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Box–Behnken Design to Optimize Standardized Mangiferin-Rich Mango Peel Extract from Agro-Industrial Waste Product

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Abstract: The light mango or "*Ma-Muang Bao*" (*Mangifere indica* L. var.) is a native mango species originating from Malaysia and southern Thailand. The whole *Ma-Muang Bao* fruit, except peels, is popular as both a raw and ripe fruit for consumption, as well as being used in various processed food products. This study aims to transform the peel of a specific mango variety, which is a byproduct of the agro-industrial sweet, pickled mangoes industry, into a valuable bioactive ingredient for healthcare products. This is achieved through the establishment of a standardized mangiferin-rich mango peel extract (SMPE). Employing the Box–Behnken design (BBD) within the framework of response surface methodology (RSM), an optimal microwave-assisted extraction procedure was developed. A total of 27 experiments, each with four independent variables, including solvent ratio, extraction power, extraction time, and ethanol (EtOH) ratio, were conducted to optimize the extraction method in terms of mangiferin content and extraction yield. The optimized extraction conditions encompassed a solvent ratio of 120 mL EtOH/100 g sample, an extraction power of 450 W, an extraction time of approximately 4.3 min, and an EtOH ratio of 69.44% (EtOH in water). Small-scale extractions were carried out using the following specified parameters: solvent ratio of 120 mL, extraction power of 450 W, extraction time of 4 min, and EtOH ratio of 70% EtOH. These extractions yielded an extract with a mangiferin content of 27.24 ± 2.05 mg/g and an extraction yield of 3.71 ± 0.17% *w*/*w*. Notably, these outcomes were better from the mangiferin content of 19.62 mg/g and a yield of fresh peel of 5.61% estimated through BBD analysis. Furthermore, a pilot-scale extraction was performed using 7 kg of fresh mango peel and 70% EtOH (8.4 L) for 4 min, resulting in an extract with a mangiferin content of 51.85 ± 0.35 mg/g and a fresh peel yield of 4.35% *w*/*w*. This method emerges as the most suitable for mango peel extraction and forms the basis of the SMPE. The results from biological activities highlight the potential use of SMPE as the active ingredient for cosmeceutical or healthcare products for wound-healing and skin-brightening agents. Additionally, the knowledge from this study presents an alternative approach to various plant sources and sustainable extraction methods for the herbal extract industry.

Keywords: mango peel; mangiferin; agro-industry waste; extraction; optimization; standardized extract; healthcare product

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1. Introduction

Mango (*Mangifera indica* L.) of the Anacardiaceae family is a well-known tropical and subtropical fruit that has been widely cultivated in Asia (77% mango production), Amer-

ica (13%), and Africa (9%) [1,2]. Mango has numerous chemical constituents that reflect its high nutritional value and health benefits. Moreover, mango is also listed as an important traditional and Ayurvedic medicine with a long history of over 4000 years for antioxidant, wound-healing, anti-inflammatory, immunomodulatory, tonic, and antidiabetic activities [3–5]. In addition to macronutrients and micronutrients, the phytochemical constituents of mango, such as polyphenols, carotenoids, flavonoids, and triterpenoids, also contribute to its health benefits [6]. Mangiferin, a natural phenolic compound in the form of xanthone glycoside, is the major bioactive compound found in various parts of mango, including the bark, leaves, fruit, and fruit peel [5–8]. In mango fruit, mangiferin is more abundant in the peel compared to the pulp, estimated at approximately 1.69 g/kg dry weight of peel [9]. Mangiferin and its derivatives have exhibited a wide range of pharmacological activities, especially antioxidant effects. They have also shown potential for anticancer, antimicrobial, antiatherosclerotic, antiallergenic, antidiarrhea, anti-inflammatory, analgesic, hepatoprotective, immunomodulatory, hypolipidemic, antiobesity, and antidiabetic activities [7–10]. Mangiferin is also utilized as an active ingredient in cosmeceutical products, including sunscreen. It has been reported to diminish the appearance of skin wrinkles, mitigate the degradation of collagen in the skin, provide skin protection against sun damage, and extend sunscreen effectiveness [11,12].

The light mango (*Mangifere indica* L.var.), or "*Ma-Muang Bao*" in Thai, is a native mango species originating from Malaysia and southern Thailand. The variety name "light" or "Bao" is attributed to its weight and its ability to yield a large quantity of agricultural produce rapidly in summer. While a wide range of mango varieties are available, only a few are cultivated on a commercial scale. *Ma-Muang Bao* has been grown in Singha Nakhon, Songkhla, Thailand for over 100 years, for household consumption and creating a green space around the house, but it has been commercially available for less than 30 years [13]. *Ma-Muang Bao* has become a geographical indication (GI) fruit of Singha Nakhon, Songkhla, Thailand since it has a specific sour taste and smell. *Ma-Muang Bao* has gained increasing popularity as both a raw and ripe fruit for consumption, as well as being used in various processed food products. The most famous product from *Ma-Muang Bao* is sweet pickled mangoes, which are produced from peeled raw mango and preserved in sugar for 3 d [13,14]. From this process, a large amount of mango peel is discarded as agro-industrial waste.

Based on previous reports, the agro-food industry has been associated with a high amount of waste production (approximately 30–50% of processed food), resulting in significant environmental issues (including pollution and greenhouse gas emissions), health concerns (related to microbial and animal-borne diseases), and negative economic impacts [15,16]. The fruit-manufacturing industry alone can generate over 0.6 billion tons of agro-industrial waste annually. Within the mango-processing factory, substantial quantities of fruit peels (approximately 7–24% of the total weight of a mango) and seeds (approximately 20% of the entire fruit) are discarded as waste [17]. In recent times, mango peels have attracted increased attention due to their potential as renewable natural sources of polyphenols, carotenoids, and tocopherols for use as active ingredients in healthcare products such as dietary supplements, functional foods, and cosmeceuticals [17,18].

The utilization of *Ma-Muang Bao* peel for the creation of standardized mangiferin-rich mango peel extract (SMPE) could be a suitable option to maximize the benefits of mango peel waste. This sustainability approach aligns with the principles of a biobased, circular, and green economy (referred to as the BCG economy), facilitated by technological innovation or green extraction [19,20]. Hence, the objectives of this study were to optimize the extraction and preparation process of a standardized mangiferin-rich mango peel extract (SMPE) through the utilization of the Box–Behnken design (BBD) response surface methodology. Additionally, we evaluated its biological activities, with the intention of advancing healthcare product development from agro-industrial waste based on sustainability.

2. Materials and Methods

2.1. Chemicals and Materials

Mangiferin (standard reference) was obtained from Chengdu Biopurity Phytochemicals Ltd., Chengdu, Sichuan, China. Acetonitrile (ACN), ethanol (EtOH), and methanol (MeOH), both analytical and HPLC grade, were purchased from LabScan Asia Co., Bangkok, Thailand. Dimethyl sulfoxide (DMSO), Triton X-100, phosphate-buffered saline (PBS), mushroom tyrosinase, kojic acid, and 3,4-dihydroxy-L-phenylalanine (L-DOPA) were purchased from Sigma Aldrich, Singapore. Water was purified in a Milli-Q system (Millipore, Bedford, MA, USA). All solvents were used for extraction, bioactivity evaluation, and HPLC analytical processing of the obtained extract.

For cell-based assays, primary human dermal fibroblast (HDF) cells (ATCC® PCS-201-012™) and RAW264.7 cells (ATCC® TIB-71™) were obtained from ATCC®, Manassas, VA, USA. Fetal bovine serum (FBS), 0.25% trypsin–EDTA, trypan blue dyes, penicillin/streptomycin, and cell culture media (Roswell Park Memorial Institute (RPMI) 1640 medium and Dulbecco's modified Eagle medium (DMEM)) were purchased from Gibco, California, USA. 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) for cell viability determination, lipopolysaccharide (LPS) from *Escherichia coli* for inflammatory process activation in RAW264.7 cells, Griess reagent for determination of nitric oxide (NO) production in RAW264.7 cells, and standard indomethacin were purchased from Sigma Aldrich Inc., St. Louis, MO, USA. The Sircol Soluble Collagen Assay kit for analyzing collagen production in HDFs was purchased from Biocolor, UK.

For machines, a microplate reader (model SPECTRO star Nano spectrometer-based absorbance, multimode detector) from BMG Labtech Ltd., Cary, NC, USA was used to measure the absorbance in biological activity testing. High-performance liquid chromatography (HPLC) was performed on a Shimadzu® instrument (Shimadzu® LC-20A series, Tokyo, Japan) with a quaternary pump, autosampler, and photodiode array detector.

2.2. Plant Material

The peel of *Ma-Muang Bao* from agro-industrial waste products was collected from Singha Nakhon District, Songkhla Province, Thailand. Fresh mango peel materials were washed, cut into small pieces, and kept in a refrigerator at 4 °C (if used as fresh raw material) or dried at 60 °C for 48 h in a hot-air oven. The dried mango peel was ground into a powder by an electric blender and kept at 4 °C in a well-closed container until use.

2.3. Determination of a Suitable Extraction Method

The dried powder of mango peel (2 g) was separately extracted using three different methods between conventional methods, including maceration (ME), reflux extraction (RE), and microwave-assisted extraction (MAE), as described in our previous study [21]. All methods were performed using either absolute EtOH or water as the extractive solvent (100 mL). For maceration, the dried powders were soaked in the solvent and then shaken by a shaker machine at 60 rpm for 72 h at room temperature. For reflux extraction, the Soxhlet apparatus was used for plant powder extraction for 30 min and then cooled to room temperature. For microwave-assisted extraction, a household microwave was used for dried powder extraction at 800 W for 180 s. The extract from each method (3 times) was filtered through filter paper and dried at 45–60 °C under reduced pressure conditions using a rotary evaporator.

2.4. Optimization of a Suitable Extraction Method

The optimization of the microwave-assisted extraction method was achieved using Minitab Version 19.2 (Minitab Inc., State College, PA, USA) through the implementation of the Box–Behnken design (BBD) within the framework of response surface methodology (RSM) [22]. This study employed 4 independent variables (solvent ratio (X_1), extraction power (X_2), extraction time (X_3), and EtOH ratio (X_4)), with each variable having three levels (high (1), medium (0), and low (-1)) chosen based on a suitable extraction method

(2.3). These variables were applied to fresh mango peel with approximately 80% humidity, adhering to the principles of sustainability and the green extraction concept, which aimed to minimize energy consumption and process steps, particularly reducing the need for drying in a hot-air oven. Subsequently, fresh mango peel was utilized instead of dried mango peel powder to BBD optimize the microwave-assisted extraction method [23,24]. The solvent ratio ranged from 20 to 120 mL/100 g of sample. Microwave power was applied to extract the mango peel at 3 different levels from 450–800 W. The extraction time was also optimized, and the pulse extraction time ranged from 1 min to 5 min (1 min = 1 min power on; 3 min = 2 min power on followed by 1 min power off and then 1 min power on; 5 min = 2 min power on followed by 1 min power off 2 times and then 1 min power on). The EtOH ratio was also examined for the suitable extraction method, which ranged from 25–75% EtOH in water (Table 1). We applied variable conditions based on the results from our previous study, which demonstrated that microwave energy could enhance the efficiency of the extraction method, resulting in reduced time and energy consumption compared to conventional methods [22]. The outcomes of the designed experimental study utilizing the BBD to evaluate the impact of 4 variables (X_1, X_2, X_3, and X_4) are summarized in Table 1, which encompasses 27 experiments (F1 to F27). Table 1 also provides a comprehensive overview of all the variables used for optimization within the BBD. Each extraction method was measured in triplicate. The 27 experimental runs were subjected to assessment of mangiferin content (Y_1) and % yield (Y_2). The experimental design was employed to study the influence of diverse independent variables. Interaction terms (X_1X_2, X_1X_3, X_1X4, X_2X_3, X_2X_4, and X_3X_4) have been included to understand how the response changes when two factors are concurrently adjusted. Polynomial terms (X_1^2, X_2^2, X_3^2, and X_4^2) were introduced to investigate nonlinearity. The polynomial equation for the experiments can be expressed as shown in Equation (1).

$$Y = A_0 + A_1X_1 + A_2X_2 + A_3X_3 + A_4X_4 + A_{11}X_1^2 + A_{22}X_2^2 + A_{33}X_3^2 + A_{44}X_4^2 + A_{12}X_1X_2 + A_{13}X_1X_3 + A_{14}X_1X_4 + A_{23}X_2X_3 + A_{24}X_2X_4 + A_{34}X_3X_4 \quad (1)$$

Table 1. Independent variables, their levels, and experimental runs of Box–Behnken design (BBD) for suitable extraction methods.

Formulations (Run)	Independent Variables with Coded Levels			
	X_1	X_2	X_3	X_4
F1	1	1	0	0
F2	1	0	0	1
F3	1	0	1	0
F4	0	0	1	−1
F5	0	0	−1	−1
F6	0	1	1	0
F7	0	−1	−1	0
F8	−1	0	0	1
F9	0	0	1	1
F10	0	−1	0	1
F11	−1	0	1	0
F12	−1	0	−1	0
F13	0	0	0	0
F14	0	1	−1	0
F15	1	−1	0	0
F16	−1	1	0	0
F17	1	0	0	−1
F18	0	1	0	−1
F19	1	0	−1	0
F20	0	−1	0	−1
F21	0	0	−1	1

Table 1. *Cont.*

Formulations (Run)	Independent Variables with Coded Levels			
	X_1	X_2	X_3	X_4
F22	0	−1	1	0
F23	−1	0	0	−1
F24	−1	−1	0	0
F25	0	1	0	1
F26	0	0	0	0
F27	0	0	0	0

Names of factors	Symbol	Level of independent variables		
		−1	0	1
Solvent ratio (volume of solvent/100 g sample)	X_1	20 mL	70 mL	120 mL
Extraction power	X_2	450 W	600 W	800 W
Extraction time	X_3	1 min	3 min	5 min
EtOH ratio (ethanol in water)	X_4	25%	50%	75%

The statistical validity was established through an analysis of variances (ANOVA) using Minitab software version 19.2 (Minitab Inc., State College, PA, USA). Subsequently, feasibility and grid searches were conducted to identify the optimal composition of formulations. Contour plots were then generated using the output data produced by Minitab software. Upon the development of polynomial equations for the response variables Y_1 and Y_2, in relation to the independent variables X_1, X_2, X_3, and X_4, the most favorable formulation was determined by employing the response optimizer plot.

2.5. Quantitative Analysis of Mangiferin Contents

Mangiferin contents in the extract were quantified by HPLC (Shimadzu) analysis using a column TSK-gel ODS-100 V column (250 × 4.6 mm i.d.) (Tosho Bioscience, Japan) at 30 °C. The isocratic mobile phase (2% acetic acid: acetonitrile (85:15)) was run at a rate of 1 mL/min for 20 min. The sample injection volumes were 20 µL. The absorption spectrum was detected at 348 nm. The mangiferin standard solution was prepared in the concentration range of 6.25–200 µg/mL for the standard curve. For analysis of the data, Labsolutions software for client PC version 5.96 was used. The sample (15 mg) was prepared by dissolving in MeOH and then adjusting to 10 mL in a volumetric flask. Before the analysis, the sample solution was filtered through a polyvinylidene fluoride membrane (0.45 micron) filter. The mangiferin content in each sample was determined by comparing the area under the curve with the standard curve of mangiferin, represented by the linear equation Y= 18,549X + 28,508 (r2 = 0.9992). The results are expressed in milligrams per gram of the dry extract.

2.6. Bioactivity Determination of Standardized Mangiferin-Rich Mango Peel Extract (SMPE)

2.6.1. Anti-Inflammatory Activity Assay (Anti-NO Production)

The anti-inflammatory activity was evaluated by the inhibition of LPS-induced nitric oxide (NO) production from murine macrophages (RAW264.7) [22]. RAW264.7 cells were cultured in a CO_2 incubator at 37 °C using RPMI medium supplemented with 10% fetal bovine serum (FBS), 0.1% sodium bicarbonate, 2 mM glutamine, and a penicillin–streptomycin solution (100 µg/mL). The cell monolayer was detached using trypsin–EDTA, suspended in fresh RPMI medium, and allowed to adhere to 96-well plates at a density of 1×10^5 cells/well for 60 min. After that, the supernatant was removed, and the cells were rinsed with PBS. The cells were stimulated for NO production with 100 µL of RPMI medium containing LPS. The samples and a positive control (standard indomethacin) were prepared in RPMI medium with 1% DMSO at various concentrations (3–100 µg/mL). Griess reagent was used to assess the accumulation of NO in the cell supernatant through

spectrophotometry at 570 nm. The NO inhibition (%) value of the samples and positive control was determined using the concentration necessary to inhibit 50% of NO production (IC_{50}) (n = 4). The examined samples were considered cytotoxic if the % cell viability of treated cells was less than 80% in comparison to untreated control cells.

2.6.2. In Vitro Wound Healing Assay

Cell Proliferation

The MTT assay was used to evaluate HDF cell proliferation at 37 °C in a humidified incubator containing 5% CO_2 according to the report of Rachpirom and coworkers [22]. HDF cells (2×10^3 cells/well) were seeded in DMEM containing 10% FBS for 24 h. Cells were then treated with or without the sample (using 1% DMSO as solvent) in DMEM containing 2% FBS for 48 h. Then, the supernatant was replaced with 100 µL of fresh media containing 10% MTT solution (5 mg/mL in PBS) for 2 h. Afterward, the medium was replaced with 150 µL of DMSO to dissolve the precipitate of formazan crystals of living cells. The cell proliferation of each well was measured by the absorbance of the solution at 570 nm. The % cell proliferation was calculated by comparison of cell densities from treated cells with control (n = 4).

Wound-Healing Assay

The wound-healing assay was assessed by the wound area at each time point using a migration assay as described in our previous study [22]. These HDFs (1×10^5 cells/well in 6-well plates) were grown for 2 d to confluence of monolayer cells. On day 0, the culture medium was removed, and then the monolayer cells were gently scraped using sterile pipette tips to create a small wound with a universal size and distance of linear scratch for all samples. After that, the cells were rinsed with PBS to remove any debris before being treated with the different treatment solutions at a concentration of 10 µg/mL. The images of 3 distinct areas for each sample at each time point were taken at various time intervals, as specified in the Results section. ImageJ software version 1.4.7 was used to quantify the area of wound closure caused by infiltration of migratory HDFs. The percentage of wound closure was expressed as 100 × ((cell linear distance on day 0 − cell linear distance on day 1, 2 or 3)/cell linear distance on day 0).

Collagen Production Assay

The Sircol Soluble Collagen Assay kit was used to measure the amount of collagen released from HDFs into the supernatant medium [22]. HDF cells (2×10^3 cells/well) were seeded in 96-well plates and cultured in DMEM with 2% FBS as the medium for 24 h. Following the removal of the medium, the cells were treated with or without the test sample for 48 h. From each well, 100 µL of supernatant was collected and then centrifuged. Subsequently, 500 µL of Sircol dye reagent was added to each tube, and the mixture was agitated for 30 min at room temperature. Afterward, the mixture underwent centrifugation at 10,000× *g* for 10 min, and the supernatants were decanted. The precipitate was washed with ethanol (EtOH) and subsequently dissolved in 500 µL of an alkali reagent. The solutions were assessed at 540 nm using a spectrophotometer. The absorbance value of each sample was used to determine collagen production through comparison with standard collagen equivalents (mg/g).

2.6.3. In Vitro Assay for Tyrosinase Inhibition

Tyrosinase inhibitory activity was evaluated for whitening effects using the mushroom tyrosinase enzyme [25]. The samples and positive control (kojic acid) were prepared by dissolving in 15% Triton-100 in DMSO. In a 96-well plate, the reaction mixture was composed of 20 µL of samples, 40 µL of 100 units/mL of enzyme solution (blank control was prepared using sample without enzyme), and 100 µL of PBS (pH 6.8). The mixture was incubated for 10 min at room temperature, and then 40 µL of 12.5 mM L-DOPA was added. The absorbance of each sample was measured immediately and every minute for 4 min at

490 nm by a microplate reader. The results were compared with a control. The percentage tyrosinase inhibition was compared with the blank control and reported as IC_{50} values.

2.7. Statistical Analysis

The results are expressed as the mean ± standard deviation (SD). The group comparisons were conducted through one-way analysis of variance (ANOVA) at a 95% confidence level (p value < 0.05). Statistical analysis was carried out using IBM SPSS software (version 22) for Windows (SPSS Inc., Chicago, IL, USA.)

3. Results and Discussion

3.1. Determination of a Suitable Extraction Method

3.1.1. Determination of a Suitable Extraction Method for Mango Peel Extract

The dried mango peel powder was extracted with three different methods, including ME, HE, and MAE, using absolute EtOH and water as extraction solvents. As shown in Table 2, MAE revealed the highest percentages of mangiferin content and % yield when compared to ME and HE. MAE using absolute EtOH as solvent exhibited the highest mangiferin content and % yield when compared with other methods and solvents (water). The results revealed that MAE was the most suitable extraction method for standardized mangiferin-rich mango peel extract (SMPE) preparation according to a previous report on the advantages of MAE compared to the conventional extraction method by providing a shorter extraction time and better effective extraction [21,22]. This effect can be caused by the efficient delivery of microwave energy through molecular interaction with the electromagnetic field, which leads to increased temperatures within the plant cells, causing cell wall disruption and subsequent release of desired compounds into the extraction solvent [21,22]. Further optimization of the MAE process could provide the most suitable conditions for mangiferin extraction from mango peel. In addition, whether employing high water content (using water as the extraction solvent) or low water content (using EtOH as the extraction solvent) in the extraction process, MAE consistently demonstrated superior effectiveness. Therefore, we chose to utilize fresh mango peel rather than dry powder for further extraction method optimization. This decision aligns with the principles of green extraction, aiming to minimize the drying process and, consequently, decrease both time and energy consumption [19].

Table 2. The mangiferin content and % yield of mango peel extract obtained from different extraction methods.

Methods	Solvent	Mangiferin Content (mg/g)	% Yield (Dry)
MAE	Water	29.34 ± 1.35^{b}	18.83 ± 0.80^{b}
	EtOH	38.80 ± 1.61^{a}	20.86 ± 0.46^{a}
RE	Water	15.49 ± 0.78^{e}	12.95 ± 0.65^{de}
	EtOH	22.78 ± 0.33^{c}	12.30 ± 2.18^{ef}
ME	Water	10.51 ± 0.23^{g}	10.96 ± 0.26^{f}
	EtOH	19.08 ± 0.55^{d}	14.71 ± 0.37^{c}

Note: Results are expressed as the mean ± SD based on triplicate determinations (N = 3). Different letter superscripts in the column indicate significant differences (p < 0.05), while values with the same superscript are not significantly different. RE = reflux extraction, MAE = microwave-assisted extraction, ME = maceration.

3.1.2. Optimization of a Suitable Extraction Method

A suitable extraction method for the MAE technique using BBD was evaluated. The ranges of Y_1 and Y_2 were 0.00–20.22 mg/g and 0.00–5.62%, respectively, as shown in Table 3. From 27 experiments, 4 experiments (F6, F11, F16, and F24) did not yield enough extract for further mangiferin content evaluation, while 2 experiments (F8 and F23) had missing data because some replications yielded extracts lower than 15 mg (only one replication could be evaluated). Moreover, F13, F26 and F27 were performed according to BBD as the

baseline of four variables. Among all experiments, F15 showed the highest mangiferin content, followed by F10 and F12 at 20.22 ± 0.38, 18.57 ± 0.34, and 17.28 ± 0.95 mg/g extract, respectively. The mango peel with the highest mangiferin content from F15 (fresh 100 g equal to dry power 20 g) was extracted using a microwave power of 450 W for 3 min with 50% EtOH in water (120 mL) as the solvent for extraction.

Table 3. Mangiferin content and % yield of the extract from all experiments following BBD.

Samples	Y_1: Mangiferin Content (mg/g) (Mean ± S.D.)	Y_2: % Yield (100 g Fresh)
F1	11.66 ± 0.83	3.55
F2	16.87 ± 2.08	5.62
F3	11.87 ± 0.83	4.04
F4	12.69 ± 1.38	0.23
F5	12.19 ± 0.51	3.32
F6	0.00 ± 0.00	0
F7	14.47 ± 0.50	1.25
F8	8.21 ± 0.21	0.09
F9	11.58 ± 0.02	2.31
F10	18.57 ± 0.34	3.88
F11	0.00 ± 0.00	0
F12	6.61 ± 0.57	1.74
F13	17.28 ± 0.95	1.65
F14	11.70 ± 0.35	2.95
F15	20.22 ± 0.38	3.18
F16	0.00 ± 0.00	0
F17	16.94 ± 2.62	4.23
F18	8.57 ± 0.21	3.51
F19	16.12 ± 0.61	2.98
F20	13.40 ± 0.35	2.86
F21	11.29 ± 0.63	5.25
F22	16.09 ± 0.48	1.41
F23	54.8 ± 0.11	0.08
F24	0.00 ± 0.00	0
F25	12.22 ± 0.20	2.67
F26	16.22 ± 0.10	1.74
F27	17.59 ± 0.23	1.53

The data collected from all 27 experiments were employed to concurrently establish the second-order polynomial equation as depicted in Equation (1). Furthermore, Table 4 provides correlation values, coefficients of determination (R^2), adjusted coefficients of determination (adjusted R^2), and ANOVA results. These tables also include the regression equations formulated for each response variable.

Table 4. Statistical analysis (ANOVA) summary results for the response surface model of the mangiferin content (Y_1) and % yield of fresh peel (Y_2).

Source	DF	Adj. SS	Adj. MS	F Value	*p* Value
Model: Mangiferin Content (Y_1)	14	878.82	62.77	2.77	0.0423
Solvent ratio (per 100 g of sample): X_1	1	450.86	450.86	19.89	0.0008
Extraction power: X_2	1	124.16	124.16	5.48	0.0374
Extraction time: X_3	1	120.1	120.1	5.3	0.0401
EtOH ratio (EtOH in water): X_4	1	3.51	3.51	0.15	0.7009

Table 4. *Cont.*

Source	DF	Adj. SS	Adj. MS	F Value	*p* Value
X_1^2	1	75.76	75.76	3.34	0.0925
X_2^2	1	25.31	25.31	1.12	0.3114
X_3^2	1	12.6	12.6	0.56	0.4703
X_4^2	1	18.11	18.11	0.8	0.3890
X_1X_2	1	13.97	13.97	0.62	0.4476
X_1X_3	1	78.45	78.45	3.46	0.0875
X_1X_4	1	0.0012	0.0012	0.0001	0.9943
X_2X_3	1	42.82	42.82	1.89	0.1944
X_2X_4	1	0.083	0.083	3.67×10^{-3}	0.9527
X_3X_4	1	0.011	0.011	4.86×10^{-4}	0.9828
Residual	12	272.01	22.67	-	-
Lack of fit	10	200.41	20.04	0.56	0.7829
Pure error	2	71.60	35.80	-	-
Corrected total	26	1150.83	-	-	-
R^2 = 0.7636	-	-	-	-	-
Adjusted R^2 = 0.4879	-	-	-	-	-
Model: % Yield of Fresh Peel (Y_2)	14	63.69	4.52	5.17	0.0035
Solvent ratio (per 100 g of sample): X_1	1	40.79	40.79	46.62	<0.0001
Extraction power: X_2	1	8.33×10^{-4}	8.33×10^{-4}	9.53×10^{-4}	0.9759
Extraction time: X_3	1	9.74	9.74	11.13	0.0059
EtOH ratio (EtOH in water): X_4	1	2.03	2.03	2.32	0.1539
X_1^2	1	0.019	0.019	0.022	0.8848
X_2^2	1	1.84×10^{-3}	1.84×10^{-3}	2.10×10^{-3}	0.9642
X_3^2	1	0.017	0.017	0.02	0.8901
X_4^2	1	3.59	3.59	4.11	0.0655
X_1X_2	1	0.023	0.023	0.027	0.8730
X_1X_3	1	2.9	2.9	3.32	0.0935
X_1X_4	1	0.4800	0.4800	0.5400	0.4749
X_2X_3	1	2.29	2.29	2.62	0.1316
X_2X_4	1	1.09	1.09	1.24×10^{0}	0.2866
X_3X_4	1	5.63×10^{-3}	5.63×10^{-3}	6.43×10^{-3}	0.9374
Residual	12	10.5	0.87	-	-
Lack of fit	10	10.47	1.05	71.22	0.0139
Pure error	2	0.029	0.015	-	-
Corrected total	26	73.79	-	-	-
R^2 = 0.8577	-	-	-	-	-
Adjusted R^2 = 0.6917	-	-	-	-	-

DF = degree of freedom, Adj. SS = adjusted sums of squares, Adj. MS = adjusted mean squares.

In this study, the contour plots illustrated the interaction between two factors displayed as a two-dimensional graph. The contour plots for the six responses under investigation, namely, Y_1 and Y_2, can be found in Figures 1 and 2, respectively. For Y_1, focusing on its impact on the mangiferin content, the optimization suggests a subsequent linear equation.

$$\text{Mangiferin content } (Y_1) = -60.0933 + 0.4238\ X_1 + 0.1507\ X_2 + 4.7311\ X_3$$

Based on the ANOVA results, the selection of a linear model for the mangiferin content was found to be the most appropriate choice compared to two-factor, quadratic, or cubic models. This preference is substantiated by the linear model's F value of 2.77, indicating that the model terms are statistically significant at a p value = 0.0423 (p value < 0.05), suggesting a reasonable fit to the experimental results (Table 4). The linear terms of solvent ratio (X_1), extraction power (X_2), and extraction time (X_3) exhibited a significant influence on the mangiferin content, as indicated by their p values (0.0008, 0.0374, and 0.0401, respectively). Other terms in the model do not show significant effects. The lack of fit value (F value = 0.56) was nonsignificant due to noise (p > 0.05), ensuring the validity of the model. This suggests

that the linear model captures all the variability in the data, with a 78.29% chance that such a discrepancy could be due to random noise. The N-probability plot, each point aligning along a straight line with an "S" shape, demonstrates that the residuals conform to a normal distribution (Figure 3). This pattern suggests that employing response transformation can lead to a valid analysis. Consequently, this model is suitable for the navigation of the design space. The contour plots (Figure 1) illustrate the influence of various independent variables on the mangiferin content (Y_1).

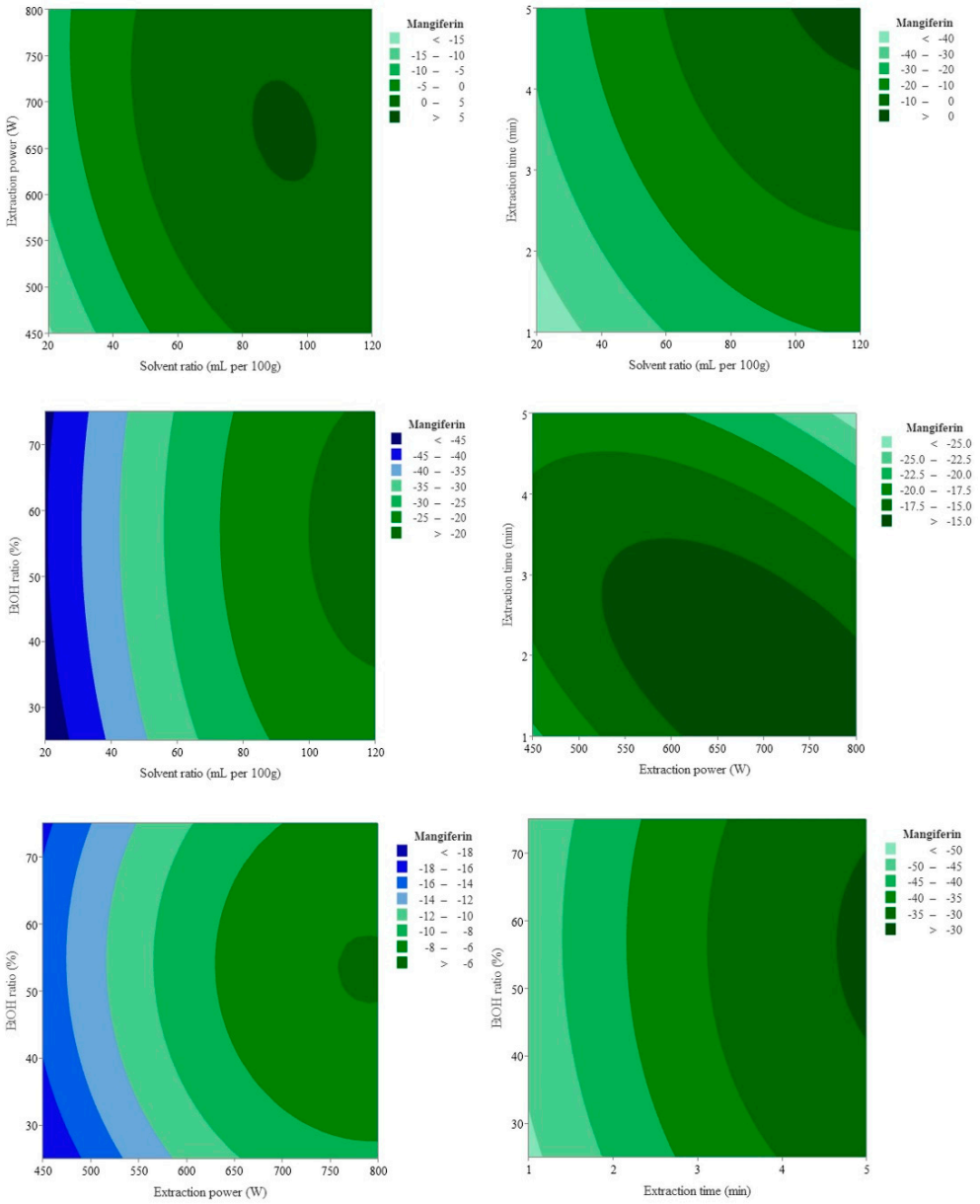

Figure 1. Contour plots of the extraction method influence on the mangiferin content.

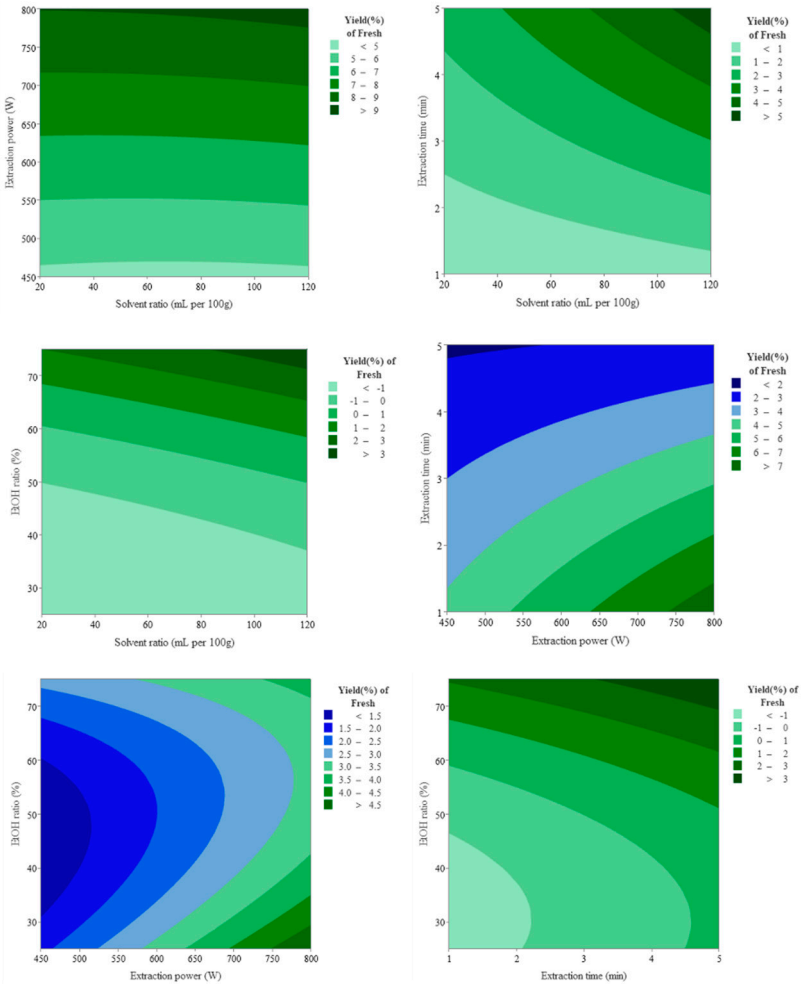

Figure 2. Contour plots of extraction method influence on % yield.

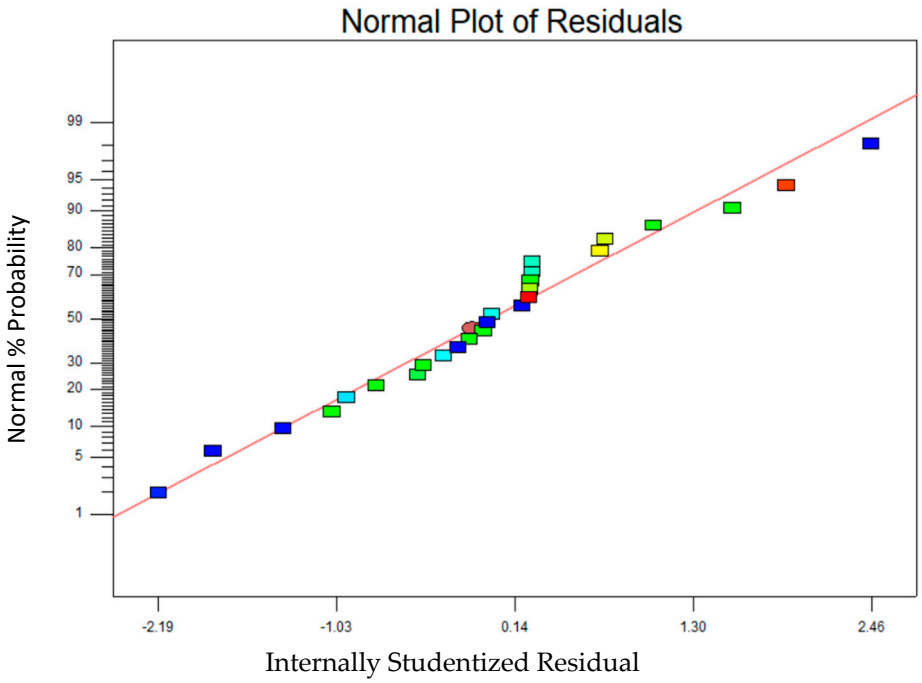

Figure 3. Normal plot of residuals of extraction method influence on mangiferin content.

For Y_2, focusing on its impact on the % yield of the extract per 100 g of fresh mango peel, the optimization suggests the subsequent linear equation.

$$\% \text{ Yield } (Y_2) = 0.0574 - 0.0102\ X_1 + 0.2252\ X_3$$

Based on the ANOVA results, the selection of a linear model for the % yield was found to be the most appropriate choice compared to two-factor, quadratic, or cubic models. This preference is substantiated by the linear model's F value of 5.17, which, with a p value lower than 0.05 (indicating that the model terms are statistically significant), suggests a reasonable fit to the data. Notably, only the linear terms of solvent ratio (X_1), extraction power, and X_3 exhibited a significant influence on the % yield, as indicated by their p values (<0.0001 and 0.0059, respectively). Other terms in the model do not show significant effects. However, a notable concern is the significant lack of fit, as evidenced by an F value of 71.22 (p value = 0.0139). This suggests that the linear model might not be capturing all the variability in the data, with a 1.50% chance that such a discrepancy could be due to random noise. This significant lack of fit indicates that while the linear model is the best among the models tested, it might not be an ideal representation of the underlying process. For future studies, it is advisable to explore other modeling approaches or refine the current linear model. This could involve investigating potential interaction effects, nonlinear relationships, or additional variables that were not included in the current model but may have a significant impact on the % yield. A more comprehensive model that reduces the lack of fit could lead to more accurate predictions and a deeper understanding of the factors influencing the yield. Additionally, further validation with different data sets would be crucial to ensure the robustness and generalizability of the model. The N-probability plot, each point aligning along a straight line with an "S" shape, demonstrates that the residuals conform to a normal distribution (Figure 4). This pattern suggests that employing response transformation can lead to a valid analysis. Consequently, this model is suitable for the navigation of the design space. The contour plots (Figure 2) illustrate the influence of various independent variables on % yield (Y_2).

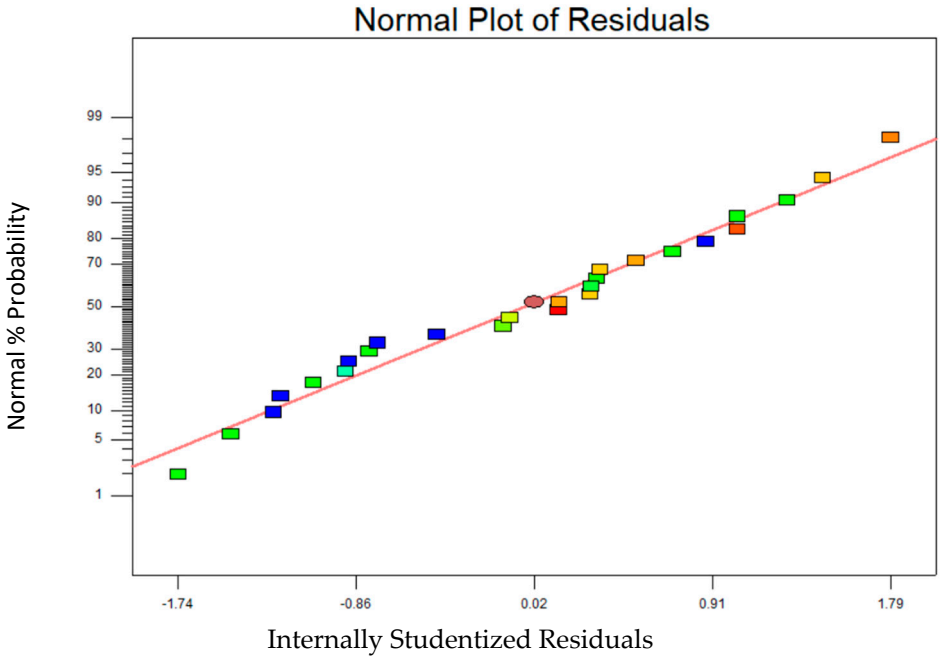

Figure 4. Normal plot of residuals of extraction method influence on % yield.

In this study, we optimized a suitable extraction method from a total of 27 experiments. The ideal formulation was determined using a response optimizer plot with a composite desirability (D) value of 0.9843. The optimization plot, displayed in Figure 5, reveals the

influence of each parameter on the responses or composite desirability (rows). The vertical red lines on the graph indicate the current parameter settings, while the horizontal blue lines represent the responses corresponding to those parameter levels. To achieve the best results, two parameters were adjusted to their maximum levels, specifically mangiferin content and % yield. Based on these criteria, the optimal formulation comprised a solvent ratio of 120 mL per 100 g of sample, extraction power of 450 W, an extraction time of 4.335 min, and an EtOH ratio (EtOH in water) of 69.4444%. Subsequently, a small-scale extraction experiment was conducted using the same parameters: solvent ratio of 120 mL, extraction power of 450 W, extraction time of 4 min, and an EtOH ratio of 70% EtOH (n = 3).

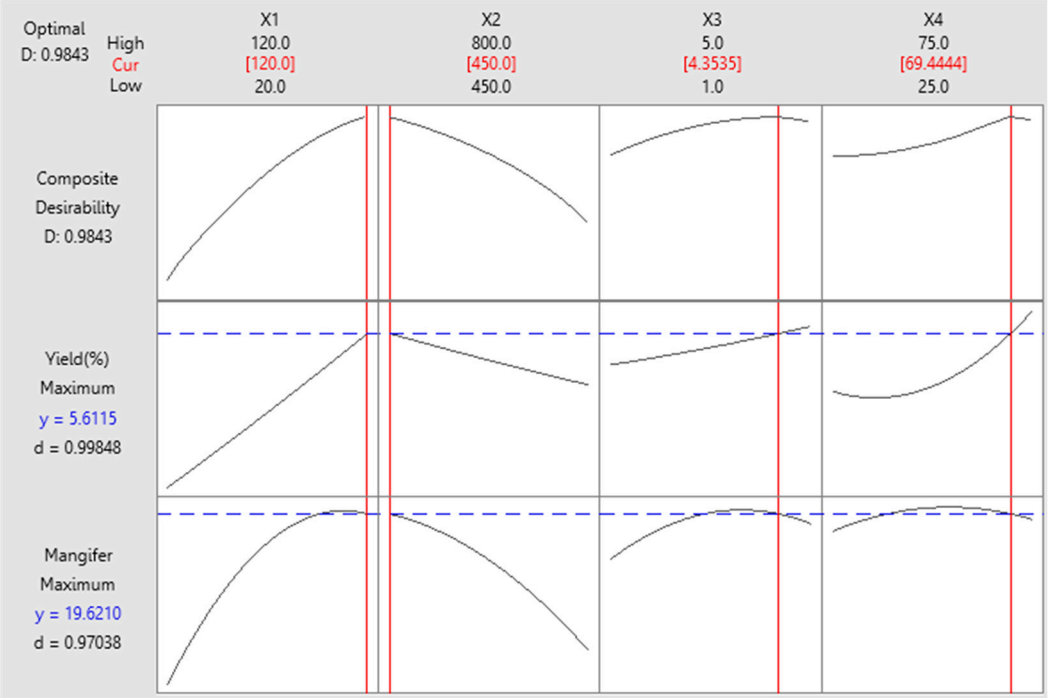

Figure 5. Composite desirability and optimization conditions obtained using BBD.

The resulting extract showed a mangiferin content of 27.24 ± 2.05 mg/g and a fresh peel yield of 3.71 ± 0.17%. These results show the difference from the BBD analysis estimates that gave a mangiferin content of 19.62 mg/g and a yield of fresh peel of 5.61%. From the actual experiments, the data show that this method is a suitable extraction method for extracting mangiferin from fresh peels of mango due to the higher mangiferin content, even if it decreases the yield. Moreover, the extraction method on a small scale was prepared on a pilot scale by using a microwave-assisted extraction machine. The extract was prepared from a fresh peel of mango (7 kg) and extracted with 70% EtOH (8.4 L) for 4 min. The results showed a mangiferin content of 51.85 ± 0.35 mg/g and a yield of fresh peel of 4.35%. These results support the higher extraction capacity of MAE compared to conventional methods (ME and HE), resulting in a more than twofold increase in mangiferin content (Table 2), which is consistent with our previous studies on other medicinal plants [21,22]. Our findings show promising data that support the use of an optimized extraction method for mango peel waste utilization at both the small and pilot scales. This method could be applied as the most suitable extraction method for the peel of *Ma-Muang Bao* from agro-industrial waste products. Moreover, the extract obtained from this method was set as standardized mangiferin-rich mango peel extract (SMPE).

3.2. Bioactivities of Standardized Mangiferin-Rich Manaifera indica Linn. Peel Extract (SMPE)

The wound-healing, anti-inflammatory, and tyrosinase inhibitory effects of standardized mangiferin-rich mango peel extract (SMPE) were assessed to provide additional evi-

dence for utilizing these extracts as active ingredients in cosmeceutical or healthcare products.

The wound-healing activities of SMPE were evaluated through three different mechanisms in HDF cells, including proliferation, migration, and collagen production. For fibroblast proliferation activity, standard mangiferin and SMPE showed toxicity to HDFs at all tested concentrations (0.25–10 μg/mL) (Table 5). At a concentration of 0.25 μg/mL, standard mangiferin displayed the most significant proliferation activity, whereas SMPE demonstrated its highest proliferation activity at a concentration of 1 μg/mL. It was observed that the proliferation activity of SMPE could be influenced by the mangiferin content within the extract.

Table 5. Proliferation and collagen production activities of mangiferin and SMPE.

Sample	Concentration (μg/mL)				
	0.25	**0.5**	**1**	**3**	**10**
	% Viability				
Mangiferin	175.46 ± 5.05	145.23 ± 0.46	105.31 ± 6.13	100.40 ± 0.46	103.05 ± 11.49
SMPE	106.10 ± 2.45	110.61 ± 3.98	130.64 ± 1.99	99.73 ± 1.23	89.39 ± 6.43
	% Collagen content				
Mangiferin	99.26	99.36	99.44	99.34	99.37
SMPE	99.53	99.60	99.82	99.50	99.27

The findings from the migration assay demonstrated that SMPE accelerated cell migration in comparison to the control, and this rate was comparable to that of standard mangiferin. The migration rate of the control group was notably lower than that of cells treated with SMPE and standard mangiferin (Figure 6). The results align with other studies suggesting that mangiferin can enhance wound-healing activity [26,27]. Moreover, the synthesis of type I collagen was assessed in HDFs after 48 h of exposure to mangiferin or SMPE at concentrations ranging from 0.25 to 10 μg/mL (Table 5). The results indicated that neither mangiferin nor SMPE could stimulate the generation of type I collagen from HDFs in comparison to the control.

Overall, the wound-healing capabilities of SMPE compared with standard mangiferin were proven through mechanisms involving fibroblast proliferation and migration. Our results confirmed the previous pharmacological activity evaluations of mangiferin and mango peel extract for wound healing and the treatment of skin diseases [10,12,26,27]. Moreover, SMPE exhibited nontoxic effects across the tested concentrations (0.25–10 μg/mL) and contributed to fibroblast proliferation at the optimal concentration of 1 μg/mL. Notably, SMPE demonstrated significant cell migration enhancement similar to standard mangiferin, highlighting the potential of SMPE in promoting wound healing. Although SMPE could not stimulate collagen production in HDFs when compared to the control group, these findings contribute to the broader understanding of the effects of SMPE, emphasizing their potential for wound-healing applications.

For anti-inflammation evaluation through the inhibition of NO production from macrophages, the maximum NO inhibition of SMPE was detected at a concentration of 6.25 μg/mL (21.76 ± 1.14%), while that of mangiferin was detected at a concentration of 100 μg/mL (38.87 ± 1.37%). SMPE and mangiferin exhibited NO inhibitory activity lower than that of the standard drug (IC_{50} of indomethacin = 26.51 ± 0.83 μg/mL) with IC_{50} > 100 μg/mL. Although the NO inhibitory activity of SMPE and mangiferin was lower than that of indomethacin, some previous reports also revealed the anti-inflammatory effect of mangiferin in various skin disease models, such as dermatitis [10].

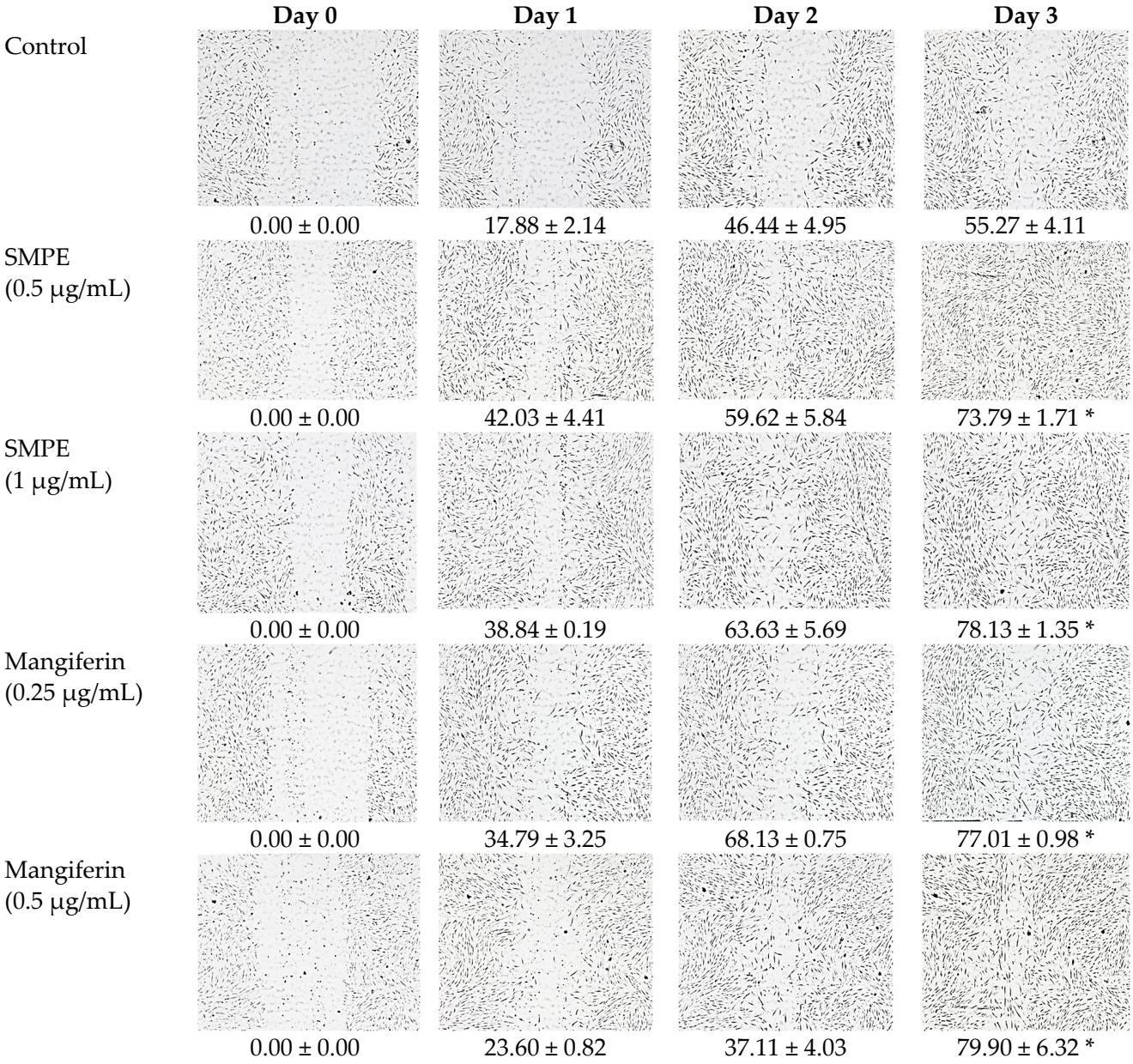

Figure 6. Effects of SMPE (0.5–1 μg/mL) and mangiferin (0.25–0.5 μg/mL) on HDF migration. The migration pictures were recorded at 0, 1, 2, and 3 d. The analysis of the migration area was calculated by computing software (ImageJ version 1.4.7) (Control: 0.1% DMSO in DMEM containing 2% FBS). * $p < 0.05$ vs control at Day 3 was considered to be statistically significant.

Tyrosinase is an enzyme in many organisms that modulates melanogenesis and skin pigmentation. The inhibition of the tyrosinase enzyme in skin leads to brighter skin, which is attractive in cosmeceutical industries as a whitening agent. In this study, the tyrosinase inhibitory activity of SMPE and mangiferin compared with kojic acid (positive control) was evaluated. SMPE exhibited antityrosinase activity, with an IC_{50} value of 132.20 ± 0.77 μg/mL. In contrast, mangiferin showed lower tyrosinase inhibitory activity at concentrations of 295.77 ± 0.58 μg/mL (Table 6). This implies that other compounds in SMPE, such as phenolics or flavonoids, which can be found in mango peel, may modulate tyrosinase inhibitory activity better than mangiferin [6]. The findings of this study affirm the notion that the chemical complexity in the high-yielding standardized extract offers a broader spectrum of pharmacological effects compared to individual isolated pure compounds, which are less expensive [21,22,28,29].

Table 6. Tyrosinase inhibitory activity of SMPE, mangiferin, and standard kojic acid.

Samples	Concentration (μg/mL)	% Inhibition	IC_{50} (μg/mL)
Kojic acid	50	85.84 ± 0.56	14.14 ± 1.47
	25	69.44 ± 1.83	
	12.5	48.92 ± 1.42	
	6.25	20.97 ± 0.81	
SMPE	800	69.53 ± 0.31	132.20 ± 0.77
	400	66.58 ± 0.56	
	200	57.80 ± 1.23	
	100	43.82 ± 0.97	
Mangiferin	800	74.28 ± 0.68	295.77 ± 0.58
	400	61.83 ± 0.71	
	200	38.89 ± 0.41	
	100	28.23 ± 0.54	

Overall, the pilot-scale MAE method resulting from the BBD optimization process demonstrated superior selectivity, yielding elevated mangiferin content and exhibiting good bioactivities in wound healing and tyrosinase inhibition. This study demonstrated the successful development of a standardized extraction method using the alternative green extraction concept and the utilization of agro-industrial waste to reduce the environmental impact of waste while also increasing its value according to sustainability principles and the BCG model [19,20,23,24,30]. This approach should be adopted for the formulation of SMPE as a bioactive component, particularly for cosmeceutical product development in further investigations.

4. Conclusions

This study demonstrated the utilization of *Ma-Muang Bao* peel, an agro-industrial waste, as a valuable resource by establishing a method for preparing SMPE, a bioactive ingredient for healthcare products. Employing a response surface methodology (RSM) known as Box–Behnken design (BBD), we optimized the mangiferin content and extraction yield of SMPE across 27 experiments with four independent variables: solvent ratio, extraction power, extraction time, and EtOH ratio. The outcomes of this optimization guided the preparation of SMPE on both the laboratory and pilot scales. The optimal extraction method, achieved using a solvent ratio of 120 mL, extraction power of 450 W, extraction time of 4 h, and EtOH ratio of 70%, yielded an extract with a mangiferin content of 51.85 ± 0.35 mg/g and a fresh peel yield of 4.35% *w*/*w*. This approach emerges as the best extraction method for *Ma-Muang Bao* peel and therefore applies to other types of mango peel. This strategy aligned with considerations of economic viability, environmentally friendly extraction, and sustainability within the broader context of the BCG economy. Notably, SMPE exhibited substantial bioactivities in wound healing and tyrosinase inhibition. This promising approach should be embraced for the formulation of SMPE as a bioactive component, particularly in the advancement of cosmeceutical product development in future studies.

5. Patents

The results from this paper were used as a part of a patent submission for the preparation of standardized mangiferin-rich mango peel extract from agro-industrial waste products in Thailand (https://www.ipthailand.go.th/th/ accessed on 3 November 2023).

Author Contributions: Conceptualization, P.S. (Punnanee Sumpavapol) and P.P.; methodology, P.S. (Punnanee Sumpavapol) and P.P.; software, P.P.; validation, P.S. (Punnanee Sumpavapol), M.R., and P.P.; formal analysis, P.S. (Punnanee Sumpavapol), A.W., P.S. (Paranee Suklim), M.R., and P.P.; investigation, P.S. (Punnanee Sumpavapol), A.W., P.S. (Paranee Suklim), M.R., and P.P.; resources,

P.S. (Punnanee Sumpavapol) and P.P.; data curation, P.S. (Punnanee Sumpavapol), M.R., and P.P.; writing—original draft preparation, P.S. (Punnanee Sumpavapol), M.R., and P.P.; writing—review and editing, P.S. (Punnanee Sumpavapol), M.R., and P.P.; visualization, M.R. and P.P.; supervision, P.S. (Punnanee Sumpavapol) and P.P.; project administration, P.P.; funding acquisition, P.P. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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