Ultrasonic-assisted virgin coconut oil based extraction for maximizing polyphenol recovery and bioactivities of mangosteen peels

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Abstract Virgin coconut oil (VCO) and propylene glycol (PG) have received more attention as bio-based solvents for natural bioactive recovery in green extraction process. Here, maceration extraction and ultrasound-assisted extraction (UAE) of bioactive phenolics from mangosteen peel (MP) by VCO, PG and VCO-PG mixture were compared. The goal was to maximize the phenolic extraction and improve bioactivities. Based on a single-factor experiment for UAE with VCO, the optimal condition was sample to solvent ratio of 1:6.6 g/mL, amplitude of 55 μ m, and extraction time of 7 min, which yielded total phenolic content of 365 mg GAE/100 g. Regarding the extraction methods and bio-based solvents, UAE with mixed VCO-PG was not only provided greater polyphenol yield in a shorter time, but it also enhanced the bioactivities (radical scavenging, antibacterial, and antidiabetic activities) of the extract. Therefore, UAE can be potentially used in combination with bio-based solvents, especially mixed VCO-PG, for maximizing bioactive phenolic isolation from MP. This study provided an alternative method for production of bio-based oil solution from MP which can be directly used as a functional ingredient in emulsion based food, nutraceutical and cosmetic products.

Keywords Mangosteen peel · Virgin coconut oil · Propylene glycol · Ultrasound-assisted extraction · Phenolic compounds · In vitro bioactivities

Introduction

Phytochemicals in particular phenolic compounds have been evidenced so far for their health benefits. Mangosteen (*Garcinia mangostana* Linn.) is one of the important fruits in Thailand with the total production of approximately 351,760 tons in 2019 (Office of Agricultural Economics 2019). In the mangosteen processing, the desired arils are separated and the mangosteen peel (MP) are generally discarded as by-products. The MP composed of 60% or about two times of the edible portion (Fu et al. 2007). Recent studies suggested that MP extracts showed excellent biological activities e.g. antioxidant, antimicrobial and antidiabetes activities (Chen et al. 2018; Suttirak and Manurakchinakorn 2014; Adnyana et al. 2016). These activities are attributed to the types and quantities of phytochemicals in the MP. The MP has been reported as a rich source of a variety of phytochemicals and polyphenols such as phenolic acids, tannins, xanthones, anthocyanins and others (Suttirak and Manurakchinakorn 2014). Different methods have been reported to extract phenolic compounds from MP but organic solvents were intensively used (Sungpud et al. 2019, 2020). This was contributed to an environmental impact and the residual solvent in the extract was harmful to human health. Thus, the use of greener, bio-based solvents for extraction of chemical constituents from plant origins and agricultural waste is paid more attention. The alternative bio-based solvents such as coconut oil can be used to replace classical organic solvents (Pujirahayu et al. 2015). The coconut oil with high hydrophilicity can

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dissolve a variety of polar substances which are insoluble in conventional fats and oils (Krishna et al. 2010). In addition, the coconut oil is more oxidative stable compared to other vegetable oils because a few unsaturated fatty acids are presented (Krishna et al. 2010). The coconut oil also has high nutritive values and bioactivities with little or no adverse effect to human health (Krishna et al. 2010). Furthermore, the coconut oil based extract can be directly applied into numerous emulsion based foods and cosmetics without removal of solvent which are more convenient and cost effective to the industries.

According to our study on the phenolic recovery from MP, the coconut oil showed lower extraction power than propylene glycol (PG) (Sungpud et al. 2020). The extracting efficacy can be potentially improved by mixing coconut oil with PG and thus it was able to reduce the amount of PG used. Although, PG is defined as “generally regarded as safe” (GRAS) by the Food and Drug Administration (FDA), the use in food is limited due to its toxicity. World Health Organization (WHO) suggests a maximum oral dose of 25 mg/kg/day of PG and no more than 25 mg/dL in blood serum (Lim et al. 2014). Therefore, the reduction of PG in the extraction by replacing with coconut oil, a nontoxic natural solvent, is the possible strategy for reducing its content in food and drug (Sungpud et al. 2019). However, the polyphenol recovery and bioactivities of the extract obtained by mixed solvent were still lower than that done by pure PG even at the highest PG content employed (70% PG + 30% coconut oil) (Sungpud et al. 2019). To overcome this problem, an efficient extraction assisted method like ultrasound-assisted extraction (UAE) should be simultaneously used with the bio-based solvents to maximize the phenolic recovery and improve the bioactivity of MP extracts. The main advantages of the UAE are simple equipment and low overall cost compared to supercritical CO₂ extraction (Abad et al. 2010). The UAE has been widely used for the extraction of bioactive flavonoids and phenolic compounds from plant origins (Chemat et al. 2017). The results markedly varied among studies according to the operating conditions (Rocha et al. 2018; Bruno Bamba et al. 2018). Moreover, each plant material has its own unique properties in terms of chemical compositions and physical characteristics. Therefore, the UAE condition must be optimized to be suitable for plant material considered and the phenolic of interest.

Material and methods

Reagents and samples

Virgin coconut oil (VCO) was prepared by fermentation method. In brief, the coconut milk of mature coconut from

tall tree cultivar *Cocos nucifera* Linn was stored at $-18\text{ }^{\circ}\text{C}$ for 2 h. Thereafter, the upper cream layer was taken out. The coconut cream was subjected into glass bowl and incubated at $35\text{ }^{\circ}\text{C}$ for 24 h. The oil settling on the upper layer was poured out and filtered. Then, the oil was dried by using rotary evaporator (Buchi, Rotavapor R-124) at $50\text{ }^{\circ}\text{C}$, 100 mbar for 15 min. PG was purchased from Fisher Chemical (Thermo Fisher Scientific, USA). Other reagents were obtained from Sigma Aldrich (St. Louis, MO, USA). The pericarp of fresh dark reddish purple mature fruits of mangosteen (*Garcinia mangostana* Linn) harvested from an agroforestry farm in Nakhon Si Thammarat, Thailand was dried at $50\text{ }^{\circ}\text{C}$ using a tray dryer and ground using Cyclotec™ 1093 Sample Mill (Foss Tecator Co., Hillerød, Denmark). The fine powder was passed through 100 mm sieve meshes before used.

Full factorial design for UAE

Three-level and three-factor full factorial experiments were determined using Central Composite Design (CCD) to cover the ranges of 3 factors (combinations between the -1.682 , -1 , 0 , $+1$ and 1.682 levels); sonication time (X_1), MP powder to solvent ratio (X_2) and amplitude (X_3) as independent variables. Total phenolic content (TPC), total flavonoid content (TFC) and 2,2-diphenyl-1-picrylhydrazyl radical (DPPH•) scavenging activity were response of the design with 15 different experimental conditions. Table 1 summarizes the coded and real values of the independent variables used in the CCD. In this section, VCO was used as an extracting medium.

Ultrasound-assisted extractor (High Intensity Ultrasonic Processor, VCX 500 W, 20 kHz, USA) was used for the extraction of phenolic compounds from MP powder by VCO. For the experimental design, the extraction parameters were optimized using CCD followed by Response Surface Design (RSM). MP powder and solvents with different sample to solvent ratios (1:6.6, 1:10, 1:15, 1:20 and 1:23.5 w/v) were added in a 200 mL beaker and soaked with the probe maintaining a gap of one cm between probe (13 mm diameter cylindrical titanium alloy head) and the bottom of the beaker. Sample solutions were extracted at different amplitudes (38, 45, 55, 65 and 72 μm) and different extraction times (4, 5, 7, 9 and 10 min). Thereafter, the extracts were centrifuged at 5000 rpm for 10 min and the supernatant was collected. Each experiment was conducted in triplicates. The full factorial experimental design for each response of individual solvent was analyzed using CCD. The second order response surface model was implemented by considering R-square (R^2) value. The selected model was used to determine the coefficients of three independent variables.

Table 1 Total phenolic content (TPC), total flavonoid content (TFC) and DPPH[•] scavenging activity of mangosteen pericarp (MP) extract recovered by virgin coconut oil (VCO) at different ultrasonic-assisted extraction (UAE) conditions

Treat	Central composite design for UAE condition			Phenolic recovery and antioxidant activity		
	Extraction times (min)	Sample to solvent ratio (g/mL)	Amplitude of ultrasound (μm)	TPC (mg GAE/100 g)	TFC (mg RE/100 g)	DPPH [•] scavenging activity (mmol TE/100 g)
1	– 1, (5)	– 1, (1:10)	– 1, (45)	280.58 ± 9.53 ^C	51.80 ± 1.74 ^C	876.85 ± 62.86 ^B
2	– 1, (5)	– 1, (1:10)	1, (65)	290.05 ± 10.81 ^B	57.31 ± 4.68 ^B	822.43 ± 30.96 ^C
3	– 1, (5)	1, (1:20)	– 1, (45)	200.47 ± 17.03 ^D	28.07 ± 3.45 ^H	634.12 ± 46.51 ^E
4	– 1, (5)	1, (1:20)	1, (65)	189.49 ± 8.08 ^E	29.60 ± 2.07 ^{HG}	632.44 ± 19.53 ^E
5	1, (9)	– 1, (1:10)	– 1, (45)	283.24 ± 11.62 ^{BC}	50.93 ± 1.91 ^C	910.56 ± 30.48 ^B
6	1, (9)	– 1, (1:10)	1, (65)	284.75 ± 8.91 ^{BC}	58.86 ± 2.03 ^B	913.21 ± 36.62 ^B
7	1, (9)	1, (1:20)	– 1, (45)	178.12 ± 9.49 ^F	29.67 ± 1.75 ^{HG}	647.13 ± 27.69 ^E
8	1, (9)	1, (1:20)	1, (65)	178.12 ± 5.65 ^F	31.06 ± 2.23 ^G	645.44 ± 42.41 ^E
9	– 1.682, (4)	0, (1:15)	0, (55)	203.50 ± 6.42 ^C	33.58 ± 1.01 ^F	713.83 ± 20.29 ^D
10	+ 1.682, (10)	0, (1:15)	0, (55)	205.40 ± 9.53 ^D	36.17 ± 1.67 ^E	735.98 ± 55.41 ^D
11	0, (7)	– 1.682, (1:6.6)	0, (55)	360.32 ± 13.92 ^A	82.72 ± 4.87 ^A	1154.73 ± 49.51 ^A
12	0, (7)	+ 1.682, (1:23.5)	0, (55)	168.84 ± 9.51 ^G	24.72 ± 2.53 ^I	606.92 ± 44.00 ^E
13	0, (7)	0, (1:15)	– 1.682, (38)	205.21 ± 4.24 ^D	35.77 ± 1.52 ^E	704.92 ± 47.53 ^D
14	0, (7)	0, (1:15)	+ 1.682, (72)	201.61 ± 4.21 ^D	39.62 ± 1.36 ^D	699.14 ± 46.61 ^D
15	0, (7)	0, (1:15)	0, (55)	201.61 ± 8.40 ^D	36.52 ± 1.79 ^E	644.60 ± 40.96 ^E

Results are mean ± SD from 3 replications

Different letters in the same column are indicate significant difference at $p < 0.05$

GAE = gallic acid equivalent, RE = rutin equivalent, TE = Trolox equivalent

The predicted response (model) was calculated by a second-order polynomial equation. The response (Y) function is divided into linear component, quadratic and interaction components, as expressed in Eq. 1:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_{11} X_1^2 + \beta_{33} X_3^2 + \beta_{12} X_1 X_2 + \beta_{13} X_1 X_3 + \beta_{23} X_2 X_3 + \beta_{22} X_2^2 \quad (1)$$

where β_0 is the constant coefficient (intercept), β_i is the linear coefficient, β_{ii} is the quadratic coefficient, β_{ij} is the coefficient of interaction and X_i is the level of the independent variable (X_1 = extraction times (t), X_2 = MP powder to solvent ratio (M) and X_3 = amplitude of ultrasound (A)).

Effects of the extraction techniques and solvents

Dried MP powder was extracted by the conventional maceration extraction (ME) and UAE methods. The optimum UAE condition was used in this study. The corresponded extracts were measured for TPC, TFC and bioactivities including in vitro antioxidative, antibacterial and antidiabetic activities. For ME, the MP powder to solvent ratio was the same as optimized condition of UAE. In brief, MP powder (13.33 g) was mixed with 100 mL (ratio of 1:7.5 w/v) of individual solvent (VCO, PG and mixed VCO-PG at a ratio of 1:1, v/v) at 40 °C with a

magnetic stirrer in the dark for 24 h. From our previous study, the optimum ratio of VCO and PG was 1:1 (v/v) which can effectively recovery TPC, TFC, α -mangostin and γ -mangostin from MP (Sungpud et al. 2019). For UAE, MP powder and solvent were added into beaker and soaked with the probe as described above. The mixture was ultrasonically extracted at amplitude of 55 μ m for 7 min. Thereafter, the extracts were centrifuged at 5000 rpm for 10 min and the supernatant was collected. Each experiment was conducted in triplicates.

Separation of polyphenol fractions from MP extracts

The MP phenolic compounds were separated from MP extract according to the method of Nevin and Rajamohan (2006). A sample of individual MP extract dissolved in 5 mL hexane was mixed with the same volume of methanol/water (60:40, v/v) and vortexed for 2 min. Phase separation was done by centrifugation at 3500 rpm for 10 min and the hexane phase was re-extracted with 5 mL methanol/water (60:40, v/v) as the same manner. The pool fraction was analyzed for TPC, TFC, phenolic profile, antioxidative activity, antimicrobial activity and antidiabetic activity.

Determination of TPC, TFC and phenolic profiles

The method of Gutfinger (1981) and Meda et al. (2005) was used to estimate the TPC and TFC, respectively. The reverse phase high performance liquid chromatography (HPLC) system (Prominence-I LC-2030C 3D Plus, Shimadzu, Kyoto, Japan) coupling with A Shim-pack GIST C-18 column (4.6 × 150 mm, 5 µm size) and photodiode array detector were used to identify the phenolic constituents present in the MP extracts (Owen et al. 2000).

Determination of antioxidative activities

The method of Shimada et al. (1992) was used to evaluate the DPPH[•] scavenging activity in comparison with Trolox. The method of Mukhopadhyay et al. (2016) was used for hydrogen peroxide (H₂O₂) scavenging activity in comparison with ascorbic acid. The half-maximal effective concentration (EC₅₀; mg/mL) values were reported.

Determination of antibacterial activity

The minimal inhibitory concentration (MIC) of the MP extract against the food borne pathogens, *Escherichia coli* and the major acne bacteria, *Staphylococcus aureus* were determined by the agar dilution method (Topuz et al. 2016).

In vitro α-amylase and α-glucosidase inhibitory activities

The α-amylase inhibitory activity was determined as method described by Ademiluyi and Oboh (2013) and the α-glucosidase inhibitory activity was determined using the method of Jayasri et al. (2009). Pure acarbose (Sigma Aldrich) was used as a positive control.

Statistical analysis

All experiments were carried out in triplicates and results were expressed as mean values with standard deviation (± SD). Data from the optimization experiments were analyzed for the regression coefficients by stepwise linear regression. For effect of solvents and extraction methods, one-way analysis of variance (ANOVA) and Duncan's new multiple range test (DMRT) were carried out to determine the significant differences ($p < 0.05$) between means by using SPSS statistical software package (SPSS, version 20.0).

Results and discussion

Optimization of MP phenolics recovery by UAE with VCO

In the first step, the recovery of MP phenolics by UAE with VCO was optimized using response surface methodology (RSM). The results obtained from the 15 randomized experiments are displayed in Table 1. Among the experiments, the experiment 11 (MP powder to solvent ratio of 1:6.6, extraction times of 7 min and amplitude of 55 µm) showed the highest phenolic recovery, followed by the experiments 6, 2, 5 and 1, respectively. Similarly, the highest DPPH[•] scavenging activity was observed in the experiment 11 (1154.73 ± 49.51 mmol TE/100 g), followed by the experiments 6, 5, 1 and 2 (822–913 mmol TE/100 g).

Compared between experiment 1 and 3 with the same processing factors except for sample to solvent ratio (1:10 and 1:20, w/v for experiment 1 and 3, respectively), the TPC was 200.47 ± 17.03 and 280.58 ± 9.53 mg GAE/100 g, respectively. This result suggested that the higher the solvent ratio, the greater the extraction rate of phenolic compounds. An increasing solvent proportion reduces the energy needed to separate the molecules, thus, leading to the higher molecular mobility of solute molecules to the solvent (Rocha et al. 2018; Pompeu et al. 2009). When increasing the sonication time to 9 min (experiment 7), the amplitude to 65 µm (experiment 4) and both parameters (experiment 8), TPC (178–189 mg GAE/100 g) tended to decrease but TFC was slightly increased from 28 to 31 mg RE/100 g. No significant differences in DPPH[•] scavenging activities (634–645 mmol TE/100 g) were observed ($p > 0.05$) among the experiments 3, 4, 7 and 8, having the similar sample to solvent ratio with different extraction time and ultrasound amplitude. This indicated that the solvent ratio was an important parameter influencing the antioxidant activity of the MP extracts. With stronger ultrasonic amplitude and longer reaction time, the higher temperature can be generated. At higher temperature, the sonochemical effects due to collapse of cavitation bubbles may be reduced (Chemat et al. 2017). Some heat-sensitive phenolic compounds possibly underwent degradation, oxidation and polymerization (Dent et al. 2013), while flavonoid compounds were more heat tolerant. This result was in agreement with Bruno Bamba et al. (2018) who applied UAE for recovery of phenolic compounds from blueberry pomace. An increasing operation temperature in the ranges of 20–60 °C resulted in a decrease in TPC but increases in TFC and DPPH[•] scavenging activity. The differences in DPPH[•] scavenging activities between this study and previous report of Bruno Bamba et al. (2018)

were probably due to the different phenolic species presented in the samples. From the results, TPC played an important role in the free radical scavenging activity of MP extract. Also, the UAE with higher amplitude and longer time seemed to show negative effect on both TPC and free radical scavenging activity of MP extract.

Statistical models and response surface for TPC, TFC and DPPH[•] scavenging activity

Statistical models were validated by analysis of variance and F-test at a confidence level of 95% to build the response surface graphs as depicted in Fig. 1. If the insignificant lack-of-fit and the R^2 -values of the models are taken into account, the models are highly suitable to predict the TPC, TFC and DPPH[•] scavenging activity of MP extracts. The effects of the parameters M (MP powder to solvent ratio), t (extraction time) and A (amplitude) were further studied by determining the significance of the coefficients according to F-test, and evaluating the p-values. All three variables had 95% significant effect on TPC, TFC and DPPH[•] scavenging activity whereas the combined effects of two among three variables were significant except for the combined effect of amplitude and extraction time. The regression equation following the second order polynomial regression model was used to determine the effect of processing parameters on TPC, TFC and DPPH[•] scavenging activity and the significant regression terms are shown in Table 2. It can be observed in Eqs. 2–4 that the MP powder to solvent ratio (M) possessed a positive linear correlation with the TPC, TFC and DPPH[•] scavenging activity whereas extraction time (t) had a negative effect. On the other hand, the amplitude (A) did not significantly influence the TPC and DPPH[•] scavenging activity ($p > 0.05$).

Figure 1 illustrates the contour plot and response surface graphs of TPC from three different optimum regions. Three contour plots were obtained at different combination of variable parameters as (a) sample to solvent ratio and extraction time, (b) ultrasound amplitude and extraction time and (c) amplitude and sample to solvent ratio. The optimum regions were area which presented the highest amount of phenolic compounds. The optimum point is the middle point of the optimum ranges. The optimum condition was sample to solvent ratio of 1:6.6 (w/v), sonication time of 7 min and amplitude of 55 μ m, which was selected for further experiment. Linear regression equation (Eq. 2 in Table 2) was used to predict the TPC at optimum condition and compared with the experimental values. The predicted value (335 mg GAE/100 g) was closed to experimental value (365 mg GAE/100 g). From the result, the model used in this study was fitted well and highly correlated with the experimental data. This indicated the successful

optimization of the UAE parameters for maximizing polyphenol recovery.

Effects of extraction methods and bio-based solvents on the recovery of MP polyphenols

TPC and TFC

The TPC and TFC of MP extracts through ME and UAE using VCO, PG and its mixture as bio-based solvent are depicted in Fig. 2a, b, respectively. In the case of ME, PG extract showed the highest TPC (664 mg GAE/100 g) and TFC (107 mg RE/100 g) whereas VCO extract did the lowest. The moderate TPC and TFC were observed in mixed VCO-PG extract. Owing to the lipophilic and hydrophilic parts of VCO and PG, respectively, the mixture can extract more MP phenolic compounds than VCO alone but it was still less efficient than PG alone. For UAE, mixed VCO-PG was the most effective solvent for phenolic and flavonoid recovery, followed by PG and VCO, respectively. The TPC and TFC of the extract done by mixed VCO-PG was 718 mg GAE/100 g and 139 mg RE/100 g, respectively. The TPC of extract done by mixed VCO-PG was 1.96 and 1.24 folds higher than those done by VCO and PG, respectively whereas the TFC was 1.36 and 1.16 folds higher. This suggested the extraction efficiency improvement by UAE, particularly in the mixed solvent system. In comparison between ME and UAE, no significant differences in TPC were observed among VCO based extracts ($p > 0.05$), which was unexpected. Interestingly, the TPC of PG extracts were significantly decreased when the UAE was used as compared to ME. It was probably due to the degradation of some phenolic compounds induced by cavitation under PG environment during the UAE. This indicated a negative effect of this technique on MP phenolic recovery when PG was used as an extractant. However, roughly 1.2-fold increase in TPC of mixed VCO-PG based extract was noticeable by using UAE when compared to ME (Fig. 2a). On the other hand, the TFC of all extracts tended to increase by using UAE compared to ME (Fig. 2b) which was accounted for 1.13, 1.42 and 1.10 folds for VCO, mixed VCO-PG and PG based extracts, respectively, indicating the enhancement of flavonoid extraction by UAE. The flavonoids such as anthocyanin may tightly associate with other cell components in which the implement of UAE is capable of destroying the plant cell walls and thereby leaching out of such compounds. It should be noted that using the UAE together with mixed VCO-PG could typically improve the TPC and TFC recovery from MP and it was even better than pure PG, the most effective extractant for MP phenolic recovery from our preliminary study. From the

Fig. 1 The optimum region of contour plot and response surface methodology of total phenolic content (TPC) from mangosteen peel (MP) recovered by ultrasound-assisted extraction (UAE) with virgin coconut oil (VCO)

results, the highest TPC and TFC recovery from MP were observed in UAE with mixed VCO-PG. Overall, the extraction techniques and solvent types had a profound effect on the phenolic recovery from MP.

The phenolic profiles

Identification and quantification of phenolics and flavonoids in MP extracts were done using HPLC. Total 6

phenolic compounds were found in MP extracts (Table 3). It was clearly seen that phenolic profiles among the MP extracts varied considerably as a function of extraction technique and solvent type. Among ME, PG extract provided the highest (-) epicatechin, vanillic acid, α -mangostin and γ -mangostin, followed by mixed VCO-PG extract and VCO extract ($p < 0.05$), respectively. A comparable amount of rutin and xanthone were observed in extracts done by PG and mixed VCO-PG ($p > 0.05$). The ME and

Table 2 Second-order response surface model of total phenolic content (TPC), total flavonoid content (TFC) and DPPH[•] scavenging activity of mangosteen pericarp (MP) extract recovered by virgin coconut oil (VCO) at different ultrasonic-assisted extraction (UAE) conditions

Response variable (Y)	R	R ²	SE _{est}	Regression equation (predictor)
TPC (mg GAE/100 g)	0.975	0.950	± 11.15	$Y = 595.475 - 36.462M + 0.957M^2 - 0.388tM + 1.048t^2 - 10.192t$ (2)
TFC (mg RE/100 g)	0.974	0.948	± 3.12	$Y = 119.125 - 8.937M + 0.243M^2 + 0.005A^2 - 0.025MA + 0.021tM$ (3)
DPPH [•] scavenging (mmol TE/100 g)	0.942	0.888	± 48.18	$Y = 1921.175 - 111.306M + 3.074M^2 + 6.862t^2 - 70.251t - 1.231tM$ (4)

Sonication times (t), sample to solvent ratio (M) and amplitude of ultrasound (A)

R, Multiple correlation coefficient

R², Coefficient of determination

SE_{est}, Standard error of the estimate

GAE = gallic acid equivalent, RE = rutin equivalent, TE = Trolox equivalent

UAE with VCO could liberate 3 (xanthone, α -mangostin and γ -mangostin) out of 6 phenolic compounds compared to those with PG and mixed VCO-PG, indicating the less efficiency of this extracting medium in phenolic isolation from MP. With the same solvent used, UAE showed a similar phenolic pattern as ME but the content of some compounds increased or decreased differently. Alpha-mangostin content slightly increased by using UAE when compared to ME for VCO based extracts whereas the amount of the other two phenolic compounds was remained constant (Table 3). The obvious extraction improvement of three phenolic compounds including (-) epicatechin, vanillic acid and rutin was noticed in mixed VCO-PG extract done by UAE compared to ME while a slight reduction in γ -mangostin in UAE treatment was detected. No significant differences in α -mangostin were observed among UAE and ME extracts employed by mixed VCO-PG ($p > 0.05$). It was noted that additional unidentified peaks of unknown phenolic compounds were observed in the extract done by UAE with mixed VCO-PG (data not shown), suggesting the more released phenolic compounds from MP matrix. These additional phenolic substances may contribute to the superior bioactivities of this extract. Surprisingly, most of phenolic compounds in PG extract were significantly decreased by UAE when compared to ME except for xanthone (Table 3). The loss of major phenolic compounds in PG extract during ultrasonic extraction was not fully understood. However, the degradation of PG and some reaction between PG and certain phenolic compounds e.g. polymerization induced by cavitation and/or high temperature during UAE possibly occurred. PG is a sound-conducting medium (Mason 1999) and thus its structure can be altered during sonication due to cavitation effect. Suksamrarn et al. (2002) reported that MP contained a broad variety of phenolics such as xanthone (α -mangostin, γ -mangostin), anthocyanins, phenolic acids (protocatechuic acid, vanillic acid, syringic acid, *p*-coumaric acid, caffeic acid and ferulic acid), condensed

tannins, and others, which can participate in different chemical reactions. From the results, UAE with mixed VCO-PG can potentially leach out rutin, vanillic acid and (-) epicatechin to greater extents and it can extract additional phenolics from MP with a shorter extraction time compared to ME.

Effects of extraction method and bio-based solvent on bioactivities of MP extracts

Antioxidant activity

Several studies reported that MP extracts had excellent antioxidant effects (Chen et al. 2018; Suttirak and Manurakchinakorn 2014) because of their polyphenols acting as primary antioxidant or free radical terminator. The antioxidant activities of MP extracts as evaluated by EC₅₀ values of DPPH[•] and H₂O₂ scavenging activities are shown in Fig. 2c, d, respectively. The lower the EC₅₀ value indicated the higher the antioxidant activity. According to ME, the highest DPPH[•] and H₂O₂ scavenging activities were found in PG extract, followed by mixed VCO-PG extract and VCO extract, respectively. For UAE, the highest DPPH[•] and H₂O₂ scavenging activities were noticed in mixed VCO-PG extract, followed by PG extract and VCO extract, respectively, which was highly correlated with the TPC and TFC of those extracts (Fig. 2a, b). Compared among ME and UAE, no significant difference in DPPH[•] scavenging activity was observed in PG extract with ME and mixed VCO-PG extract with UAE ($p > 0.05$). So, UAE can improve the radical scavenging activity of mixed VCO-PG extract to show the same activity of the extract with PG, a powerful extractant for MP extraction. Surprisingly, the PG extract with UAE had a lower DPPH[•] scavenging activity when compared to that with ME. It was corresponded to a reduction in TPC in this treatment (Fig. 2a). This phenomenon was not clearly

Fig. 2 Effect of extraction method on total phenolic content (TPC) (a), total flavonoid content (TFC) (b), the EC₅₀ of DPPH• scavenging activity (c), the EC₅₀ of H₂O₂ scavenging activity (d), the EC₅₀ of α-amylase inhibition activity (e) and the EC₅₀ of α-glucosidase inhibition activity (f) bioactivity of mangosteen pericarp (MP) extracts. Different letters on the bars indicate significant differences ($p < 0.05$). VCO = virgin coconut oil, PG = propylene glycol, ME = maceration extraction and UAE = ultrasound-assisted extraction. Total phenolic

understood but the same results were obtained after several replications. The side reaction between phenolic compounds and PG during sonication possibly occurred led to

content and total flavonoid content of VCO was 3.20 ± 0.40 mg GAE/100 g and 0.10 ± 0.01 mg RE/100 g, respectively. The EC₅₀ value for DPPH• scavenging activity of Trolox was $22.86 \mu\text{g/mL}$. The EC₅₀ value for H₂O₂ scavenging activity of ascorbic acid was $162.2 \mu\text{g/mL}$. The EC₅₀ value for α-amylase inhibitory activity of acarbose was $5.84 \mu\text{g/mL}$. The EC₅₀ value for α-glucosidase inhibitory activity of acarbose was $667 \mu\text{g/mL}$.

the loss of certain phenolic compounds with decreased antioxidant activity. Comparable DPPH• scavenging activities between VCO extracts done by ME and UAE

Table 3 The phenolic profiles of crude mangosteen peel (MP) extracts done by different solvents and extraction methods

Polyphenol content (mg/100 g)	VCO		Mixed VCO and PG (1:1)		PG	
	ME	UAE	ME	UAE*	ME	UAE
Gallic acid	ND	ND	ND	ND	ND	ND
(+) Catechin	ND	ND	ND	ND	ND	ND
Trans-ferullic acid	ND	ND	ND	ND	ND	ND
(-) Epicatechin	ND	ND	4.85 ± 0.12a	6.48 ± 0.10b	5.37 ± 0.55b	3.31 ± 0.09a
Vanillic acid	ND	ND	11.91 ± 0.27a	17.36 ± 0.55b	13.14 ± 1.52b	7.28 ± 0.77a
Rutin	ND	ND	10.38 ± 1.02a	19.64 ± 2.66b	9.65 ± 2.25b	6.20 ± 0.00a
Xanthone	10.30 ± 0.03a	10.09 ± 0.08a	9.57 ± 0.17b	8.67 ± 0.54a	9.62 ± 0.10a	9.57 ± 0.10a
γ-mangostin	197.61 ± 2.79a	201.48 ± 3.97a	183.38 ± 7.73a	169.83 ± 2.90b	225.67 ± 4.37b	204.70 ± 0.59a
α-mangostin	359.44 ± 4.70b	339.92 ± 4.89a	454.13 ± 14.73a	431.19 ± 1.47a	626.98 ± 13.05b	591.04 ± 1.19a

The values are mean ± standard deviation

Different letters in the same column are indicate significant difference at $p < 0.05$

ME and UAE present maceration (24 h) and ultrasonic-assisted extraction (7 min)

ND = not detected

*Unidentified peaks were observed under this condition

VCO = virgin coconut oil, PG = propylene glycol

were obtained. This was correlated well with their TPC and TFC (Fig. 2a, b). Tjahjani et al. (2014) reported that α-mangostin, non-polar substance, had relative poorly DPPH• scavenging activity. The mixed VCO-PG extract made by UAE had lower content of α-mangostin than PG extract (Table 3) but it showed the highest inhibitory activity against the DPPH•. This effect may be attributed to the highest TFC (Fig. 2b) such as rutin which presented more content in mixed VCO-PG extract with UAE. For H₂O₂ scavenging activity, similar results were found, except that the greater H₂O₂ scavenging activity was detected in VCO extract made by UAE compared to ME. This was due to the fact that different types of phenolic compounds extracted had different antioxidant activities. The efficiency of phenolic compounds as anti-radicals and antioxidants is diverse and depends on many factors, such as the number of hydroxyl groups bonded to the aromatic ring, the site of bonding and mutual position of hydroxyls in the aromatic ring (Halliwell and Gutteridge 1999). Taken together, the UAE had a synergistic effect in MP polyphenol extraction and resulted in high antioxidant activities when mixed VCO-PG was used as an extractant. Also, antagonistic effects on TPC recovery and antioxidant activities were highlighted when UAE with PG was applied. This was out of our expectation and the further research should be carried out.

In vitro antidiabetic activity

To reduce blood glucose levels as close as the normal is challenging goal in the management of patients with diabetes mellitus (DM). Inhibition of carbohydrate-

hydrolyzing enzymes, such as α-amylase and α-glucosidase is one of approaches to therapeutic DM (Bhandari et al. 2008). Nowadays, polyphenol is reported as an alternative approach for therapeutic DM.

Figure 2e shows the EC₅₀ values of α-amylase inhibitory activity of MP extracts from different solvents and extraction methods. Regarding to ME, the highest α-amylase inhibitory activity (EC₅₀ = 2.8 mg/mL) was observed in PG extract while the lowest activity (EC₅₀ = 16 mg/mL) was found in VCO extract. The moderate α-amylase inhibitory activity was found in mixed VCO-PG extract. These were in line with the TPC and TFC of those extracts (Fig. 2a, b). For UAE made extracts, the highest α-amylase inhibitory activity was found in PG extract (EC₅₀ = 3.0 mg/mL) and mixed VCO-PG extract (EC₅₀ = 3.1 mg/mL). This suggested the improved efficiency of UAE to extract the anti-amylase compounds from MP powder, particularly, when the mixed solvent was used. The lowest α-amylase inhibitory activity was noticed in VCO extract (EC₅₀ = 13.9 mg/mL) as expected. Regarding the extraction method, VCO extract and mixed solvent extract made by UAE had higher α-amylase inhibitory activity than those done by ME ($p < 0.05$). No significant difference in such activity was observed among PG based extracts made by ME and UAE. PG alone may efficiently isolate the anti-enzyme substances from MP. This result was different with the radical scavenging activity in which the lower radical scavenging activity was found in PG extract made by UAE compared to ME (Fig. 2b, c). It should be noted that the α-amylase inhibitory activity of all MP extracts were less effective than acarbose drug (EC₅₀ = 5.84 μg/mL). Acarbose is a noninsulinotropic oral

antidiabetic drug that is used to control blood glucose levels in people type 2 diabetes in conjunction with diet, exercise, and other diabetes drugs (Rosak and Mertes 2012). Typically, the anti-type II diabetes property of polyphenols is type and dose dependent. Bhandari et al. (2008) reported that two active compounds, (–)-3-O-galloylepicatechin and (–)-3-O-galloylcatechin, of *Bergenia ciliata* were responsible for the strong inhibition of porcine pancreatic α -amylase and rat intestinal maltase activity in a dose dependent manner. In addition, Tachibana (2009) stated that the (–)-epigallocatechin-3-O-gallate (EGCG) has been recognized as the most beneficial component for anti-diabetes among the four other catechins isolated from green tea. The starch digestive enzymes inhibitory efficiency is correlated with the number of hydroxyl groups of phenolic compounds (Tadera et al. 2006). Among the major 7 phenolic compounds found in MP extracts, rutin (10 –OH groups) and (–) epicatechin (5 –OH groups) may exhibit a greater α -amylase inhibitory activity than the others. This was in agreement with phenolic profile of mixed VCO-PG extract made by UAE, which had higher contents of rutin and (–) epicatechin than those done by ME (Table 3). However, non-significant changes in rutin and (–) epicatechin were noticed among VCO and PG extracts made by ME and UAE (Table 3), resulting in the negligible changes in α -amylase inactivation of those extracts (Fig. 2e). From the results, the α -amylase inhibitory activity of MP extracts was not only dependent on the amount of phenolic compounds but it also corresponded to the phenolic profiles and its individual contents.

For in vitro α -glucosidase inhibitory activity of ME made extracts, the highest activity was obtained in PG extract ($p < 0.05$), followed by mixed VCO-PG extract and VCO extract, respectively (Fig. 2f). The highest α -glucosidase inhibitory activity of UAE made extracts was found in mixed VCO-PG extract ($p < 0.05$), followed by PG extract and VCO extract, respectively. The extraction of MP using VCO provided the lowest TPC, TFC, and bioactivities than other media. Ultrasonic approach has been used during extraction but the extraction efficacy was not improved, indicating the more importance of the extraction media than the extraction technique. However, mixed VCO-PG can effectively liberate more bioactive compounds from MP in both classical extraction and UAE methods, resulting in the higher α -glucosidase inhibitory activity than VCO extract and PG extract. Regarding to the extraction technique, VCO extract and mixed VCO-PG extract made by UAE had higher α -glucosidase inhibition than those done by ME for 1.10 and 1.70 folds, respectively. This indicated the enhancement efficacy of UAE for isolation of α -glucosidase inhibitory compounds from MP (Fig. 2f). No significant differences in α -glucosidase inhibitory activity among PG extracts made by ME and UAE

were detected ($p > 0.05$) (Fig. 2f). Based on the phenolic profiles and contents in Table 3, mixed VCO-PG extract made by UAE had higher amounts of rutin and (–) epicatechin than the other extracts, which may contribute to the superior α -glucosidase inhibitory activity. Wang et al. (2010) reported that flavonoids such as rutin, showed potential inhibition against α -glucosidase. Interestingly, all MP extracts had higher potential to inhibit α -glucosidase than that of clinically acarbose drug ($EC_{50} = 667 \mu\text{g/mL}$) for 2–4 folds.

Antibacterial activity

The inhibitory effect of MP extracts done by different extractants and extraction methods as evaluated by MIC value on gram-negative bacteria, *E. coli* and gram-positive bacteria, *S. aureus* are shown in Table 4. The results showed that the types of solvents and extraction methods were mutually beneficial for promoting anti-microbial activity. Among ME made extracts, mixed VCO-PG and PG extracts had a comparable inhibitory effect against *E. coli* (MIC = 1563 $\mu\text{g/mL}$), which was higher than VCO extract (MIC = 3125 $\mu\text{g/mL}$). For *S. aureus*, VCO and mixed VCO-PG extracts provided lower MIC (1563 $\mu\text{g/mL}$) than PG extract (MIC = 3125 $\mu\text{g/mL}$). The results indicated that the antimicrobial activity of MP extracts was varied among microbial species and it might be influenced by the amount of polyphenols and their constituents in the MP extracts. Li and Xu (2008) mentioned that the antimicrobial activity of MP extract is dependent on the polyphenol type such as phenolic acids, flavonoids, anthocyanins and tannins. Moreover, the antimicrobial activity is substantially influenced by the position and number of hydroxyl groups because these groups may interact with the bacterial cell membrane, disrupt its structure and lead to cellular components leakage (Xue et al. 2013).

The highest antimicrobial activities against both species were observed in mixed VCO-PG extract made by UAE, which exhibited the lowest MIC of 781 $\mu\text{g/mL}$ (Table 4). However, VCO extract and PG extract showed conversely in inhibition of *E. coli* and *S. aureus* where the less *E. coli* inhibition observed in VCO extract (MIC = 3125 $\mu\text{g/mL}$) compared to PG extract (MIC = 1563 $\mu\text{g/mL}$). On the other hand, the higher *S. aureus* inhibition was detected in VCO extract (MIC = 1563 $\mu\text{g/mL}$) than PG extract (MIC = 3125 $\mu\text{g/mL}$). The difference was might be contributed to the ability of antimicrobial compounds from various MP extracts to pass through the microbial cell membrane. The results suggested the importance of type and content of polyphenol and the microbial species on the degree of microbial inactivation.

Table 4 Minimum inhibitory concentration (MIC) against food borne pathogens of mangosteen peel (MP) extracts done by different solvents and extraction methods

Extraction methods	Solvents	MIC values against the pathogen (µg/mL)	
		<i>E. coli</i>	<i>S. aureus</i>
ME	VCO	3125	1563
	Mixed VCO and PG	1563	1563
	PG	1563	3125
UAE	VCO	3125	1563
	Mixed VCO and PG	781	781
	PG	1563	3125

ME and UAE present maceration (24 h) and ultrasonic-assisted extraction (7 min)

MIC values against *E. coli* and *S. aureus* by ampicillin were 4 µg/mL

As compared between ME and UAE methods, no significant differences in *E. coli* and *S. aureus* inhibition of the VCO or PG extracts were observed ($p > 0.05$). The results suggested that UAE had no effect on the liberation of the antimicrobial agents from MP using VCO and PG (Table 4). The UAE combined with mixed VCO-PG potentially increased the inactivation against both *E. coli* and *S. aureus* by 2 folds compared to ME method. This suggested the synergistic effect of UAE and mixed solvent to isolate the antimicrobial agents from MP. In this study, mixed VCO-PG extract made by UAE method presented the higher TPC and TFC (Fig. 1a, b) and had the greatest ability to inhibit the growth of *E. coli* and *S. aureus*. This was possibly due to the synergistic effect of natural lauric acid and monolaurin found in the original VCO together with polyphenols recovered from MP (Loung et al. 2014).

Conclusion

The RSM was successfully applied to optimize UAE parameters including amplitude, sonication time and solid to solvent ratio for maximizing bioactive phenolic compounds extraction from MP. The UAE was confirmed to be more efficient process to enhance the bioactive compounds isolation from MP when using together with mixed VCO-PG. This method consumed a shorter period of extraction time than the ME and the extracts contained potential antioxidant, antimicrobials and anti-diabetics substances. This study demonstrated an effective method by combining the bio-based solvent with the ultrasound technique to enhance the recovery of bioactive compounds from agricultural waste with superior amount and bioactivities. This method can be used for producing polyphenol bio-oils based agent in the desired function for functional food, agrochemicals, cosmetics, and pharmaceuticals industries.

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Compliance with ethical standards

Conflict of interest Authors would like to declare that they do not have any conflict of interest.

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