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Alkali Extraction of Phenolic Compounds from Tomato Peel: Optimization of Extraction Conditions and Investigation of Phenolic Profile by LC-MS/MS[#]

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ABSTRACT

With the increasing world population, the food need of humanity is increasing proportionally. Agricultural wastes constitute an important potential for the global economy as they contain components that are less preferred to be consumed as food due to their low bioavailability due to their indigestion in the human body or due to their sensory properties, but that may be beneficial to human health such as antioxidant substances and antimicrobial agents. The benefits of using these wastes in terms of economy and reducing environmental pollution are obvious. Tomato, which is one of the most used agricultural products in our country and the world, is processed by removing its skins in the processing of many products. Tomato skins cause serious environmental problems and economic losses unless they are valorized. In this regard, this study aims to optimize the extraction efficiency, the antioxidant capacity, and total phenolic content of the tomato peel extract according to the independent variables of temperature and time, while the alkaline extraction process applied to tomato skins is cheap and industrially applicable. Using response surface methodology, the highest extraction yield (28.77 g/100 g dry extract), total phenolic content (3819.32 mg GAE/100 g dry extract), and total antioxidant capacity (2737.82 µmoL Trolox/100 g dry extract) were obtained under extraction conditions at 100°C for 5.26 h. According to LC-MS/MS results, tomato skins treated with alkali contain various phenolic acids and some flavonoids. The phenolic component found in the highest amount in the tomato peel extract was determined as p-coumaric acid (429.99 ± 38.53 mg/100 g dry extract). Other important phenolic components are ferulic acid (12.44 ± 2.06); 4-hydroxy benzoic acid (7.13 ± 1.01) and vanillin (2.47 ± 0.22) mg/100 g dry extract.

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Introduction

Tomato (*Solanum lycopersicum* L.) is one of the most popular vegetables with an annual production of 187 million tons worldwide (FAOSTAT, 2020). It contains several bioactive compounds that have been associated with health-promoting aspects such as the prevention of diseases related to oxidative stress (Pinela et al., 2016), treatment of cancer and cardiovascular diseases (Boehm V. 2012. Lycopene and heart health. Molecular Nutrition, 2012; Friedman, 2013).

About a quarter of annual tomato production is processed into soups, pastes, ketchup, juices, sauces, and dried and preserved foods, resulting in various wastes such as peels, seeds, and pulp (Szabo et al., 2019a). These byproducts lead to serious environmental problems (Kumar Saini et al., 2018) if not recycled in a way that satisfies food consumers. It has been reported that several available nutrients abundant in these by-products could be efficiently extracted and used as functional food ingredients (Andres et al., 2017; Belovic et al., 2017). Foods containing these ingredients have been very well received by consumers (Szabo et al., 2018).

Agro-industrial tomato waste accounts for about 5-30% of tomatoes (Nincevic-Grassino et al., 2020) and contains a variety of valuable nutrients such as polyphenols, carotenoids, pectin, fiber, and fatty acids (Szabo et al., 2019b). Phytochemicals present in industrial tomatoes and their by-products are composed of polyphenols, sterols, carotenoids, terpenes, and some tocopherols (Kalogeropoulos et al., 2012). Among them, phenolic compounds have attracted particular interest due to their role in preventing various oxidative stress-related diseases (Shahidi and Ambigaipalan, 2015) and their anti-inflammatory activity and antimicrobial potential (Calinoiu and Vodnar, 2018). Caffeic acid, chlorogenic acid, p-coumaric acid, ferulic acid, rosmarinic acid, quercetin, and

rutin have been described as phenolic compounds in tomato peels (Cetkovic et al., 2012). It has also been suggested that tomato wastes should be considered as potential nutraceuticals due to their significant antioxidant and antiproliferative activities (Cetkovic et al., 2012). Naringenin, p-coumaric acid, quercetin, and rutin have been detected in tomato peel fibers by using different enzymes in the extraction, maceration, and ultrasound (Navarro-Gonzalez et al., 2011).

Several methods have been used to extract bioactive compounds from tomato peels. These methods include i) ultrasound-assisted extraction (Szabo et al., 2019a; Tamasi et al., 2019; Valdez-Morales et al., 2014), (ii) multi-step extraction with an ethanol-water mixture (70:30; 96:4) followed by Soxhlet extraction with a chloroform-methanol mixture (50:50) for extended periods (22 h) (Nincevic-Grassino et al., 2020); iii) sequential hydroalcoholic extraction with methanol and water for 24 h (El-Badrawy and Sello, 2016); iv) multi-fractional separation of free and bound phenols based on acid or alkali hydrolysis (Perea-Dominguez et al., 2018); v) microwave-assisted extraction (Bakic et al., 2019) combined with heat application. Alkali extraction with/without heat treatment has been recognized as an alternative method, especially for the recovery of bound phenols closely related to cell wall polysaccharides in plant tissues and their agro-industrial by-products. Alkali treatment was reported to facilitate the extraction of more polyphenols from kiwifruit peels, pulp, and seeds with higher resolution in HPLC compared to extraction with organic solvents (Sun-Waterhouse et al., 2009). Several studies emphasized that alkali treatment can favor the extraction of some bound phenols such as p-coumaric acid, ferulic acid, and caffeic acid from wheat bran (Kim et al., 2006; Verma et al., 2009) and rice husk (Nenadis et al., 2013) by contributing significantly to the antioxidant capacity.

In terms of economic aspects, an optimization process is required to design the extraction conditions to achieve the maximum antioxidant capacity, the maximum amount of total phenols, and the maximum extraction yield. To our knowledge, there are no data on the optimization of alkaline extraction from tomato waste. Moreover, there is no evidence that the use of an alkaline medium in extraction could be beneficial for the recovery of phenolic compounds from tomato peels. In this context, this study aims to determine the optimized extraction conditions and TAC of tomato peels and to further evaluate the possible contribution of each phenolic compound abundant in tomato peels to the TAC by revealing the phenolic profile of tomato peel extracts. We believe that the results of this study will help valorize food wastes and point to new studies on the production of functional foods from tomato waste.

Material and Method

Materials

Sodium hydroxide, hydrochloric acid, folin-ciocalteu, DPPH (1, 1-diphenyl-2-picyrlhydrazyl) reagents, gallic acid, Trolox standards, sodium carbonate, ethanol (99.96% purity), methanol (99.99% purity), and formic acid (99.99% purity) were purchased from Merck & Millipore.

Sample Preparation

Fresh tomato pomace was provided by a tomato paste processing factory (TUKAŞ Inc., Izmir, Turkey). The pomace was sedimented in containers filled with water to separate the seeds from the skins. Then, the peels were dried in an oven dryer (Lab T2-Eksis, Turkey) at 60°C for 8 h with an airflow velocity of 1 m/s. The dried tomato peels were then ground using a hammer mill (Brook Crompton 2000 Series, UK) and sieved with a pore diameter of 500 µ (Retsch, Germany). The dried peels were then stored at -20°C in vapor-tight, airtight packaging until the extraction process began.

Alkaline Extraction of Tomato Peels

The extraction was performed according to the procedure described in the literature (Cifarelli et al., 2016; Benitez et al., 2018). In each experiment, samples were treated with NaOH solution (3% w/v) at a solvent: solute ratio of 10:1. After filtration, the residue was rinsed twice with excess distilled water, and the supernatant was combined with the filtrate. The supernatant was then acidified with 3 M HCl until the pH of the solution reached 4.3. The samples were then centrifuged at 4000 rpm for 15 min and rinsed three times with alkaline water (pH=8.45) until the pH reached 6.5. This procedure was performed to remove acid-insoluble lignin from the tomato peel extracts (Mussatto et al., 2007). Since lignin can bind the phenols, this procedure facilitated the release of phenols. The precipitates were then freeze-dried using a freeze dryer (Christ, Alpha 1-2 LD plus, Sweden). The precipitates were then immediately weighed and stored at -18°C until the start of the analysis.

Experimental Design

Response Surface Methodology (RSM) was used to determine the effect of two independent variables (temperature and time) on total antioxidant capacity (TAC), total phenolic content (TPC), and extraction yield (EY). Three levels of 60ºC, 80ºC, and 100ºC for temperature and 2, 4, and 6 h for extraction time were chosen as independent variables. RSM can be chosen as a tool to find the best alternative solution for the relationship between the independent variables and the responses in such cases where it is not possible to easily predict this relationship.

The face-centered central composite design (CCD) was used; 19 runs (4 factorial points and 4 axial points with two replicates each and one central point with triple runs) were performed using Design-Expert software (version 7.0, Stat-Ease Inc., Minneapolis, USA). Variables were coded using the following equation:

$$X_k = \frac{x_k - x_i}{\Delta x_k} \quad (1)$$

where x_k is the corresponding real value, x_i is the real value in the middle of the range, and Δx_k is the increment of x_k corresponding to a change of 1 unit from x

The experimental results of the CCD were evaluated using equation 2.

$$y = \beta_0 + \sum_{i=0}^{k} \beta_i X_i + \sum_{i=0}^{k} \beta_{ii} {X_i}^2 + \sum_{i\leq 1}^{k} \sum_{i=1}^{k} \beta_{ij} X_i X_j + \cdots + e \quad (2)$$

where y is the predicted response, β_0 is the constant coefficient, β_{ii} is the linear coefficient, β_{ij} is the strength of interaction between variables i and j, k is the number of factors, and e is the random error (Liu et al., 2011; Khor and Abdullah, 2012).

Determination of Total Phenolic Content (TPC)

The TPC of tomato peel extracts (TPE) was determined by the Folin-Ciocalteu method (Xu and Chang, 2007). Gallic acid was used as a standard and the results were expressed as gallic acid equivalents (GAE). For extraction of phenolic compounds, the dried extract was treated with ethanol (96% v/v), then 50 µL of the mixture was shaken for 30 seconds after the addition of 250 µL Folin-Ciocealtau reagent and 3 mL distilled water. 750 µL sodium carbonate solution (7% w/v) was added to the mixture and shaken for another 30 seconds. Then 950 µL of distilled water was added to each sample and gently stirred. The mixture was allowed to stand at room temperature in the dark for 2 h. The absorbance of the mixture was measured at 765 nm using a spectrophotometer (Cary 60 UV-VIS, Agilent Technologies, USA). A calibration curve of gallic acid in ethanol (96%) at different concentrations was plotted against the absorbance values. The TPC for each sample was calculated from the linear function of this curve. The results were expressed as mg of gallic acid (GAE)/100 g of dried extract.

Determination of TAC (DPPH Radical Scavenging Activity)

The experiment was based on a method described in the literature (Kumaran and Joel Karunakaran, 2006; Tezcan et al., 2009). The absorbance was measured at 517 nm against ethanol and subtracted from the blank values. Quantification was performed based on the calibration curve of Trolox in ethanol (10, 15, 20, 30, 40, 60, and 80 mg/L). The radical scavenging activity was calculated using Equation 3:

$$\% \text{ reduction in DPPH} = (A_{blank}-A_{sample})/A_{blank} \times 100 \quad (3)$$

The computed antioxidant capacities were expressed in terms of µM Trolox/100 g dried extract.

Determination of Individual Phenolic Compounds by LC-MS /MS

The LC-MS /MS analysis of the TPEs obtained under optimized conditions was performed using an Agilent 6420 Series (Agilent Technologies, Italy) equipped with an electrospray ion source (ESI) and a triple quadrupole analyzer-mass spectrometer. Calibration standards ranging from 25 µg/L to 1000 µg/L were prepared for each of the following phenolic compounds: 2-hydroxycinnamic acid, 2,5-dihydroxybenzoic acid, 3-hydroxybenzoic acid, 3,4-dihydroxyphenylacetic acid, 4-hydroxybenzoic acid, apigenin, apigenin-7-glucoside, caffeic acid, chlorogenic acid, eriodictyol, ferulic acid, gallic acid, hesperidin, hyperoside, kaempferol, luteolin, luteolin 7-glucoside, pinoresinol, protocatechuic acid, pyrocatechol, quercetin, rosmarinic acid, sinapic acid, syringic acid, taxifolin, vanillic acid, vanillin, verbascoside, (+)-catechin, (-)-epicatechin, p-coumaric acid. Poroshell EC (C18, 2.7 µ, 4.6 x 100 mm) column was used at 25°C for the separation of phenols according to the analytical method described by Valdez-Morales et al. (2014) with some modifications. Elution was performed with a gradient of two solvents: deionized water acidified with formic acid (0.1%) (A) and methanol (B). The gradient for the phenolic compounds was 98% phase A, 2% phase B, from 0 to 3 min; 75% phase A and 25% phase B from 3 to 10 min; 50% phase A and 50% phase B from 10 to 14 min; 5% phase A and 95% phase B from 14 to 17 min, 98% phase A and 2% phase B from 17 to 17.5 min. The maximum pressure was 400 bar at a flow rate of 0.4 mL/min. The samples (0.1 g) were dissolved in 5 mL of ethanol. The solution was first filtered through a coarse paper filter. The filtrate was filtered again using 0.22 µm Durapore syringe filters (Millipore, Carrigtwohill, Co. Cork, Ireland). It was then injected into the column using an injection volume of 2 µL. Chromatographic peaks were identified by comparing the retention times of the pure standards. Mass Hunter software was used to manage the instrument, collect and analyze the data.

Statistical Data Analysis

A one-way ANOVA was performed using Design-Expert to determine the significance of the effects of the independent variables on the response. TPC and TAC were examined twice in duplicate. The mean values of the associated antioxidant capacities were reported with their standard deviations (±).

Results and Discussion

The experimental results of the RSM are shown in Table 1. The extraction yield ranged from 10.20 to 32.04 g /100 g dry peel. The highest yield (32.04) was obtained at 100°C for 6 h. The highest TPC (4232.32 mg GAE /100 g dry extract) was determined at 100°C for 4 h, and the highest TAC (2814.30 µmol Trolox/100 g dry extract) was determined at 100°C for 6 h. The optimal conditions for maximum EY, TPC and TAC were determined as 100°C for 5.26 h. which were within the range of the performed experiments. Design-Expert proposed a solution of 28.77 g/100 g dry peel; 3819.32 mg GAE /100 g dry extract; 2737.82 µmol Trolox/100 g dry extract as the responses of EY, TPC, and TAC at 100°C and 5.26 h, respectively. Validation of the proposed models was performed in triplicate and found for EY, TPC, and TAC as 28.07 ±0.69 g/100 g dry peel; 3762.15 ± 56.66 mg GAE /100 g dry extract; 2678.63 ± 59.26 µmol Trolox/100 g dry extract respectively. All validated results were determined within the confidence intervals (± 5%) of the expected results suggested by the Design Expert program.

The effects of the two independent variables (extraction temperature and time) on the responses were examined and individually optimized with CCD (Table 2a, 2b, and 2c). The adjusted coefficients of determination (R^2) for EY, TPC, and TAC were 0.9603, 0.9066 and 0.9614, respectively. For all responses, the quadratic model with the highest adjusted R^2 proved to be the best solution.

The proposed optimized parameters and the recommended models for all responses were able to satisfactorily explain the relationship between the independent variables and the responses.

Table 1. RSM Design and the Responses for the EY, TPC and DPPH of TPE

Run	Temperature (ºC)	Time (h)	EY (g/100 g dry peel)	TPC (mg GAE/100 g dry extract)	DPPH (µmol Trolox/100 g dry extract)
1	100	4.00	24.85	3769.42	2740.80
2	60	6.00	17.94	2929.70	1313.90
3	80	4.00	16.00	3425.82	1698.00
4	60	6.00	16.26	2635.82	1405.70
5	100	6.00	32.04	3332.62	2771.90
6	100	4.00	25.90	4232.32	2577.50
7	80	4.00	19.00	3487.34	1640.70
8	100	6.00	30.58	3498.12	2814.30
9	100	2.00	20.45	2854.12	2068.80
10	60	2.00	10.20	2394.22	1301.20
11	80	2.00	13.30	2371.20	1502.20
12	80	4.00	17.15	3694.17	1645.20
13	60	2.00	13.30	2349.50	1329.80
14	60	4.00	11.85	3348.13	1456.60
15	100	2.00	20.50	2875.58	2316.70
16	80	6.00	23.45	3035.90	1490.00
17	80	6.00	22.20	3040.42	1668.30
18	80	2.00	16.20	2464.94	1630.60
19	60	4.00	12.65	2999.37	1457.20

Table 2a. ANOVA table indicating the statistical data of EY for phenolic compounds from tomato peels

Source of variation	Sum of Squares	Degree of Freedom	Mean of Squares	F	P
Model [c]	663.15	5	132.63	88.16	< 0.0001 [a]
A-temperature	433.44	1	433.44	288.11	< 0.0001
B-time	196.18	1	196.18	130.40	< 0.0001
AB	15.04	1	15.04	10.00	0.0075
A^2	8.51	1	8.51	5.66	0.0334
B^2	8.21	1	8.21	5.46	0.0362
Residue	19.56	13	1.50		
Lack of Fit	1.84	3	0.61	0.35	0.7934 [b]
Pure Error	17.72	10	1.77		
Overall	682.71	18			

$EY = +24.02507 - 0.39419 \times A - 3.45866 \times B + 0.034281 \times A \times B + 3.4847 \times 10^{-3} \times A^2 + 0.34223 \times B^2$

[a] statistically significant at α=0.05

[b] statistically insignificant at α=0.05

[c] Adjusted R^2 = 0.9603 ; Predicted R^2 = 0.9375 ; Adequate Precision = 29.171

*A: Temperature (°C) ; B:Time (h)

Table 2b. ANOVA table indicating the statistical data of TPC of TPE obtained by alkali extraction

Source of variation	Sum of Squares	Degree of Freedom	Mean of Squares	F	P
Model [c]	4.645×10^6	5	9.290×10^5	35.94	< 0.0001 [a]
A-temperature	1.271×10^6	1	1.271×10^6	49.17	< 0.0001 [a]
B-time	8.337×10^5	1	8.337×10^5	32.25	< 0.0001 [a]
AB	9746.87	1	9746.87	0.38	0.5498
A^2	43510.23	1	43510.23	1.68	0.2170
B^2	2.527×10^6	1	2.527×10^6	97.77	< 0.0001 [a]
Residue	3.360×10^5	13	25849.41		
Lack of Fit	66050.42	3	22016.81	0.82	0.5141 [b]
Pure Error	2.700×10^5	10	26999.19		
Overall	4.981×10^6	18			

$TPC = +514.91014 - 27.08096 \times A + 1581.05685 \times B + 0.87263 \times A \times B + 0.24914 \times A^2 - 189.88429 \times B^2$

[a] statistically significant at α=0.05

[b] statistically insignificant at α=0.05

[c] Adjusted R^2 = 0.9066 ; Predicted R^2 = 0.8616 ; Adequate Precision = 18.142

*A: Temperature (°C) ; B:Time (h)

Table 2c. ANOVA table indicating the statistical data of TAC (DPPH) of TPE obtained by alkali extraction

Source of variation	Sum of Squares	Degree of Freedom	Mean of Squares	F	P
Model [c]	5.025×10^6	5	1.005×10^6	90.61	< 0.0001 [a]
A-temperature	4.113×10^6	1	4.113×10^6	370.87	< 0.0001 [a]
B-time	1.441×10^5	1	1.441×10^5	12.99	0.0032 [a]
AB	1.546×10^5	1	1.546×10^5	13.94	0.0025 [a]
A^2	5.796×10^5	1	5.796×10^5	52.26	< 0.0001 [a]
B^2	64698.17	1	64698.17	5.83	0.0312
Residue	1.442×10^5	13	11090.81		
Lack of Fit	68429.00	3	22809.67	3.01	0.0811 [b]
Pure Error	75751.49	10	7575.15		
Overall	5.169×10^6	18			

$TAC = +5564.77826 - 130.11835 \times A + 19.80616 \times B + 3.47531 \times A \times B + 0.90932 \times A^2 - 30.38098 \times B^2$

[a] statistically significant at α=0.05

[b] statistically insignificant at α=0.05

[c] Adjusted $R^2 = 0.9614$; Predicted $R^2 = 0.9377$; Adequate Precision = 24.484

*A: Temperature (°C) ; B:Time (h)

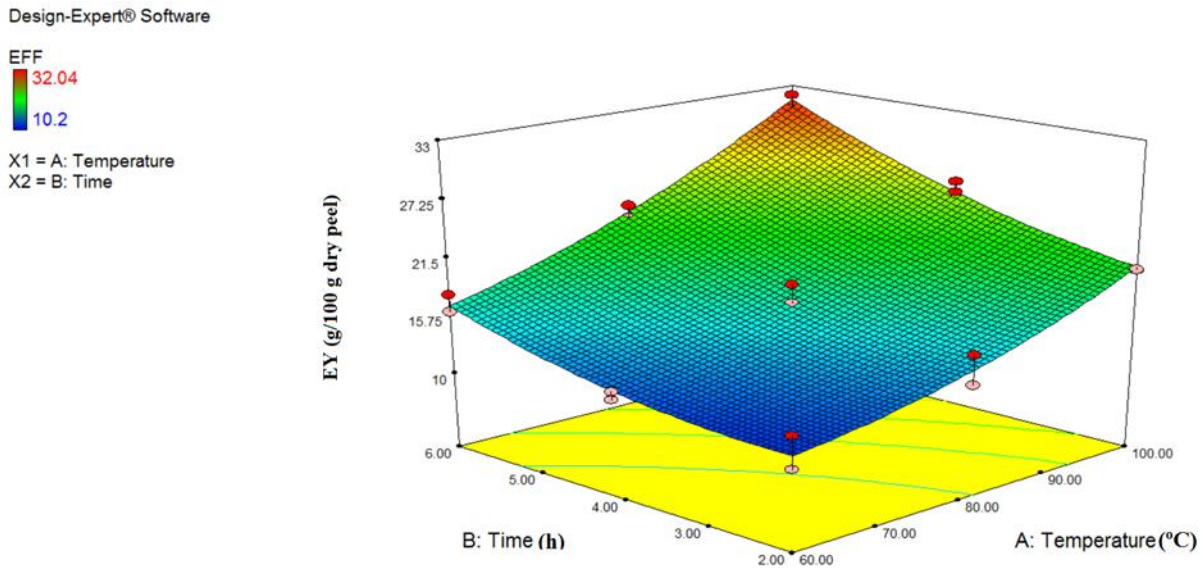

Figure 1. Effect of temperature and time on EY of tomato peels

The P-values reported in Table 2a, 2b, and 2c demonstrate the significance of the model (P<0.0001). Lack of fit was not significant (P>0.05), further confirming the significance of the model as the optimized conditions with acceptable desirability (D = 0.853).

Influence of Extraction Parameters on the EY of TPE

The significance of each variable was determined using the F-test and the p-value listed in Table 2 a. All the parameters investigated in this study (temperature, time, temperature-time interaction, square of temperature, square of time) significantly influenced EY (P<0.05). All parameters were found to have a positive effect on EY. Temperature and time as individual factors had the greatest effect. In other words, higher temperatures and longer extraction times improved the extraction yield (Figure 1). Bakic et al. (2019) reported that higher temperatures (90°C) facilitated the extraction of phenolic compounds from tomato peels, leading to an increase in the yield of microwave-assisted extraction. Recent studies reported an increase in EY of tomato peels with extraction time when extractions were performed at 130°C for 15 min and 2 h, with yields of 18% and 28%, respectively (Cifarelli et al., 2016). It was highlighted that longer extraction times (4-5 h) with alkali treatment of blueberries favoured the extraction of non-extractable polyphenols in the aqueous-organic solvent mixtures and significantly increased the yield (Cheng et al., 2014). These results are consistent with the findings of this study. The EY of tomato peels is also associated with the recovery of several alkali-and heat-labile cell wall polysaccharides such as cellulose, lignin, and pectin, which are present in considerable amounts in industrial tomato wastes (Nincevic Grassino et al., 2020; Szymanska-Chargot and Zdunek, 2013; Montoya Arbelaez et al., 2015; Mangut et al., 2006; Lopez-Casado et al., 2007). Depolymerization of pectin to galacturonic acid under alkaline conditions (Abang-Zaidel et al., 2017); depolymerization of phenolic lignin by oxidation with molecular oxygen to oxidation byproducts (i.e.., oxirane, muconic esters, or carbonyl structures) at strongly alkaline pH (Kalliola et al., 2015); and degradation of cellulose to arabinose and xylose by alkali hydrogen peroxide treatment (Sun et al., 2000) have been reported in previous studies. Therefore, it can be assumed that these polysaccharides may have made a significant contribution to the EY of TPE.

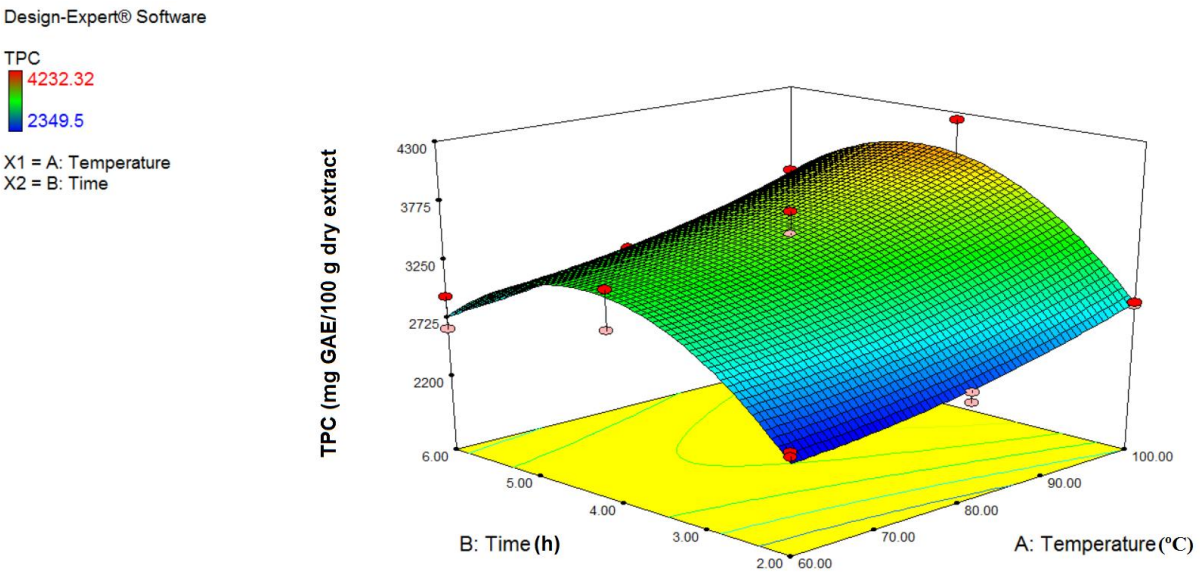

Figure 2. Effect of temperature and time on TPC of TPE

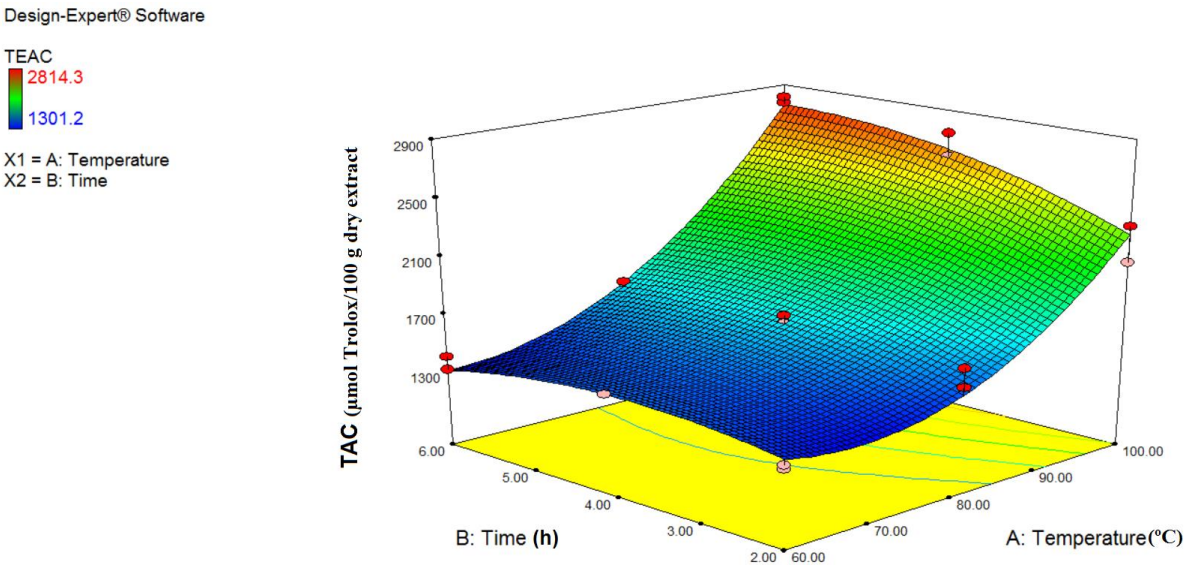

Figure 3. Effect of temperature and time on TAC of TPE

Influence of Extraction Parameters on the TPC of TPE

The influence of the independent variables on the TPC using ANOVA is shown in Table 2b. Among the parameters, temperature, time, and time square were found to be significant ($P<0.05$). The three-dimensional response surface diagram related to the total phenolic content of TPE is shown in Figure 2. The TPC increased linearly as the temperature increased from 60°C to 100°C. On the other hand, the TPC increased up to a certain period (5.26 h) and then decreased with time. According to Fick's second diffusion law, excessive time is unnecessary to extract more phenols if a final equilibrium between the solution concentration in the solid matrix and the bulk solution is reached after a certain time (Silva et al., 2007). This argument explains why time showed a quadratic effect on the TPC of TPE. The results are consistent with the study on RSM optimization of phenol extraction by alkali treatment from purple sweet potato (Meng et al., 2019) and blueberry (Cheng et al., 2014).

Influence of Extraction Factors on the TAC of TPE

The influence of the independent variables on TAC using the one-way method ANOVA was presented in Table 2c. It was found that all the parameters studied in the RSM have a significant influence on the TAC ($P<0.05$). It is obvious that temperature was the predominant driving force of alkali extraction as it affected TAC the most ($P<0.05$). Temperature showed a pronounced hyperbolic effect, leading to a significant increase in TAC when the temperature increased from 60°C to 100°C. On the other hand, extraction time had a slightly parabolic effect on TAC. That is, at low temperatures (60 and 80°C), longer extraction times resulted in an increase in TAC up to a certain period (4 h) and TAC decreased slightly after 6 h. At 100°C, TAC also increased with increasing duration, although TPC at this temperature decreased after 6 h. This result indicates that, in addition to the phenolic compounds extracted from tomato peels by the alkali treatment, there could be other compounds that could also have contributed significantly to the antioxidant capacity. These compounds could consist of different fatty acids such as linoleic and linolenic acids present in the outermost layer of tomato

peel (Benitez et al., 2018; Cifarelli et al., 2016), which do not react with the Folin-Ciolcalteu reagent (Everette et al., 2010).

Overall Evaluation of TPC and TAC

The results of this work show that alkali extraction combined with longer heat treatment allows higher TPC values (3762.15 ± 56.66 mg GAE /100 g dry extract) compared to the results of most studies using different extraction methods for tomato peel and pomace. Szabo et al. (2019a) reported an average TPC of 76 ± 4 mg GAE /100 g (ranging from 37 ± 2 to 155 ± 2 mg/100 g) in tomato peels of 10 cultivars by ultrasonic treatment for 60 min at 30°C using methanol (80% v/v). In another study, the TPC of 4 different cultivars of tomato peels was reported to range between 71-351 mg GAE /100 g DW obtained by ultrasonic extraction with methanol for 1 h (Valdez-Morales et al., 2014). The lower TPC of tomato peels compared to our result might be related to the different extraction methods. For example, Bryan-Gonzales et al. (2014) reported 6.5 ± 0.27 mg GAE /g dry waste TPC of alkali-treated cauliflower waste at 60°C for 2 h, which was extremely higher compared to the TPC of ultrasonicated cauliflower waste extract at 60°C for 15 min using methanol (1.5 ± 0.12 mg GAE /g dry waste) in the same study. Alkaline hydrolysis was the most commonly used and is generally considered the most effective method for releasing bound phenols (Bryan-Gonzales et al., 2014). The authors also noted that longer extraction times and higher temperatures may be required to extract more bound phenols from vegetable sources in which highly bound phenolic acids were present (Bryan-Gonzales et al., 2014). In addition, Nincevic Grassino et al. (2020) reported 2866 and 2626 mg GAE /100 g TPC from tomato peels extracted with 70% and 96% ethanol, respectively, for 6 h at solvent boiling temperatures. The results reported by Nincevic Grassino et al. (2020) were more comparable to our results, in contrast to those of other relevant studies. This could be due to the fact that in both studies heat was applied at high temperatures for a prolonged period of time during the extraction process.

Perea-Dominguez et al. (2018) performed sequential extraction of phenols including alkali/acid treatment from tomato pomace and found 7.33 mg GAE /g DW in the alkali fraction of the extracts. Although a multi-fractional separation process followed by acid and alkali treatment was performed, the TPC of industrial tomato by-products in the study by Perea-Dominguez et al. (2018) was much lower than our results, probably due to the absence of a heating process. Nenadis et al. (2013) reported that heating rice husks at 120°C for 2 h with 1 M NaOH improved the total polar phenolic content from 13206 (at 25°C for 24 h) to 14889 mg/kg DW. This result suggests that the extraction of polar phenols, which contribute more to the TAC of tomato peels compared to that of the lipophilic part of tomato peels (Navarro Gonzales et al., 2011) could be favoured by heat-induced alkali treatment.

On the other hand, various novel extraction methods such as microwave-assisted extraction (MAE) combined with heat application (Bakic et al., 2019) could be another alternative to extract phenolic compounds from TPE, since polar compounds are most affected by microwave radiation due to their high dielectric heat absorption capacity (Deepak and Gaikar, 2002). Bakic et al. (2019), conducted MAE and reported 78.06 g GAE / kg DW as TPC of tomato peels at 90°C for 10 min with methanol (70% v/v) at an irradiation power of 500 W, which was much higher than the TPC of TPE found in our study. However, compared to alkali extraction, the main disadvantage of MAE is the higher capital and operating costs, which limit its feasibility on an industrial basis.

It is also interesting that the TPC of TPE determined in this work was higher than those yielded by alkali extraction and reported for several agro-industrial wastes in literature. TPC of rice hull extracts was reported as 24300 mg GAE/kg dry hulls (Nenadis et al., 2013). TPC of carob wastes, potato peel, and white grape peels were determined as 13830; 9770 and 9700 mg GAE/kg DW respectively (Makris et al., 2007). All these issues indicate that tomato peels contain the highest amount of TPC among the agricultural wastes of several investigated fruits and vegetables. That's why the valorization of tomato peels should be considered with a higher priority.

Table 3. The phenolic profile of TPE by LC-MS/MS

Compound	Mean value (mg/100 g dry extract)	Std
3-4 Dihdroxyphenyl acetic acid	0.179	0.011
3 Hydroxy benzoic acid	0.358	0.032
4- hydroxy benzoic acid	7.131	1.005
Apigenin	0.061	0.018
Caffeic acid	0.135	0.009
Ferulic acid	12.442	2.057
Homovanillic acid	1.223	0.331
Luteolin-7 glucoside (Cynaroside)	0.010	0.001
p-Coumaric acid	429.989	38.532
Pinoresinol	0.015	0.001
Protocatechuic acid	0.166	0.013
Quercetin	0.300	0.018
Sinapic acid	0.083	0.005
Syringic acid	0.041	0.004
Vanillin	2.467	0.218
Verbascoside	0.011	0.002
TOTAL	454.610	53.234

TAC values in our study (2678.63 ± 59.26 µmol Trolox/100 g dry extract) represented higher or lower values compared to the results of several studies. In these studies, tomato peels were extracted by ultrasonication or maceration techniques. Szabo et al. (2019a) and Valdez-Morales et al. (2014) reported lower TAC values of industrially processed tomato peels which were ultrasonicated for 1 h using organic solvents as 201 ± 44 µmol TE /100 g and 47.9 ± 5.0 - 405.7 ± 29.7 µmol Trolox/100 g Trolox, respectively. On the other hand, Tamasi et al. (2019) reported higher TAC values of fresh tomato peels ultrasonicated for 15 min with methanol as 4691.2 ± 220.4 µmol Trolox/kg fresh weight. Muthukumarasamy et al. (2017) also reported lower TAC values for tomato peels extracted by maceration technique at room temperature for 14 days.

These results revealed that the method as well as the type of raw material (thermal history, pre-treatment, and processing conditions) play an important role on the extraction yield of the antioxidants and phenolic compounds from tomato peels. Furthermore, the difference in the results might also depend on genetic factors and different extraction conditions (temperature, time, solvent/solute ratio, and concentration of the solvent).

As a result, compared to ultrasound-assisted extraction and maceration, alkali-heat treatment is a more effective and powerful technique based on the extraction of phenolic compounds from tomato wastes. Furthermore, the results yielded by this method are higher than those obtained by ultrasound-assisted extraction and maceration method (Szabo et al., 2019a; Carillo Lopez and Yahia, 2013; Valdez-Morales et al., 2014; Muthukumarasamy et al., 2017)

Evaluation of Phenolic Compounds Profile by LC-MS/MS

Sixteen compounds (10 phenolic acids; 3 flavonoids; 1 phenolic aldehyde; 1 lignan; 1 acteoside) were identified and quantified in the TPE at optimized conditions. The quantification was shown in Table 3.

The results of LC-MS/MS analysis indicated that heat-induced alkali treatment of tomato peels for a prolonged time resulted in tremendous amounts of p-coumaric acid as the most abundant phenolic compound (430 mg/100 g dry extract) in the investigated samples. In the literature, its abundance in the tomato peels was reported in diverse quantities ranging from 0.64 to 1.57 mg/100 g DW in the unprocessed tomato peels (Valdes-Moralez et al., 2014); 0.40 mg/g DW in the alkali hydrolyzed fractions of tomato pomace as tomato paste by-product (Perea-Dominguez et al., 2018), in trace amounts in the unprocessed tomato peels (Tamasi et al., 2019). All of these results reported in literature are far below the content of p-coumaric acid in the tomato peels found in this study. We anticipate several factors such as the type of raw material (whether pomace or peel; either fresh or processed by-product), the type of solvent, the extraction conditions (temperature, time), the type of cultivar, and harvesting conditions might have had a crucial impact on this difference. The health-promoting aspects of p-coumaric acid was reported as i) the inhibition of the proliferation and migration of cancer cells (Janicke et al., 2011; Nasr Bouzaiene et al., 2015; Jaganathan et al., 2013; Roy et al., 2016) ; ii) acting as an antioxidant and antimicrobial agent (Boz, 2015; Lou et al., 2012); iii) antimelanogenic effect based on the inhibition of tyrosinase (An et al., 2010; Seu et al., 2011; Boo, 2019) ; iv) as a copolymer of biomaterials produced to heal wounded skins (Contardi et al., 2019); v) anti-inflammatory effect based on increasing serum immunoglobulin levels (Pragasam et al., 2013). All these arguments indicate the health benefits of TPE rich in p-coumaric acid yielded by alkali-heat treatment. Thus, the use of alkali-digested TPE in cosmetics and medicine should be strongly recommended.

Ferulic acid was found as the second most abundant phenolic compound in our study. Its abundance (12.44 mg/100 g DW) was considerably lower compared to the results 0.70 mg/g DW) reported by Perea-Dominguez et al. (2018). A fractional separation process was performed on the dewaxed tomato by-products with hydroalcoholic solvent extraction followed by alkali and acid hydrolysis to recover free and bound phenolics separately (Perea-Dominguez et al., 2018). On the other hand, the results of this study were substantially higher than the amounts (1.36-4.56 mg/100 g DW) reported by Valdes-Moralez et al. (2014). The authors performed an ultrasonication for 1 h using methanol for the extraction of bioactive compounds from freeze-dried tomato peels.

It seems that processing tomatoes into pastes and using alkali treatment might have increased the amount of some individual phenolics substantially when compared to the results of Tamasi et al (2019). Tamasi et al. (2019) investigated the phenolic profile of fresh tomato skins and found p-coumaric acid and ferulic acid amounts in trace amounts and below the limits of quantification respectively. The dominant effect of alkali treatment on the substantial increase in the individual content of p-coumaric acid and ferulic acid was also shown in wheat bran (Kim et al., 2006). In addition, the superiority of alkali treatment during the extraction of phenolics from rice husk compared to other methods (75% ethanol-soxhlet, acid hydrolysis) was also reported (Vadivel and Brindha, 2015). The same scientists pointed out 25 times and 43 times increase in the p-coumaric acid and ferulic acid contents by alkali treatment compared to those obtained by acid hydrolysis respectively.

We consider that the temperature has a positive effect on the alkali extraction of tomato peels because the results obtained without heat treatment (Perea-Dominguez et al., 2018) were much lower compared to our results. Several monocyclic phenolic compounds such as chlorogenic and gallic acid were not detected in TPE probably due to their low stability at alkali pH where strong alkali medium destroyed the structure of these polyphenols after they were released from the food matrice (Meng et al., 2019). On the other hand, caffeic acid was detected in minor amounts in the TPE in spite of its monocyclic structure probably, because of the conversion of chlorogenic acid into caffeic acid at alkali pH (Carrillo-Lopez and Yahia, 2013). Since ionized and resonance form of multi-ring aromatic structures such as p-coumaric acid, and ferulic acid was more resistant to severe alkalinity (Sun et al., 2017), they were highly abundant in TPE investigated in this study.

Conclusion

Consequently, tomato peels contain an appreciable amount of phenolic compounds with a wide variety and substantial TAC. Among all investigated phenolic substances, p-coumaric acid is the most abundant phenolic present in alkali-digested tomato peels. From the ecological and economic point of view, the valorization of tomato peels is necessary to reduce the food losses created by food processing. Heat-induced alkali treatment is an effective method to extract the bound phenolics in tomato peels. The results of the optimization revealed that temperature and time have crucial roles in the EY, TPC and TAC of TPE. It is expected that the gained knowledge based on this work could be also practiced for other agro-industrial wastes within the framework of sustainability to produce functional ingredients to be used by different industries.

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Declaration of Conflict of Interest

The authors hereby declare no conflict of interest.

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