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Ultrasound-assisted green extraction methods: An approach for cosmeceutical compounds isolation from *Macadamia integrifolia* pericarp

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ABSTRACT

This study aimed was to examine the potential of several green extraction methods to extract cosmetic/cosmeceutical components from *Macadamia integrifolia* pericarps, which were a by-product of the macadamia nut industry. *M. integrifolia* pericarps were extracted by conventional solvent extraction process using 95% v/v ethanol and various green extraction methods, including infusion, ultrasound, micellar, microwave, and pulsed electric field extraction using water as a clean and green solvent. The extracts were evaluated for total phenolic content using Folin-Ciocalteu method. The antioxidant activities were evaluated by 1,1-diphenyl-2-picrylhydrazyl (DPPH), 2,2′-azinobis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), ferric reducing/antioxidant power, and ferric-thiocyanate method. The anti-skin ageing activities were investigated by means of collagenase, elastase, and hyaluronidase inhibition using enzyme-substrate reaction assay. The irritation profile of the extracts was evaluated by the hen's egg test-chorioallantoic membrane (HET-CAM) test. The results noted that ultrasound-assisted extraction yielded the significantly highest extract amount with the significantly highest total phenolic content ($p < 0.05$), especially when the extraction time was 10 min. The aqueous extract from ultrasound-assisted extraction possessed the most potent antioxidant and anti-skin ageing activities ($p < 0.05$). Its antioxidant activities were comparable to ascorbic acid and Trolox, whereas the anti-skin ageing activities were equivalent to epigallocatechin-3-gallate and oleanolic acid. Besides, the extract was safe since it induced no irritation in the HET-CAM test. Therefore, ultrasound-assisted extraction was suggested as an environmentally friendly extraction method for *M. integrifolia* pericarp extraction and further application in the cosmetic/cosmeceutical industries.

1. Introduction

Organic solvents, employed in a variety of manufacturing processes on a regular basis, such as benzene, toluene, xylene, etc., may represent potential risks to the ecological environment and human health due to their low flash points, easy volatility, and high toxicity [29,4]. It has been estimated that they account for over 60% of all industrial emissions and 30% of all volatile organic compound emissions globally [4]. Therefore, solvent-free processes or using green solvents, such as water, would be ideal for both the environment and human health [43]. Nowadays, "green chemistry" is currently employed to reduce harmful solvents and reducing hazardous solvents in industry is one of their priorities since environmental issues are increasingly reacquainting the attention of global corporate leaders [16]. Innovative alternatives with durable and environmentally friendly principles have been widely adopted in various industries, including food, cosmetic, perfume, and pharmaceuticals [14]. Green extraction, focusing on environmental consciousness, is thus regarded one of the latest main trends. Green solvents, particularly water, have a constraint in extraction efficiency as they are relatively hydrophilic. However, other methods can extraction efficiency, including ultrasound-assisted, microwave-assisted, pulsed electric field (PEF), micellar extractions, etc. [43].

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Macadamia integrifolia, native to Australia and now produced commercially worldwide, is a demanding plant that is rich in minerals and vitamins [8]. The macadamia nut is mostly marketed as the kernel, which contributes to only about 20% of the overall weight of the nut and is extensively consumed as a snack, while the remaining 80% of the nut consisting of the pericarp (42%) and husk (38%), is usually discarded as waste [20]. As a result, around 80% of *M. integrifolia* nuts end up as industrial debris [17–20], which could be a significant problem due to environmental effects and high management costs. The majority of this waste is disposed of in landfills, with only a small portion of it being used as a fuel source, garden mulch, and animal feed filler [61,19]. Encouraging the use of *M. integrifolia* waste would also result in lower waste disposal costs and an increase in the value of the agricultural and industrial waste. Our realted study revealed the potential of ethanolic extract from *M. integrifolia* pericarp extracts in cosmeceuticals due to its considerable antioxidant, anti-tyrosinase, and anti-ageing effects [55], which piqued curiosity for future research.

Therefore, this study aimed to investigate the potential of several green extraction methods to extract cosmetic and cosmeceutical components from *M. integrifolia* pericarps, which are a by-product of the macadamia nut industry. The *M. integrifolia* pericarp extract from various extraction methods using water as a green solvent, including infusion, ultrasound-assisted, micellar, microwave-assisted, and PEF extractions, was compared with the ethanolic extract from the conventional maceration method in the aspects of biological activity and safety regarding cosmetic/cosmeceutical applications.

2. Materials and methods

2.1. Plant materials

Fresh *M. integrifolia* pericarp was obtained from Power Plus Strong Company Limited (Thep Sadet, Doi Saket, Chiang Mai, Thailand). They were dried in a tray dryer at 50° C for 3 days until dry and the dried *M. integrifolia* pericarp was then ground into fine powder using Panasonic blender (Berkshire, UK) and subsequently passed through a sieve of mesh number 60. The fine powder of dried *M. integrifolia* pericarp with a particle size <250 μm was kept in the sealed plastic bag at ambient temperature until further use.

2.2. Chemical materials

Clostridium histolyticum collagenase (EC.3.4.23.3), porcine pancreatic elastase (PE–E.C.3.4.21.36), bovine testis hyaluronidase (E.C.3.2.1.3.5), N-[3-(2-furyl) acryloyl]-Leu-Gly-Pro-Ala (FALGPA), *N*-Succinyl-Ala-Ala-Ala-p-nitroanilide (AAAPVN), hyaluronic acid, tricine, sodium chloride, calcium chloride, 1,1-diphenyl-2-Picrylhydrazyl (DPPH), 2,2′-azinobis 3-ethylbenzothiazoline-6-sulfonic acid (ABTS), potassium persulphate ($K_2S_2O_8$), 2,4,6-tri (2-pyridyl)-s-triazine (TPTZ), sodium dihydrogen phosphate, disodium phosphate, sodium phosphate, sodium acetate, sodium thiocyanate, ferric chloride ($FeCl_3$), Folin–Ciocalteu reagent, sodium carbonate, 3,4,5-trihydroxybenzoic acid (gallic acid), L-ascorbic acid (purity ≥ 99.0%), (±)-6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid (Trolox), epigallocatechin-3-gallate (EGCG), ferrous sulfate, linoleic acid, oleanolic acid, lauryl glucoside (Plantacare® 1200), sorbitan Laurate (Span® 20), and polysorbate 20 (Tween® 20) were acquired from Sigma-Aldrich (Schnelldorf, Germany). Ethanol and dimethyl sulfoxide (DMSO), were analytical grade acquired from Labscan (Dublin, Ireland). Tris base, acetic acid, and hydrochloric acid were analytical grade acquired from Fisher Chem Alert (Fair Lawn, NJ, USA). HPLC grade methanol and acetonitrile was acquired from Carlo Erba Reagents (Cornaredo, Italy).

2.3. Extraction of M. integrifolia pericarp

2.3.1. Conventional solvent extraction method

The dried *M. integrifolia* pericarp powder was macerated in 95% v/v ethanol at a weight ratio of 1:5 for 3 cycles of 24 h each at an ambient temperature. After filtration through qualitative filter paper (Whatman grade 1, diameter 125 mm, Merck KGaA, Darmstadt, Germany), the *M. integrifolia* pericarp residue was removed. Then 95% v/v ethanol was removed by a Buchi rotary evaporator (Essen, Germany). The extractions were performed in duplicate. An extract from solvent extraction was obtained and kept at 4° C until further experiments.

2.3.2. Green extraction methods

2.3.2.1. Infusion. The dried *M. integrifolia* pericarp powder was infused in a boiling DI water (100° C) at a weight ratio of 1:5 for various durations (5, 10, and 15 min) with constant stirring of 300 rpm using an AM4 multi-position heating magnetic stirrer (Velp Scientifica, Italy). After filtration through qualitative filter paper (Whatman grade 1, diameter 125 mm, Merck KGaA, Darmstadt, Germany), the *M. integrifolia* pericarp residue was removed. The filtrate was then further concentrated using the freeze-drying process.

2.3.2.2. Ultrasound extraction. The dried *M. integrifolia* pericarp powder was extracted by DI water at a weight ratio of 1:5 with the assistance of ultrasound by an ultrasonic bath S30H (Elmasonic S, Germany) with a maximum capacity of 2.75 L (37 kHz, 80 W) at various durations (5, 10, 15 min). After filtration through qualitative filter paper (Whatman grade 1, diameter 125 mm, Merck KGaA, Darmstadt, Germany), the *M. integrifolia* pericarp residue was removed. The filtrate was then further concentrated using the freeze-drying process.

2.3.2.3. Micellar extraction. Micellar solutions of Tween® 20 (T20), Span® 20 (S20), and Plantacare® 1200 (P1200) at a concentration of 20 mM was used as the solvents for micellar extraction. This concentration was higher than their critical micellar concentrations (CMC), which were 0.05 [44], 0.24 [36], and >7 mM [49], respectively. The dried *M. integrifolia* pericarp powder was extracted using micellar solutions at a weight ratio of 1:5 for various durations (5, 10, and 15 min) with constant stirring of 300 rpm using an AM4 multi-position heating magnetic stirrer (Velp Scientifica, Italy). After filtration through qualitative filter paper (Whatman grade 1, diameter 125 mm, Merck KGaA, Darmstadt, Germany), the *M. integrifolia* pericarp residue was removed. The filtrate was then further concentrated using the freeze-drying process.

2.3.2.4. Microwave extraction. The dried *M. integrifolia* pericarp powder was extracted by DI water at a weight ratio of 1:5. The microwave extraction was carried out using a Toshiba microwave oven (Toshiba, Thailand) at 200, 400, and 800 W microwave power for 1, 1.5, or 2 min. After filtration through qualitative filter paper (Whatman grade 1, diameter 125 mm, Merck KGaA, Darmstadt, Germany), the *M. integrifolia* pericarp residue was removed. The filtrate was then further concentrated using the freeze-drying process.

2.3.2.5. Pulsed electric fields (PEF) extraction. The dried *M. integrifolia* pericarp powder was extracted by DI water at a weight ratio of 1:5 using a coaxial-cylindrical PEF chamber composed of 20 mm and 60 mm inner and outer electrode diameter, respectively. The extraction process was adapted from a related work conducted by Chaiyana et al [13]. Both electrodes were made of stainless steel and had a 300 mL capacity for plant materials. While the outer electrode was attached to the ground, the inner electrode comprised a 20-kV positive unipolar-exponential decay type. The flyback circuit, producing the high PEF voltage, is powered by a 24 V, 200 W direct current (DC) switching

power source. The high-voltage capacitor had accumulated multiple voltages. The PEF treatment chamber received the rotating gap. Different electric fields (3, 4, and 5 kV/cm) and PEF treatments were investigated (10, 15, and 20 kV). After filtration through qualitative filter paper (Whatman grade 1, diameter 125 mm, Merck KGaA, Darmstadt, Germany), the *M. integrifolia* pericarp residue was removed. The filtrate was then further concentrated using the freeze-drying process.

2.3.3. Freeze-drying process

The filtrates from green extraction methods, including infusion, ultrasound extraction, micellar extraction, microwave extraction, and PEF extraction, were frozen at the temperature of −40° C, and the solvent was discarded using a FreeZone 4.5 freeze dryer (Labconco, Kansas, MO, USA). All extracts were kept at 4° C until further experiments.

2.4. Determination of total phenolic content of M. integrifolia pericarp extract

The total phenolic content of each *M. integrifolia* pericarp extracts were assessed using the Folin-ciocalteu method [12,57]. After the incubation of the mixture containing the sample solution, 10% v/v Folin-Ciocalteu reagent, and 75 g/L sodium carbonate solution at a volume ratio of 1:5:4 for 2 h, the optical density was measured at 760 nm using a multimode microplate reader (BMG Labtech GmbH, Ortenberg, Germany). The gallic acid equivalent (GAE) of each sample was calculated and reported in terms of mg gallic acid per g extract. The experiment was performed in triplicate.

2.5. Determination of antioxidation activities of M. integrifolia pericarp extracts

2.5.1. 1,1-Diphenyl-2-picrylhydrazyl (DPPH) assay

The free radical scavenging on $DPPH^{\bullet}$ of each *M. integrifolia* pericarp extracts was assessed [9,12]. After the incubation of the mixture containing the sample solution and DPPH solution at a volume ratio of 1:9 for 30 min, the optical density was assessed at 540 nm using a multimode microplate reader (BMG Labtech GmbH, Ortenberg, Germany). The DPPH inhibition was calculated as follows: $DPPH^{\bullet}$ inhibition (%) = [(*OD1* − *OD2*)/*OD1*] × 100, where *OD1* is the optical density of the combination without *M. integrifolia* pericarp extracts and *OD2* is the optical density of the combination with *M. integrifolia* pericarp extracts. The positive control was L-ascorbic acid. The experiment was performed in triplicate.

2.5.2. 2, 2′-azinobis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assay

The free radical scavenging on $ABTS^{\bullet+}$ of each *M. integrifolia* pericarp extracts was assessed [11,57]. After the incubation of the combination containing the sample solution and ABTS solution at a volume ratio of 1:9 for 5 min, the optical density was assessed at 750 nm using a multimode detector (BMG Labtech GmbH, Ortenberg, Germany). Trolox was used to construct a calibration curve (R^2 = 0.9876) and the Trolox equivalent antioxidant activity (TEAC) of each sample was calculated and reported. The positive control was L-ascorbic acid. The experiment was performed in triplicate.

2.5.3. Ferric reducing/antioxidant power (FRAP) assay

The ferric reducing/antioxidant power of each *M. integrifolia* pericarp extracts was assessed [12,52]. After the incubation of the combination containing the sample solution and FRAP solution at a volume ratio of 1:9 for 5 min, the optical density was assessed at 595 nm using a multimode microplate reader (BMG Labtech GmbH, Ortenberg, Germany). Ferrous sulfate ($FeSO_4$) was used to construct a calibration curve (R^2 = 0.9926) and the equivalent capacity (EC_1) of each sample was calculated and reported. The positive control was L-ascorbic acid. The experiment was performed in triplicate.

2.5.4. Lipid peroxidation by ferric-thiocyanate method

The lipid peroxidation inhibition of each *M. integrifolia* pericarp extracts was assessed using ferric-thiocyanate method [12,46]. After the incubation of the combination containing the sample solution, 50% linoleic acid in DMSO, 5 mM NH_4SCN solution, and 2 mM $FeCl_2$ solution in a volume ratio of 1:1:1:1 at a temperature of 37 ± 2° C for 60 min, the optical density was assessed at 490 nm using a multimode microplate reader (BMG Labtech GmbH, Ortenberg, Germany). The lipid peroxidation inhibition was calculated was calculated as follows: lipid peroxidation inhibition (%) = [(*OD1* − *OD2*)/ *OD1*] × 100, where *OD1* is the optical density of the combination without *M. integrifolia* pericarp extracts and *OD2* is the optical density of the combination with *M. integrifolia* pericarp extracts. The positive control was Trolox. The experiment was performed in triplicate.

2.6. Determination of the anti-skin ageing activities of M. integrifolia pericarp extracts

2.6.1. Determination of anti-collagenase activity

The anti-collagenase activity of each *M. integrifolia* pericarp extracts was assessed [59,11]. After the incubation of the combination containing the sample solution and collagenase solution in a volume ratio of 1:2, the FALGPA solution in tricine buffer (pH 7.5) was added. The optical density was immediately continuously assessed at 340 nm for 10 min using a multimode microplate reader (BMG Labtech GmbH, Ortenberg, Germany). The collagenase inhibition was calculated was calculated as follows: collagenase inhibition (%) = [(*OD1* − *OD2*)/ *OD1*] × 100, where *OD1* is the optical density of the combination without *M. integrifolia* pericarp extracts and *OD2* is the optical density of the combination with *M. integrifolia* pericarp extracts. A positive control was epigallocatechin-3-gallate (EGCG). The experiment was performed in triplicate.

2.6.2. Determination of anti-elastase activity

The anti-elastase activity of each *M. integrifolia* pericarp extracts was assessed [59,11]. After the incubation of the combination containing the sample solution and 2 μg/mL elastase solution in a volume ratio of 1:2 for 15 min, 0.27 mM AAAPVN solution in tris-HCl buffer pH 8.0 was added. The optical density was immediately continuously assessed at 410 nm for 20 min using a multimode microplate reader (BMG Labtech GmbH, Ortenberg, Germany). The elastase inhibition was calculated was calculated as follows: elastase inhibition (%) = [(*OD1* − *OD2*)/*OD1*] × 100, where *OD1* is the optical density of the combination without *M. integrifolia* pericarp extracts and *OD2* is the optical density of the combination with *M. integrifolia* pericarp extracts. A positive control was EGCG. The experiment was performed in triplicate.

2.6.3. Determination of anti-hyaluronidase activity

The anti-hyaluronidase activity of each *M. integrifolia* pericarp extracts was assessed [11]. After the incubation of the combination containing the sample solution and 1.5 units of hyaluronidase in a volume ratio of 1:20 at the temperature of 37° C for 10 min, 1 mL of bovine serum albumin solution in the buffer of pH 3.7 was added. The optical density was assessed at 600 nm after the incubation at room temperature for 10 min using a multimode microplate reader (BMG Labtech GmbH, Ortenberg, Germany). The hyaluronidase inhibition was calculated was calculated as follows: hyaluronidase inhibition (%) = [(*OD1* − *OD2*)/ *OD1*] × 100, where *OD1* is the optical density of the combination without *M. integrifolia* pericarp extracts and *OD2* is the optical density of the combination with *M. integrifolia* pericarp extracts. A positive control was oleanolic acid. The experiment was performed in triplicate.

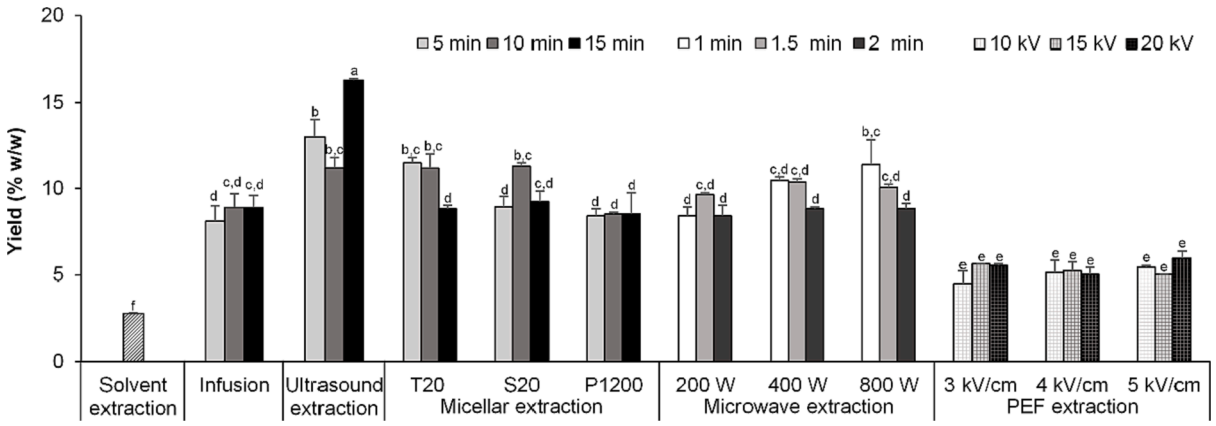

Fig. 1. Yields of *M. integrifolia* pericarp extracts from different extraction methods. The letters a, b, c, d, e, and f denote significant differences among the yields ($p < 0.05$).

2.7. Irritation properties by hen's egg test on the chorioallantoic membrane (HET-CAM) assay

The *M. integrifolia* pericarp extract with the most potent biological activities was chosen to be tested for irritation using the HET-CAM test [54,56]. The irritation potential of each sample was classified after the sample solutions were applied to the CAM. The irritation on the CAM was immediately monitored for 5 min, and the exact moment the irritation signals appeared was noted. Irritation is graded based on the severity and rapidity with which the irritation sign occurs. Irritation score (*IS*) = [(301 - *t(h)* 5]/300 + [(301 - *t(l)*) 7]/300 + [(301 - *t(c)*) 9]/300, where the first vascular bleeding, vascular lysis, and vascular coagulation were detected at *t(h)*, *t(l)*, and *t(c)*, respectively. is the time when the first is observed. The results could be graded into four categories, including no irritation (*IS* = 0.0–0.9), slight level of irritation (*IS* = 1.0–4.9), moderate level of irritation (*IS* = 5.0–8.9), and severe level of irritation (*IS* = 9.0–21.0) [23]. In the present study, DI water was used as a vehicle control since it was used as a solvent for *M. integrifolia* pericarp extracts. Besides, normal saline solution and 1% w/v sodium lauryl sulfate were employed as positive and negative controls, respectively.

2.8. Statistical analysis

The analyzed data were presented in terms of mean and standard division (S.D.). The statistical analysis was carried out using the *t*-test and ANOVA using SPSS Statistics 17.0 (IBM Corporations, New York, NY, USA). Statistically significant difference was designated when $p < 0.05$. In addition, the Pearson correlation coefficient (r) was employed to assess the strength and direction of a linear relationship between phenolic content and biological activities of the *M. integrifolia* pericarp extracts using the Graphpad Prism Program Version 2.01 (Graphpad Software Inc., La Jolla, CA, USA). The following criteria were used to interpret the level of a correlation coefficient: 0.90 to 1.00 (−0.90 to −1.00) as very high level of positive (negative) correlation; 0.70 to 0.90 (−0.70 to −0.90) as high level of positive (negative) correlation; 0.50 to 0.70 (−0.50 to −0.70) as moderate level of positive (negative) correlation; 0.30 to 0.50 (−0.30 to −0.50) as low level of positive (negative) correlation; and 0.00 to 0.30 as negligible correlation [6].

3. Results and discussion

3.1. Yields of M. integrifolia pericarp extracts

In the present study, 95% ethanol was used as a representative of an organic solvent to investigate if the green solvent (DI water) could be used as a substitute. Since conventional solvent extraction with water is not possible because microbial growth would occur during the three cycles of a 24 h extraction, a shorter extraction duration is necessary. High temperature, ultrasound, micellar solution, microwave, and PEF are required to improve extraction efficiency. Regarding the unique mechanism to enhance the extraction efficiency of each green extraction technique, distinct variables were set for each extraction method. In brief, 5 – 10 min was set for infusion, ultrasound, and micellar, while microwave was 1 – 2 min, whereas the variable of PEF was electric fields (10 – 20 kV). Solvent extraction and green extraction using DI water or micellar aqueous solution yielded *M. integrifolia* pericarp extracts with different external appearances. The extract from solvent extraction was a dark green semisolid mass, whereas all extracts from green extraction methods had the same external appearances, i.e. dried powder with a light brown color. This might be attributed to the different solvents utilized in the separation process. The coloring matter responsible for the greenish color might be chlorophyll, which is insoluble in water but soluble in ethanol [47].

The yields of each *M. integrifolia* pericarp extracts are shown in Fig. 1. The solvent extraction process yielded a significantly lower yield than the others from green extraction methods ($p < 0.05$). Among different green extraction methods, ultrasound extraction yielded the significantly highest extract yield, especially after extraction for 15 min (yield = 16.3 ± 0.1% w/w). On the other hand, infusion, micellar extraction, and microwave extraction yielded a comparable extract content, while PEF yielded a significantly lower extract content. Although the extraction duration is an important factor affecting the extract yield, no effect has been observed during 5 to 15 min in the infusion, micellar extraction, or microwave extraction. In addition, no effect has been observed during 1 to 2 min of the microwave extraction. Another factor affecting the extraction yield was energy input, but no difference has been observed in microwave and PEF extraction.

Each green extraction method has a different extraction mechanism. Infusion is a traditional procedure for extracting medicinal plants, which is simple to execute by quickly pouring hot water into plant materials. The extraction process is associated with the diffusion of water through the plant cell, resulting in the expansion of plant tissue, and the active chemicals consequently released from the cell end up in the solvent [42]. The main factors influencing on the extraction efficiency included the temperature of the water, the time of the extraction, and the surface area of the plant material [15].

The present study used boiling water (100° C) to reach the maximum extraction capacity of the infusion. Besides, micellar extraction is another efficient and environmentally acceptable approach for isolating bioactive chemicals from plant materials [50,53]. This approach employs nonionic surfactants at an amount higher than their critical micellar concentrations (CMC), so they can be aggregated and form the micelles that enhance the solubility of the bioactive compound in the

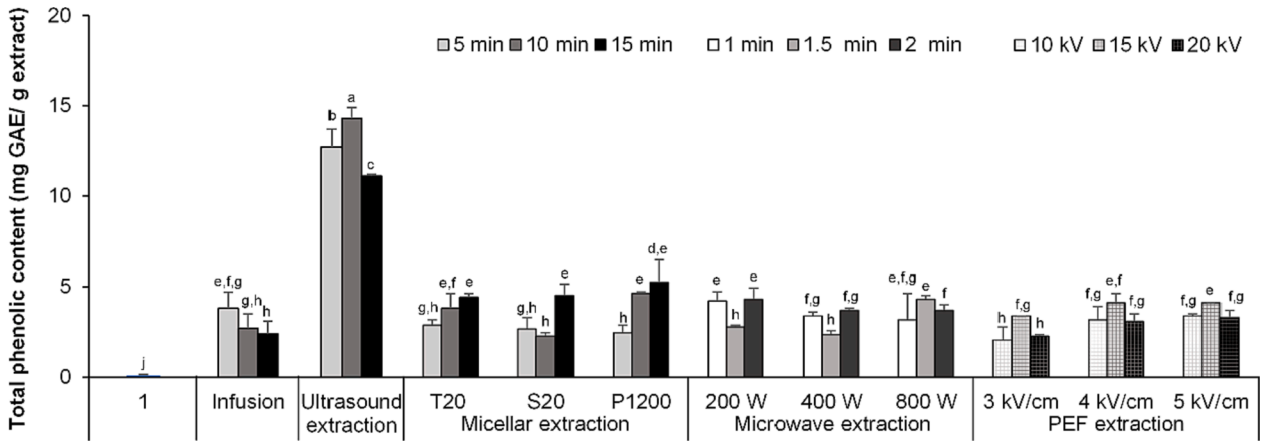

Fig. 2. Total phenolic content of *M. integrifolia* pericarp extracts from different extraction methods. The letters a, b, c, d, e, f, g, and h denote significant differences among the total phenolic content of each extract ($p < 0.05$).

extracting solvent [34,41]. Microwave-assisted extraction is based on the ability to rapidly heat the sample solvent mixture and disrupt the cell structure, resulting in the diffusion of the solvent into a plant cell and the extraction of bioactive substances from the cells. On the other hand, ultrasound-assisted and PEF extraction can create cavitation or electroporation on the plant cell wall using ultrasonic radiation and PEF, resulting in an increase of solvent carried into the plant cell and the active chemicals liberated from the plant components. [35,14,48,30,51,22]. In the case of *M. integrifolia* pericarp, ultrasonic energy might be more capable of increasing the permeability of active compounds through the cell membrane and facilitating their facile release from the cells compared with that of PEF. This could be explained by an additional acoustic cavitation phenomenon in the ultrasound-assisted extraction, which had a considerable influence on the solid surface and resulted in a larger extraction rate [21,39].

3.2. Total phenolic content of *M. integrifolia* pericarp extracts

The total phenolic contents of *M. integrifolia* pericarp extracts are shown in Fig. 2. Solvent extraction yielded the significantly lowest total

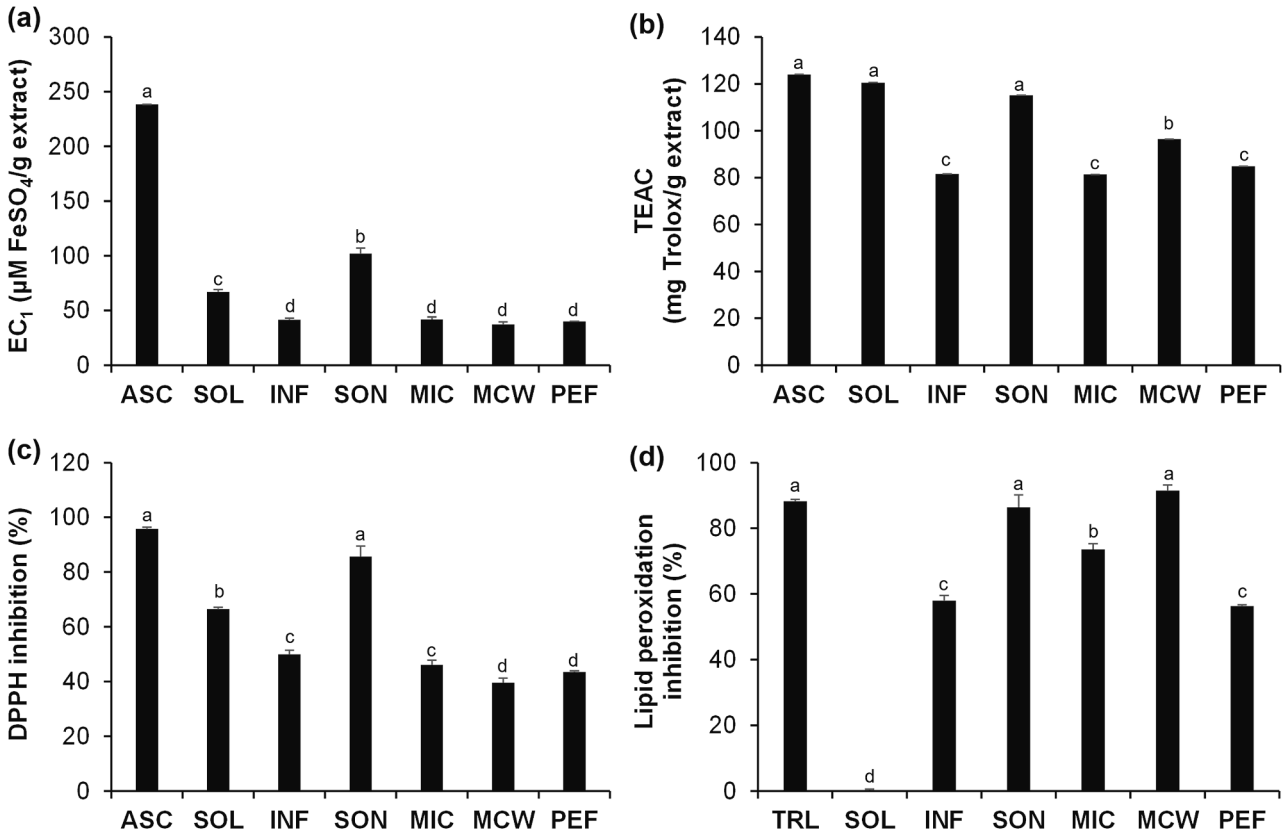

Fig. 3. Antioxidant activities of ascorbic acid (ASC), Trolox (TRL), and *M. integrifolia* pericarp extracts from different extraction methods, including solvent extraction (SOL), 5 min infusion (INF), 10 min sonication (SON), 15 min micellar extraction using Plantacare® 1200 (MIC), 1 min microwave extraction at 200 W (MCW), and PEF extraction with an intensity electric field of 5 kV/cm and a pulse of 20 (PEF), represented in terms of equivalent concentration (EC_1) (a), Trolox equivalent antioxidant capacity (TEAC) (b), DPPH inhibition (c), and lipid peroxidation inhibition (d). The letter a, b, c, and d denote significant differences among samples analyzed using one-way analysis of variance (ANOVA) with post-hoc Tukey test at $p < 0.05$.

phenolic content of only 0.39 ± 0.04 mg GAE per g extract ($p < 0.05$). In contrast, the *M. integrifolia* pericarp extracts from ultrasound-assisted extraction had the significantly highest phenolic content, ranging from 11.1 ± 0.4 to 14.3 ± 0.5 mg GAE per g extract ($p < 0.05$), whereas the extracts from infusion, micellar, microwave, and PEF extraction yielded a comparable total phenolic content (2.0 ± 0.2 to 5.1 ± 0.2 mg GAE per g extract). Therefore, ultrasound-assisted extraction not only yielded the significantly highest extract yield, but also the significantly total highest phenolic content.

Generally, the duration of extraction had an impact on the concentrations of all of the phenolic compounds tested. In virtually all situations, longer extraction had a beneficial effect on the concentration of these chemicals [27]. However, the findings in this study noted that longer than 10 min of ultrasound-assisted extraction led to the lower phenolic content. The results were well related to the exceptions reported by Horzic et al. [27] who described the decrease content of epigallocatechin, epigallocatechin-3-gallate, and gallic acid after 30 min of extraction using ultrasound probe or ultrasound bath [27]. The likely explanation was due to the phenolic compound susceptibility to prolonged extraction time, particularly at higher temperatures [58,24,60]. In the previous investigation, a 15-min extraction period was shown to be more acceptable in terms of bioactive chemical production and energy efficiency compared with a longer duration of 30 min [27]. Likewise, the current investigation revealed that ultrasound-assisted extraction with a sonication bath for 10 min was the most acceptable condition for *M. integrifolia* pericarp extraction. Although infusion is simple, quick, and requires only a brief extraction time, a prolonged extraction duration, particularly at high temperatures, results in the destruction of biological active chemicals. The findings from this research showed that a longer extraction period resulted in a lower total phenolic content. Therefore, only 5 min of infusion was suggested. In contrast, a prolonged extraction period was suggested for micellar extraction, which does not require high temperatures. Generally, surfactants have been extensively acknowledged for their ability to solubilize a wide range of solutes owing to their amphiphilic molecular structure and both hydrophilic and lipophilic substances may be extracted in a single extraction procedure [40]. Different types of nonionic surfactants in the present study, did not influence the content of total phenolic compounds extracted. However, extraction with an aqueous solution of an environmentally friendly nonionic surfactant (Plantacare® 1200) for 15 min was suggested since it tended to yield the highest total phenolic content.

On the other hand, decreased phenolic levels were observed after applying the greater energy of the microwave-assisted extraction when comparing each extraction period. The explanation might be due to the decomposition of phenolic compounds at high temperatures, even after only a few minutes of extraction, since a rapid heating of microwave energy and one-tenth of the processing time was required when compared with the conventional methods [2,10]. Regarding the PEF extraction, higher rate of energy input tended to cause the extract to contain a higher content of total phenolic, whereas total energy input (from 10 to 20 kV) had no effect. However, the total phenolic contents of *M. integrifolia* pericarp from infusion, micellar, microwave, and PEF extractions were significantly lower than those from ultrasound-assisted extraction. Therefore, it could be concluded that ultrasound-assisted extraction was the green extraction method that resulted in the significantly highest extract yield and total phenolic content. However, one *M. integrifolia pericarp* extract out of each green extraction procedure was chosen based on extract yield and total phenolic content for further assessment of biological activities. Aside from the extract from solvent extraction (SOL), there were five *M. integrifolia* pericarp extracts from green extraction methods, including 5 min infusion (INF), 10 min sonication (SON), 15 min micellar extraction using Plantacare® 1200 (MIC), 1 min microwave extraction at 200 W (MCW), and PEF extraction with an intensity electric field of 5 kV/cm and a pulse of 20 (PEF).

Table 1
The relationship between the total phenolic content and antioxidant activities of *M. integrifolia* pericarp extracts.

Correlation	Ferric reducing antioxidant power (EC_1)	Radical scavenging activities		Lipid peroxidation inhibition
		TEAC	DPPH inhibition	
Green extraction methods				
Pearson r (P value)	0.9895(0.0013) **	0.8853 (0.0458) *	0.9715 (0.0058) **	0.5227 (0.3662)
Correlation level	Very high positive	High positive	Very high positive	Moderate positive
Green extraction methods and solvent extraction				
Pearson r (P value)	0.7101 (0.1139)	0.2218 (0.6728)	0.6343 (0.1761)	0.6533 (0.1595)
Correlation level	High positive	Negligible correlation	Moderate positive	Moderate positive

Note: Asterisks denote significant strong correlations, * $p < 0.05$, ** $p < 0.01$.

3.3. Antioxidant activities of *M. integrifolia* pericarp extracts

Antioxidant activities of *M. integrifolia* pericarp extracts from solvent extraction and different green extraction methods are shown in Fig. 3. Since several oxidative processes are associated with the oxidation process [45], the antioxidant activities of *M. integrifolia* pericarp extracts were confirmed using four different antioxidant assays in the current study. The free radical scavenging capacity of the extracts was assessed using the DPPH and ABTS, which were related to the electron transfer process [1,32]. On the other hands, FRAP assay was used to demonstrate the reducing ability, i.e., the capacity of the extracts to convert ferric ion (Fe^{3+}) to ferrous ion (Fe^{2+}) [54,7]. Besides, ferric thiocyanate method was used to investigate the inhibition on lipid peroxidation of the extracts [25].

SON was found to have the most outstanding antioxidant activities among *M. integrifolia* pericarp extracts from various extraction methods, with the significantly highest EC_1 (101.9 ± 5.0 μM $FeSO_4$/g extract), TEAC (115.1 ± 4.9 mg Trolox/g extract), $DPPH^{\bullet}$ radical scavenging activity (85.7 ± 3.8%), and lipid peroxidation inhibition (86.4 ± 1.8%) ($p < 0.05$). Notably, SON had a potent antioxidant activity via free radical scavenging capacity and inhibition on lipid peroxidation. The antioxidant activities of SON were equivalent to ascorbic acid in $ABTS^{\bullet+}$ radical scavenging activity with a TEAC value of 124.0 0.4 mg Trolox/g extract and $DPPH^{\bullet}$ radical scavenging activity with an inhibition of 95.8 ± 0.6%. Furthermore, the lipid peroxidation inhibition of SON was comparable to that of Trolox, with an inhibition of 88.2 ± 0.5%. The antioxidant activities of *M. integrifolia* pericarp extracts from the green approach were attributed to phenolic compounds. Different levels of correlation between the phenolic content and biological activities of *M. integrifolia* pericarp extracts were observed in the analysis with and without the solvent extraction, particularly in the antioxidant activities. Among *M. integrifolia* pericarp extracts from green extraction methods, total phenolic content was found to have a very strong positive correlation with ferric reducing antioxidant power and $DPPH^{\bullet}$ radical scavenging activities, as well as a strong positive correlation with $ABTS^{\bullet+}$ radical scavenging activities, but a moderate positive correlation with lipid peroxidation inhibition (Table 1). However, lower correlations were found when SOL was included. The most plausible explanation involves chemicals other than the water-soluble (hydrophilic) phenolic compounds, such as some flavonoids, proanthocyanidins, etc. [18,28].

3.4. Anti-ageing activity of *M. integrifolia* pericarp extracts

Skin is the largest organ of the body, having significant defensive functions that deteriorate over time owing to both internal and extrinsic ageing processes [38]. Collagen accounts for 80% of skin dry weight and is responsible for skin tensile strength, whereas elasticity is attributable

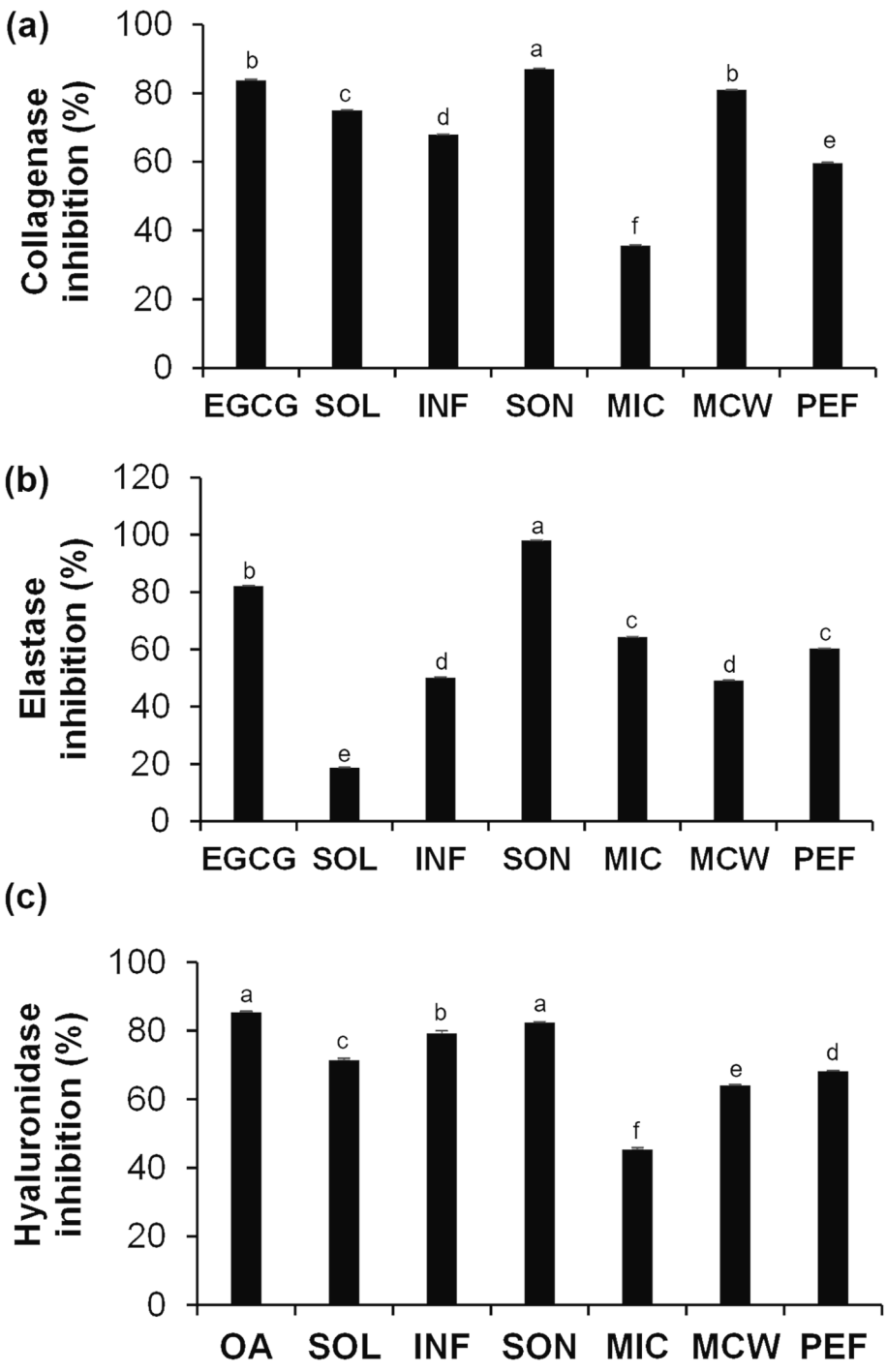

Fig. 4. Inhibitory activities against collagenase (a), elastase (b), and hyaluronidase (c) of epigallocatechin-3-gallate (EGCG), oleanolic acid (OA), and *M. integrifolia* pericarp extracts from different extraction methods, including solvent extraction (SOL), 5 min infusion (INF), 10 min sonication (SON), 15 min micellar extraction using Plantacare® 1200 (MIC), 1 min microwave extraction at 200 W (MCW), and PEF extraction with an intensity electric field of 5 kV/cm and a pulse of 20 (PEF). The letter a, b, c, d, e, and f denote significant differences among samples analyzed using one-way analysis of variance (ANOVA) with post-hoc Tukey test at $p < 0.05$.

to the elastic network, which accounts for 2–4% of the ECM [59]. On the other hand, hyaluronan is one of the natural moisturizing factors important in skin hydration [26]. However, when dermal fibroblasts were influenced by photoaging, less dermal ECM was produced, resulting in apparent changes in the skin, such as wrinkles, pigmentation, skin thickness alterations, etc. [59,38]. Apart from the reduction of ECM production, skin ageing is also induced using a destruction of dermal ECM, which comprises collagen fibers, elastin fibers, and hyaluronan, all of which are primarily degraded by matrix metalloproteinase-1 (MMP-1), elastase, and hyaluronidase, respectively [5,33]. As a result, inhibiting these enzymes can interrupt ECM breakdown and postpone the formation of skin wrinkles. The anti-skin aging activities of *M. integrifolia* pericarp extracts are shown in Fig. 4. SON was the most significantly potent and effective at inhibiting collagenase, elastase, and hyaluronidase ($p < 0.05$). Remarkably, the anti-skin ageing activities of SON were more potent than those of EGCG in terms of anti-collagenase and anti-elastase activities ($p < 0.05$), whereas its anti-hyaluronidase activity was equivalent to that of oleanolic acid. Both EGCG and oleanolic acid are well-known potent anti-ageing enzymes that are widely employed in the health care industry, including the cosmetic and cosmeceutical fields [3,31].

Phenolic compounds were proposed as the primary components responsible for anti-elastase activity of *M. integrifolia* pericarp extracts because they displayed a very strong positive correlation both including and excluding the SOL from solvent extraction (Table 2). In contrast, anti-collagenase and anti-hyaluronidase actions were attributed to

Table 2
Relationship between the total phenolic content and anti-skin ageing activities of *M. integrifolia* pericarp extracts.

Correlation	Anti-collagenase	Anti-elastase	Anti-hyaluronidase
Green extraction methods			
Pearson r (P value)	0.4999 (0.3911)	0.9515(0.0127) *	0.4471 (0.4503)
Correlation level	Low positive	Very high positive	Low positive
Green extraction methods and solvent extraction			
Pearson r (P value)	0.3237 (0.5314)	0.9334(0.0065) **	0.3259 (0.5284)
Correlation level	Low positive	Very high positive	Low positive

Note: Asterisks denote significant strong correlations, * $p < 0.05$, ** $p < 0.01$.

Table 3
Irritation score (IS) of *M. integrifolia* pericarp extracts.

Sample	IS	Irritation level
Positive control (1% w/v SLS)	11.94 ± 0.01	Severe
Negative control (0.9% w/v NaCl solution)	0.00 ± 0.00	No irritation
Vehicle control (DI water)	0.00 ± 0.00	No irritation
SOL (10 mg/mL aqueous solution)	2.30 ± 0.01	Slight
SON (10 mg/mL aqueous solution)	0.00 ± 0.00	No irritation

Note: M. integrifolia pericarp extracts from different extraction methods, including solvent extraction (SOL) and 10 min sonication (SON).

bioactive molecules other than phenolic compounds since the correlations were at a low level.

3.5. In vitro irritation properties of M. integrifolia pericarp extract

The irritation test was another important assessment required to validate the safety of further topical application. The HET–CAM test, which was suitable *in vitro* tests widely used in international cosmetics industries during the last decade [56], was used to investigated the irritation effect of *M. integrifolia* pericarp extracts in the present study. According to the data presented in Table 3, the positive control, 1% w/v SLS solution, generated severe irritation with an IS of 11.94 ± 0.01, but the negative control, 0.9% w/v NaCl solution, induced no irritation. After 60 min of exposure to the positive control, all irritation signs, including bleeding, coagulation, and vascular lysis, were observed as shown in Fig. 5. It was in line with our related study reporting that 1% w/v SLS solution caused significant severe irritation with an IS of 10.60 ± 0.80 [54].

M. integrifolia pericarp extracts, particularly SON from ultrasound-assisted extraction, exhibited potent antioxidant and anti-ageing effects. As a result, it has the potential to be exploited as an active cosmetic/cosmeceutical ingredient. Therefore, the irritating potential of SON from green extraction was evaluated compared with SOL, an extract from solvent extraction. The findings revealed that SON caused no irritation and presented no irritation signs on the CAM even after 60 min of exposure, but SOL caused mild irritation and vascular bleeding. Despite the fact that using ethanol might cause skin irritation or contact dermatitis [37], all ethanol was eliminated from the *M. integrifolia* pericarp extract during the evaporation process. The irritation of SOL could be due to some chemical components of the *M. integrifolia* pericarp dissolved in ethanol but not DI water. As a consequence, the green extraction method not only produced a greater bioactive content and biological activities associated with the cosmetic/cosmeceutical, but it also produced a safe *M. integrifolia* pericarp extract with no irritation generation.

4. Conclusion

The bioactive components associated with cosmetic/cosmeceutical were successfully extracted from *M. integrifolia* pericarp using the green extraction techniques. The ultrasound-assisted extraction produced the extract with the greatest yield and the largest amount of phenolic content, resulting in the extract (SON) having the most effective antioxidant and anti-skin ageing activities. When compared with traditional solvent extraction, the ultrasound-assisted extraction yielded not only a higher quality of the extract but was also safer. As the ethanolic extract generated mild irritation and vascular bleeding on the CAM, whereas

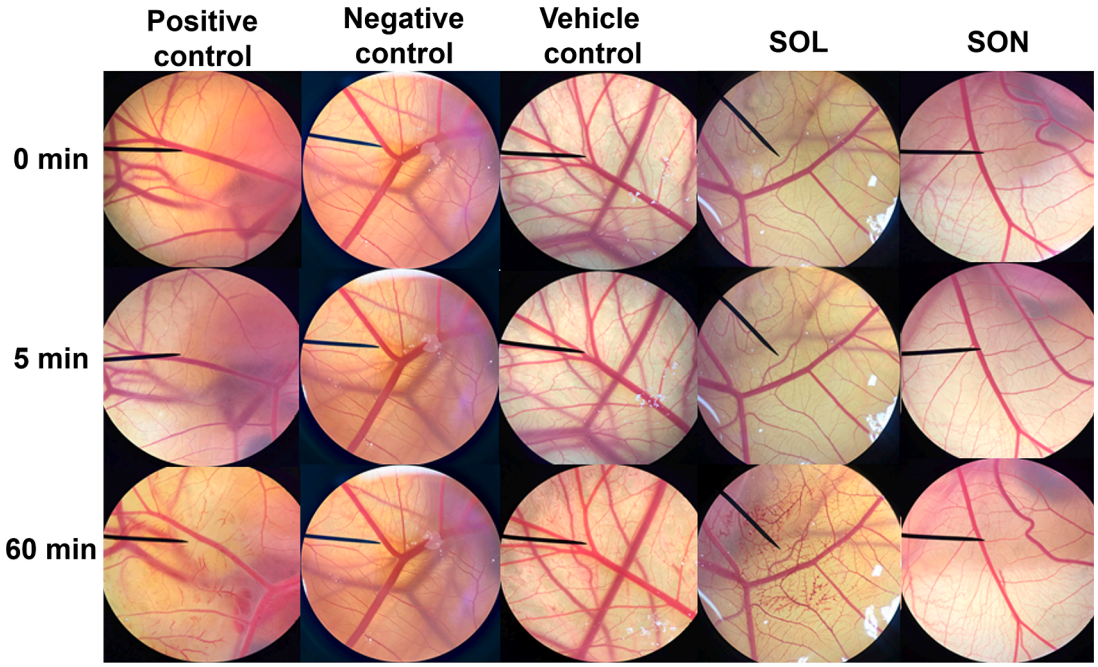

Fig. 5. Chorioallantoic membrane after being exposed to a positive control (1% w/v sodium lauryl sulfate aqueous solution), a negative control (0.9% w/v sodium chloride aqueous solution), a vehicle control (DI water), and *M. integrifolia* pericarp extracts from various extraction methods, including solvent extraction (SOL) and 10 min sonication (SON), for 0, 5, and 60 min.

SON caused zero irritation. Therefore, ultrasound-assisted extraction with aqueous, a clean and green solvent, was proposed as an environmentally acceptable extraction method for extracting the cosmetic/cosmeceutical bioactive components from *M. integrifolia* pericarp. Further investigations concerning the main phenolic compounds were suggested for quality control of the extract in a prospective application.

CRediT authorship contribution statement

Suvimol Somwongin: Investigation, Formal analysis, Writing – original draft, Funding acquisition. **Sasithorn Sirilun:** Conceptualization, Validation. **Panuwan Chantawannakul:** Conceptualization. **Songyot Anuchapreeda:** Conceptualization, Validation. **Artit Yawootti:** Investigation, Validation. **Wantida Chaiyana:** Conceptualization, Validation, Writing – original draft, Writing – review & editing, Funding acquisition, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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