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Potential antioxidant, anti-aging enzymes, and anti-tyrosinase properties of Macadamia (*Macadamia integrifolia*) pericarp waste products

Suvimol Somwongin[1], Sasithorn Sirilun[1], Panuwan Chantawannakul[2], Songyot Anuchapreeda[3] and Wantida Chaiyana[1*]

[1]Department of Pharmaceutical Sciences, Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand
[2]Department of Biology, Faculty of Science, Chiang Mai University, Chiang Mai, Thailand
[3]Division of Clinical Microscopy, Department of Medical Technology, Faculty of Associated Medical Sciences, Chiang Mai University, Chiang Mai, Thailand
[*]Corresponding author: wantida.chaiyana@gmail.com

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Abstract

Macadamia integrifolia pericarps are waste products from *M. integrifolia* nut production. This study aimed to investigate the potential use of *M. integrifolia* pericarp extracts as cosmeceutical active ingredients. The pericarp of *M. integrifolia* was extracted by sequential maceration using various solvents, starting with *n*-hexane, followed by ethyl acetate and 95% v/v ethanol. The extracts were then investigated for their antioxidant activities using 2,2'-diphenyl-1-picrylhydrazyl (DPPH), 2'-azinobis (3-ethylbenzothiazoline-6-sulfonic acid), and ferric reducing/ antioxidant power assay. The whitening effects of the extracts were determined through tyrosinase inhibition when the substrates were L-tyrosine and L-3,4-dihydroxyphenylalanine (L-DOPA). In addition, anti-ageing activities were determined through collagenase and elastase inhibitions. The results revealed that the ethanolic extract yielded the highest content, contained the highest phenolic content, and displayed the highest biological activities, including antioxidant, anti-tyrosinase, and anti-ageing effects ($p < 0.05$). This extract possessed the highest DPPH inhibition (57.0 ± 2.2%), equivalent concentration (EC_1) (51.9 ± 0.7 mM $FeSO_4$/g extract), Trolox equivalent antioxidant capacity (118.8 ± 0.9 mM Trolox/g extract), anti-tyrosinase activity on the conversion of L-tyrosine (26.4 ± 3.2%) and L-DOPA (27.1 ± 2.4%), anti-collagenase (65.4 ± 2.4%), and anti-elastase (68.3 ± 2.3%). Therefore, the ethanolic extract of *M. integrifolia* pericarp is a promising natural extract for use as antioxidant, anti-aging, and whitening active ingredient and is suggested for further cosmetic and cosmeceutical product development.

Keywords: Antioxidant, Anti-ageing, Anti-tyrosinase, Cosmeceutical, *Macadamia integrifolia*

1. Introduction

Macadamia is known as the "King of nut" because of its popularity and valuable nutritional value. Therefore, it is grown for commercial consumption purposes. *Macadamia* spp. is a plant in the Proteaceae family, native to Northeast New South Wales and the Southeast coast of Queensland, Australia. It is also cultivated in Brazil, Central America, Hawaii, Kenya, and South Africa [1]. *M. integrifolia* trees can also be grown in Thailand, especially in the Northern region of the country. Only two of ten species are edible: *M. integrifolia* (smooth shell) and *M. tetraphylla* (rough shell).

M. integrifolia is a common species grown for its nut, which is rich in carbohydrates, dietary fiber, minerals, various vitamins, unsaturated fat, and plant sterols [2,3]. *M. integrifolia* nuts have also become popular in bakery products such as cookies, cakes, snacks, and cuisine [4]. Furthermore, *M. integrifolia* nut oil is employed in the food, pharmaceutical, and cosmetic industries because it contains monounsaturated fatty acids, vitamin E, and sterols [5-7].

The fruits of *M. integrifolia* are spherical and have a smooth shell. The kernel, which accounts for only 20% of the overall weight, is often consumed as a snack. The remaining 80% of the overall weight was split into two

parts: 42 percent pericarp and 38 percent nutshell. The pericarp is thick, compact, and green, whereas the nutshell is firm and brown [8,9]. As a result, over 80% of *M. integrifolia* nuts end up in the industrial waste stream [8,10]. Around 40,000 tons of macadamia nuts are used in the food and cosmetic production process each year, resulting in 16,800 tons of pericarp and 15,200 tons of nutshell, both of which are waste products with high management costs [8,9]. These waste products are frequently discarded in landfills, resulting in high processing costs [8,11]. Finding a way to consume and increase the value of the pericarp of *M. integrifolia* is difficult because it is considered to be a waste of no value that needs to be eliminated [12]. These waste products have been used as furniture materials, animal feed fillers, and garden mulch; however, there is a need to eliminate this waste from landfill, which entails considerable costs for disposal operations. Although the skin of *M. integrifolia* has been reported to contain proanthocyanidins, phenolic compounds, and flavonoids, which were known as antioxidants [8], the bioactivities and utilization of *M. integrifolia* pericarp apart from activated carbon have not been reported before.

Therefore, the aims of this study were to investigate the potential of *M. integrifolia* pericarp extract to be an active cosmeceutical component with the inhibitory properties against oxidation, tyrosinase, collagenase, elastase, and hyaluronidase.

2. Materials and methods

2.1 Plant materials

The pericarps of *M. integrifolia* were supplied by the Power Plus Strong Company Limited (Thep Sadet, Doi Saket, Chiangmai, Thailand). They were dried in a tray dryer and then milled into a fine powder.

2.2 Chemical Materials

2,2'-azinobis 3-ethylbenzothiazoline-6-sulfonic acid (ABTS), 2,4,6-tripyridyl-striazine (TPTZ), 2,2'-diphenyl -1-picrylhydrazyl (DPPH), (±)-6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid (Trolox), collagenase from Clostridium histolyticum (ChC-EC.3.4.23.3), ascorbic acid, calcium chloride ($CaCl_2$), elastase from porcine pancreatic (PE-E.C.3.4.21.36), Epigallocatechin-3-gallate (EGCG), ferrous sulfate ($FeSO_4$), Folin-Ciocalteu reagent, sodium carbonate (Na_2CO_3), N-Succinyl-Ala-Ala-Ala-*p*-nitroanilide (AAAPVN), gallic acid, L-tyrosine, L-DOPA, kojic acid, N-[3-(2-furyl) acryloyl]-Leu-Gly-Pro-Ala (FALGPA), potassium persulphate ($K_2S_2O_8$), ferric chloride ($FeCl_3$), sodium acetate (CH_3COONa), tricine, sodium chloride (NaCl), and Tyrosinase from mushroom lyophilized powder (EC.1.14.18.1) were purchased from Sigma-Aldrich (Schnelldorf, Germany). Hydrochloric acid, acetic acid, and Tris base were purchased from Fisher Chem Alert (Fair Lawn, NJ, USA).

2.3 Extraction of M. integrifolia pericarp

The pericarp of *M. integrifolia* was extracted using a sequential maceration method that involved *n*-hexane, ethyl acetate, and 95% v/v ethanol. Briefly, 400 g of *M. integrifolia* pericarp powder was macerated for 24 h and three cycles in 2000 mL of *n*-hexane. The macerate was filtered using Whatman No. 1 filter paper. Finally, a rotary evaporator was used to extract each fractionated macerate (Buchi Labortechnik GmbH, Essen, Germany). Three pericarp extracts of *M. integrifolia* were obtained: Macadamia Pericarp Hexane Extract (MPH), Macadamia Pericarp Ethyl acetate Extract (MPA), Macadamia Pericarp Ethanolic Extract (MPE). The extracts were then stored at 4℃ until they were utilized.

2.4 Determination of the total phenolic content

The total phenolic content of *M. integrifolia* pericarp extract was determined using the Folin-Ciocalteu technique [13]. Briefly, 20 µL of sample solution was mixed with 100 µL of Folin-Ciocalteu reagent that had been diluted 10-fold in DI water and incubated at 37℃ for 4 min. Then, 80 µL of sodium carbonate solution (Na_2CO_3) with a concentration of 75 g/L was added. The UV absorbance was measured using the multimode detector at 750 nm after 2 h incubation at 37℃ in the dark. Gallic acid is the standard chemical for this reaction. The data were expressed in mg/g gallic acid equivalents (GAE).

2.5 Measurement of antioxidant activity

2.5.1. 2,2'-diphenyl-1-picrylhydrazyl (DPPH) assay

The ability of *M. integrifolia* pericarp extracts to scavenge DPPH radicals was investigated. [13,14]. Briefly, 20 µL samples of extracts were mixed with 180 µL of DPPH reagent. The UV absorbance was measured by the multimode detector at 540 nm after 30 min incubation at 37℃. DPPH inhibition (%) = [(C- M)/C] 100, where C represents the absorbance of the combination without *M. integrifolia* pericarp extracts and M represents the absorbance of the combination with *M. integrifolia* pericarp extracts. The positive control was ascorbic acid. The experiment was repeated in triplicate.

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

The ability of *M. integrifolia* pericarp extracts to scavenge free radicals on ABTS was investigated [13,14]. Briefly, in order to form an ABTS free radical solution, 7 mM of ABTS reagent and 2.45 mM of potassium persulphate ($K_2S_2O_8$) solution were mixed in a 2:3 ratio and incubated in the dark for 16 h. Subsequently, 20 µL of the extract was mixed with 180 µL of ABTS free radical reagent (diluted 20-fold in ethanol). After 5 min incubation at 37℃, the UV absorbance was assessed using the multimode detector at 750 nm. A calibration curve was generated with Trolox. The findings were expressed as Trolox equivalent antioxidant activity (TEAC). The experiment was repeated in triplicate.

2.5.3 Ferric reducing/antioxidant power (FRAP) assay

The free radical scavenging activity of *M. integrifolia* pericarp extracts was evaluated using the FRAP assay technique [13,14]. Briefly, in the ratio 10:1:1, the freshly made FRAP reagent contained 0.3 M of acetate buffer with a pH of 3.6, 10 mM of TPTZ solution in 40 mM of HCl, and 20 mM of $FeCl_3$. Then, 20 µL of extract and 180 µL of FRAP reagent were mixed together. A multimode detector was used to assess UV absorbance at 595 nm after 5 min of incubation at 37℃. A calibration curve was created using ferrous sulfate ($FeSO_4$). The results were given as the equivalent capacity (EC_1), which means that 1 mg of sample could decrease the number of ferric ions. The experiment was repeated in triplicate.

2.6 In vitro determination of the anti-ageing activities

2.6.1 In vitro collagenase inhibitory activity

Collagenase inhibitory assays were used to test *M. integrifolia* pericarp extracts for anti-ageing efficacy [15,16]. Briefly, extract was incubated for 15 min with 5 units/mL of collagenase enzyme. Then, tricine buffer with a pH of 7.5 and 2.0 M FALGPA was added. Immediately following the enzyme reaction, the multimode detector was utilized to analyze the kinetic reaction at 340 nm within 20 min. The following equation was used to determine collagenase inhibition: Collagenase inhibition (%) = [(B - M)/B] × 100, where B represents the absorbance of the combination without *M. integrifolia* pericarp extracts, and M represents the absorbance of the combination with *M. integrifolia* pericarp extracts. As a positive control, EGCG was used. The experiment was repeated in triplicate.

2.6.2 In vitro elastase inhibitory activity

The elastase inhibitory technique was used to test *M. integrifolia* pericarp extracts for skin anti-ageing effects [15,16]. Briefly, for 15 min, the extract was incubated with 4.5 unit/L of elastase. After that, 1.6 mM succinyl-Ala-Ala-Ala-*p*-nitroanilide (AAAVPN) was added to a Tris HCI buffer at a pH of 8.0. Immediately following the enzyme reaction, the multimode detector analyzed the kinetic reaction at 410 nm within 20 min. The following equation was used to determine elastase inhibition: Elastase inhibition (%) = [(B - M)/B] × 100, where B represents the absorbance of the combination without *M. integrifolia* pericarp extracts, and M represents the absorbance of the combination with *M. integrifolia* pericarp extracts. As a positive control, EGCG was used. The experiment was repeated in triplicate.

2.7 Anti-tyrosinase activity measurements

The anti-tyrosinase activity of *M. integrifolia* pericarp extracts was measured using ultraviolet spectrophotometry, utilizing L-tyrosine and L-DOPA as substrates [17]. Briefly, 10 µL of extract was treated with

30 µL of tyrosinase reagent, 60 µL of AAAVPN with a pH of 6.8, and 100 µL of each substrate. A multimode detector was used to assess UV absorbance at 492 nm after 30 min of incubation at 37°C. The inhibition of tyrosinase was determined using the following equation: Tyrosinase inhibition (%) = [(B - M)/B] × 100, where B represents the absorbance of the combination without *M. integrifolia* pericarp extracts, and M represents the absorbance of the combination with *M. integrifolia* pericarp extracts. As a positive control, kojic acid was used. The experiment was repeated in triplicate.

2.8 Statistical analysis

All of the data were analyzed and reported as the mean and standard deviation (S.D.). SPSS software was used to perform a T-test and a one-way ANOVA in the statistical study (SPSS Statistics 17.0, IBM Corporations, New York, NY, USA). A p-value < 0.05 was determined to be statistically significant.

3. Results

3.1 Yields and phenolic contents of M. integrifolia pericarp extracts

The yields and total phenolic contents of *M. integrifolia* pericarp extracts are shown in Table 1 MPE and MPA yielded higher extract contents compared to MPH. On the other hand, MPE contained the significantly highest phenolic content, followed by MPA and MPH.

Table 1 Yields and total phenolic contents of *M. integrifolia* pericarp extracts.

Extracts	Yield (%w/w)	Total phenolic content (µg GA/g extract)
MPH	0.58 ± 0.02^{a}	0.0 ± 0.0^{a}
MPA	2.67 ± 0.11^{b}	52.9 ± 1.7^{b}
MPE	2.71 ± 0.01^{b}	108.6 ± 5.0^{c}

Notes: MPH: Macadamia Pericarp Hexane Extract, MPA: Macadamia Pericarp Ethyl acetate Extract, MPE: Macadamia Pericarp Ethanolic Extract. Using one-way analysis of variance (ANOVA) with post hoc Tukey's test ($p < 0.05$), the letters a, b, and c indicate significantly different yields and total phenolic contents across different extracts.

3.2 Antioxidant activities of M. integrifolia pericarp extracts

The antioxidant activities of *M. integrifolia* pericarp extracts are shown in Table 2 Among different *M. integrifolia* pericarp extracts, MPE possessed the significantly highest antioxidant activities with the highest EC_1, TEAC, and DPPH inhibition ($p < 0.05$), followed by MPA and MPH. MPE possessed antioxidant activities via both mechanisms. Although MPE was not as potent as L-Ascorbic acid, the TEAC value of MPE (118.8 ± 0.9 mg I/g extract) was very close to that of L-Ascorbic acid (124.0 ± 0.4 mg I/g L-Ascorbic acid).

Therefore, MPE was the most potent antioxidant since it inhibited DPPH• radicals by 57.0 ± 2.2% and possessed the significantly highest EC_1 and TEAC values, which were 51.9 ± 0.7 mM $FeSO_4$/g extract and 118.8 ± 0.9 mM I/g extract, respectively.

Table 2 Antioxidant activities of *M. integrifolia* pericarp extracts.

Samples	EC_1 (µM $FeSO_4$/g extract)	TEAC (mg Trolox/g extract)	DPPH inhibition (%)
L-Ascorbic acid	238.3 ± 0.2^{a}	124.0 ± 0.4^{a}	95.8 ± 0.6^{a}
MPH	4.7 ± 0.5^{d}	13.3 ± 1.5^{d}	0.0 ± 0.0^{d}
MPA	22.0 ± 0.8^{c}	96.1 ± 1.8^{c}	14.9 ± 0.7^{c}
MPE	51.9 ± 0.7^{b}	118.8 ± 0.9^{b}	57.0 ± 2.2^{b}

Notes: Data are the mean ± S.D. (n = 3), MPH: Macadamia Pericarp Hexane Extract, MPA: Macadamia Pericarp Ethyl acetate Extract, MPE: Macadamia Pericarp Ethanolic Extract . Using one-way analysis of variance (ANOVA) with post hoc Tukey's test ($p < 0.05$), the letters a, b, and c indicate significantly different yields and total phenolic contents across different extracts.

3.3 Anti-ageing activities of M. integrifolia pericarp extracts

The inhibitory activities of *M. integrifolia* pericarp extracts against collagenase and elastase enzyme are shown in Figure 1 Although MPE was not as potent as EGCG in the inhibitory effects on collagenase and elastase, it possessed the significantly highest inhibition against both collagenase and elastase, followed by MPA and MPH. MPE showed potential to inhibit skin ageing by reducing the activities of collagenase by 65.4 ± 2.4% and elastase by 68.3 ± 2.3%. Therefore, ethanol would be suggested for extracting the anti-ageing compounds from *M. integrifolia* pericarp.

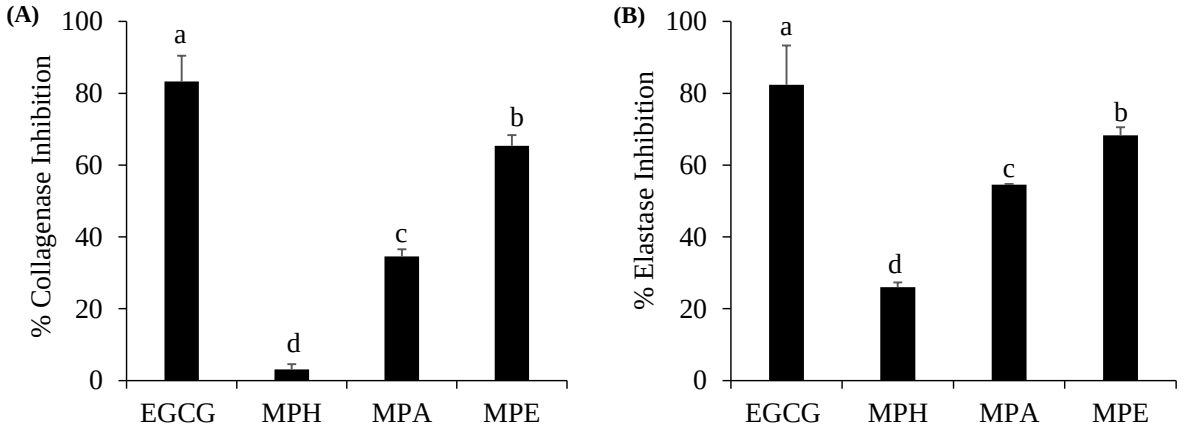

Figure 1 Collagenase inhibition (A) and elastase inhibition (B) of EGCG and *M. integrifolia* pericarp extracts extracted by Macadamia Pericarp Hexane Extract (MPH), Macadamia Pericarp Ethyl acetate Extract (MPA), and Macadamia Pericarp Ethanolic Extract (MPE). The letters a, b, c, and d indicate that there are significant differences between the extracts ($p < 0.05$).

3.4 Anti-tyrosinase activity of M. integrifolia pericarp extracts

The anti-tyrosinase activities of *M. integrifolia* pericarp extracts are shown in Figure 2 Since tyrosinase has long been recognized as a crucial melanosome enzyme in the complex pathway of melanin production, any compounds possessed anti-tyrosinase activities were suggested for skin whitening effects. Tyrosinase is a melanin-producing enzyme that catalyzes the conversion of L-tyrosine to L-DOPA [18]. Afterwards, tyrosinase rapidly converts L-DOPA to L-dopaquinone and lastly resulting in melanin [18]. Among three *M. integrifolia* pericarp extracts, MPE possessed the significantly highest anti-tyrosinase activity in both substrates, including L-tyrosine and L-DOPA.

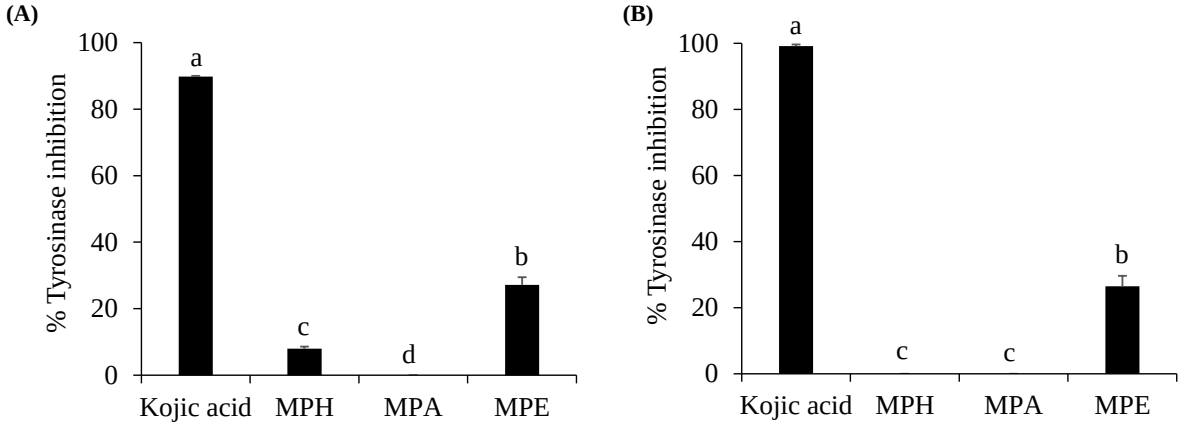

Figure 2 Tyrosinase inhibition by kojic acid and *M. integrifolia* pericarp extracts extracted by Macadamia Pericarp Hexane Extract (MPH), Macadamia Pericarp Ethyl acetate Extract (MPA), and Macadamia Pericarp Ethanolic Extract (MPE). when the substrates were L-tyrosine (A) and L-DOPA (B). The letters a, b, c, and d indicate that there is a significant difference between the extracts ($p < 0.05$).

4. Discussion

Since more than 30,000 tons of pericarp and nutshell of *M. integrifolia* are generated as waste products each year [8-10], the utilization which could increase its value would be worth studying. Besides, there have been many studies reported that the pericarp of some fruits and the waste products from food processing industry are abundant source of bioactive compounds [19-21]. Therefore, the potential of *M. integrifolia* pericarp extracted using various types of solvents to be used in the cosmetic and cosmeceutical areas was investigated in the present study.

Different extracting solvents significantly affected the extraction of bioactive chemicals from plant materials because bioactive components from natural sources are variety and range from very polar to extremely non-polar molecules [8]. MPE was identified as the *M. integrifolia* pericarp extract which yielded the significantly highest extract content and contained the significantly highest number of phenolic compounds ($p < 0.05$). Therefore, phenolic compounds in *M. integrifolia* pericarp contained more polar components compared non-polar components. In general, highly polar solvents can extract phenolic compounds, and the total phenolic content is clearly related to the kind of solvent and its polarity index [22]. The present study employed the sequential extraction method to remove some non-polar components. Previously processes with low polar solvents, which were *n*-hexane ($\varepsilon = 1.88$) and ethyl acetate ($\varepsilon = 6.02$), could rarely extract the phenolic compounds. Therefore, 95% v/v ethanol was suggested for the extraction of phenolic compounds from *M. integrifolia* pericarp.

MPE had the highest biological activity related to cosmeceutical applications among three different *M. integrifolia* pericarp extracts, including antioxidant, anti-tyrosinase, and anti-ageing capabilities. The most likely explanation would be its significant content of total phenolic compounds. Phenolic compounds have been reported to be able to neutralize free radicals either by donating a hydrogen atom transfer or by a single electron transfer mechanism; therefore, the MPE that contained the significantly highest phenolic content tended to be useful for defense against the generation of free radicals and the skin ageing process [23,24].

There are several oxidative processes involved in oxidation; therefore, three different antioxidant assays were employed in this investigation to confirm the antioxidant capacity of *M. integrifolia* pericarp extracts [25]. The DPPH and ABTS assays were both associated with the same electron-transfer reaction, but the FRAP assay was associated with the conversion of ferric ions (Fe^{3+}) to ferrous ions (Fe^{2+}). Oxidative stress caused by the overproduction of free radicals could induced cell damage, cell death, and result in the skin ageing process [26-28]; therefore, MPE which possessed potent antioxidant activities via various mechanisms would be an attractive natural anti-ageing ingredient in future cosmetic/cosmeceutical product development for the inhibition of skin ageing.

To ensure the anti-ageing potential of *M. integrifolia* pericarp extracts, inhibitory activities on the degradation of the dermis extracellular matrix (ECM) were investigated. Type I collagen fibrils produced by fibroblasts are the most common structural protein in the dermis. They are in charge of the skin's firmness and elasticity [29]. During the ageing process, these collagen fibrils are gradually degraded by the enzyme named collagenase, or MMP-1 [30]. Moreover, the deterioration of fibroblast function with older age results in a further decrease in collagen production [31]. In addition, other ECM components, including elastic fibers, hyaluronan, glycosaminoglycans (GAGs), and proteoglycans (PGs), are also degraded, and eventually result in a reduction in functional parts. Lower levels of these ECM components in the dermis layer leads to clinical ageing features, such as wrinkles and sagging skin [31]. Consequently, the inhibitory activities of the enzymes associated with dermal ECM degradation are important for youthful skin [31,32]. Various solvents, ranging from *n*-hexane, ethyl acetate, and 95% v/v ethanol, were used in the extraction of *M. integrifolia* pericarp since a variety of compounds, ranging from polar to non-polar, could be active ingredients for anti-aging activity. Previous studies have reported that polyphenols, especially catechin and epigallocatechin gallate, have demonstrated considerable inhibitory effects on both collagenase and elastase activity due to non-covalent binding [33-35]. On the other hand, oleanolic acid, a natural pentacyclic triterpene, has been widely known and used as a standard collagenase and elastase inhibitor [36-38]. In the present study, the inhibitory activities of *M. integrifolia* pericarp extracts against collagenase and elastase enzyme are presented to reveal their anti-ageing effects. Although MPE was not as potent as EGCG in the inhibition against collagenase and elastase, its inhibitory activities were about 80% of the standard EGCG. The results showed that MPE and EGCG inhibited collagenase by $65.4 \pm 2.4\%$ and $83.3 \pm 7.1\%$, when inhibited elastase by $68.3 \pm 2.3\%$ and $82.4 \pm 11.0\%$. In brief, the anti-ageing effects of *M. integrifolia* pericarp extracts have been revealed and MPE has been identified as a potential natural anti-ageing ingredient due to its potent inhibitory activities on collagenase and elastase, along with potent antioxidant activities.

Apart from antioxidant and anti-ageing activities, MPE exhibited a potential whitening effect because it could inhibit the activity of tyrosinase, which is an important rate-limiting enzyme in the melanogenesis process that leads to the melanin overproduction. Normally, natural extracts, which can inhibit this enzyme, are considered as a good choice for skin-whitening agents in cosmetic products [39]. The present study was the first to reveal the tyrosinase inhibitory activities of *M. integrifolia* pericarp extracts. Although the tyrosinase inhibition of MPE was at a very low level comparing to kojic acid, it could be used at higher concentrations in the formulation to achieve similar inhibitory activity to kojic acid. However, there is a need to be concerned about safe concentrations for topical applications.

5. Conclusion

This study is the first to reveal the cosmeceutical properties of *M. integrifolia* pericarp extracts. Among three *M. integrifolia* pericarp extracts, MPE yielded the significantly highest extract content and contained the

significantly highest number of phenolic compounds ($p < 0.05$), which were suggested to be responsible for its antioxidant, anti-collagenase, and anti-elastase activities. Therefore, MPE is suggested to be a potential active cosmeceutical ingredient for use in the development of further cosmeceutical and cosmetic products. However, safe concentrations need to be determined and clinical evaluations of *M. integrifolia* pericarp extracts should be performed. The utilization of these *M. integrifolia* pericarp extracts could not only lead to a reduction in waste materials, but also enhance the value of these waste products.

6. Conflicts of interest

There are no conflicts of interest declared by the authors.

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