Antioxidant properties, selected enzyme inhibition capacities, and a cosmetic cream formulation of Thai mango seed kernel extracts

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Abstract

Purpose: To investigate the antioxidant properties, the inhibition of selected enzyme activities of ultrasonication-assisted mango seed kernel extract (MSKE), and to evaluate the physical stability and skin irritation properties of a cosmetic cream formulated with MSKE.

Methods: Choke-Anan MSKE and a Kaew cultivar of Thai mangoes were prepared by ultrasonication-assisted extraction. Antioxidant activities (DPPH, FRAP, H₂O₂ scavenging assay, ABTS), antityrosinase, anti 5-lipoxygenase, antihyaluronidase and anti α-glucosidase were determined. Cosmetic creams containing 0, 1, 2 and 3 % of MSKE were prepared and evaluated for physical stability. The most stable formulation was subjected to the clinical skin irritation test.

Results: The yield, total polyphenol content, antioxidant properties and inhibition of 5-lipoxygenase, hyaluronidase and α-glucosidase were higher (p < 0.05) for MSKE from Choke-Anan than from Kaew cultivar. The MSKE from both cultivars showed no significant difference (p > 0.05) in tyrosinase inhibition activity compared to arbutin. However, a slightly lower α-glucosidase inhibition activity than acarbose was observed. The cosmetic cream containing 1 % Choke-Anan MSKE had good physical stability with no skin irritation.

Conclusion: MSKE exhibits good antioxidant and enzyme inhibitory activity. Thus, it is a potentially natural functional ingredient for use in food and cosmetic industries.

Keywords: Mango, Antioxidant, Enzyme inhibitory activities, Cosmetic product stability, Skin irritation

INTRODUCTION

Polyphenol phytochemicals have been extensively studied and are the most well-known bioactive compounds found in plants. Polyphenols are secondary metabolites found in higher plants that contain one or more phenol units [1]. They have strong antioxidant activity, and can scavenge a variety of free radicals including reactive oxygen species (ROS) and reactive nitrogen species (RNS) [2]. Previous studies have shown the protective action of polyphenols on human health and indicate their potential use as key components of a healthy and balanced diet [3]. Currently, the use of natural antioxidants in cosmetics is of increasing interest. Previous studies show that oxidative stress, is the major cause of skin ageing and is an over production of ROS and a reduction of antioxidant activity with age [4]. Moreover, plant polyphenols have been reported to be used as sunscreens, whitening and anti-ageing agents in cosmetic products [5].

The mango (Mangifera indica L.) fruit belongs to the Anacardiaceae family and is a good source of various polyphenols, which are found in the pulp, peel and seed [6]. The mango fruit and its processed products are in increasing demand in the world market. Consequently, mango seed and peel, which account for 35-60% of the fruit depending on the variety, are the main by-products [7]. There are several mango varieties grown in Thailand. The most well-known cultivars are Choke-Anan, Ok-Long, Kaew, Nam-Dorkmai, Rad and Keow-Savoey. The Choke-Anan and Kaew cultivars are commonly used for processing in factories, and represent for 29.5% and 27.9%, respectively, for all mango varieties. It has been reported that industrial mango seed waste generation is as high as 1 ton annually [8].

The bioactive compounds in the mango seed kernel are tannin, gallic acid, coumarin, cafeeic acid, vanillin, mangiferin, ferulic acid, and cinamic acid [9]. Mango seed kernel extracts have been reported to have anti-tyrosinase, anti-inflammatory and hepatoprotective activities [10]. Therefore, mango seed kernels could be a potential source of ingredients for functional foods and cosmetics [11].

The present study aimed to determine a suitable ultrasonication time for the extraction of two cultivars of Thai mango seed kernel. The bioactivity, antioxidant activity and the effect on tyrosinase, 5-lipoxygenase, hyaluronidase and α-glucosidase activities were also studied. The application of the mango seed kernel extract in a cosmetic cream was evaluated.

EXPERIMENTAL

Plant materials

Two mango cultivars (Mangifera indica L.) were studied. The cultivars, Kaew and Choke-Anan were obtained from a local orchard in Nakornratchasima Province, Thailand between March and May, 2015. Mature green mangoes were selected by weight (200 - 250 g / kg). The peel and pulp were removed from the fruits using a fruit peeler and a knife, and the seeds were kept at -18 °C (Ultra Cold Freezer -80 °C, CTL 821, Thailand) for no longer than 1 month. Before use, the frozen kernels were separated from their shell with scissors.

Preparation of mango seed kernel extract (MSKE)

Crude MSKE were prepared by ultrasonic-assisted extraction as previously described [12]. All of the samples were ground and blended with 95% ethanol (100 ml) in a blender for 5 min. The samples were incubated in a sonication water bath, at a frequency of 20 KHz and a temperature of 25 °C for 15-60 min. The samples were further incubated in a water bath at 80 °C and stirred every 10 min for 1 h. The mixtures were cooled at room temperature and the supernatant from each mixture was passed through Whatman filter paper no. 4. All filtrates were evaporated in a rotary evaporator at 50 °C under a vacuum until dry, and the extracts were weighed to determine the extraction yield of the soluble components.

Determination of total polyphenol content (TPC)

TPC was analysed as previously described [13]. The TPCs of the samples were expressed as mg of gallic acid equivalents per gram of MSKE.

Determination of antioxidant activities

The antioxidant activity of MSKE was evaluated using four different methods; the 2, 2-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay, the ferric reducing antioxidant power assay (FRAP), the hydrogen peroxide scavenging assay and the 2, 2’-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) radical scavenging assay. The assays were performed according to previous reports [14]. The results were expressed as mg of trolox equivalents per gram of MSKE.

Determination of enzyme inhibition activity

The tyrosinase inhibition activity was measured using a modified dopachrome method with mushroom tyrosinase and L-3, 4-dihydroxyphenylalanine as the substrate [15]. The 5-lipoxygenase inhibition activity was studied using sodium linoleate as the substrate according to a previous study [16]. The hyaluronidase inhibition activity was determined using sodium hyaluronate as substrate following a previously described method [17]. The α-glucosidase inhibition activity was measured using p-nitrophenyl-α-D-glucopyranoside as substrate [18].
inhibitory effects of the samples were expressed as the inhibitor concentration causing a 50 % loss of enzyme activity (IC50).

Preparation of cosmetic cream

The oil-in-water emulsion creams used in this study were prepared, respectively by melting the lipophilic phase including Emulium Delta (5.0 %), stearic acid (1.5 %), stearyl alcohol (2.0 %), Captex 300 (3 %) and cetyl alcohol (1.5 %) in a water bath at 80 °C and separately mixing the hydrophilic phase; propylene glycol (3 %), xanthan gum (0.1 %), EDTA (0.1 %) and water in a water bath at 70 °C.

The 2 phases were mixed by homogenizer at 20,000 rpm for 3 min and cooled down at room temperature. MSKE (0, 1, 2, and 3 % w/w) and 0.1 % phenoxyethanol as preservative were added and mixed again at 10,000 rpm for 3 min.

Test for resistance to centrifugation

The resistance to centrifugation study was based on a previously described method [19]. The samples were stored at ambient temperature and humidity for 48 h. A 10 ml sample was centrifuged at 3000 rpm for 30 min. The Samples were evaluated for phase separation by measuring the supernatant after centrifugation.

Assessment of physical stability

The samples were stored at -4 °C for 24 h and then 25 °C for another 24 h and this was repeated for 6 cycles. Samples were taken every 48 h for the evaluation of pH, viscosity, phase separation, colour and TPC. The samples were centrifuged at 15000 g for 30 min at 4 °C and the supernatant was analysed for TPC using a previously described method [13].

The colour of the samples was expressed as L (degree of lightness), a (degree of redness) and b (degree of yellowness) values. The total colour difference (ΔE) was calculated by Eq 1.

\[ \Delta E = \sqrt{(L - L')^2 + (a - a')^2 + (b - b')^2} \]  

where L, a and b are the sample colours, and L’, a’ and b’ are the colours at time zero.

Skin irritation test

MSKE cream was subjected to in-vivo skin irritation assessment. A total of 20 Thai men and women with normal skin, 18 years old and older, volunteered to participate in this study. Patch tests were performed on a part of the back (5x4 cm) of all volunteers. After 24 h, the patch was removed and the skin was observed for redness/ irritation after 30 min and 24 h. The method used in this study was approved by the Ethical Committee for in vivo Studies of Mae Fah Luang University, Thailand (reference no. REH-50005).

Statistical analysis

The results are expressed as the mean ± standard deviation (SD, n = 3). Statistical analyses were carried out by a one-way ANOVA using SPSS version 16.0. Significant differences were at p ≤ 0.05.

RESULTS

Extraction yield and TPC

The effect of duration of ultrasonication on the extraction yield and TPC of the MSKEs from the two cultivars are shown in Table 1. The results showed that a longer ultrasonication duration (up to 45 min) gave a significantly higher (p ≤ 0.05) extraction yield and TPC of the extracts. However, the values were not significantly different (p > 0.05) after 45 min, indicating that the optimum duration of ultrasonication for the extraction of MSKEs under the conditions used in this experiment was 45 min. The Choke-Anan cultivar had a higher extraction yield and TPC than the Kaew cultivar. The MSKE obtained by ultrasonic-assisted extraction at 45 min gave a 55 and 63 % higher extraction yield and 92 and 55 % higher TPC for the Kaew and Choke-Anan cultivars, respectively compared to conventional ethanol extraction.

Antioxidant activity of MSKE

MSKEs prepared by the ultrasonication-assisted extraction of the two cultivars had approximately two-fold greater antioxidant activity for all the methods studied (Table 2). The higher polyphenol content in the MSKEs obtained by ultrasonication-assisted extraction (Table 1) likely contributed to the greater antioxidant activity. In addition, the Choke-Anan MSKE showed a higher antioxidant activity.
activity than the Kaew MSKE for all methods evaluated. The results corresponded to the content of TPC, which was also higher in the Choke-Anan MSKE (Table 1).

**Enzyme inhibition capacity of MSKEs**

As shown in Table 3, the Kaew and Choke-Anan MSKE were not significantly different (p > 0.05) for the tyrosinase inhibitory activity compared to arbutin and the IC50 values were in the range of 19.86 ± 1.2 to 20.64 ± 0.3 μg/mL. The Choke-Anan MSKE had significantly higher (p ≤ 0.05) 5-lipoxygenase inhibitory activity than that of the Kaew MSKE. However, the inhibitor concentration that caused a 50% loss of the enzyme activity (IC50) of the MSKES was approximately 3.2 - 4.3 fold higher than rutin. The hyaluronidase inhibitory activity of the Choke-Anan MSKE was not significantly different (p > 0.05) compared to vitamin C. However the Kaew MSKE showed an approximately 1.3 fold lower inhibitory activity. The Choke-Anan MSKE had a significantly higher (p ≤ 0.05) α-glucosidase inhibitory capacity than the Kaew MSKE. The Choke-Anan MSKE had an approximately 1.1 fold higher IC50 than acarbose, indicating a slightly lower α-glucosidase inhibitory activity.

**Table 1:** Effect of the ultrasonication duration on the extraction yield and TPC of MSKES

<table>
<thead>
<tr>
<th>Mango cultivars</th>
<th>Extraction time (min)</th>
<th>Yield (%)</th>
<th>TPC (mg GAE/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaew Ethanol</td>
<td>0 (Ethanol extraction)</td>
<td>1.60±0.06</td>
<td>71.74±0.97</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>1.71±0.03</td>
<td>70.93±0.63</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>2.10±0.07b</td>
<td>91.64±0.80</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>2.48±0.03b</td>
<td>137.49±1.15b</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>2.49±0.06</td>
<td>138.71±2.52</td>
</tr>
<tr>
<td>Choke-Anan</td>
<td>0 (Ethanol extraction)</td>
<td>2.16±0.02</td>
<td>110.02±1.06</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>2.29±0.04d</td>
<td>110.32±0.93d</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>2.73±0.03c</td>
<td>124.36±1.69c</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>3.52±0.03c</td>
<td>170.12±1.89c</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>3.56±0.02c</td>
<td>170.63±0.93c</td>
</tr>
</tbody>
</table>

*Values are the mean ± standard deviation; (n=3); values in the same column followed by different superscript letters are significantly different (p ≤ 0.05)*

**Table 2:** Antioxidant capacity of MSKE by different methods

<table>
<thead>
<tr>
<th>MSKE extract</th>
<th>Antioxidant capacity (mg Trolox/ g MSKE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DPPH</td>
</tr>
<tr>
<td>Kaew Ethanolic</td>
<td>92.61±3.72a</td>
</tr>
<tr>
<td>Kaew Ethanol + ultrasonication</td>
<td>197.06±5.83a</td>
</tr>
<tr>
<td>Choke-Anan ethanolic</td>
<td>117.07±4.12a</td>
</tr>
<tr>
<td>Choke-Anan ethanolic + ultrasonication</td>
<td>254.64±1.15f</td>
</tr>
</tbody>
</table>

*Values are the mean ± standard deviation; (n=3); values in the same column followed by different superscript letters are significantly different (p ≤ 0.05)*

**Table 3:** Enzyme inhibition capacity

<table>
<thead>
<tr>
<th>Sample</th>
<th>IC50 (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tyrosinase</td>
</tr>
<tr>
<td>Kaew MSKE</td>
<td>20.64±0.32a</td>
</tr>
<tr>
<td>Choke-Anan MSKE</td>
<td>19.86±1.22a</td>
</tr>
<tr>
<td>Arbutin</td>
<td>20.46±0.33a</td>
</tr>
<tr>
<td>Rutin</td>
<td>-</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>-</td>
</tr>
<tr>
<td>Acarbose</td>
<td>-</td>
</tr>
</tbody>
</table>

*Values are the mean ± SD (n=3); values in the same column followed by different superscript letters are significantly different (p ≤ 0.05). IC50 = inhibitor concentration causing 50% loss of enzyme activity*
Physical stability of MSKE cream

After centrifugation, phase separation was not observed in any sample of MSKE cream or the control base (data not shown). A physical stability evaluation of the MSKE creams is shown in Table 4. A freeze-thaw cycling test showed that the pH and viscosity of the samples from each cycle did not exhibit significant changes (p > 0.05) and no phase separation was observed in any sample. The results indicate that the pH, viscosity and appearance of the MSKE creams were stable and that the MSKE did not affect the physical properties tested. In particular, the total colour (ΔE) of the 1% MSKE and the base cream was not significantly different (p > 0.05) for any cycle (data not shown), while the (ΔE) of the 2 and 3% MSKE creams were significantly different (p ≤ 0.05).

Clinical skin irritation

No volunteer exposed to MSKE cream showed an adverse reaction. Skin exposed to the MSKE cream did not respond differently than skin exposed to the negative control (data not shown).

DISCUSSION

This study found that the Choke-Anan and Kaew MSKEs had higher extraction yields and TPC when ultrasonication was applied during extraction. A higher TPC of MSKE had previously been observed when an ultrasonic-assisted aqueous two phase extraction of mango seed kernel was used [20]. Ultrasonication was shown to disrupt the cell membrane and the cell wall structure, increasing solvent diffusion through the membrane, thus facilitating the release of the cell contents [21].

MSKEs from the two cultivars prepared by ultrasonication-assisted extraction showed greater antioxidant activity for all methods studied and the Choke-Anan MSKE had higher antioxidant activity than the Kaew MSKE. The results agree with reports of concurrent antioxidant activities indicated by DPPH and ABTS methods for Choke-Anan MSKE when compared to several other varieties of Thai mangoes [22]. Moreover, the Choke-Anan and Kaew MSKEs had the highest antioxidant properties of eleven mango varieties studied [23].

The results showed that tyrosinase inhibitory activity of the Kaew and Choke-Anan MSKEs were similar to previously reported values. Choke-Anan MSKE was previously shown to inhibit tyrosinase activity up to 1.58 fold higher than arbutin [25]. These results indicated that MSKE can be a good source of phytochemicals with tyrosinase inhibitory activity.

5-Lipoxygenase catalyses the conversion of polyunsaturated fatty acids to biologically active metabolites, which are active mediators in a variety of inflammation processes [26]. A previous study showed that the IC50 values for the 5-lipoxygenase inhibitory activity of eight plant extracts ranged from 27.4 ± 0.6 to 66.7 ± 0.6 µg / mL [27]. These 5-lipoxygenase inhibition activities imply that MSKE has a high potential for use as natural anti-inflammatory drug compared to other plant extracts reported in previous studies.

It is well understood that the degradation of hyaluronic acid by hyaluronidase can diminish amount of hyaluronic acid in the skin, which consequently becomes dry and wrinkled [28]. An extract of the bark of Terminaliaarjuna (250 µg / mL) and dried fruit rinds of Terminaliachebula (500 µg / mL) have been reported to have 90.4 ± 5.30 % and 89.65 ± 3.90 % hyaluronidase inhibition, respectively [29]. In the present study, the Kaew and Choke-Anan MSKEs respectively gave up to 80.35 % and 97.61 % inhibition at concentrations of 70 µg / mL. These results indicate that the MSKEs, and especially Choke-Anan MSKE, have a potential for cosmetic use as an anti-wrinkle agent.

The progression of diabetes mellitus can be controlled by inhibiting the absorption of dietary carbohydrates in the small intestine [30]. The α-glucosidase inhibitory activity of the Kaew and Choke-Anan MSKEs compared to acarbose showed IC50 values of 163.19 ± 2.3, 113.51 ± 5.8, and 104.42 ± 5.5 µg / mL, respectively. A methanol extract of mango seed from Nigeria has been reported to inhibit α-glucosidase with an IC50 of 340 µg / mL [31]. The results in this study revealed that MSKEs potently inhibit α-glucosidase activity.

Due to the higher bioactivity of the Choke-Anan MSKE, it was further evaluated for its potential use as a cosmetic ingredient. The results revealed that addition of MSKE at 1 % in a cosmetic cream caused no significant difference (p > 0.05) of the physicochemical
Table 4: pH, viscosity, phase separation and TPC of the MSKE creams and the base control from the freeze-thaw physical stability evaluation

<table>
<thead>
<tr>
<th>Sample</th>
<th>Parameter</th>
<th>Freeze-thaw cycle</th>
<th>Freeze-thaw cycle</th>
<th>Freeze-thaw cycle</th>
<th>Freeze-thaw cycle</th>
<th>Freeze-thaw cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Control base</td>
<td>pH(^{29})</td>
<td>5.74±0.02</td>
<td>5.67±0.06</td>
<td>5.63±0.06</td>
<td>5.43±0.38</td>
<td>5.70±0.10</td>
</tr>
<tr>
<td></td>
<td>Viscosity (cPs)(^{29})</td>
<td>1558.45±18.53</td>
<td>1554.04±14.73</td>
<td>1554.33±3.21</td>
<td>1556.22±4.04</td>
<td>1559.34±8.50</td>
</tr>
<tr>
<td></td>
<td>Phase separation</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>TPC (mg of GAE/ ml)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>1% MSKE</td>
<td>pH(^{29})</td>
<td>5.72±0.05</td>
<td>5.63±0.06</td>
<td>5.70±0.10</td>
<td>5.67±0.12</td>
<td>5.70±0.10</td>
</tr>
<tr>
<td></td>
<td>Viscosity (cPs)(^{29})</td>
<td>15540.43±7.61</td>
<td>15546.33±5.85</td>
<td>15549.66±1.1</td>
<td>15549.21±10.44</td>
<td>15551.06±10.14</td>
</tr>
<tr>
<td></td>
<td>Phase separation</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>TPC (mg of GAE/ ml)</td>
<td>1.64±0.32(^a)</td>
<td>1.65±0.40(^a)</td>
<td>1.66±0.33(^a)</td>
<td>1.62±0.33(^a)</td>
<td>1.48±0.15(^b)</td>
</tr>
<tr>
<td>2% MSKE</td>
<td>pH(^{29})</td>
<td>5.69±0.03</td>
<td>5.67±0.06</td>
<td>5.67±0.12</td>
<td>5.73±0.12</td>
<td>5.63±0.06</td>
</tr>
<tr>
<td></td>
<td>Viscosity (cPs)(^{29})</td>
<td>15543.56±11.15</td>
<td>15542.66±11.05</td>
<td>15549.66±2.50</td>
<td>15539.66±3.31</td>
<td>15547.33±12.42</td>
</tr>
<tr>
<td></td>
<td>Phase separation</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>TPC (mg of GAE/ ml)</td>
<td>3.32±0.06(^a)</td>
<td>3.34±0.14(^a)</td>
<td>3.27±0.21(^a)</td>
<td>3.23±0.17(^b)</td>
<td>2.84±0.03(^b)</td>
</tr>
<tr>
<td>3% MSKE</td>
<td>pH(^{29})</td>
<td>5.70±0.06</td>
<td>5.67±0.06</td>
<td>5.70±0.10</td>
<td>5.73±0.12</td>
<td>5.67±0.12</td>
</tr>
<tr>
<td></td>
<td>Viscosity (cPs)(^{29})</td>
<td>15527.45±5.80</td>
<td>15529.33±5.50</td>
<td>15539.33±8.32</td>
<td>15535.66±6.99</td>
<td>15539.04±5.19</td>
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<tr>
<td></td>
<td>Phase separation</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>TPC (mg of GAE/ ml)</td>
<td>4.92±0.12(^a)</td>
<td>4.90±0.21(^a)</td>
<td>4.89±0.14(^a)</td>
<td>4.86±0.21(^a)</td>
<td>4.23±0.13(^b)</td>
</tr>
</tbody>
</table>

Values are the mean ± SD (n = 3); values in the same row followed by different superscript letters are significantly different (p < 0.05). NS means non-significantly different, N means not observed, ND means not determined.
properties or the skin irritation test result of the cream. Moreover, adding MSKE to the cream contributed to the total polyphenol content of the product.

CONCLUSION

The findings of this study indicate that mango seed by-products can be used as a new ingredient source for the food, pharmaceutical and cosmetic industries. The results demonstrate that Kaew and Choke-Anan MSKEs exhibit antioxidant activities as well as inhibit tyrosinase, 5-lipoxygenase, hyaluronidase and α-glucosidase activities. A cosmetic cream containing 1% Choke-Anan MSKE is physically stable and appears safe for use on human skin.

DECLARATIONS

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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