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Optimization of ultrasound-assisted extraction of apple peel using central composite design for extractive yield, phenolic content, and antioxidant activity

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Abstract
Malaria remains a global health challenge, with increasing interest in plant-based therapies as potential The study was designed to optimize the ultrasound-assisted extraction (UAE) of apple peel using a central composite design (CCD) for extractive yield, total phenolic content (TPC), and antioxidant activity. The Lal-Ambri variety of apples was subjected to UAE in the present study. A probe sonicator was used for the extraction process with variable time (3.96 to 11.03 min) and temperature (35.85 to 64.14) as per CCD. The full quadratic model showed significant ($P < 0.05$) effects of time and temperature on extractive yield, TPC, and antioxidant activity. The model equation showed a significant ($P < 0.05$) negative coefficient of the interaction of time and temperature on extractive yield and a significant ($P < 0.05$) negative coefficient of time, temperature, and their interaction on TPC. The results indicated that extractive yield, TPC, and antioxidant activity decrease when time and temperature exceed certain limits. The optimized value for UAE time and temperature was found to be 7.29 min and 46.92 ^{0}C for maximum product response. The results suggest that 7-8 min at 45-50 ^{0}C may be sufficient for UAE extraction process. The research work is suggested to investigate additional variables to further enhance the efficiency and applicability of UAE in extracting phytoconstituents from plant materials.

Keywords: Ultrasound-assisted extraction, Central composite design, Response surface methodology, Apple peel extract, Total phenolic contents, Antioxidant activity

Introduction
It is well-known that the extraction process is the key step in recovering or isolating phytoconstituents from the plants. Currently, there are several methods available for extraction but have their limitations, like solvent extraction methods require a huge amount of solvent and time, mechanical expelling has low yield, supercritical fluid extractions enhance the economic burden, and microwave-assisted extraction requires aqueous phase [1-3]. When compared to these methods, ultrasound-assisted extraction (UAE) has many merits. UAE method is a solvent, time, economy, and energy-efficient technology for the extraction process. Besides, it allows multiple solvents (polar to non-polar) and temperatures and produces better yield as compared to conventional extraction methods [2, 4].

In the past few years, ultrasound has been an emerging technology for the food and pharmaceutical industries, such as formulation, extraction, degassing, and emulsification [5]. UAE produces a high sound wave, which destroys the tissues or cells through cavitation effects and helps in the release of phytoconstituents without changing their chemical nature [6]. There are several variables associated with the UAE technology such as frequency, power, pulse cycle, temperature, time, solvent type, and solid-liquid ratio that affect the extraction process, which needs to be optimized to enhance the efficiency of UAE [2]. A plethora of research revealed the various conditions for extraction by UEA [2, 7, 8]. Temperature and time are the most important factors in UAE which were studied in the present study. The optimum temperature must be maintained during the extraction process, generally depending on the plants and phytoconstituents that are extracted. In general hypothesis, initially increases the yield of extraction with temperature and time and further decreases, similar to the effect caused by power, additionally beyond the optimum limits phytoconstituents may be degraded, therefore it must be under critical limits [2].

It is revealed, that fruit waste like peels have more antioxidant potential than its pulp. It contains a rich amount of different phenolic compounds like carotenoids, anthocyanins,

flavonoids, and phenolic acids, even higher than that of pulp [9, 10]. In this study, we optimize the UAE process for apple peel. Apple belongs to the Rosaceae family. A plethora of epidemiological and traditional studies revealed that apples in a regular diet may have beneficial effects in a variety of diseases including diabetes, hypertension, cardiovascular diseases, asthma, and cancer [11]. additionally, it has several pharmacological activities including antioxidants [10], anticancer [12], anti-ischemic [9], antihyperlipidemic [13], and antidiabetic activity [14]. Apple peels show a variety of polyphenols like catechins, rutin, quercitrin, phloridzin, phloretin, and chlorogenic acid [15]. Therefore, in this study, we optimized ultrasound-assistant extraction of apple peel to enhance the extraction efficiency and therapeutic values.

Materials and Methods

Plant collection

Lal-Ambri variety of apples (a cross between Red Delicious and Ambari apples) were used in this study. It is widely cultivated in India, especially in Jammu-Kashmir, Himachal Pradesh, and Uttaranchal states. Apple was purchased from the local market of Bhilai-490020, India in October 2024. Apples were washed with distilled water, and peeled by a peeler knife thereafter left to natural shaded dry. Thereafter, dried apple peels were reduced to a coarse powder and kept in an airtight container until use.

Ultrasound-sound assisted extraction

Probe sonicator (Labman Pro-656, Labman Scientific Instrument Pvt. Ltd., India) was used for extraction process with constant probe (6 mm), power rate (30%), pulse rate (2 sec. on-2 sec. off), solvent (50% v/v methanol) and solid-liquid ratio (1:5) and variable time and temperature as per central composite design (CCD) of response surface methodology (RSM). The extractions were filtered by Whatman filter paper under vacuumed pressure and the solvent was evaporated under reduced pressure at 50 ^{0}C to achieve concentrated viscous extract. The final extracts were kept in an amber color bottle and stored at 2-8 ^{0}C until analysis.

Experimental design

CCD was used to assess the co-relationship between the dependent variables (extractive yield, TPC, and antioxidant activity) and two independent variables (time and temperature). Independent variables or factors, time was set to 5 (-1) and 10 (+1) and temperature was set to 40 (-1) and 60 (+1) ^{0}C in the software. CCD generated of these two factors at 5 levels (-α, -1, 0, +1, +α). Twenty-seven experiments were carried out (4x3 factorial, 4x3 axials, and 1x3 Centre) described in Table 1. Design expert-13 (Stat-Ease Inc, USA) was used to develop CCD and analyze it statistically. The full quadratic model equation is as follows:

$$Y=\beta_0 + \beta_1 A + \beta_2 B + \beta_{12} AB + \beta_{11} A^2 + \beta_{22} B^2 + \epsilon \quad (1)$$

Where Y is the product response, A and B are the selected independent variables (time and temperature), β_0 is the constant values, other β is the respective coefficients for the respective variable and ϵ is the error.

Table 1: Central composite design for the set of experiments.

Run Orders	Space Type	Time (min) (X1: A)	Temperature (^{0}C) (X2: B)	Coded Level (A, B)
1	Axial	3.96	50	-α, 0
2	Factorial	10	60	+1, +1
3	Axial	7.5	64.14	0, +α
4	Axial	7.5	64.14	0, +α
5	Factorial	5	60	-1, +1
6	Factorial	5	40	-1, -1
7	Axial	11.03	50	+α, 0
8	Factorial	10	40	+1, -1
9	Axial	7.5	35.85	0, -α
10	Factorial	5	40	-1, -1
11	Factorial	5	60	-1, +1
12	Center	7.5	50	0, 0
13	Axial	3.96	50	-α, 0
14	Factorial	5	40	-1, -1
15	Axial	11.03	50	+α, 0
16	Factorial	5	60	-1, +1
17	Axial	11.03	50	+α, 0
18	Axial	7.5	35.85	0, -α
19	Center	7.5	50	0, 0
20	Axial	3.96	50	-α, 0
21	Center	7.5	50	0, 0
22	Axial	7.5	35.85	0, -α
23	Factorial	10	60	+1, +1
24	Factorial	10	40	+1, -1
25	Axial	7.5	64.14	0, +α
26	Factorial	10	60	+1, +1
27	Factorial	10	40	+1, -1

* Time 3.96 was set to 4 11.03 was set to 11 min and temperature 64.14 was set to 64 and 35.85 was set to 36 in the probe-sonicator. -α, -1, 0, +1, +α are the coded level of the experimental design

Determination of extractive yield

The dried extract weight of each sample was measured and extractive yield was calculated by using the following formula:

Extractive yield (mg/g) = Weight of dry extract (mg)/ Weight of powdered drug (g)

Total phenolic content (TPC)

The total phenolic content in the test samples was determined by spectrophotometric method (UV-1780, Shimadzu, USA) using the Folin-Ciocalteu reagent [16]. Briefly, a 1 ml extract sample (100 ug/ml in methanol) was reacted with 2 ml of 10 % v/v Folin-Ciocalteu reagent and kept for 5 min at room temperature. Thereafter, 2 ml of 6% sodium carbonate was mixed in the reaction mixture. After 90 min, the colored product was read at 725 nm against blank. The TPC (mg gallic acid equivalent/1g dry weight) was calculated by using a standard curve of gallic acid (2-20 ug/ml).

Antioxidant activity

Antioxidant activity was determined by DPPH (2,2-diphenyl-1-picrylhydrazyl) free radicle scavenging activity [17]. Briefly, 1 ml of the test sample (100 ug/ml in methanol) was mixed with 3 ml of DPPH (0.1 mM in methanol) and kept in the dark at room temperature for 30 min. Thereafter a colored product was read at 517 nm against the blank. The percentage inhibition or scavenging activity was calculated by using the following formula:

Scavenging activity (%) = [(Ac-As)/Ac] x 100

Where Ac is the absorbance of DPPH control and as is the absorbance of the sample.

Results and Discussion

CCD is the most common and widely used statistical model or tool for optimization in RSM. It offers great flexibility and can be designed for full factorial (2^k) or fractional (2^{k-p}) design with additional axial and central points and can accommodate a full quadratic model [18]. In the current study, I have taken two independent variables time and temperature, which affect most of UAE. The variation in time and temperature was selected based on the previous study [2, 7]. The responses (extractive yield, TPC, and antioxidant activity) concerning independent variables (time and temperature) are presented in Table 2. The present work was performed to analyze the influence of time and temperature on the product response and optimize the conditions of UAE using CCD of RSM. The observed results are provided in the below-mentioned section.

Effects of individual factor

Effects of extraction time

Extraction time is one of the most important factors in achieving the desirable dependent variable. The result (Figure 1) showed that extractive yield, TPC, and antioxidant activity were considerably altered in a time-dependent manner. As per the point prediction analysis with a constant temperature at 50 ^{0}C, within 5-10 min, the extractive yield (SD = 10.31) increased from 241.65 to 275.108 mg/g, and thereafter reduced to 249.1 mg/g, when the time was over 7.7 min. Similar results were observed in TPC and antioxidant activity, TPC (SD = 16.08) increased 270.07 to 282.19 mgE GA/g and then decreased to 218.21 mgE GA/g, when the time was over 7.1 min. Antioxidant activity (SD = 1.78) increased from 84.08 to 84.76 % and then decreased to 82.67 % when the time was over 6.8 min. The results indicated that 6.5 to 7.5 min is sufficient to achieve maximum efficiency.

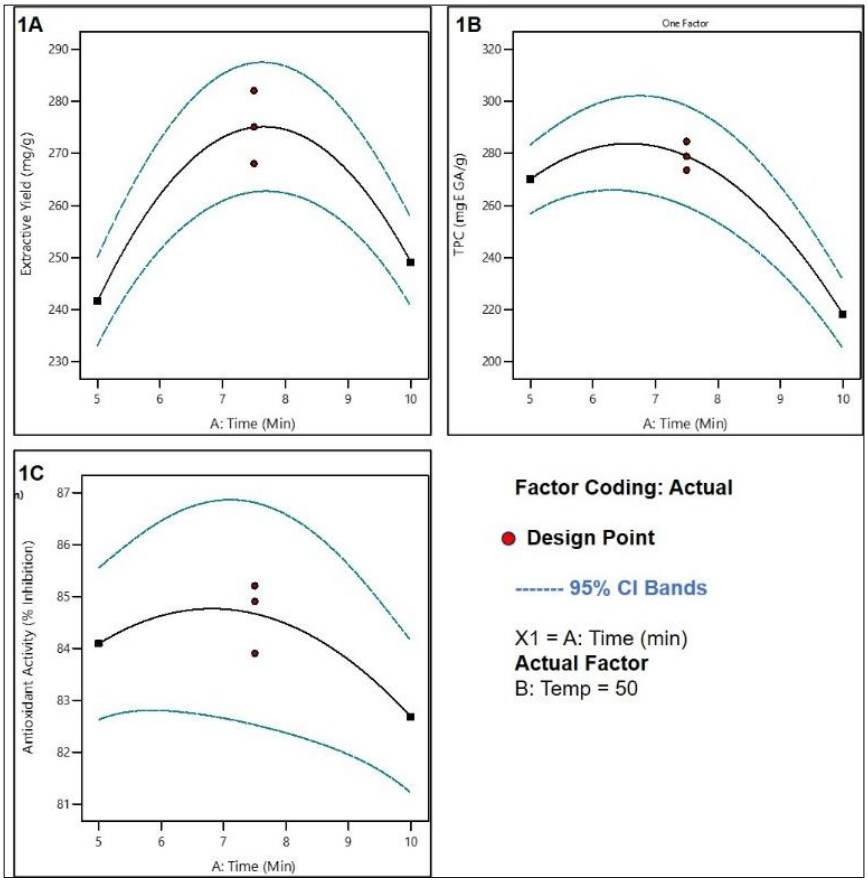

Fig 1: Effect of ultrasound-assisted extraction time on extractive yield (A), total phenolic content (B), and antioxidant activity (C).

Previously, extraction time effects on the yield of phytoconstituents have been well explored. Initially, yield increases with the sonication time and then further decreases with the time. Initially, ultrasound enhances the hydration, swelling, fragmentation, and pore formation by cavitation effect. Later long-term exposure to the ultrasound causes structural damage and decreases the yield [2]. Similar trends have been reported for phenolic content extraction from waste spent coffee grounds [19], black chokeberry waste [20], antioxidants polysaccharide extraction from signaling stem [21], pectin extraction from jackfruit peel [22], banana peel [23], and pomegranate peel [24].

Effects of extraction temperature

It is well-known that high temperature led to thermal degradation of the active compounds, which is shown in the study (Figure 2) similar to UAE time. At a constant time of 7.5 min, within 40 to 60 ^{0}C, the extractive yield increased from 257.44 to 275.07 mg/g and thereafter reduced to 252.63 mg, when the temperature was over 49.4 ^{0}C. TPC increased from 278.84 to 286.29 mgE GA/g and then decreased to 219.80 mgE GA/g when the temperature was over 45 ^{0}C. Antioxidant activity increased from 84.00 to 84.76 % and then decreased to 82.50 % when the temperature was over 47.4 ^{0}C. The results indicated that 45 to 50 ^{0}C is sufficient to achieve maximum UAE efficiency.

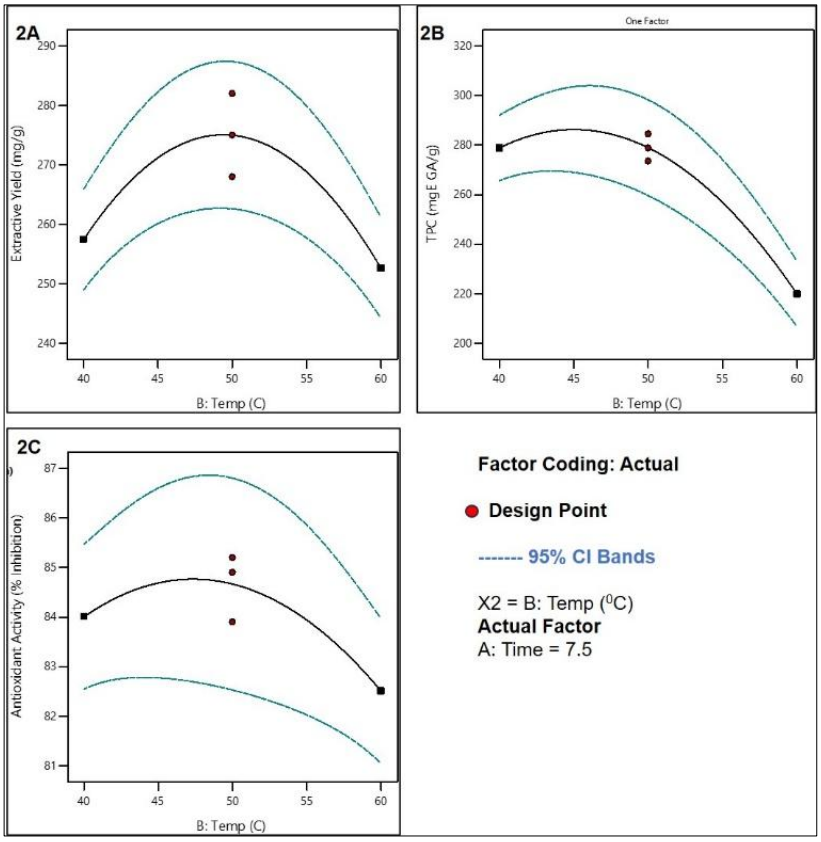

Fig 2: Effect of ultrasound-assisted extraction temperature on extractive yield (2A), total phenolic content (2B), and antioxidant activity (2C).

Initially, UAE extractive yield increases with the temperature by the dual effect on solvent and solute. Initially, temperature increases the solubility of solute and decreases the viscosity of solvent, resulting in more diffusivity of solvent in the tissue matrix. Further decreasing the UAE yield might be due to a weekend of cavitation effects and structural damages at higher temperatures [2]. This observation is corroborated by the other research. Al-Dhabi *et al*. observed that extraction of phenolic compounds from waste spent coffee ground in UAE, the initial yield increased with the temperature (30 to 45 ^{0}C), and over 45 ^{0}C the yield decreased [19]. Similar trends have been observed for pectin from pomegranate peel [24] and grapefruit peel [25], flavonoids from hawthorn seeds [26], and anti-oxidant polysaccharide from sijiaoling stem [21]

Fit of RSM model

Table 2 provides the response of combinations of independent variables (time and temperature) to dependent variables (extractive yield, TPC, and antioxidant activity). The results were fitted by the full quadratic model using Design-Expert. The analysis of variance (ANOVA) for a fitted model of various responses is presented in Table 3. As per the statistical results, the fitted model was significantly ($P < 0.05$) affected by the time and temperature. The determination coefficient (R^2) computed was more desirable for extractive yield (R^2 = 0.8169) and TPC (R^2 = 0.9073) than antioxidant activity (R^2 = 0.4190). The predicted R^2 for extractive yield (pred-R^2 = 0.7072) and TPC (pred-R^2 = 0.8514) was found better corelative between the predicted values and actual values (Figure 3) than antioxidant activity (pred-R^2 = 0.0677). This observation indicated that time and temperature majorly affect the extractive yield and TPC. The difference between pred-R2 and adj-R2 was found <0.2, suggesting reasonable agreement between them [5] in the case of extractive yield and TPC. The adequate precision was found between 5.54 to 18.42 for all, suggesting an ideal and adequacy of the model. The coefficient of variation (CV) was found in the range between 2.17 to 7.26 %, which suggests the repeatability and precision of the model. The results suggested that extractive yield and TPC are well correlated and affected by the selected dependent variable, i.e., time and temperature.

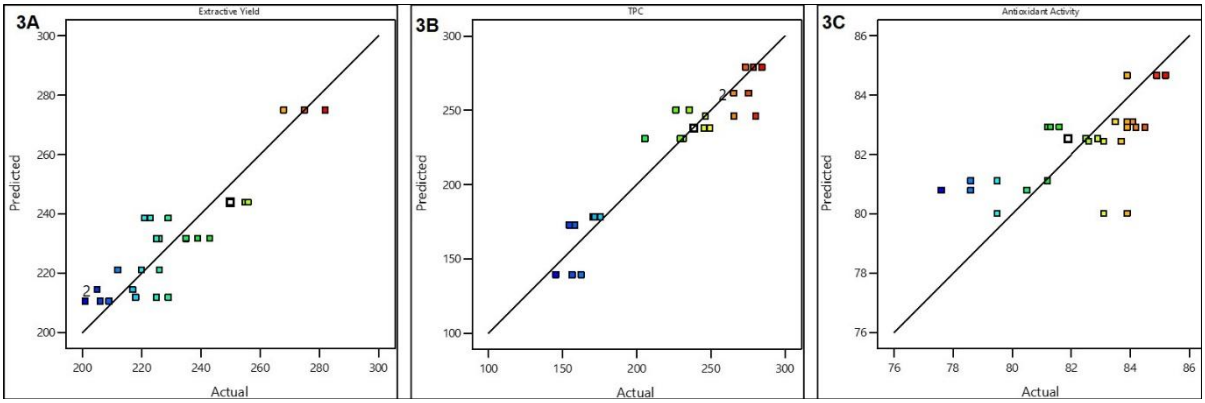

Fig 3: Predicted values vs actual values for extractive yield (3A), total phenolic content (3B), and antioxidant activity (3C).

Table 2: Effects of time and temperature on extractive yield, total phenolic content, and antioxidant activity.

Std	Run	Time (min)	Temp (^{0}C)	Extractive Yield (mg/g)	Total Phenolic content (mgE GA/g)	Antioxidant Activity (% Inhibition)
13	1	3.96	50	209	265.6	84.1
11	2	10	60	217	156.5	79.5
24	3	7.5	64.14	235	175.6	77.6
23	4	7.5	64.14	239	171.5	80.5
9	5	5	60	225	229.5	83.7
2	6	5	40	225	235.6	81.2
17	7	11.0355	50	226	158.5	78.6
6	8	10	40	256	245.5	82.5
21	9	7.5	35.85	229	265.5	84.2
1	10	5	40	218	235.5	81.6
7	11	5	60	226	205.6	82.6
27	12	7.5	50	268	278.8	83.9
14	13	3.96	50	201	280.3	83.5
3	14	5	40	229	226.5	81.3
18	15	11.03	50	212	154.6	81.2
8	16	5	60	235	231.5	83.1
16	17	11.03	50	220	156.6	79.5
20	18	7.5	35.85	221	275.6	83.9
26	19	7.5	50	282	284.5	84.9
15	20	3.96	50	206	246.5	83.9
25	21	7.5	50	275	273.5	85.2
19	22	7.5	35.85	223	265.5	84.5
12	23	10	60	205	162.6	83.9
4	24	10	40	250	238.6	81.9
22	25	7.5	64.14	243	170.6	78.6
10	26	10	60	205	145.5	83.1
5	27	10	40	255	249.5	82.9

Table 3: Analysis of variance for the fit of data to response surface model.

Source	Sum of Squares	Df	Mean Square	F-value	p-value
Extractive Yield					
Model	9974.76	5	1994.95	18.74	< 0.0001*
A-Time	332.99	1	332.99	3.13	0.0915
B-Temp	139.08	1	139.08	1.31	0.2659
AB	1825.33	1	1825.33	17.15	0.0005*
A^2	7659.41	1	7659.41	71.96	< 0.0001*
B^2	3476.38	1	3476.38	32.66	< 0.0001*
Residual	2235.09	21	106.43		
Lack of Fit	1699.76	3	566.59	19.05	< 0.0001*
Pure Error	535.33	18	29.74		
Cor Total	12209.85	26			
R^2	0.8169				
Adjusted R^2	0.7734				
Predicted R^2	0.7027				
Adeq Precision	13.2662				
CV %	4.47				
TPC					
Model	53160.97	5	10632.19	41.09	< 0.0001*
A-Time	16139.18	1	16139.18	62.37	< 0.0001*
B-Temp	20919.42	1	20919.42	80.85	< 0.0001*
AB	4720.33	1	4720.33	18.24	0.0003*
A^2	10564.02	1	10564.02	40.83	< 0.0001*
B^2	7650.79	1	7650.79	29.57	< 0.0001*
Residual	5433.90	21	258.76		
Lack of Fit	4028.14	3	1342.71	17.19	< 0.0001*
Pure Error	1405.75	18	78.10		

Cor Total	58594.87	26			
R^2	0.9073				
Adjusted R^2	0.8852				
Predicted R^2	0.8514				
Adeq Precision	18.4214				
CV %	7.26				
Antioxidant Activity					
Model	48.06	5	9.61	3.03	0.0327*
A-Time	11.98	1	11.98	3.77	0.0656
B-Temp	13.48	1	13.48	4.25	0.0519
AB	3.10	1	3.10	0.9770	0.3342
A^2	14.37	1	14.37	4.53	0.0453*
B^2	17.31	1	17.31	5.45	0.0295*
Residual	66.65	21	3.17		
Lack of Fit	45.34	3	15.11	12.77	0.0001*
Pure Error	21.31	18	1.18		
Cor Total	114.71	26			
R^2	0.4190				
Adjusted R^2	0.2807				
Predicted R^2	0.0677				
Adeq Precision	5.5439				
CV %	2.17				

*$P < 0.05$ is considered as significant.

Observation in contour and 3D surface Plot

Figure 4 depicts the influence of each variable and the interaction between them on product responses using a contour and 3-D surface graph. In a 3D surface plot, the sharper the surface plot, the more pronounced the interaction between the variables, which was observed in this study. The contour plot is the lower projection of the reaction surface and represents the interaction between two factors. In the present study, we observed the elliptical contour plots, which indicate a significant interaction between variables [5].

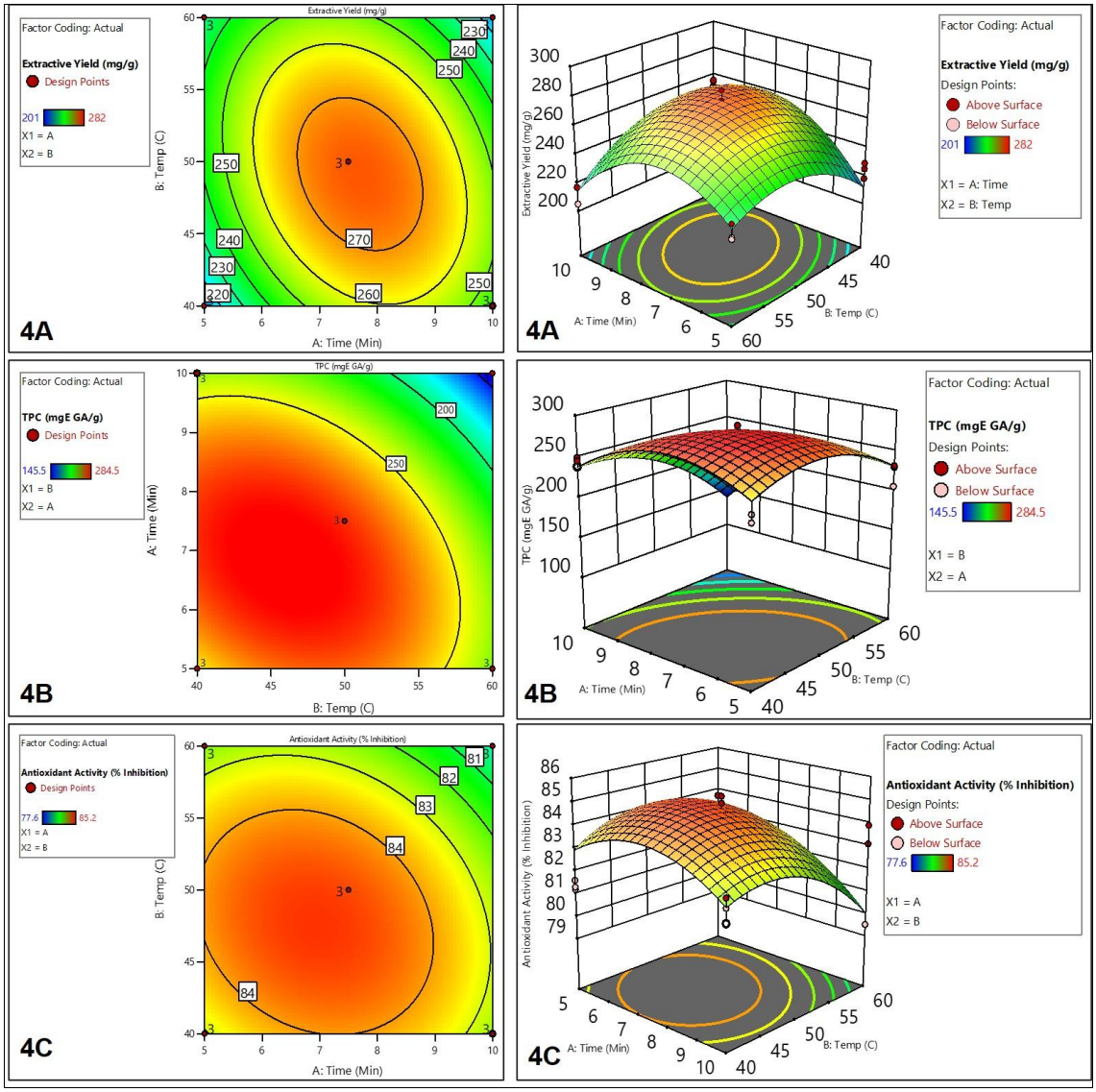

Fig 4: Contour plots and 3D response surface plots for interaction between time and temperature on extractive yield (4A), total phenolic content (4B), and antioxidant activity (4C).

Effects on product response and model equation

Extractive Yield

The extractive value was found to range between 201 to 282 mg/g (Table 2). The predicted coded equation for the extractive yield is described below (equation 2):

$$\text{Extractive yield} = 275 + 3.72\ A - 2.40\ B - 12.33\ AB - 29.62\ A^2 - 19.95\ B^2 \quad (2)$$

Equation 2 provided the information the coefficient of time (A) is positive indicating the extractive yield increases with time and the coefficient of temperature (b) is negative indicating the extractive yield decreases with the temperature, but these effects were found non-significant. Moreover, their interaction was found significant ($P < 0.05$, Table 3) negative coefficient, suggesting that a longer time with a higher temperature significantly decreased the extractive yield, which is shown in the contour and 3D surface graph (Figure 4A).

Total phenolic Contents

Total phenolic content was found in the range of 145.5 to 284.5 mgE GA/g (Table 2). The predicted coded equation for the TPC is described below (equation 3).

$$TPC = 278.93 - 25.93\ A - 25.52\ B - 19.83\ AB - 34.79\ A^2 - 29.60\ B^2 \quad (3)$$

Equation 3 and Table 3 showed significant ($P < 0.05$) negative coefficients of time, temperature, and their interaction on TPC that is reflected in the contour and 3D surface plot (Figure 4B). As discussed above, at higher temperatures for a longer time UAE may degrade the chemical nature of phytoconstituents, which was reflected in the results.

Antioxidant activity

The apple peel extracts at 100 ug/ml showed 77.6 to 85.2 % of DPPH scavenging activity (Table 2). The predicted coded equation (equation 4) showed a non-significant negative coefficient of time, temperature, and their interaction on antioxidant activity.

$$\text{Antioxidant Activity} = 84.66 - 0.70\ A - 0.74\ B - 0.50\ AB - 1.28\ A^2 - 1.40\ B^2 \quad (4)$$

A slight decrease in antioxidant activity with time and temperature might be due to TPC which is mainly responsible for antioxidant activity. Moreover, to analyze the antioxidant potential of plant extracts, a multiple mechanism and reactions may be involved. Unfortunately, no single antioxidant assay method is available to accurately reflect the total antioxidant potential due to the complexity of phytoconstituents [27].

Optimization

By using optimization numerical tools in Design expert software and covering our criteria (time and temperature goal set to in range and product response goal set to maximize with a confidence interval, alpha- 0.05), the best solution was selected for the extraction based on desirability value (0.825, Figure 5). The optimized values were found at 7.29 min and 46.92 ^{0}C. The predicted response of extractive yield, TPC, and antioxidant activity was found to be 273.0 mg/g, 286.64 mgE GA/g, and 84.80 % respectively. For confirmation, extraction was performed with 7.3 min at 47 ^{0}C in triplicate and the mean response of extractive yield, TPC, and antioxidant activity was found to be 271.56 mg/g, 283.2 mgE GA/g, and 83.6 % respectively, which is quite similar as the predicted value

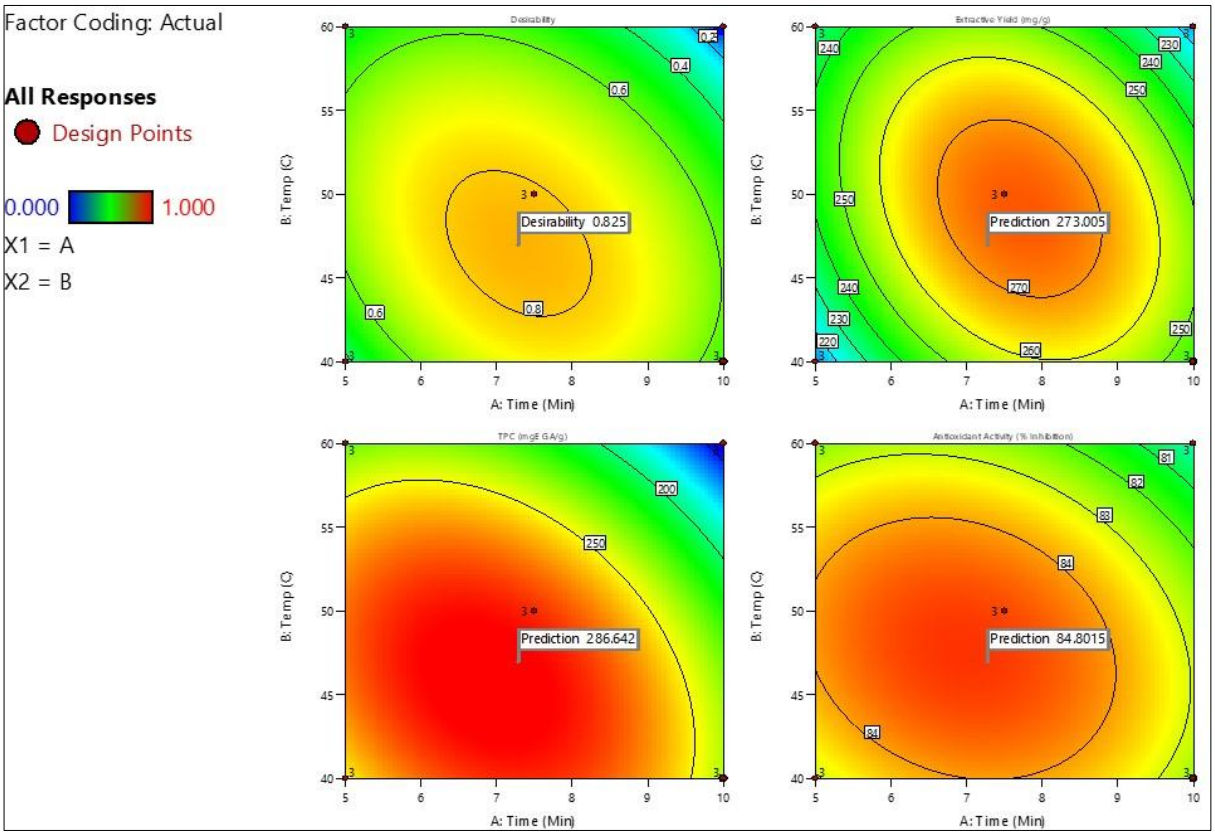

Fig 5: Desirability function response.

Conclusion

Based on the findings, the study concluded that UAE is an efficient extraction process over the conventional technique, emphasizing its ability to enhance the quality of yield while minimizing the extraction time. The study highlighted the role of UAE time and temperature in the product response. Initially, within the critical limit extractive yield, TPC and antioxidant activity increased with time and temperature and thereafter decreased due to the degradation of phytoconstituents. The UAE process was optimized by using the CCD-RSM model, which demonstrated good precision and repeatability and showed a desirable correlation between extractive yield and TPC. The RSM model showed significant effects of time and temperature on extractive yield, TPC, and antioxidant activity. The optimized value for UAE time and temperature was found to be 7.29 min and 46.92 ^{0}C for maximum product response. The results suggest that 7-8 min at 45-50 ^{0}C may be sufficient for the UAE extraction process but it also has several limitations. Other factors like plant materials, solvent type, power, and solid-liquid ratio may also influence the productive yield, which need to be explored in the future.

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Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article

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