Applied Science and Engineering Progress, Vol. 14, No. 2, pp. 156–164, 2021

Research Article

Application of Statistical Solvent Mixture Design in Optimizing the Solid-Liquid Extraction of Phenolic Compounds from Mango Seed Kernels

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Received: 9 November 2020; Revised: 21 December 2020; Accepted: 15 January 2021; Published online: 1 February 2021

Abstract
Mango seed kernel (MSK) is a waste material of the mango processing industry and is reported to significantly contain phenolic compounds with anti-oxidative properties. In this work, these compounds are isolated via solid-liquid extraction (SLE) in which solvent mixture design approach was used to evaluate the optimal quaternary solvent ratio in relation to the phenolics content of extracts from MSK. The quaternary solvent is composed of ethanol (E), methanol (M), acetone (A), and water (W). The extraction process was implemented at 40°C for 60 minutes with the ratio between solid and solvent at 1:25. Response surface methodology coupled with simplex lattice design was developed to evaluate the optimal solvent system and their interaction effects on the phenolic compounds content. The linear, two-way, and three-way interaction, except for methanol-acetone-water system, resulted in positive effects on the phenolic compounds content. The response model shows that a quaternary mixture with approximately 3:3:3:1 E:M:A:W ratio provided the highest phenolic content. A Scheffé cubic model sufficiently described the extraction process. The results of this study showed that the extraction of phenolic compounds in MSK via SLE using a mixture of solvents is possible. Higher extraction efficiencies can be achieved by optimizing the SLE process, and the optimum conditions can be applied to produce phenolic extracts with positive antioxidant activity.

Keywords: Quaternary solvent, Solid-liquid extraction, Response surface methodology, Mango seed kernel, Phenolic compounds content

1 Introduction

Mango is one of the important fruits in the Philippines in terms of volume and value. In 2019, the archipelago was able to yield over 700,000 metric tons of the fruit valued at approximately PhP20M [1]. Aside from direct consumption, mangoes are being processed to produce several commercial products in the market. The mango and mango processing industry has recently seen an increase in demand for these products [2]. However, this increase has also led to a consequential increase of by-products, in terms of volume, since only the fruit pulp is utilized. These by-products, namely the seeds and peels, amount to over 350,000 MT based on 2017 production in the country [1], [3]. The generation of these by-products has become a problem since they are merely thrown in dumpsites and landfills, posing unfavorable health and environmental risks [4], [5].

Mango peels and seeds have shown potential applications in the food and pharmaceutical sectors. The mango seed kernel (MSK), a component of the seed, is reported to contain significant amounts of carbohydrates and protein. It is also known that MSK can be an interesting feedstock of various commercial

Please cite this article as: A. A. Cabajar, F. D. C. Siacor, K. J. A. Lim, C. F. Y. Lobarbio, and E. B. Taboada, "Application of statistical solvent mixture design in optimizing the solid-liquid extraction of phenolic compounds from mango seed kernels," *Applied Science and Engineering Progress*, vol. 14, no. 2, pp. 156–164, Apr.–Jun. 2021, doi: 10.14416/j.asep.2021.02.001.

products, notably phenolic compounds [6], [7]. The demand for phenolic compounds has increased recently because of their potential human health benefits such as the possible prevention of cardiovascular and neurodegenerative diseases, cancer, and diabetes mellitus [8]. From an economic perspective, the market of phenolic compounds globally already stands at over US $800 million in 2018 from a value of more than US $500 million in 2011. The estimated annual growth rate of the market is about 7% in 2019 and this will remain constant up to 2025 [9].

To isolate phenolic compounds from MSK, the conventional solid-liquid extraction (SLE) technique is commonly employed. This mass transfer phenomenon depends on several factors, particularly extraction temperature and time, as well as feedstock-to-solvent ratio and the nature of solvent or solvent mixture [10]. Among these factors, the type of solvent to be used during extraction is of critical consideration since phenolic compounds must be highly soluble to the solvent for optimum yield. Due to a plethora of phenolic compounds with differing polarities present in plant material, a certain solvent system may not hold for different raw materials and thus proper solvent selection must be done [11].

Polar solvents such as methanol, ethanol, and acetone and their combinations in aqueous mixtures are commonly used, resulting in positive results in terms of extraction yield. Methanol was observed to excellently extract lower molecular weight phenolic compounds such as acids, anthocyanins, and flavanal monomers and oligomers. The use of acetone as a solvent successfully extracted high molecular flavonols [12] while the ethanol-water solvent system extracted phenolic acids and flavanol dimers [13]. Ethanol and acetone were also observed as optimal solvents for the extraction of phenolic compounds from barley flour [14]. Furthermore, the use of a quaternary solvent system comprising methanol, ethanol, acetone, and water led to an exhaustive extraction of phenolic compounds from *Trichilia catigua* barks [15].

A study by Dorta *et al.* [16] revealed a selection of appropriate solvents for the extraction of the phenolic compounds from MSK through SLE. The consideration of using a quaternary ethanol-methanol-acetone-water mixture was not highlighted. Hence, no formal investigation regarding the use of such a solvent system during the SLE of phenolic compounds from MSK was done yet. The major objective of this study then was to evaluate, through response surface methodology, the optimal quaternary solvent ratio consisting of ethanol, methanol, acetone, and water in relation to the phenolic compounds content of extracts from MSK during SLE.

2 Materials and Methods

2.1 *Materials*

The reagent-grade solvents used in this study, namely: ethanol, methanol, and acetone procured from Sigma-Aldrich Pte. Ltd. (Singapore). The chemicals used in the analysis of total phenolic content, specifically Folin's phenol reagent, sodium carbonate, and gallic acid were also reagent-grade and purchased from the same manufacturer. Green Enviro Management Systems (GEMS) Inc., located in Lapu-lapu City, Cebu, Philippines provided the mango seeds used in this study.

2.2 *Mango seed kernel preparation*

Mango seeds were rinsed with water to remove impurities and then dried at ~70°C to brittleness. After cracking the seeds open, MSK was recovered within the husks. MSK was further dried in a convection oven (Memmert GmbH, Germany) at 60°C until the moisture content is ≤10%. Subsequently, the dried MSK was ground to produce MSK powders (MSKP) with ≤1 mm powder size. MSKP was stored in polyethylene bags and at 4°C until further use. The characteristics of MSKP in terms of moisture, lipid, extractives, and total phenolic contents were also determined.

2.3 *Phenolic compounds extraction from mango seed kernels*

A single batch maceration procedure was adopted during phenolic compounds extraction from MSKP. About 1 g of MSKP was mixed with 25 mL solvent system in a 50 mL extraction tube and was agitated in an orbital incubator shaker (SI-64, Hanyang Scientific Equipment Co., Ltd, Korea) at 230 rpm and a temperature of 40°C for 60 minutes. The tube was sealed hermetically to prevent oxidation, and extraction was performed in total darkness. After extraction, the

mixture was filtered by vacuum to dryness and the extract was transferred in a 50 mL volumetric flask. The extract was diluted to mark using the solvent system. The resulting extract sample was then stored at –20°C for further analyses. The sample was used no later than 72 h.

2.4 *Experimental design and statistical analysis*

A simplex lattice mixture design with axial and center runs was used to precisely describe the response surface and consequently optimize the proportions of the components of the methanol-ethanol-acetone-water solvent system. This design is generally represented by Equation (1), where x_i is the composition of the ith component and q is the number of components.

$$\sum_{i=1}^{q} x_i = 1;\ 0 \le x_i \le 1 \tag{1}$$

This design was used due to its flexibility in the regression of data in quadratic and cubic models. The response used to assess solvent desirability was the corrected total phenolic content of the extracts which considers interferences from major reducing compounds such as reducing sugars and proteins. The design was unconstrained, and replication was done at the center of the design space which would serve as points for the measurement of lack-of-fit and pure error for a total of 20 experimental runs. The experimental design was orthogonally blocked using Nguyen's blocking algorithm and randomized into two experimental sets with 10 experimental runs for each set. The obtained response data were fitted in a Scheffé form of a special cubic model [17] as illustrated in Equation (2), where β_i are the regression coefficients, $E(y)$ is the response, and x_q are the compositions of q components. The degree of the model was reduced when significant lack-of-fit was detected to precisely estimate the response surface. The resulting simplex lattice augmented mixture design is shown in Table 1 with a total of 17 runs.

$$E(y) = \sum_{i=1}^{q} \beta_i x_i + \sum \sum_{i<j=2}^{q} \beta_{ij} x_i x_j + \sum \sum \sum_{i<j=2}^{q} \beta_{ijk} x_i x_j x_k \tag{2}$$

The significance of solvent composition effects was elucidated by performing Fisher analysis of variance (ANOVA) at a significance level of $\alpha = 0.05$. The statistical software R Project for Statistical Computing 3.3.2 with its base packages and packages "qualityTools" for mixture design construction and "AlgDesign" for optimal blocking was used for the design of experiments and statistical analysis.

Table 1: Simplex lattice augmented mixture design of the quaternary solvent system involving methanol(1), ethanol(2), acetone(3), and water(4)

Run Order	Standard Order	Type	x_1	x_2	x_3	x_4
1	6	2-blend	0	0	0.5	0.5
2	3	center	0.25	0.25	0.25	0.25
3	16	2-blend	0.5	0.5	0	0
4	5	1-blend	0	1	0	0
5	4	2-blend	0.5	0	0	0.5
6	7	1-blend	1	0	0	0
7	13	2-blend	0	0.5	0.5	0
8	12	axial	0.125	0.125	0.125	0.625
9	1	center	0.25	0.25	0.25	0.25
10	14	axial	0.125	0.125	0.625	0.125
11	9	axial	0.125	0.625	0.125	0.125
12	15	1-blend	0	0	1	0
13	2	2-blend	0	0.5	0	0.5
14	17	1-blend	0	0	0	1
15	11	center	0.25	0.25	0.25	0.25
16	10	2-blend	0.5	0	0.5	0
17	8	axial	0.625	0.125	0.125	0.125

2.5 *Analytical methods*

The total phenolic content (TPC) of extracts was quantified using a colorimetric method based on Folin-Ciocalteau reaction [18]. A portion of the sample (about 1.0 mL of the supernatant solution after 20-fold dilution) was added with 6 mL distilled water and mixed well. After adding Folin-Ciocalteau phenol reagent (0.50 mL), the solution was left to stand for 5 mins. Then, 1.5 mL of 20% w/v sodium carbonate solution was added and the solution was diluted to 10 mL using distilled water. The resulting mixture was allowed to react for 120 mins at 30°C. The absorbance of the colored mixture at a wavelength equal to 765 nm was read using a Spectroquant Pharo 100 spectrophotometer (Merck, United States). Gallic acid was used as a standard and a calibration curve was constructed. Results were expressed as % phenolic content (mg g^{-1}).

The %moisture of MSKP was determined based on AOAC standard method [19], while the %extractives and %lipid were obtained through Soxhlet extraction following the method developed by Sluitzer *et al.* [20] for National Renewable Energy Laboratory.

3 Results and Discussion

3.1 *Composition of mango seed kernel powders*

Table 2 presents the chemical composition of MSKP. The %moisture of MSKP is within acceptable limits for handling and storage. The %lipid of MSKP is relatively low compared to other feedstock of similar nature. In extracting phenolic compounds, it is desirable to utilize a feedstock with lower lipid concentration since lipids can possibly impede the process of extraction [21].

Table 2: Chemical composition of MSKP in dry-basis

Components	Percentage/Amount
Moisture (%)	6.47 ± 0.06
Water-soluble extractives (%)	26.33 ± 1.26
Ethanol-soluble extractives (%)	20.12 ± 0.72
Total phenolic compounds (mg/g)	78.24 ± 0.64
Lipids (%)	7.98 ± 0.12

The %water-soluble (WSE) and %ethanol-soluble (ESE) extractives signify the constituents outside the lignocellulosic structure of MSKP. WSE's are made up of structural sugars, nitrogenous compounds, and other inorganic compounds, while ESE's are composed of chlorophyll and waxes, as well as secondary compounds soluble in ethanol [20]. It can be noted from Table 2 that %WSE is higher than %ESE, with >26% difference. In most cases, %WSE is larger compared to %ESE. WSE and ESE are also obtained to initially assess the maximum amount of extractable phenolic compounds in MSKP, which is about 78 mg g^{-1} as presented in Table 2.

3.2 *Statistical analysis of the response model*

Correlation of the response variable (TPC of the extract samples) with reference to solvent composition was performed by fitting the responses in a special cubic model shown in Equation (2). The process of fitting the responses is the method of least squares which permits the estimation of model coefficients. The outcomes of the fitting after ANOVA are presented in Table 3. It is shown that the linear, two-way, and three-way interaction effects were significant at a confidence level of 95%. Hence, the preceding effects were collectively considered to build a statistical model describing the extraction process with enhanced estimation efficiencies. Table 3 also presents the values of the regression coefficients of Equation (2) and their corresponding statistical indicators. An important statistical indicator is the standard error (SE), which determines the precision of model estimation of the regression coefficients. A relatively small value of SE implies that the estimation has greater precision [22]. Based on a comparison of SE's in Table 3, the reduced cubic model in Equation (2) adequately estimated the linear (x_1, x_2, x_3, and x_4) effects with superior precision than the two-way and three-way effects.

On the other hand, the t-statistics ratio signifies the divergence of an approximated parameter from its assumed hypothetical value. The greater the value of the parameter, the more likely that there is indeed a significant difference [23]. It can be noted from Table 3 then that the linear effects, as well as the two-way effects of ethanol-water and acetone-water, have significant differences based on the t-statistics.

The results presented in Table 3 revealed that only the three-way interaction effect of methanol (x_1), acetone (x_3), and water (x_4) exhibited a negative effect on the total phenolic content of MSK extracts, while the rest of the interaction effects imparted positive

effects to the response variable. This is based on the values of each regression coefficient. Moreover, every interaction effect is dependent on one another because the two-way and three-way interaction effects were significant [24].

The coefficient values revealed in Table 3 were substituted to the variables in Equation (2) to obtain a decoded statistical response model shown in Equation (3). As can be noted in Table 3, the difference between R^2 and the adjusted R^2 is 0.74%, which is a manifestation that the statistical model imparted a better fit of the responses [25], [26]. Furthermore, the interaction effects explain 99.84% – 99.1% of the variability in TPC of extract samples based on the R^2 and the adjusted-R^2 values.

The graph of the response surface is represented by a ternary plot shown in Figure 1, where TPC (as the response variable) is plotted as a function of methanol, ethanol, and acetone with water as the balance component in the quaternary solvent mixture. Each region is indicated by the predicted TPC of the extracts. The region having the lightest shade represents the optimal solvent design, which is the range of quaternary solvent proportions that would result in higher total phenolic content. A closer examination of the plot reveals that a quaternary mixture with approximately 30% ethanol, 30% methanol, 30% acetone, and 10% water (3:3:3:1 ratio) provided the optimum TPC of the extracts. The findings of this study are closely following Lonni *et al.* [15] in which quaternary solvents mixtures composed of 1:1:1:1 water:methanol:acetone:ethanol solvents were found to provide the highest polyphenol content of crude extracts during the extraction of bioactive compounds from Trichilia catigua. However, the interaction of methanol-ethanol was found to contribute negatively to the phenolic content in the crude extract.

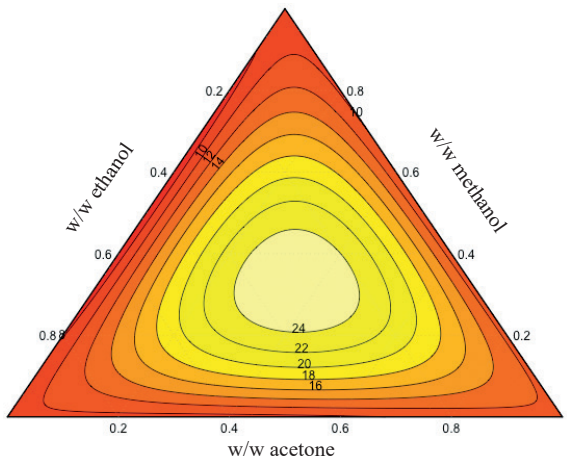

Figure 1: Ternary plot showing the total phenolic compounds content of MSK extracts as a function of ethanol, methanol, acetone, and water proportions at a temperature and time of 40°C and 60 minutes, respectively. Regions are indicated by the total phenolic content (%) of the extracts.

Table 3: Coefficients of the statistical response model describing the extraction of phenolic compounds from mango seed kernels with statistical indicators (1-methanol, 2-ethanol, 3-acetone, and 4-water)

Coefficient	Term	Value	Standard Error	t-statistics	*p*-value (> |t|)
β_1	x_1	8.915	1.063	8.385	0.00356
β_2	x_2	5.086	1.063	4.784	0.01737
β_3	x_3	3.417	1.063	3.214	0.04881
β_4	x_4	6.728	1.063	6.329	0.00798
β_{12}	$x_1 \cdot x_2$	9.558	5.211	1.834	0.16397
β_{13}	$x_1 \cdot x_3$	19.022	5.211	3.651	0.03548
β_{14}	$x_1 \cdot x_4$	16.943	5.211	3.252	0.04743
β_{23}	$x_2 \cdot x_3$	7.119	5.211	1.366	0.26527
β_{24}	$x_2 \cdot x_4$	26.477	5.211	5.081	0.01473
β_{34}	$x_3 \cdot x_4$	39.291	5.211	7.540	0.00484
β_{123}	$x_1 \cdot x_2 \cdot x_3$	2.890	129.440	0.022	0.98359
β_{124}	$x_1 \cdot x_2 \cdot x_4$	72.709	129.440	0.562	0.61354
β_{134}	$x_1 \cdot x_3 \cdot x_4$	–218.179	129.440	–1.686	0.19047
β_{234}	$x_2 \cdot x_3 \cdot x_4$	196.987	129.440	1.522	0.22541
			Residual standard error (RSE)	1.0650	
			Coefficient of determination (R^2)	0.9984	
			Coefficient of determination (R^2), adjusted	0.9910	
			F-statistic	134	

Furthermore, the extraction of phenolic compounds via batch maceration from MSKP was repeated under optimized condition of quaternary solvent mixture composition (30% ethanol, 30% methanol, 30% acetone and 10% water) and the fixed conditions (temperature = 40°C ; time = 60 minutes ; shaking speed = 230 rpm ; solid-to-solvent ratio = 1:25). This was performed to assess the validity of the response model presented in Equation (3). The response (C) of this validation experiment was compared to the predicted response from the model. About 5% difference between the values was considered acceptable [27]. The TPC of the extract produced during validation is 12.76% (± 0.61), which differs by approximately 5.09% from the value (12.13%) predicted by Equation (3). This means that the predictive accuracy of the response model and its quantifying confidence is validated.

$$\begin{aligned} C = {} & 8.915x_1 + 5.086x_2 + 3.417x_3 + \\ & 6.728x_4 + 9.558x_1x_2 + 19.022x_1x_3 + \\ & 16.943x_1x_4 + 7.119x_2x_3 + 26.477x_2x_4 + \\ & 39.291x_3x_4 + 2.890x_1x_2x_3 + 72.709x_1x_2x_4 - \\ & 218.179x_1x_3x_4 + 196.987x_2x_3x_4 \end{aligned} \quad (3)$$

3.3 *Influence of quaternary solvent mixture*

The consideration for a quaternary solvent mixture stems from the dependence of the SLE process on the properties of the solvent mixture and the solute, which in this study are phenolic compounds. The work of Lim *et al.* [28] and Masibo and He [29] showed that phenolic compounds in MSK largely comprise the following constituents: tannins, mangiferin, coumarin, and vanillin, as well as gallic, cinnamic, caffeic, and ferulic acids. The interactions of the aforementioned compounds in polar solvents are highly favorable since phenolic compounds are generally polar compounds. From the above-named phenolic compounds, tannins are more soluble in water while the rest are more soluble in acetone, ethanol, and methanol [30], [31]. The aliphatic portions of alcohols and ketones can probably explain the association of the non-polar fragments in phenolic compounds with acetone, ethanol, and methanol. On the other hand, the aromatic ring of phenolic compounds that is bounded by three hydroxyls and one carboxyl functional group could be the reason behind the attraction of the compounds towards water [32]. Hence, the consideration of a quaternary solvent mixture in extracting phenolic compounds from plant-based feedstock allows the simultaneous extraction of various phenolic compounds within its matrix.

The presence of different solvents having dissimilar polarities in the mixture also affects the extraction of phenolic compounds (solute) from the feedstock. This can be further expounded through polarity indices P' [33], [34]. This index represents the level of interaction relative to water of a particular solvent with several phenolic compounds [35]. A solvent with a higher value of polarity index signifies that its extent of interaction with phenolic compounds is also higher. For the quaternary solvent used in this study, the order of P' based on the results of Abdul Razak *et al.* [36] is as follows: water > methanol > acetone > ethanol. The presence of water molecules permits the disintegration of the feedstock, which eases penetration of the said solvent within the matrix. As a result, the capability of water in dissolving phenolic compounds is amplified [37]. Methanol, on the other hand, is efficient in extracting lower molecular weight phenolic compounds. In simultaneously extracting flavanols having high molecular weights and other non-polar phenolic compounds, the use of acetone is found to efficient [37]–[39]. Moreover, ethanol is also preferred because of lesser restrictions than organic solvents even though its capacity to extract phenolic compounds is inferior, to a certain extent, compared to the above-mentioned solvents [40].

4 Conclusions

In this work, the extraction of phenolic compounds from mango seed kernels was demonstrated via solid-liquid extraction method using a quaternary solvent mixture comprising water, ethanol, methanol, and acetone as the extraction solvent. Response surface methodology coupled with simplex lattice mixture design was applied that permitted assessment of the interaction effects (linear, two-way, and three-way) among the polar solvents. This method also led to optimizing the quaternary solvent mixture composition in relation to the total phenolic compounds content of the extracts during the extraction process. The interaction effects are significant (adjusted R^2 equal to 0.991), and they imparted positive effects on the phenolic content

of extracts except for methanol-acetone-water three-way interaction effect. The estimation of the linear effects has greater precision than the two-way and three-way effects. The response model, which is based on the Scheffé cubic equation, sufficiently described the extraction process. Furthermore, a quaternary solvent mixture with approximately 30% ethanol, 30% methanol, 30% acetone, and 10% water (3:3:3:1) ratio provided the highest phenolic content during the extraction process at 40°C for 60 minutes with a 1:25 solid-to-solvent ratio. Moreover, model validation has shown that the response model has reliable predictive accuracy. Finally, the presence of different solvents in the quaternary solvent mixture allowed simultaneous extraction of various phenolic compounds within the matrix of MSK. Hence, this has an implication during the extraction process of phenolic compounds from MSK and in identifying the appropriate application of these phenolic compounds.

Acknowledgments

The authors are indebted to the Philippine Higher Education Research Network – Commission on Higher Education (PHERNET-CHED) for the financial assistance in pursuing this study and to the following people in BioPERC for extending their help during the conduct of experiments: Engr. Ynno C. Igut, Engr. Jzia Mae Paciencia, Ms. Desiree Tangpos, and Mr. Jason Moen Pestaño.

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