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Polyphenols from Tropical Almond Leaves (*Terminalia catappa* L.): Optimized Extraction Conditions and α-Glucosidase Inhibitory Activity

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Abstract

The purpose of this study was to find the optimal conditions for extracting polyphenols from Vietnamese tropical almond leaves (*Terminalia catappa* L.) and to assess the anti-diabetic activities of the resulting extract. The polyphenol extraction from Vietnamese tropical almond leaves was optimized using the response surface methodology. A rotatable central composite design (RCCD) with three variables (ethanol concentration, temperature, and extraction time), consisting of 21 experimental runs with three replicates at the center, minimal, and maximal factorial points was applied to describe the experimental data. The experimental results properly confirmed the constructed model (R^2 = 0.8337). The optimized conditions were as follows: ethanol concentration of 62.76%, a temperature of 62.2°C, and an extraction time of 70 minutes. Five extractions were performed in parallel at the optimized conditions to validate the model. The experimental values highly agreed with the predicted value. The extract powder has powerful effects against the α-glucosidase activity and can develop as a novel natural anti-diabetic agent.

Keywords

Tropical almond, polyphenol, α-glucosidase, antioxidant, anti-diabetic

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Introduction

Polyphenol compounds are the most common group of secondary metabolites in the plant kingdom, with approximately 10,000 structures identified up to now (Kennedy & Wightman, 2011; Sridhar *et al.*, 2021). It was suggested that polyphenols are the most abundant antioxidants in the human diet (Mudgal *et al.*, 2010) and contribute up to 90% of the total antioxidant capacity in most fruits and vegetables (Wu *et al.*, 2004).

A recent study showed that the leaves of tropical almond collected in Vietnam have a high polyphenol content of 1,709.75 ± 1.99 mg GAE/g dried matter (Ha Dang Huy *et al.*, 2021), and is much higher than berries, which are considered a source of polyphenols in the human food. Polyphenol-rich extracts from the tropical almond leaf demonstrated antioxidant, anti-inflammatory, antibacterial, anti-cancer, and hepatoprotective properties (Anand *et al.*, 2015).

The tropical almond (*Terminalia catappa* L.) is one of the recent objects of researcher's interest as a highly polyphenol-containing object used in herbal medicines. The tree belongs to the family Combretaceae, which originates from Southeast Asia and is well-developed in tropical and subtropical climates. The tree can grow in arid, rocky places and is usually planted in urban areas, roadsides, temples, pagodas, and schools for landscaping and shade (Do Huy Bich *et al.*, 2006). Tropical almonds are very popular in Vietnam, but their utility is limited. The leaves are used to wrap food and to treat fever, sweating, dysentery, scabies, and tooth decay in traditional medicine; they are also used as an alternative to antibiotics to treat bacteria and fungi on ornamental fish (Rex, 2019).

There have been several studies on the extraction of the active ingredient from tropical almonds (Ha Dang Huy *et al.*, 2021; Vo Thi Thanh Kieu, 2016); however, the optimal solvent extraction conditions of polyphenols have not been reported yet. This study optimized the extraction parameters of polyphenols from tropical almond (*T. catappa* L.) leaves and evaluated the anti-diabetic properties of the afforded extract.

Materials and Methods

Plant material preparation

The green tropical almond leaves collected in Gia Lam province (**Figure 1**) were then dried at 50°C by a forced air convection oven until moisture content was less than 10%. This drying temperature was defined based on our preliminary experimentation (data not shown). Dried tropical almond leaves were ground to powder (below 0.12mm in diameter) and then preserved in zip bags with a desiccant inside at 4^{o}C. The material powder was extracted with different sets of material-to-solvent ratios, ethanol concentrations, extraction temperatures, and times.

The extract obtained at the optimal extraction conditions was evaporated by Buchi Rotavapor R-210 (Buchi Labotechnik AG, Switzerland) at 40°C under pressure of 175mbar and lyophilized at -50°C with pressure of 0.45mbar by Thermo Scientific ModulyoD Freeze Dryer (Thermo Fisher Scientific, US) to analyze α-glucosidase inhibitory ability.

Chemicals and reagents

Gallic acid, Folin-Ciocalteau reagent, 6-hydroxy - 2, 5, 7, 8 - tetramethylchroman - 2-

Figure 1. Green tropical almond leaves

carboxylicacid (Trolox), diphenyl-1-picrylhydrazyl (DPPH) radical, enzyme yeast a-glucosidase; p-nitrophenyl-α-D-glucopyranoside (pNPG), 4-Nitrophenol were purchased from Sigma-Aldrich (St. Louis, MO, USA). Na_2CO_3, ethanol, and methanol of analytical grade were obtained from Xilong, China.

Single-factor experiment

The material powder used to extract with five different sets of material-to-solvent ratios from 1/5 to 1/25, at seven different concentrations of 20, 40, 50, 60, 70, 90, and 96% of ethanol solvent, at seven different extraction temperatures from 40 to 95°C and for six extraction times (from 30 to 120 minutes) in an incubator shaker with a shaking speed of 150 rounds/min. All the solutions were then transferred to 50-mL falcon tubes and centrifuged at 6000 rounds/min for 10 minutes at 4°C. The collected supernatants were used to analyze total polyphenol. The impact of material-solvent ratio, ethanol concentration, extraction temperature, and extraction time on total polyphenol content (TPC) was evaluated to identify the suitable ranges of parameters for optimizing polyphenol extraction from tropical almond leaves (**Table 1**). All the extraction processes were carried out in three replicates, and all the analyses on each sample were done in duplicate.

Optimization of polyphenol extraction by Response Surface Methodology (RSM)

The polyphenols extraction from tropical almond leaves was further optimized through the response surface methodology (RSM) approach. The design variables were the ethanol concentration (X_1), extraction temperature (X_2), and extraction time (X_3) at five different levels assigned to the obtained set of optimum parameters (**Table 2**). A Rotatable Central Composite Design (RCCD) consisted of 21 experiment runs with eight factorial points, six axial points, and three replicates at the center point, maximal and minimal factorial points.

Those combinations then experimentally attempted to obtain the data of Y, which then fitted to the following second-order polynomial model:

$$Y = \beta_0 + \sum_{i=1}^{3} \beta_i X_i + \sum_{i}^{3} \beta_{ii} X_{ii}^2 + \sum_{i=1}^{3} \sum_{j=1}^{3} \beta_{ij} X_i X_j$$

When

Y: the response variable (total polyphenol)

X: independent variables

β: model coefficients

0, i, j, and ij: the constant, linear terms, quadratic terms, and interactive terms

The optimal conditions of the TPC extraction process were determined using JMP 10 software. The experiment & predicted values of five replicates performed at the optimal conditions were compared to validate the model.

Determination of total polyphenol content

The polyphenol content of the extract was determined using the Folin-Ciocalteu reagent as described by Singleton & Rossi (1965). First, an aliquot of 0.5mL diluted extract was mixed with 0.25mL Folin-Ciocalteu reagent 1N. The mixture was shaken and then allowed for a reaction for 5 minutes at room temperature 25°C. Then, 1.25mL Na_2CO_3 7.5% was added and mixed well. After incubation at room temperature 25°C for 30 minutes, the absorbance of the reaction

Table 1. Single-factor experiment on total polyphenol content

Experiment	Extraction parameters	Fixed parameters
Material-to-solvent ratio (g/mL)	1/5, 1/10, 1/15, 1/20, 1/25	Ethanol 70%, 40°C, 60 minutes
Ethanol concentration (%)	20, 40, 50, 60, 70, 90, and 96	Selected material-to-solvent ratio, 40°C, 60 minutes
Extraction temperature (°C)	40, 50, 60, 70, 80, 90 and 95	Selected material-to-solvent ratio, selected ethanol concentration, 60 minutes
Extraction time (minute)	15, 30, 45, 60, 90, and 120	Selected material-to-solvent ratio, selected ethanol concentration, selected extraction temperature

Table 2. The response surface methodology experimental

Factor	Symbol	Coded level				
EtOH concentration (%)	X1	-1.68	-1	0	+1	+1.68
Temperature (°C)	X2	-1.68	-1	0	+1	+1.68
Time (minute)	X3	-1.68	-1	0	+1	+1.68

solution was measured at 755nm by UV-1800 UV-VIS spectrophotometer (Shimadzu, Japan). Gallic acid was used as the standard for building calibration curves. The TPC was expressed as mg of gallic acid equivalent (GAE) per gram dry weight (mg GAE/g DW).

Determination of α-glucosidase inhibitory ability

The extract powder was sent to the Biological test laboratory, Institute of Biotechnology, Vietnam Academy of Science and Technology to determine the α-glucosidase inhibitory ability. The α-glucosidase enzyme inhibitory activity of the extract powder performed as follows:

First, extract powder was dissolved in DMSO 100% (v/v) to obtain 20 mg mL^{-1} concentration and diluted in phosphate buffer 10 mM (pH = 6.8). The reaction mixture containing 130µL of phosphate buffer (100mM, pH = 6.8), 20µL of the enzyme α-glucosidase (0.5 U/mL), and 50µL of the extract dilution was incubated at 37°C for 15 minutes to obtain final concentration at 500-100-20-4 µg mL^{-1}. Then, 40µL of p-nitro-phenyl-α-D glucopyranoside (5mM) was added to the above mixture and kept at 37°C for 60 minutes. The reaction stopped by adding 80µL of Na2CO3 (0.2M). The absorbance of the released p-nitrophenol was measured at 405nm by an ELISA Plate Reader (Biotek). Acarbose, a commercial α-glucosidase inhibitor that is considered a first-line treatment for diabetic individuals used as the standard.

The α-glucosidase inhibitory activity of the extracts was calculated by the formula: % inhibitory activity = 100 – absorbance of sample/absorbance of control*100.

IC_{50} was defined by TableCurve2Dv4.

Statistical analysis

The experiment results were expressed as mean ± standard deviation (SD) and analyzed using the SAS 9.4 software (SAS Institue, Cary, NC). One-way analysis of variance (ANOVA) and the Duncan test were used to determine the differences among the means at *P*-value <0.05. In the RSM experiment, multiple linear regression analysis was performed using the software JMP 10 (SAS Institue, Cary, NC).

Results and Discussion

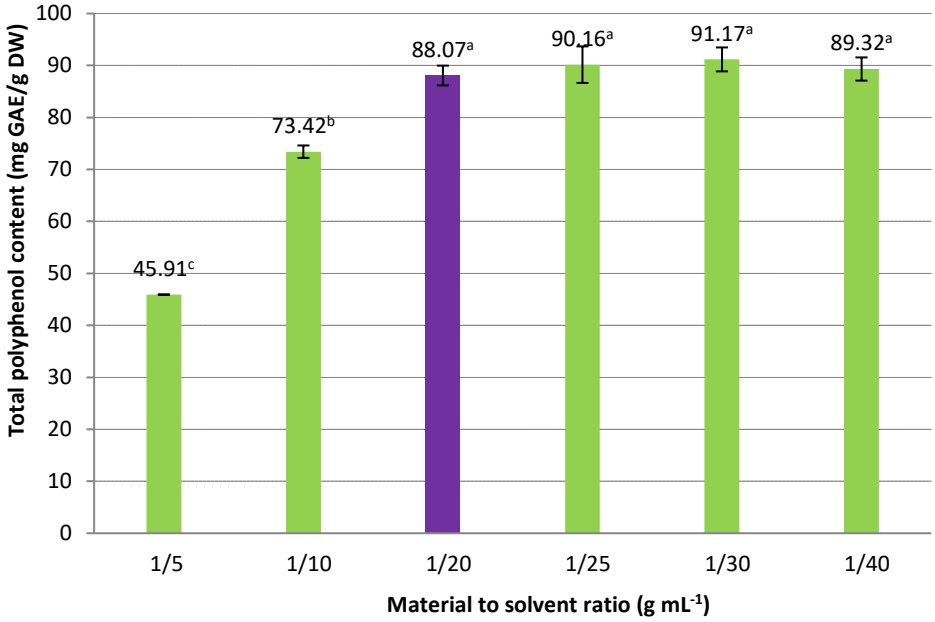
Single-factor experiment

Effect of material-to-solvent ratio

The material-to-solvent ratio showed a significant effect on the TPC extraction ($P < 0.05$) (**Figure 2**). The total polyphenols yield from the tropical almond extracts increased when the ratio raised from 1/5 to 1/20 (w/v) and remained stable at a further higher in the material-to-solvent. This increase could be due to the enhanced penetration of solvent through the cell membrane under thermal treatment, which helps push active compounds out, resulting in greater extraction of materials by solvent (Cacace & Mazza, 2003). However, the component yield did not increase once equilibrium was achieved (Herodez *et al.*, 2003). With the material-to-solvent ratio of 1/20 (w/v), the TPC of the extract was at the maximum level, indicating a sufficient amount of extraction solvent used, and this ratio was chosen for the consequent experiment.

Effect of ethanol concentration

The TPC of the extracts as a function of ethanol concentration follows a parabolic shape, and the ethanol concentration had a significant effect (P <0.05) on the extraction efficiency of total polyphenol from Vietnam's tropical almond



Note: Values are means ± standard deviation. Values marked by different letters indicate significant difference (P <0.05)

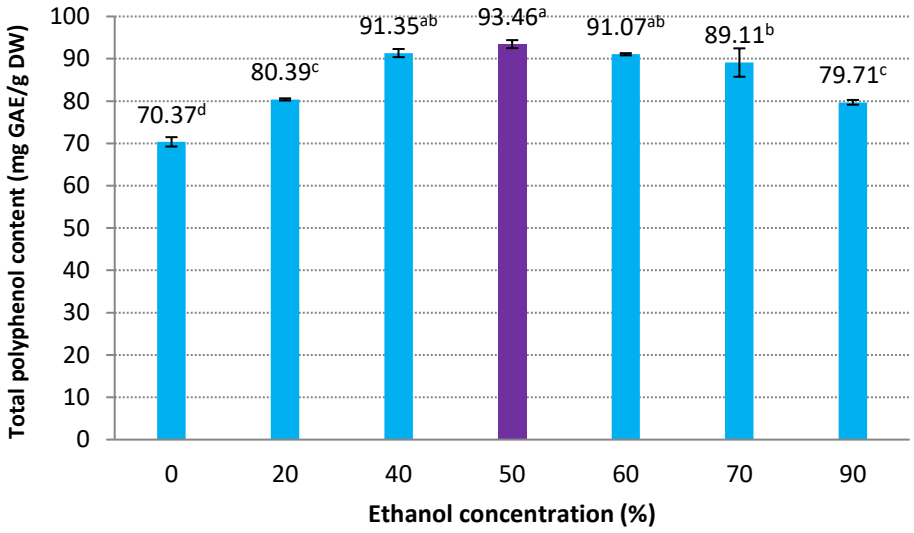
Figure 2. Effect of material-to-solvent ratio on total polyphenol content of the extracts

leaf (**Figure 3)**. The TPC gained from the extract at 50% ethanol (93.46 mg GAE/g DW) was significantly higher than those recovered at lower ethanol concentrations (0, 20, and 40%). Rising the ethanol concentration from 50 to 60% slightly decreased the TPC yield to 91.07 mg GAE/g DW, and with ethanol concentration higher than 60%, the TPC of the extracts significantly dropped (P <0.05). The impact of the ethanol concentration could be due to its effect on the polarity of the extraction solvent and the resulting solubility of the polyphenol compounds; It is interesting to note that the numbers of water and ethanol are 1.000 and 0.654, respectively (Reichardt, 2003). The polyphenols in the extracts increased with increasing ethanol concentration according to the like dissolves-like principle (Chirinos *et al.*, 2007). The highest total polyphenol content at 50% ethanol (v/v) indicated that the solvent had similar polarity to polyphenols in tropical almond leaves. And solvents higher than 60% were not suitable polarities resulting in lowered total polyphenols content. A solvent of 50% ethanol (v/v) was chosen as the central value in the RSM experiment.

Effect of temperature extraction

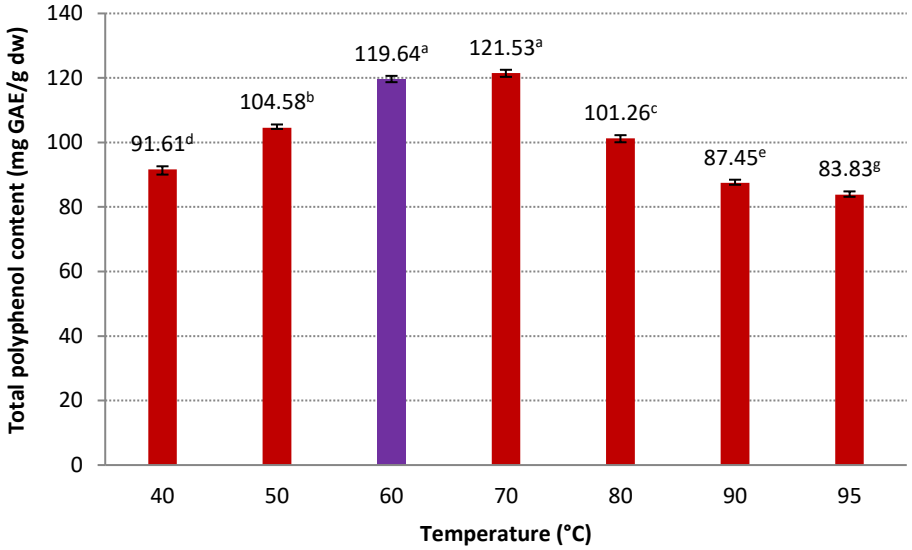
The extraction temperature significantly affected the TPC extraction from tropical almond leaves **(Figure 4).** Results indicated a significant increase in the extraction of TPC when the temperature elevated from 40 to 70°C, and a further temperature rise noticeably downed the level of polyphenols in the extracts (P <0.05). This effect of temperature followed studies on glucosinolates extraction from by-products of white cabbage (Nga, 2016). The whole polyphenol extraction process could speed up by the enhanced mass transfer with the penetrated solvent into the plant matrix and the increased solubility and diffusion coefficient of polyphenol (Al-Farsi & Chang, 2007). However, extraction yields decreased when the extraction temperature raised more than 70°C, indicating that polyphenols in tropical almond leaves are not thermo-resistant phenolic compounds. This result agreed with a previous report where 60°C determined as the extraction temperature of TPC of ethanolic rosemary leaf extract (Tam *et al.*, 2021).

The polyphenols level extracted at 60°C did not significantly improve from that at 70°C (P >



Note: Values are means ± standard deviation. Values marked by different letters indicate significant difference (P <0.05).

Figure 3. Effect of ethanol concentration on total polyphenol content of the extracts.



Note: Values are means ± standard deviation. Values marked by different letters indicate significant difference (P <0.05).

Figure 4. Effect of temperature on total polyphenol content of the extracts

0.05), 65°C used as the central point in the experiment of polyphenols extraction optimization from tropical almond leaves.

Effect of extraction time

The efficiency was equivalent to the extraction time. The efficiency can not rise anymore when it gets all the polyphenols on the plant matrix. The maximum level of polyphenols was at sixty minutes (**Figure 5),** and this result agreed with studies by Tam *et al.* (2021) that the highest solutes reached at sixty extraction minutes.

According to our results, the polyphenols extraction process split into two phases: a fast one, which accounted for the first 30 minutes, and a slow one, which accounted for the rest of the studied time. The extraction achieved equilibrium from forty-five to ninety minutes without significant difference in statistical

analysis of the total polyphenol content (P >0.05), and prolonging the extraction time up to 120 minutes, the TPC downed considerably (P <0.05).

This result agreed with the study of Silva *et al.* (2007). The choice of a long extraction time led to no significant effect on the TPC, so forty-five minutes and twenty-five minutes were chosen as the central value and variation of the extraction time, respectively, so that the variable time in the RSM experiment covered both phases of the extraction.

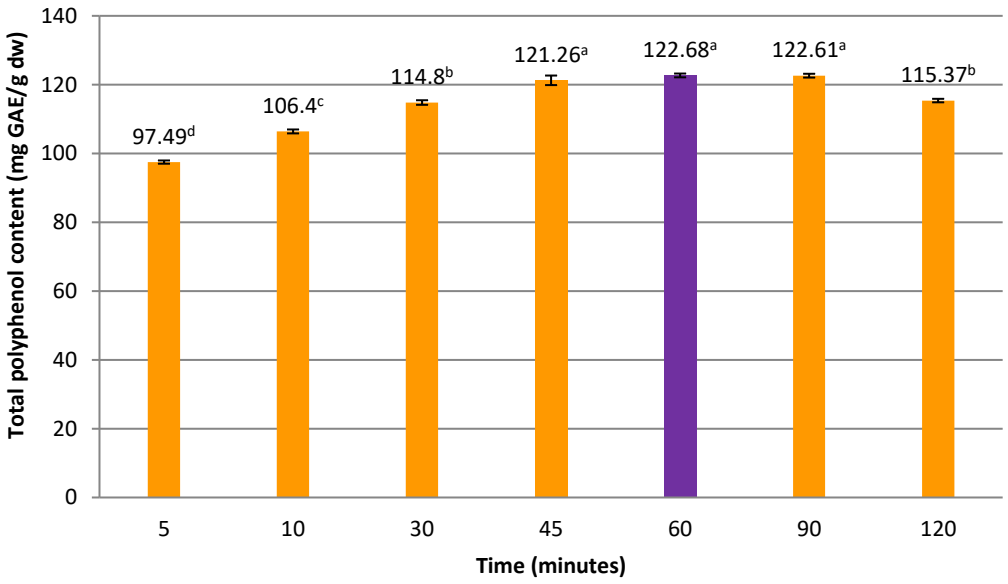
Optimization of polyphenol extraction by Response surface methodolody

The total polyphenols extraction from tropical almond leaves was further optimized through the RSM approach. Based on the single-factor experiment results, a fixed material-to-solvent (1/20, w/v) was chosen while three factors, namely ethanol concentration X_1 (30-70 % v/v), temperature X_2 (45-85°C) and time X_3 (20-70 minutes) considered as variables in the model. Their ranges are presented in **Table 2**. The experimental design of a five-level, three-variable RCCD and the experimental results of the extraction are shown in **Table 3**. By applying multiple regression analysis, the relation between the tested independent variables and the response is explained by **Equation 1**, in which Xi was the coded variable.

$$Y= 126.83779 + 1.863547*X1 + 2.1350615*X2 + 2.115998*X3 +0.1500095*X1*X2 + 2.0525095*X1*X3 – 2.58749*X2*X3 – 3.049965*X12 – 1.271592*X22 – 0.071278*X32 \quad \textbf{(Equation 1)}$$

To fit the response function and experiment data, the linear and quadratic effects of the independent variables, and their interactions in the response, were evaluated by analysis of variance (ANOVA), and regression coefficients were determined (**Table 4** and **Table 5**).

The ANOVA of the regression model showed that the model was highly significant due to a low probability value (P <0.0033) (**Table 4**). As illustrated by **Table 5**, the ethanol concentration, temperature, and time showed significant linear effects for the TPC (P < 0.05), so the TPC increased when increasing ethanol concentration (Runs 9 and 10 in **Table 3**), temperature (Runs 11 and 12 in **Table 3**) and time (Runs 13 and 14 in **Table 3**). Besides, the interaction between temperature and time was negative (**Table 5**), which could mean high temperature requires less time and vice versa. The quadratic ethanol concentration appeared to



Note: Values are means ± standard deviation. Values marked by different letters indicate significant difference (P <0.05).

Figure 5. Effect of time on total polyphenol content of the extracts

Table 3. Experimental results of the Rotatable central composite design (Total polyphenol content of extract from tropical almond leaves)

Runs	Coded forms			Real values			Response – TPC (mg GAE/g DW)	
	X1	X2	X3	EtOH (%)	T (°C)	Time (min)	Y (actual)	Y (predicted)
1	-1	-1	-1	30	45	20	114.13	115.9454
2	-1	-1	1	30	45	70	125.03	120.9758
3	-1	1	-1	30	85	20	127.13	124.838
4	-1	1	1	30	85	70	117.08	121.756
5	1	-1	-1	70	45	20	119.37	115.4564
6	1	-1	1	70	45	70	127.88	124.3284
7	1	1	-1	70	85	20	122.37	120.099
8	1	1	1	70	85	70	130.02	125.0395
9	-1.68	0	0	16.4	65	45	117.01	118.3493
10	1.68	0	0	83.6	65	45	117.80	118.2296
11	0	-1.68	00	1.68	0	45	119.13	119.6619
12	0	1.68	0	50	98.6	45	125.74	126.8358
13	0	0	-1.68	50	65	3	124.63	123.0817
14	0	0	1.68	50	65	87	127.03	130.1915
15	0	0	0	50	65	45	126.29	126.8378
16	0	0	0	50	65	45	127.47	126.8378
17	0	0	0	50	65	45	127.03	126.8378
18	-1	-1	-1	30	45	20	114.04	117.8089
19	1	1	1	70	85	70	129.94	126.311
20	-1	-1	-1	30	45	20	114.48	117.8089
21	1	1	1	70	85	70	130.89	126.311

Table 4. Analysis of variance of the response surface quadratic model of total polyphenol content from tropical almond leaves

Source of variance	Degree of Freedom	Sum of Square	Mean Square	F ratio
Model	9	530.33179	58.9258	6.1283
Error	11	105.76820	9.6153	*P* = 0.0033*
Total	20	636.09998		

be the most affecting factor of the TPC extraction process from tropical almond leaves, as its coefficient had the highest value (**Table 5**). Three replicates at the minimal-, center-, and maximum points showed an increase from 114,22 mg GAE/g DW (the average value for runs 1, 18, and 20 in **Table 3**) to 126.93 mg GAE/g DW (the average value for runs 15, 16, and 17 in **Table 3**) and 130,28 mg GAE/g DW (the average value for runs 8, 19, and 21 in **Table 3**), respectively. Combining all information indicated a maximum TPC content at a specific ethanol concentration, temperature, and time between two latter points (**Figure 6**).

The R^2 value for the regression model of the TPC of tropical almond leaves was 0.8337, which means 83.37% of the variation for the TPC based on the studied factors of ethanol concentration, temperature, and time. The regression model did not cover all the information to control the variation in TPC extraction from the tropical almond leaves. Our

Table 5. Parameter estimates of the predictec second-order model for the responses

Term	Estimate	Standard Error	t Ratio	Prob>|t|
Intercept	126.83779	1.786526	71.00	<0.0001*
X1 EtOH (30, 70)	1.863547	0.770907	2.42	0.0342*
X2 Temperature (45, 85)	2.1350615	0.770907	2.77	0.0182*
X3 Time (20, 70)	2.115998	0.770907	2.74	0.0191*
X1X2 EtOH*Temperature	0.1500095	0.993652	0.15	0.8827
X1X3 EtOH*Time	2.0525095	0.993652	2.07	0.0632
X2X3 Temperature*Time	-2.58749	0.993652	-2.60	0.0245*
X12 EtOH*EtOH	-3.049965	0.917792	-3.32	0.0068*
X22 Temperature*Temperature	-1.271592	0.917792	-1.39	0.1934
X32 Time*Time	-0.071278	0.917792	-0.08	0.9395

Note: Parameter estimates are coefficients of the model with coded variables.

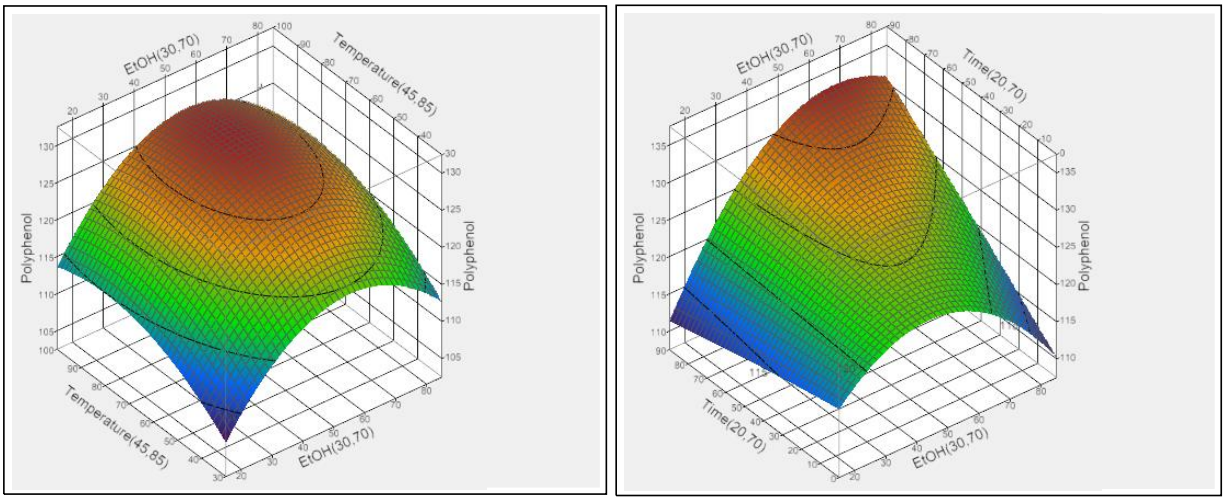


Figure 6. Response surface for the total polyphenol content in the function of the ethanol concentrations, temperature, and time of extraction

study used the popular size of extraction material and ethanol for application in the food industry; maybe the size of the sample material, type of solvent, or unknown factors could affect the 16.63% variation for the TPC in extraction, so our optimal model should have considered these factors in the future.

The optimum conditions of the TPC extraction from tropical almond leaves were acquired using JMP 10. The software set to search the optimum desirability of the response, meaning the highest value TPC content of the Vietnamese tropical almond leaves. The optimum condition was as follows: ethanol concentration of 62.76%, a temperature of 62.2°C, and an extraction time of 70 minutes (**Figure 7**).

The extraction was performed with five replicates under these conditions to examine the model's validity. The measured values (130.06, 130.88, 132.08, 130.37, and 131.61 mg GAE/g DW) lay within a 95% mean confidence interval of the predicted value (130.16 mg GAE/g DW). These results confirmed the predictability of the model. The second-order polynomial model can thus be effectively applied to predict the TPC content of extracts from tropical almond leaves.

The α-glucosidase enzyme inhibitory activity

The α-glucosidase enzyme converts carbohydrates into α-glucose, resulting in increased blood glucose levels; inhibition of this enzyme is used as a drug to treat some forms of

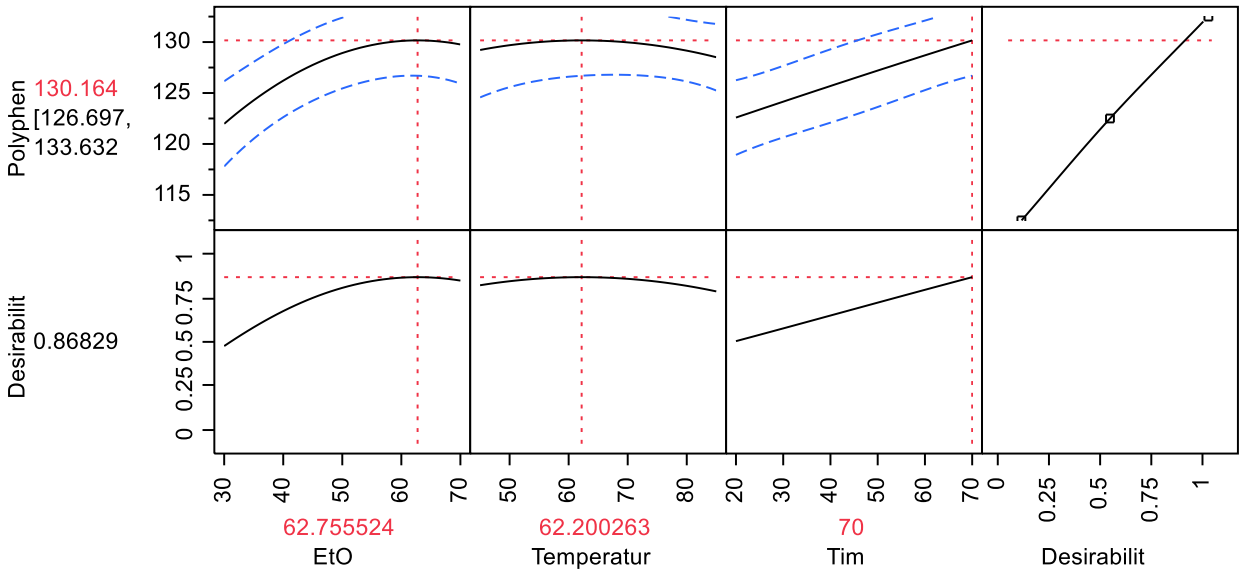


Figure 7. Desirability and responses in the function of the ethanol concentration, temperature, and time of extraction

diabetes. Acarbose, commonly prescribed for managing type 2 diabetes, was a control for the α-glucose inhibitory activity test. The α-glucosidase enzyme inhibitory activity of the extracts depended on the concentration used and presented in **Table 6**.

All seven concentration extracts displayed inhibitory activity against α-glucosidase; even at the lowest concentration of 0.032 µg mL^{-1} of the extract, the inhibition was 11.2% and close to the inhibition of Acarbose at a concentration of 20 µg mL^{-1}. The inhibition showed concentration-dependent but nonlinear behavior. Based on the IC50 value of 123.81 ± 3.58 µg mL^{-1} of the control drug Acarbose, this tropical almond leaf extract with the IC50 value 0.098 ± 0.003 µg mL^{-1} had an effective against α-glucosidase activity higher 1263 times than Acarbose. It is noteworthy that this plant extract tested herein is not associated with gastrointestinal side effects such as diarrhea, abdominal pain, cramping, bloating, and flatulence as Acarbose (DiNicolantonio *et al.*, 2015).

Besides, the α-glucosidase inhibitory activity of tropical almond leaf extract is also better than that of green coffee bean *Coffea canephora* (IC50 value of 2.21 ± 0.04 µg mL^{-1}) (Dang Kim Thu *et al.*, 2019), of the *Cyperus rotundus* tubers (IC50 value of 3.98 ± 0.55 µg mL^{-1}), of *Plumbago zeylanica* root (IC50 value of 3.46 ± 0.53 µg mL^{-1}), of *Symplocos racemosa* bark (IC50 value of 8.16 ± 0.28 µg mL^{-1}) (Ankita *et al.*, 2011). The methanol extracts of *Terminalia arjuna* bark, the most potential α-glucosidase inhibitor medicinal plants in India, had the IC50 value of 0.69 ± 0.04 µg mL^{-1} (Ankita *et al.*, 2011), and our extracts were still more effective seven times than that ability. These findings demonstrate that Vietnamese tropical almond leaf extracts can be used in diabetic treatment due to their inhibition power of the α-glucosidase enzyme.

Conclusions

The present study demonstrates that the optimal conditions for polyphenol extracts of Vietnamese tropical almond leaves (*Terminalia catappa* L) were as follows: an ethanol concentration of 62.76%, a temperature of 62.2°C, and an extraction time of 70 minutes. This extract possesses powerful effects against α-glucosidase activity and can develop as a novel antidiabetic agent. This study should be considered the first step for polyphenol-rich products from Vietnamese tropical almond leaves used as nutraceuticals for diabetes.

Table 6. The α-glucosidase enzyme inhibitory activity of the extracts and Acarbose

Concentration (µg mL^{-1})	Tropical almond leaves extracts		Acarbose	
	% inhibition	SD	% inhibition	SD
500	100.0	1.50	81.8	2.11
100	100.0	0.25	51.0	0.94
20	99.8	0.15	14.8	1.07
4	99.6	0.10	8.3	0.22
0.8	99.4	0.20		
0.16	68.8	1.45		
0.032	11.2	0.30		
IC50	0.098 ± 0.003		123.81 ± 3.58	

Acknowledgments

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