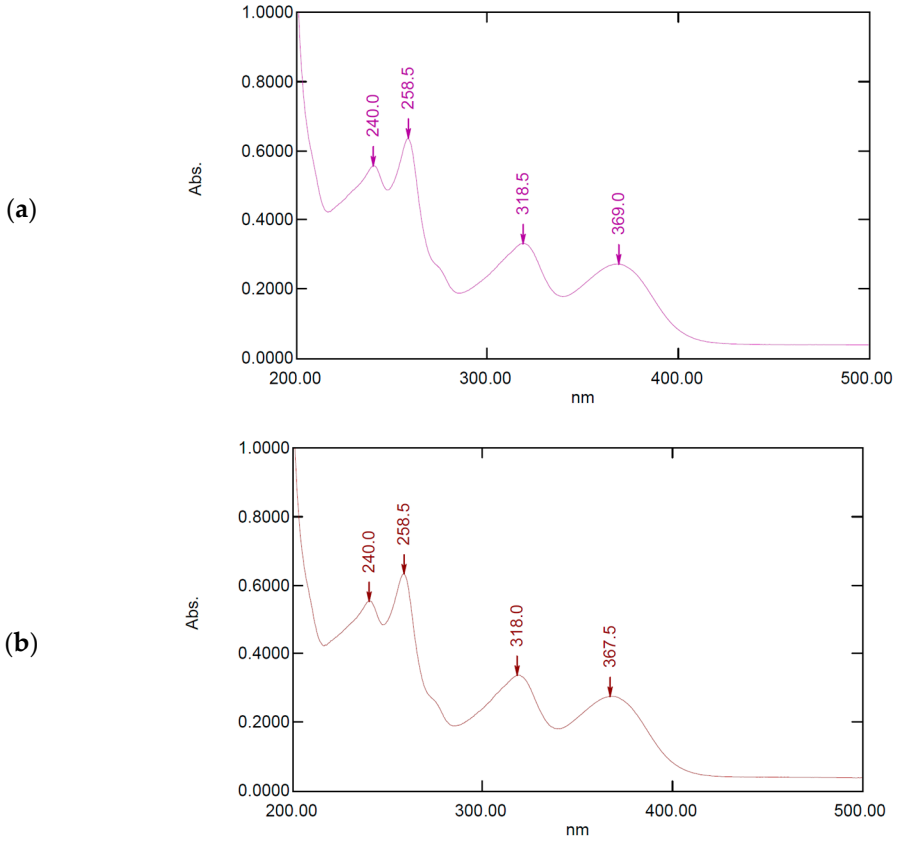

Figure 1. UV-VIS spectrum of (**a**) purified mangiferin and (**b**) mangiferin standard.

3.2.3. In Vitro SPF

Using the UV–visible spectroscopic method, the in vitro SPF values of 0.2% (*w*/*v*) PM and the MNP solution in 20% polysorbate 20 in ultrapure water were found to be 10.25 ± 0.15 and 19.73 ± 0.27, respectively. Moreover, the in vitro SPF values for F1 and F2 were found to be 12.19 ± 0.27 and 20.43 ± 0.13, respectively. The SPF value of a formulation containing MNPs was significantly higher than that containing PM at the same concentration.

3.2.4. In Vitro Anti-Oxidant Activity

Anti-oxidant activity, i.e., the ability to neutralize free radicals, plays a crucial role in repairing UV-induced skin damage and skin aging [8]. Consequently, evaluating the anti-oxidant activity of mangiferin in a formulation is important. The concentrations of PM and MNPs in the formulation were determined according to the IC_{50} value obtained using the biological activity from our related study, which was approximately 2 mg/mL [23]. The formulation was enriched with PM and MNPs (0.2% *w*/*v*) based on their significant in vitro anti-oxidant activity. The inhibition percentages of the anti-oxidant activity of the formulation containing PM and MNPs were found to be 74.47 ± 2.19 and 80.52 ± 1.05%, respectively. F2 showed an insignificant higher percentage of inhibition than F1 (unpair *t*-test, $p > 0.05$).

3.2.5. Stability Test

F2 did not show significant changes in the pH, viscosity, in vitro anti-oxidant activity, and in vitro SPF parameters compared with day 0 ($p > 0.05$), as shown in Table 2 and Figures 2 and 3. F1 did not show significant changes in the pH or viscosity after the stability test. In contrast, the results of the tests on the in vitro anti-oxidant activity and in vitro SPF parameters in F1 revealed significant changes after 30 days and the accelerated stability test. Compared to day 0, the in vitro anti-oxidant activity (Figure 3a) of F1 showed a

significant decrease under all stability conditions ($p < 0.05$). However, the in vitro SPF of F1 remained stable under most conditions, except for storage at 45 °C for 30 days (Figure 3b). Interestingly, F2 did not exhibit significant differences in its in vitro anti-oxidant activity or in vitro SPF value following the stability test. The physical appearance of F1 revealed a clear separation between mangiferin and the gel formulation. Moreover, F2 exhibited a homogeneous appearance as a pale yellow transparent gel devoid of any phase separation. The results are shown in Figure 2.

Table 2. Physicochemical characteristics of gel formulations.

Formulation/ Parameter	Stability Condition	Physical Appearance	pH	Viscosity (mPas)	In Vitro Anti-Oxidant Activity (% Inhibition)	In Vitro SPF
F1	Day 0	Homogenous	5.57 ± 0.03	14.68 ± 0.40	74.47 ± 2.19	12.19 ± 0.27
	Accelerated test	Separation of mangiferin	5.54 ± 0.04	15.68 ± 0.54	62.18 ± 1.57 *	11.76 ± 0.16
	Day 30 (RT)	Separation of mangiferin	5.57 ± 0.03	15.67 ± 0.40	56.07 ± 1.00 *	12.52 ± 0.29
	Day 30 (4 °C)	Separation of mangiferin	5.51 ± 0.03	13.63 ± 0.43	69.43 ± 1.65 *	12.13 ± 0.26
	Day 30 (45 °C)	Separation of mangiferin	5.53 ± 0.03	16.34 ± 0.37	54.85 ± 1.29 *	11.11 ± 0.36
F2	Day 0	Homogenous	5.52 ± 0.03	13.80 ± 0.56	80.52 ± 1.05	20.43 ± 0.13
	Accelerated test	Homogenous	5.56 ± 0.05	15.00 ± 0.31	79.42 ± 1.12	19.33 ± 1.39
	Day 30 (RT)	Homogenous	5.50 ± 0.02	14.80 ± 0.56	80.13 ± 2.28	18.78 ± 0.57
	Day 30 (4 °C)	Homogenous	5.52 ± 0.02	12.97 ± 0.29	78.41 ± 2.39	19.15 ± 0.75
	Day 30 (45 °C)	Homogenous	5.50 ± 0.06	15.13 ± 0.52	79.97 ± 1.71	18.51 ± 0.12

All data are presented as mean ± SD based on three measurements ($n = 3$). * denotes results that significantly differ from day 0 according to *t*-test statistics ($p < 0.05$); RT = room temperature.

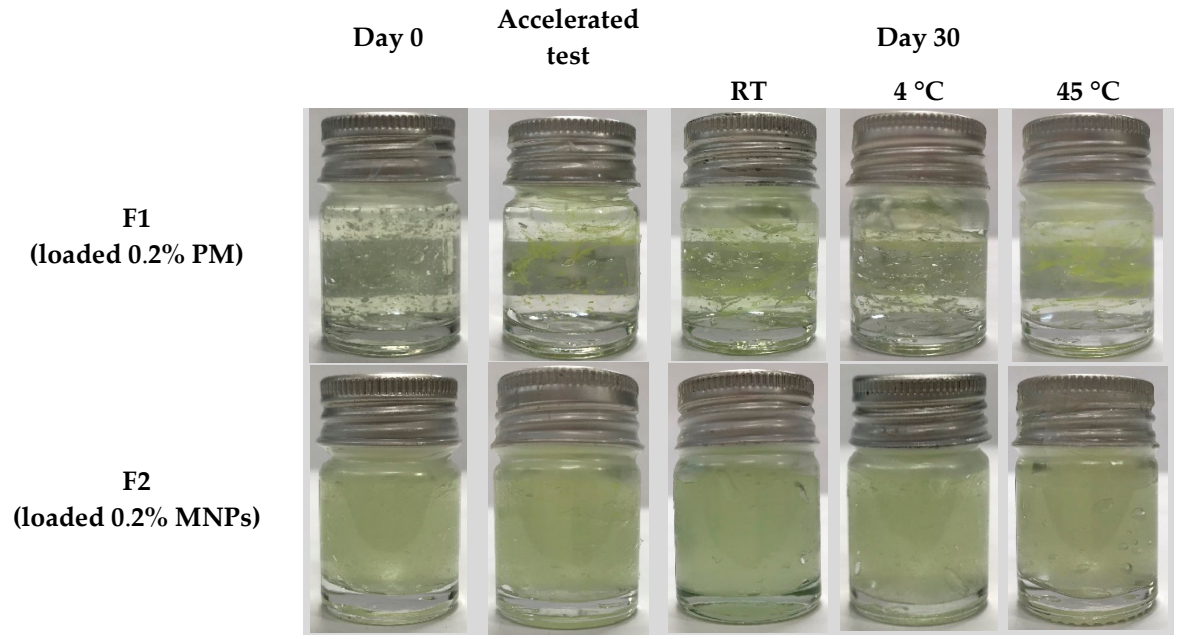

Figure 2. Physical appearance of formulations F1 (loaded 0.2% PM) and F2 (loaded 0.2% MNPs) before (day 0) and after stability test; accelerated and 30-day storage under various conditions (day 30). RT = room temperature.

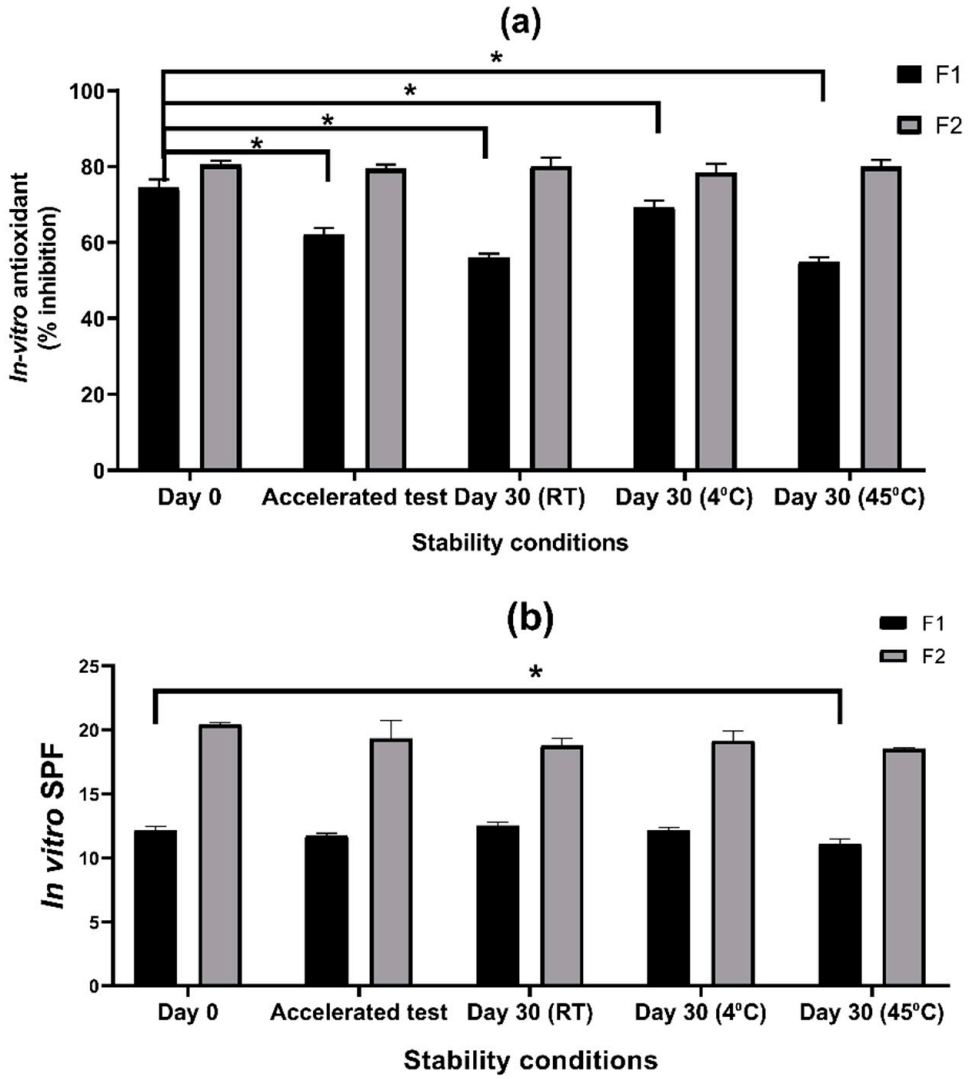

Figure 3. Stability study of formulations F1 (loaded 0.2% PM) and F2 (loaded 0.2% MNPs) for in vitro anti-oxidant activity (**a**), and in vitro SPF (**b**) parameters compared with day 0. All data are presented as mean ± SD based on three measurements ($n = 3$). * denotes results that significantly differ from day 0 according to *t*-test statistics ($p < 0.05$).

3.3. In Vitro Release Study

The release profiles of the formulation containing PM and MNPs were assessed in PBS pH 7.4, as shown in Figure 4. After 60 to 480 min, the results demonstrated significant changes in the samples. The formulation containing MNPs emitted significantly more mangiferin than the PM formulation at 60–480 min ($p < 0.05$). F1 showed a normal release pattern at first and then a continuous release pattern until 480 min, but F2 displayed a persistent release pattern. MNPs showed 76.97 ± 0.06% of released mangiferin, whereas the equivalent amount of PM only showed 36.89 ± 0.78% at 480 min.

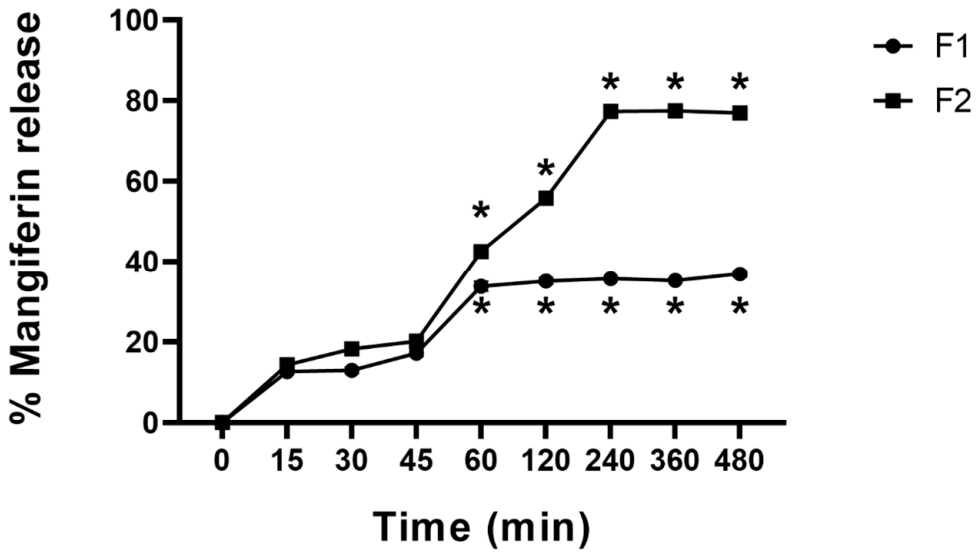

Figure 4. Mangiferin release profile of formulations F1 (loaded 0.2% PM) and F2 (loaded 0.2% MNPs) in PBS pH 7.4. All data are presented as mean ± SD based on three measurements (n = 3). * denotes results that significantly differ from day 0 according to t-test statistics ($p < 0.05$).

3.4. Ex Vivo Permeation Study

The ex vivo permeation of the formulation containing PM and MNPs was evaluated by measuring the amount of mangiferin in the skin layer (stratum corneum and viable epidermis and dermis) as well as by administering solutions every 1 h until a total of 8 h was reached. Skin permeability was examined using Franz diffusion cells. The mangiferin content in the stratum corneum layer was also detected. F2 had a larger mangiferin content in the viable epidermis to dermis compared with that of F1. The amount of mangiferin from F2 was 37.01 ± 2.61 in the stratum corneum and 22.39 ± 1.59% in the viable epidermis and dermis, whereas the amounts were 23.85 ± 1.57% and 14.84 ± 1.93% for F1 (Figure 5). The results show that more mangiferin infiltrated skin layers from F2 than from F1.

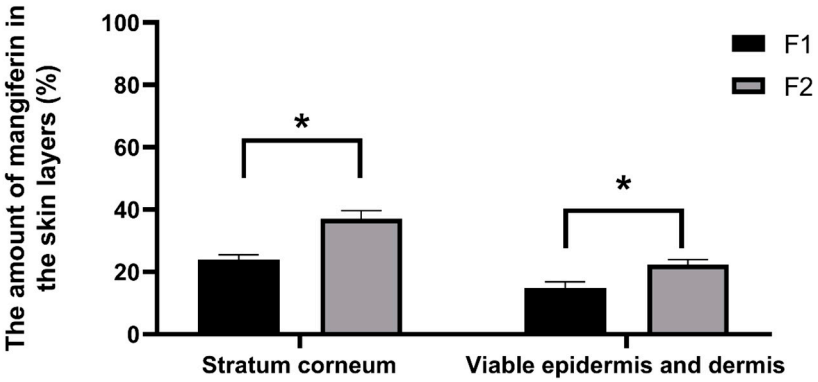

Figure 5. The mangiferin content in the skin layers from using formulations F1 (loaded 0.2% PM) and F2 (loaded 0.2% MNPs): the percentage of stratum corneum, viable epidermis, and dermis. The quantitative content of mangiferin in all of the skin layers was determined using HPLC after 8 h. All data are presented as the mean ± SD based on three measurements (n = 3). * denotes the results that significantly differ from day 0 according to the t-test statistics ($p < 0.05$).

4. Discussions

The gel formulation loaded with MNPs was successfully formulated for anti-aging effects and UV protection. Using the electrospraying technique, it was shown that both PM (purity 95.71%) and MNPs displayed anti-oxidant and anti-aging activities in vitro. The average particle size was 295.47 ± 5.58 nm, the PDI was 0.29 ± 0.01, and the zeta

potential was 21.25 ± 1.20 mV, which was produced under circumstances of an applied voltage of 15 kV and a distance of 10 cm between the needle tip to the collector. The encapsulation efficacy of MNPs was found to be 85.31% [23]. The fundamental advantage of electrospray is its high encapsulation efficiency, which appeals to many researchers [31]. A recent study revealed that calcium alginate microbeads created by electrospraying an aqueous alginate solution into ultrapure water containing calcium ions might be utilized as ecologically friendly cosmetic additives [32]. Moreover, the electrospraying technique fabricated nanoparticles containing mangiferin-rich extract from mango Talabnak variety leaves, which demonstrated a high encapsulation of 84.9% [33]. Meanwhile, the emulsion solvent evaporation approach yielded approximately 55% of mangiferin-loaded polymeric nanoparticles [34]. Another study discovered that electrospraying cashew gum microparticles is a promising method for improving the medicine encapsulation and dissolution rate of a poorly water-soluble material and a highly sensitive bioactive ingredient such as beta-carotene [35].

Several studies have shown that X-ray diffractometry was also used to detect the physical state of a drug within polymeric matrices because the features of the peaks indicate the degree of crystallization of the drug with the matrix [36]. The typical peaks of pure intact mangiferin confirmed that it was in crystalline form, whereas no definite peak was found for the amorphous polymer. However, these peaks totally disappeared in the diffractograms of the MNPs, showing that the crystallinity of mangiferin was significantly reduced during the production process. Electrospraying has proven to be a promising method of producing amorphous solid dispersions, which is an established formulation strategy for enhancing the bioavailability of poorly soluble medicinal compounds [37]. Various studies of formulation strategies have been developed in recent years to address solubility issues, with amorphous solid dispersion emerging as a popular and successful approach [38,39]. Solid dispersions can be created by solvent evaporation, heat-based procedures, and electrospraying [40,41]. As a result, MNPs from our previous study were detected in an amorphous solid dispersion. Thus, these electrospraying settings can be exploited to generate nanoparticles for cosmetic delivery systems [23]. Furthermore, related investigations indicated that N, N-dimethylacetamide and acetone in a ratio of 2:1 (v/v) is a useful solvent for electrospinning/electrospraying CA nanofibers.

The preparation of gel formulations showed that both formulations exhibited suitable viscosity and spreadability. The UV-VIS spectrum of PM at a concentration of 0.00001% in 50% (v/v) isopropanol resulted in absorption peaks at 240, 258.5, 318.5, and 369.5 nm, similar to the spectrum of MS and a related study [30]. Moreover, the UV spectrum of PM shows the absorption from 320 to 290 nm, which is important to the photoprotective effect [8]. The SPF value of the formulation containing MNPs was significantly higher than that containing PM at the same concentration. However, the reported SPF of mangiferin isolated from *Phaleria macrocarpa* fruits in the gel formulation was observed to be 11.2, 38.6, or 88.53 depending on whether mangiferin was used at concentrations of 1.25, 2.5, or 5%, respectively [13]. Compared with other phytochemicals, such as resveratrol and green tea, the in vitro SPF values of the sunscreen formulation containing resveratrol and green tea extract at a concentration of 10% (w/v) were found to be 16.91 ± 1.20 and 14.59 ± 0.64, respectively [8]. Considerately, cellulose acetate can be photochemically disintegrated by UV wavelengths less than 280 nm; however, it has limited photodegradability in sunlight due to a lack of UV-absorbing chromophores [42]. Culica et al. found, by evaluating their UV-Vis absorption and transmittance spectra, that cellulose acetate film does not absorb UV or visible light at wavelengths ranging from 200 to 700 nm [43], so CA was not a UV absorber. Several studies have demonstrated the benefits of sunscreen through nanotechnology, including reduced permeability, increased efficacy, and improved photostability. Vieira et al. found that the nanoencapsulation of the drug increased SPF and reduced toxicity in vitro and in vivo [44]. MNPs with an amorphous structure were similarly found to have greater in vitro SPF than PM. Finally, mangiferin is an effective photoprotective ingredient for cosmetic compositions, and nanoparticles have demonstrated considerable advantages

over traditional delivery techniques. Electrospraying MNPs successfully preserves labile organic filters from chemical degradation by entrapping them inside the particle core rather than molecularly dissolving them in an oil or water phase [45]. Thus, sunscreen formulations with mangiferin are applicable for photoprotective purposes.

The stability results of the formulations did not reveal significant changes in the pH, viscosity, in vitro anti-oxidant activity, or in vitro SPF parameters compared with day 0 in formulation 2. On the other hand, the results of the tests on the in vitro anti-oxidant activity and in vitro SPF parameters in formulation 1 showed that remarkable changes occurred after 30 days and during the accelerated stability test. DPPH is a stable free radical molecule that can be used to quickly assess the anti-radical or hydrogen donor capacity of unknown substances [46,47]. Hydrogen peroxide is an unstable compound that can be produced by a variety of oxidative stressors. It can create hydroxyl and singlet oxygen radicals, which cause lipid peroxidation, cell damage, and senescence [48,49]. DPPH and hydrogen peroxide scavenging tests are commonly used to determine the anti-oxidant activity of natural extracts and compounds [50]. According to Jutiviboonsuk et al., 2017, the anti-oxidant activity of a 1% (w/w) mangiferin lotion was reported to be 90.85 $\pm$ 0.69%, which is related to the results presented in this study [51]. Hence, the mangiferin used in that study likely had a potential for in vitro anti-oxidant activity. Incorporating anti-oxidants in a specific formulation is a promising way to maintain their efficiency as anti-oxidants against free radicals [52] and providing photoprotection. Stability studies are crucial as they guarantee a product's long-term stability and allow for accurate shelf-life determination. The physical appearance of formulation 1 revealed a clear separation between mangiferin and the gel formulation. In contrast, formulation 2 exhibited a homogeneous appearance. The study by Sirirungsee et al. reported that the emulsion gel containing electrosprayed nanoparticles loaded with mangiferin from mango leaf using the UV–visible spectroscopic method was found to remain in the skin and be stable after the accelerated test [33]. Cosmetic formulations loaded with nanoparticles have several benefits, including increased stability and efficacy, greater skin penetration of the ingredients, and improved tolerance as UV filters [45,53]. MNPs fabricated using the electrospraying technique show promising potential for applications in cosmetic and cosmeceutical sunscreens. After 60 to 480 min, the release profiles of the formulation including PM and MNPs differed significantly among the samples. MNPs released much more mangiferin than PM at 60 to 480 min. Mangiferin release from β-lactoglobulin nanoparticles is controlled under both kinetic and thermodynamic circumstances, which is consistent with our findings [54]. Other investigations have demonstrated that it originated from a polymer owing mostly to the interactions between the existing molecules (electrostatic interactions and forming hydrogen bonds) and the dispersion of the nanoparticles [16]. Additionally, it is widely established that the breakdown of polymeric particles begins in amorphous regions and slowly progresses to the crystalline sections [55]. According to Freiberg et al., reduced crystallinity enhances drug dispersion and increases drug–polymer interactions [56]. The degree of crystallinity of a drug can influence its dissolution rate, with a drug in the metastable or amorphous state having the highest dissolution rate due to its significant molecular activity and superior internal energy, which raises the thermodynamic properties in comparison to crystalline substances. Hence, this study found that CA was utilized as a polymer, which may have influenced the amount and pace of drug release from the nanoparticles. The ex vivo permeation results of the formulation containing PM and MNPs were applied to newborn dorsal pig skin, which has been shown to have identical structure and biochemical properties to human skin [57]. Mangiferin has a branching glycoside structure, allowing it to permeate and pass through human skin (ex vivo investigation) [18]. Mangiferin was not restrained by the stratum corneum barrier. This could be explained by the knowledge that the mangiferin log P ranges between 1 and 3 (log P of mangiferin = 2.73), indicating a molecular weight of less than 500 Da (MW of mangiferin = 422.34 Da) [18]. After 8 h, there were no detectable quantities of mangiferin in the receiving chamber. The mangiferin concentrations in viable epidermis and dermis differed considerably ($p < 0.05$).

The mangiferin concentrations in the stratum corneum were also determined. F2 had a larger mangiferin content in the viable epidermis to dermis compared with that of F1. The results show that more mangiferin infiltrated skin layers from F2 than from F1. The findings are consistent with related research indicating that using CA as a polymer within a formulation enhances the distribution of active compounds. This effect is attributed to CA's ability to function as a semipermeable membrane, specifically for hydrophobic chemicals. CA can improve the diffusion of aqueous solution into polymer networks, resulting in the greater capture of analyte molecules in an aqueous solution [20].

This study indicates that the gel formulation containing MNPs from electrospraying technology can improve skin permeation, the in vitro SPF value, and the stability of the gel formulation under various conditions. A related study has reported that nanoparticles can improve the penetration rate and manage release, and they have proven to be successful in a weakly water-soluble material [27]. Additionally, the anti-oxidant activity and SPF value of the formulation must be evaluated in further studies to confirm its efficacy for skin.

5. Conclusions

Gel formulations containing electrospray MNPs aimed to introduce double-action photoprotective and anti-aging properties. In the present study, MNPs were prepared using electrospraying techniques and loaded in gel formulations. They were evaluated based on their physical appearances, viscosity, in vitro anti-oxidant activity, and in vitro SPF and compared with the formulations containing PM. The formulations containing MNPs were notable in terms of their photoprotectivity and anti-oxidation activity, indicating adequate stability in all parameters. The in vitro release and ex vivo permeation of formulations containing MNPs demonstrated a higher amount of mangiferin penetrated in skin layers than the formulations containing mangiferin dispersion. The in vitro release profile exhibited a sustained release. Therefore, this study indicated that the gel formulation with electrosprayed MNPs with double action enhanced its penetration in skin layers, exhibiting suitability for skin application. This presents a promising delivery system characterized by sustained mangiferin release. It produces MNPs in an amorphous form, leading to an increased dissolution rate, permeability, and biological activity compared to crystalline mangiferin. These findings suggest favorable prospects for developing cosmetic products by leveraging this delivery approach.

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Abbreviations

The following abbreviations are used in this manuscript:

MNPs	Mangiferin nanoparticles
PM	Purified mangiferin
MS	Mangiferin standard
SPF	Sun protection factor
DMSO	Dimethyl sulfoxide
IPN	Isopropanol
CA	Cellulose acetate
F1	Formulation 1
F2	Formulation 2

References

1. Orazio, J.D.; Jarrett, S.; Amaro-Ortiz, A.; Scott, T. UV radiation and the skin. *Int. J. Mol. Sci.* **2013**, *14*, 12222–12248. [CrossRef] [PubMed]
2. Lintner, K. Benefits of anti-aging actives in sunscreens. *Cosmetics* **2017**, *4*, 7. [CrossRef]
3. Mishra, A.K.; Mishra, A.; Chattopadhyay, P. Herbal cosmeceuticals for photoprotection from ultraviolet B radiation: A review. *Trop. J. Pharm. Res.* **2011**, *10*, 351–360. [CrossRef]
4. Donglikar, M.M.; Deore, S.L. Development and Evaluation of Herbal Sunscreen. *Pharmacogn. J.* **2016**, *9*, 83–97. [CrossRef]
5. Kumar, D.; Rajora, G.; Parkash, O.; Himanshu; Antil, M.H.; Kumar, V. Herbal cosmetics: An over view. *Int. J. Adv. Sci. Res.* **2016**, *1*, 36–41.
6. Chen, Q. Evaluate the Effectiveness of the Natural Cosmetic Product Compared to Chemical-Based Products. *Int. J. Chem.* **2009**, *1*, 57–59. [CrossRef]
7. Romanhole, R.C.; Fava, A.L.M.; Tundisi, L.L.; Macedo, L.M.; Santos, E.M.; Ataide, J.A.; Mazzola, P.G. Unplanned absorption of sunscreen ingredients: Impact of formulation and evaluation methods. *Int. J. Pharm.* **2020**, *591*, 120013. [CrossRef] [PubMed]
8. Bhattacharya, S.; Sohini, B.; Sherje, A.P. Development of resveratrol and green tea sunscreen formulation for combined photoprotective and antioxidant properties. *J. Drug Deliv. Sci. Technol.* **2020**, *60*, 102000. [CrossRef]
9. Sayuti, N.A. Formulation and physical stability test gel formulation from leaves Ketepeng Cina (*Cassia alata* L.). *J. Kefarmasian Indones* **2015**, *5*, 74–82.
10. Khumpook, T.; Saenphet, S.; Tragoolpua, J.; Saenphet, K. Anti-inflammatory and Antioxidant activity of Thai mango (*Mangifera indica* Linn.) Leaf Extracts. *Comp. Clin. Pathol.* **2018**, *28*, 157–164. [CrossRef]
11. Fujita, M.; Inoue, T. Biosynthesis of mangiferin in *Anemarrhena asphodeloides Bunge*. II. C-glucosylation of mangiferin. *Chem. Pharm. Bull.* **1980**, *28*, 2482–2486. [CrossRef]
12. Tayana, M.; Inthakusol, W.; Duangdee, N.; Chewchinda, S.; Pandith, H.; Kongkiatpaiboon, S. Mangiferin content in different parts of mango tree (*Mangifera indica* L.) in Thailand. *Songklanakarin J. Sci. Technol.* **2019**, *41*, 522–528.
13. Eff, A.R.Y.; Rahayu, S.T.; Saraswati, H.; Mun'im, A. Formulation and Evaluation of Sunscreen Gels Containing Mangiferin Isolated from *Phaleria macrocarpa* Fruits. *Int. J. Pharm. Investig.* **2019**, *9*, 141–145.
14. Kawakami, C.M.; Gaspar, L.R. Mangiferin and Naringenin Affect the Photostability and Phototoxicity of Sunscreens Containing Avobenzone. *J. Photochem. Photobiol. B Biol.* **2015**, *151*, 239–247. [CrossRef] [PubMed]
15. Ma, H.; Chen, H.; Sun, L.; Tong, L.; Zhang, T. Improving Permeability and Oral Absorption of Mangiferin by Phospholipid Complexation. *Fitoterapia* **2014**, *93*, 54–61. [CrossRef]
16. Allaw, M.; Pleguezuelos-Villa, M.; Manca, M.L.; Caddeo, C.; Aroffu, M.; Nacher, A.; Diez-Sales, O.; Saur, A.R.; Ferrer, E.E.; Fadda, A.M.; et al. Innovative Strategies to Treat Skin Wounds with Mangiferin: Fabrication of Transfersomes Modified with Glycols and Mucin. *Nanomedicine* **2020**, *15*, 1671–1685. [CrossRef]
17. Zou, T.B.; Xia, E.Q.; He, T.P.; Huang, M.Y.; Jia, Q.; Li, H.W. Ultrasound-Assisted Extraction of Mangiferin from Mango (*Mangifera indica* L.) Leaves Using Response Surface Methodology. *Molecules* **2014**, *19*, 1411–1421. [CrossRef]
18. Ochocka, R.; Hering, A.; Stefanowicz, H.J.; Cal, K.; Baranska, H. The effect of mangiferin on skin: Penetration, permeation and inhibition of ECM enzymes. *PLoS ONE* **2017**, *12*, e0181542. [CrossRef] [PubMed]
19. Chanikanda, T.; Channarong, S.; Wongtrakul, P. Development of Aqueous Formulation Containing the Extracted Mangiferin. *Key Eng. Mater.* **2021**, *901*, 40–47.
20. Sridhar, R.; Ramakrishna, S. Electrosprayed nanoparticles for drug delivery and pharmaceutical applications. *Biomatter* **2013**, *3*, e24281. [CrossRef]
21. Jaworek, A.; Sobczyk, A.T. Electrospraying route to nanotechnology: An overview. *J. Electrost.* **2008**, *66*, 197–219. [CrossRef]
22. Xie, J.; Jiang, J.; Davoodi, P.; Srinivasan, M.P.; Wang, C. Electrohydrodynamic atomization: A two-decade effort to produce and process micro-/nanoparticulate materials. *Chem. Eng. Sci.* **2015**, *125*, 32–57. [CrossRef] [PubMed]
23. Chomchoei, N.; Leelapornpisid, P.; Tipduangta, P.; Sangthong, P.; Papan, P.; Sirithunyalug, B.; Samutrtai, P. Potential of electrosprayed purified mangiferin nanoparticles for anti-aging cosmetic applications. *RSC Adv.* **2023**, *13*, 34987–35002. [CrossRef] [PubMed]
24. Bhatia, M.; Saini, M. Formulation and evaluation of curcumin microsponges for oral and topical drug delivery. *Prog. Biomater.* **2018**, *7*, 239–248. [CrossRef] [PubMed]

25. Nanjo, F.; Goto, K.; Seto, R.; Suzuki, M.; Sakai, M.; Hara, Y. Scavenging effects of tea catechins and their derivatives on 1, 1-diphenyl-2-picrylhydrazyl radical. *Free Radical Biol. Med.* **1996**, *21*, 895–902. [CrossRef] [PubMed]
26. Vinood, K.; Mahesh, P.; Neerupma, D. Determination of sun protection factor in different extract of *Eulaliopsis binate*. *Plant Arch.* **2019**, *19*, 185–187.
27. Junior, E.R.; Kollias, N.; Cole, C. New noninvasive approach assessing *in vivo* sunprotection factor (SPF) using diffuse reflectancespectroscopy (DRS) and *in-vitro* transmission. *Photodermatol. Photoimmunol. Photomed.* **2012**, *30*, 202–211. [CrossRef] [PubMed]
28. Schieber, A.; Berardini, N.; Carle, R. Identification of Flavonol and Xanthone Glycosides from Mango (*Mangifera indica* L. Cv. "Tommy Atkins") Peels by High-Performance Liquid Chromatography-Electrospray Ionization Mass Spectrometry. *J. Agric. Food Chem.* **2003**, *51*, 5006–5011. [CrossRef]
29. Kim, J.H.; Byun, J.C.; Bandl, A.K.R.; Hyun, C.G.; Lee, N.H. Compounds with elastase inhibition and free radical scavenging activities from *Callistemon lanceolatus*. *J. Med. Plant Res.* **2009**, *3*, 914–920.
30. Vo, T.H.T.; Nguyen, T.D.; Nguyen, Q.H.; Ushakova, N.A. Extraction of Mangiferin from the Leaves of the Mango Tree *Mangifera indica* and Evaluation of its Biological Activity in Terms of Blockade of α-glucosidase. *Pharm. Chem. J.* **2017**, *51*, 806–810. [CrossRef]
31. Bock, N.; Woodruff, M.A.; Hutmacher, D.W.; Dargaville, T.R. Electrospraying, a Reproducible Method for Production of Polymeric Microspheres for Biomedical Applications. *Polymers* **2011**, *3*, 131–149. [CrossRef]
32. Bae, S.B.; Nam, H.C.; Park, W.H. Electrospraying of environmentally sustainable alginate microbeads for cosmetic additive. *Int. J. Biol. Macromol.* **2019**, *133*, 278–823. [CrossRef] [PubMed]
33. Sirirungsee, V.; Samutrtai, P.; Sangthong, P.; Papan, P.; Leelapornpisid, P.; Saenjum, C.; Sirithunyalug, B. Electrosprayed Nanoparticles Containing Mangiferin-Rich Extract from Mango Leaves for Cosmeceutical Application. *Nanomaterials.* **2023**, *13*, 2931. [CrossRef] [PubMed]
34. Razura, C.F.F.; Perez, L.A.; Gonzalez, S.N.; Herrera, M.M.; Medina, T.L.; Sayago, A.S.G. Mangiferin-Loaded Polymeric Nanoparticles: Optical Characterization, Effect of Anti-topoisomerase I, and Cytotoxicity. *Cancers* **2019**, *11*, 1965. [CrossRef] [PubMed]
35. Vazquez, G.; Yuliana, E. Electrosprayed cashew gum microparticles for the encapsulation of highly sensitive bioactive materials. *Carbohydr. Polym.* **2021**, *264*, 118060. [CrossRef] [PubMed]
36. Xie, J.W.; Tan, J.C.; Wang, C.H. Biodegradable films developed by electrospray deposition for sustained drug delivery. *J. Pharm. Sci.* **2008**, *97*, 3109–3122. [CrossRef] [PubMed]
37. Smeets, A.; Clasen, C.; Van den Mooter, G. Electrospraying of polymer solutions: Study of formulation and process Parameters. *Eur. J. Pharm. Biopharm.* **2017**, *119*, 114–124. [CrossRef] [PubMed]
38. Kawabata, V.; Wada, K.; Nakatani, M.; Yamada, S.; Onoue, S. Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: Basic approaches and practical applications. *Int. J. Pharm.* **2011**, *420*, 1–10. [CrossRef] [PubMed]
39. Van den Mooter, G. The use of amorphous solid dispersions: A formulation strategy to overcome poor solubility and dissolution rate. *Drug Discov. Today Technol.* **2012**, *9*, 79–85. [CrossRef]
40. Janssens, S.; Van den Mooter, G. Review: Physical chemistry of solid dispersions. *J. Pharm. Pharmacol.* **2009**, *61*, 1571–1586. [CrossRef]
41. Vasconcelos, T.; Marques, S.; das Neves, J.; Sarmento, B. Amorphous solid dispersions: Rational selection of a manufacturing process. *Adv. Drug Deliv. Rev.* **2016**, *100*, 85–101. [CrossRef] [PubMed]
42. Puls, J.; Wilson, S.A.; Hölter, D. Degradation of Cellulose Acetate-Based Materials: A Review. *J. Polym. Environ.* **2011**, *19*, 152–165. [CrossRef]
43. Culica, M.E.; Chibac-Scutaru, A.L.; Melinte, V.; Coseri, S. Cellulose Acetate Incorporating Organically Functionalized CeO_2 NPs: Efficient Materials for UV Filtering Applications. *Materials* **2020**, *13*, 2955. [CrossRef]
44. Vieira, C.O.; Grice, J.E.; Roberts, M.S.; Haridass, I.N.; Duque, M.D.; Lopes, P.S.; Leite-Silva, V.R.; Martins, T.S. ZnO: SBA-15 Nanocomposites for Potential Use in Sunscreen: Preparation, Properties, Human Skin Penetration and Toxicity. *Skin Pharmacol. Physiol.* **2019**, *32*, 32–42. [CrossRef]
45. Shi, L.; Shan, J.; Ju, Y.; Aikens, P.; Prud'homme, R.K. Nanoparticles as delivery vehicles for sunscreen agents. *Colloids Surf. A* **2012**, *396*, 122–129. [CrossRef]
46. Kim, M.; Hyun, J.M.; Kim, S.S.; Seong, K.C.; Lim, C.K.; Kang, J.L.; Hyun, J.A.; Kyo, S.P.; Young, H.C.; Nam, H.L.; et al. In vitro screening of subtropical plants cultivated in Jeju Island for cosmetic ingredients. *Orient. J. Chem.* **2016**, *32*, 807–815. [CrossRef]
47. Lee, J.H.; Renita, M.; Fioritto, R.J.; St. Martin, S.K.; Schwartz, S.J.; Vodovotz, Y. Isoflavone characterization and antioxidant activity of Ohio soybeans. *J. Agric. Food Chem.* **2004**, *52*, 2647–2651. [CrossRef]
48. Ko, E.Y.; Kim, D.K.; Roh, S.W.; Yoon, W.J.; Jeon, Y.J.; Ahn, G.; Kim, N.K. Evaluation on antioxidant properties of sixteen plant species from Jeju Island in Korea. *EXCLI J.* **2015**, *14*, 133–145.
49. Heo, S.J.; Park, E.J.; Lee, K.W.; Jeon, Y.J. Antioxidant activities of enzymatic extracts from brown seaweeds. *Bioresour. Technol.* **2005**, *96*, 1613–1623. [CrossRef]
50. Kim, M.J.; Park, M.H.; Jeong, M.K.; Yeo, J.D.; Cho, W.I.; Chang, P.S.; Chung, J.H.; Lee, J.H. Radical scavenging activity and anti-obesity effects in 3T3-L1 preadipocyte differentiation of Ssuk (*Artemisia princeps* Pamp.) extract. *Food Sci. Biotechnol.* **2010**, *19*, 535–540. [CrossRef]

51. Jutiviboonsuk, A.; Leeprechanon, W. Stability of Mangiferin in Lotion and its Antioxidant Activity. *Key Eng. Mat.* **2019**, *819*, 79–84. [CrossRef]
52. Shamsuddin, A.M.; Sekar, M.; Musa, A.Z. Formulation and evaluation of antiaging cream containing mangiferin. *Int. Res. J. Pharm.* **2018**, *9*, 55–59. [CrossRef]
53. Mu, L.; Sprando, R.L. Application of nanotechnology in cosmetics. *Pharm. Res.* **2010**, *27*, 1746–1749. [CrossRef] [PubMed]
54. Samadarsi, R.; Dutta, D. Design and characterization of mangiferin nanoparticles for oral delivery. *J. Food Eng.* **2019**, *247*, 80–94. [CrossRef]
55. Sokolsky-Papkov, M.; Agashi, K.; Olaye, A.; Shakesheff, K.; Domb, A.J. Polymer carriers for drug delivery in tissue engineering. *Adv. Drug Deli. Rev.* **2007**, *59*, 187–206. [CrossRef]
56. Freiberg, S.; Zhu, X. Polymer microspheres for controlled drug release. *Int. J. Pharm.* **2004**, *282*, 1–18. [CrossRef] [PubMed]
57. Avo, S.L.; Wood, R.E. Porcine skin as an in-vivo model for ageing of human bite marks. *J. Forensic Odonto-Stomatol.* **2005**, *9*, 30–38.