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Box-Behnken design based optimization of phenolic extractions from *Polygonum equisetiforme* roots linked to its antioxidant and antibacterial efficiencies

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Purpose: The *Polygonum equisetifome* is a prospective plant source of high protein, unsaturated fatty acids, and useful safe bioactive molecules. Therefore, the aim of this study was to optimize the ultrasonic aqueous extraction of phenols from *P. equisetifome* roots using Box-Behnken design based statistical modeling, and to evaluate the antioxidant and antibacterial efficiencies of *P. equisetifome* root extracts against pathogenic bacteria.

Methods: In this study, the box-behnken design was used to optimize the extraction of phenols. The extraction temperature (30–70°C), ultrasound assisted extraction (UAE) time (1–9 min), and liquid-solid ratio (35–45 mL/g) were investigated as the factors that influence the phenolic yield (Y1) and their DPPH (1,1-diphenyl-2-picrylhydrazyl) scavenging activity (Y2).

Results: The optimal conditions for both responses were 50°C, 5 min, and 40 mL/g. At these conditions, Y1 reached its maximum to be 45.321 mg GAE/g dry weight and Y2 to be 120.354 μmol Trolox/g dry weight. The *P. equisetifome* roots contained water soluble phenol, high anthocyanin, and condensed tannins. Interestingly, the *P. equisetifome* extracts showed a relation to its antioxidant and antibacterial activities, FRAP (Ferric-reducing/antioxidant power), and ABTS scavenging activity were determined. The morphological and physico-chemical features of the extract were analyzed using SEM-EDX, FT-IR, and minimum inhibitory concentration (MIC) was analyzed against several pathogenic bacteria. The antibacterial activity of the extract showed that the extract is more efficient against Staphylococcus aureus, while the *P. equisetifome* extracts showed efficient MIC against *S. aureus*, followed by Bacillus cereus.

Suggestions: The relation of *P. equisetifome* extracts to its antioxidant, and antibacterial efficiencies open a new avenue of their potential uses in the food and pharmaceutical industries.

KEYWORDS

biological activities, Box-Behnken design, chemical characterization, *P. equisetiforme* roots, water-soluble phenolic compounds, ultrasonic-assisted extraction

Introduction

Polygonaceae family composes over that 40 genera are the excellent source of food and potential pharmacological agents wherein several species of the *Polygonum* genus are extensively used in folk medicine globally (Mahmoudi et al., 2018). The polygonum genus comprises over 150 species in Asia, America and Europe, which are used to treat dermatitis, dysentery, diarrhea, and skin infections, (Koochak et al., 2010; Mahmoudi et al., 2018). Thus, extensive study in polygonum genus is crucial from food and pharmacological interest. *Polygonum equisetiforme* is a perennial herb belongs to the Polygonaceae family (Asensi and Díez-Garretas, 2011). *P. equisetiform* grows in large area in Tunisia, platicity of plants help to adapt dryland to moist soils (Belgacem et al., 2013). The resistance to such extreme climatic events was strongly related to many compounds that were used for adaptive functions. Plants of Polygonum genus contains rich secondary metabolites including (flavonoids, tannins, terpenoids, and gallic acid) Mir et al., 2019; Rodrigues et al., 2019; Cai et al., 2020; Mahmoudi et al., 2021, which are known for their potent total antioxidant capacity that reaches 30.80 mg/g dried plant material Korovkina et al., 2020 along with their antibacterial, anti-fungal, and anti-inflammatory activities (Phatik et al., 2014; Thiruvengadam et al., 2014; Chansiw et al., 2019). These studies suggest that bioactive compounds of *P. equisetiform* neutralize free radical damage in living organisms due to their antioxidant effect (Mahmoudi et al., 2018; Kaurinovic and Vastag, 2019).

P. equisetiform contains several phenolic acids compounds including gallic acid, quinic acid, protocatechuic acid, catechin, and quercetin-3-O-galactoside, which were quantified using GC-MS, and LC-ESI/MS approaches (Mahmoudi et al., 2018). However, the structure of the phenolic compounds in plant species can be affected by the extent solubility, degree of separation etc. For instance, molecular weight, degree of polarity, and conjugation characteristics of a phenolic compounds were found to be influenced by the degree of solubility during extraction processes (Alara et al., 2021). Additionally, the recovery of bioactive compounds solely relies on the extraction method, and stability of phenolic compounds depends on the distribution pattern in the plant organs as well as on the extraction conditions. Thus, some phenolic compounds are stable while others are liable to heat, oxidation, or volatilization. Thus, the selection of the extraction protocol and optimization process is of utmost importance to obtain the target phenolic compound without degradation or alteration (Robards, 2003).

Despite of these recent advancements in synthetic chemistry, there are still several challenges that require more investigations from a pharmaceutical and food processing perspective. Several techniques have been used which are time consuming, and needs large amount of solvent consumption even though mostly of them are not eco-friendly (Rincón et al., 2019). Therefore, an ecofriendly extraction technique is highly desirable. In this context, several modern techniques are recommended for extracting active ingredients from plant parts. The ultrasonic assisted-extraction (UAE) is frequently utilized as an alternative and practical method for environmentally friendly extraction (Shirsath et al., 2012). The breakdown of tissues through ultrasound waves leads to the development of cavitations inducing tissue fragmentation, high shear forces, pore formation, enhanced absorption and swelling in the tissue matrix, finally resulting in higher solubility of bioactive compounds (Kumar et al., 2021). As a proven technique, its cavitational forces improve solute dissolution rates significantly, leading to high reproducibility and faster extraction (Liu et al., 2018; Omidi et al., 2019). The ultrasound causes numerous physical events such as shock waves, micro jets and turbulence (Phatik et al., 2014).

The quality and quantity of bioactive compounds extracted using UAE depend on several quality variables, including ultrasonic power, the solvent of extraction, frequency of ultrasonic, duty cycle of the process, the ratio of solvent to solid (LSR), pH of the solvent, temperature, and time of the extraction (Kumar et al., 2021). The ultrasound-assisted extraction is generally performed at a low temperature, so the thermal degradation of phenolic compounds will be minimal. Reports have highlighted that the effect of temperature on phenolic content is conditioned by extraction time, liquid-solid ratio, particle size, nature of the solvent, and other factors (Mokrani and Madani, 2016; Opriş et al., 2021). The use of non-toxic solvents and eco-friendly extraction is consistently recommended. Water is known to be non-toxic and it has been verified to be the solvent of choice to achieve a high yield of phenolic compounds from plant matrix (Galvan d'Alessandro et al., 2012; Azizi, 2021). The response surface methodology (RSM) is a technique recommended to define the interactions between the studied factors, anticipate the aimed responses, evaluate the relationship between the chosen factors and the aimed responses, and optimize the extraction with the use of a limited number of conditions (Le et al., 2019; Naghdi et al., 2020).

The aim of this study was to analyze a second-order polynomial equation based UAE process. In this study also the effects of temperature, UAE extraction time, and liquid-solid ratio on the phenolic content and DPPH scavenging activity were investigated. At the optimal extraction conditions, the total phenolic content, anthocyanin content, and ABTS inhibition activity, the morphological and physico-chemical properties of

TABLE 1 Experimental ranges and codes of independent factors in the RSM.

Independent variables	Units	Factors	Variable ranges		
			−1	0	+1
Temperature	°C	X_1	30	50	70
UAE extraction time	min	X_2	1	5	9
Liquid-solid ratio	mL/g	X_3	35	40	45

the extract was characterized using scanning electron microscopy (SEM) and Fourier transform infrared spectroscopy (FT-IR) approaches, along with antioxidant and antibacterial efficiencies of the *P. equisetifome* extract were also evaluated.

Materials and methods

Plant material collection and extraction

Fresh roots of *P. equisetiforme* roots were collected in October 2019 from Hazeg, Sfax, Tunisia. The roots were washed thoroughly with distilled water, dried in an oven at 37°C for a week and then milled with a grinder. One gram of the sample was added to a milli-Q-water. The extraction process was done according to the method of Pardo-Muras et al. (2020) with slight modifications using the USE apparatus (Bandelin Sonorex RK 510 H, 35 kHz, Germany). The supernatant was collected after centrifugation at 4,000 rpm for 15 min, and then it was filtered through a 0.45 μm membrane. The final solution was concentrated using a freezer dryer (FD8518, llShin Lab Co. Ltd., Korea) at −72°C. All subsequent analyses were performed using the freeze-dried sample at optimal phenolic content and DPPH scavenging activity.

Experimental design and equation analyses

A Box-Behnken experimental design with three experimental levels defined as low, medium, and high were labeled as −1, 0, and +1, respectively, was chosen to establish a model and investigate the pattern responses affected by three independent factors [X1: temperature (30–70°C); X2: UAE extraction time (1–9 min); and X3: ratio liquid-solid (35–45 mL/g)] (Table 1). A total of 17 experiments were operated with five replicates at the center point in order to evaluate experimental error. A second-order polynomial equation (Equation 1) was used to investigate the mutual interactions of the independent variables, their optimum levels, and their effects on the fitted responses.

$$Y_{1,2} = \beta_0 + \Sigma_{i=1}^{3}\beta_i X_i + \Sigma_{i=1}^{3}\beta_{ii} X_{i^2} + \Sigma_{i=1}^{3}\Sigma_{i=1}^{2}\beta_{ij} X_i X_j \quad (1)$$

Where Y_1: the response of the water-soluble phenolic compounds content, Y_2: the response of the DPPH scavenging activity, β_0: the regression coefficient of the model (intercept coefficient), X_i and X_j were the independent factors, β_{ij}, β_{ii}, and β_i were the coefficient of interaction, squared and linear coefficient, respectively. The analysis of variance (ANOVA) was accomplished to find out the influence of the factors and their relations on the intended responses. In order to verify the fit of the model, the coefficient of determination noted R^2, the adjusted R^2, the significance of lack of fit, as well as the regression coefficient (β) were used. The R^2 was utilized to measure the quality of the prediction regression. The regression helps to determine the strength of the relationship between the independent variables, while the lack of fit tells us whether the regression model fits well or not. The F value was used to compare the average between the experimental and predicted values as well as to validate the designed model.

Determination of total phenol content

The total phenol content was determined by the folin-Ciocalteu method (Singleton and Rossi, 1965). In brief, 125 μL of the sample extracted at optimum conditions was added to 12 μL folin-Ciocalteu and incubated for 6 min in the dark at room temperature. Then, 1,250 μL of 7% Na_2CO_3 was added to the mixture, and the solution was maintained at a volume of 3 mL with the addition of water. The mixture was incubated for 2 h in the dark at room temperature and the absorbance was read at 760 nm. Each assay was performed in triplicate. The result was expressed as mg gallic acid GAE/g dry weight.

Measurement of anthocyanin accumulation

The anthocyanin accumulation was determined according to the method of Giusti and Wrolstad (2001) based on the difference in pH with slight modifications. In brief, 100 μL of the sample at the optimal conditions was added to 900 μL of KCl 0.025 M (pH = 1) and 900 μL HCl 0.4 M (pH = 4.5). The mixture was incubated for 15 min in the dark at room temperature and the absorbance was determined at 520 and 700 nm. The total anthocyanin content was expressed as mg Cy3G/L and it was determined as follows (Equation 2):

$$\text{Anthocyanin} = \frac{A \times MW \times 1000}{E \times l} \quad (2)$$

Where: A [A= (A520 – A700) pH 1 – (A520 – A700) pH 4.5] was the absorbance of the sample, MW: molecular weight (449.2 g mol^{-1}), DF: dilution factor, E: molar extinction coefficient of cyaniding-3-glucoside (26.9000), and l: the path length of the cuvette (1 cm). All assays were carried out in triplicate.

Determination of condensed tannins

The condensed tannins content was determined according to the Broadhurst and Jones (1978) method using catechin as a standard. In brief, 1,500 μL vanillin solution (4%) was added to 25 μL aqueous sample. Afterward, 750 μL of concentrated H_2SO_4 was added to the mixture. The latest was incubated for 15 min in the dark at room temperature and then the absorbance was read at 500 nm. The total condensed tannins ware expressed as mg equivalents of catechin (CTE) per gram dry weight. Each assay was performed three times.

Evaluation of antioxidant potential using free radical scavenging performances

The antioxidant potential of *P.equisetifome* root extract was evaluated using following assays:

DPPH scavenging activity of PCRPE

The scavenging activity of water-soluble phenolic compounds from *P. equisetiforme* roots was carried out according to the method of Brand-Williams et al. (1995) with slight modifications. Briefly, 1 mL of aqueous extract was added to 4 mL DPPH (0.1 mM). The mixture was shaken and incubated in the dark at room temperature for 1 h. The absorbance was read at 517 nm. Then, the scavenging activity was expressed as μmol Trolox/g dry weight.

ABTS scavenging activity of PCRPE

The ABTS scavenging activity of the extract was conducted following the method of Ozgen et al. (2006) with slight modifications. Briefly, 2.45 mM of potassium persulfate was added to a freshly prepared methanolic solution of ABTS (7 mM). The mixture was shaken and incubated for 12 h in the dark at room temperature; then the absorbance was fixed at 0.700 ± 0.01. Afterwards, 100 μL of the sample was added to 900 μL of the mixture, and the absorbance was read at 734 nm. The results were calculated as mean ± SD ($n = 3$) and expressed as μmol Trolox/g dry weight.

Ferric reducing antioxidant power assay

FRAP assay was performed according to the method of Benzie and Strain (1996). Briefly, the FRAP mix (300 mM acetate buffer, pH 3.6, 10 mM TPTZ, 40 mM HCl, and 20 Mm $FeCl_3$) was freshly-prepared. A volume of 2,950 μL of FRAP mix was added to a 50 μL aqueous sample at optimum conditions of extraction. The mixture was incubated in the dark at room temperature for 4 min and then the absorbance was read at 593 nm against a blank. The results were expressed as μmol Trolox/g dry weight.

Morphological and physico-chemical characterization of the extract

SEM-EDX analysis

The morphological features of the sample was analyzed using Scanning Electron Microscopy-Energy Dispersive X-ray Spectroscopy (SEM-EDX, FEI, QUANTA FEG 650). Micrographs were captured using an installed camera in SEM at the Research and application center (ÇÜMERLAB), Adana, Turkey.

Fourier transform infrared spectroscopy analysis

The FTIR spectra of water-soluble phenolic compounds were recorded on a Jasco FTIR-6800 spectrometer connected to a TGC detector. The spectrum was obtained between the frequency ranges of 400–4,000 cm^{-1} with a resolution of 4 cm^{-1}.

Determination of antibacterial activity of water-soluble phenolic compounds

The water-soluble phenolic compounds obtained from *P. equisetiforme* roots were tested for their antibacterial activity by the disk diffusion method against gram-positive strains *Escherichia coli*, *Klebsiella pneumonia*, and gram-negative strains *Staphylococcus aureus*, *Bacillus cereus* which were purchased from the Faculty of Medicine, Çukurova, Turkey. Bacterial cultures were inoculated onto Muller-Hinton agar plates after 24 h of incubation. A volume of 50 μL aqueous extract with a concentration of 100 mg/mL was dissolved in 5% DMSO and added to the wells. Ampicillin (10 μg/well) and kanamycin (10 μg/well) were used as positive controls, and 5% DMSO was used as a negative control. The diameter of the inhibition zone was estimated after 1 day of incubation at 37°C (mm). The broth micro-dilution method was also used to determine the minimum inhibitory concentration (MIC) (Mazzola et al., 2009).

Statistical analysis

The analysis of experimental data was performed using the graphical and statistical software Minitab (Version 2021-USA). ANOVA analysis was executed to verify the significance of the model.

Results and discussion

Validation of models

The experimental data were fitted to a second-order polynomial mathematical model. ANOVA analysis was used to evaluate the procured regression equation. The significance of the coefficient was assessed at a 95% confidence level. The *F*-test data revealed the significance of each coefficient factor, and *p*-values were used to determine the significance of variable interactions. It would be evaluated if the *p*-value decreased and the *F* value increased. If the *p*-value is <0.05, then the model is considered statistically significant. The observed values for Y_1 (*F*-value = 91.30; *p*-value < 0.05) and Y_2 (*F*-value = 107.7; *p*-value < 0.05) proved that the models were statistically significant. Furthermore, the adequacy and fitness of models were evaluated by the significance of a lack of fit and by the correlation coefficient (R^2).

Consequently, the multiple regression model of water-soluble phenolic content (Y_1) (Equation 3) with an R^2 = 99.16% and DPPH scavenging activity response (Y_2) (Equation 4) with a R^2 = 99.28% (Table 2) showed a strong relationship between the relative factors and the intended responses, indicating that the model can be used in a design space. According to Le Man et al. (2010) and Kunjiappan et al. (2020), the model is considered adequate when R^2 is above 0.7. Further, the adjusted coefficient of determination (Adjusted-R^2) for both responses was >98%, confirming that the model was adequate. Additionally, the lack of fit for both responses was non-significant, indicating that the model

TABLE 2 Analysis of variance (ANOVA) of both responses.

Factor/interaction	df	Sum square		Mean square		*F*-value		*p*-value	
		Y_1	Y_2	Y_1	Y_2	Y_1	Y_2	Y_1	Y_2
Model	9	435.761	6,490.48	48.418	721.16	91.30	107.73	0.00	0.00
Linear	3	74.695	1,996.07	24.898	665.36	46.95	99.40	0.00	0.00
X_1	1	40.347	1,581.81	40.347	1,581.81	76.08	236.30	0.00	0.00
X_2	1	26.729	298.64	26.729	298.64	50.40	44.61	0.00	0.00
X_3	1	7.619	115.62	7.619	115.62	14.37	17.27	0.007	0.00
Two way interaction	3	0.317	160.11	0.106	53.37	0.20	7.97	0.894	0.012
X_1X_2	1	0.277	92.32	0.277	92.32	0.52	13.79	0.494	0.008
X_1X_3	1	0.031	29.62	0.031	29.62	0.06	4.42	0.815	0.073
X_2X_3	1	0.009	38.17	0.009	38.17	0.02	5.70	0.899	0.048
Square	3	360.749	4,334.30	7.619	1,444.77	226.75	215.83	0.00	0.00
X_1^2	1	232.512	3,080.70	120.250	3,080.70	438.44	460.22	0.00	0.00
X_2^2	1	59.017	366.88	232.512	366.88	111.29	54.81	0.00	0.000
X_3^2	1	38.322	548.89	59.017	548.89	72.26	82.00	0.00	0.00
R^2		99.16%	99.28%						
R^2-adjusted		98.07%	98.36%						
Lack of fit	3	3.704	46.75	1.235	15.58	590.87	591.17	0.0654	0.0754
Pure error	4	0.008	0.11	0.002	15.58				
Total	16	439.474	6,537.34						

fits well.

$$Y_1 = -183.9 + 1.727\,X_1 + 2.143\,X_2 + 9.43\,X_3 - 0.018\,X_1^2 - 0.234\,X_2^2 - 0.120\,X_3^2 - 0.003\,X_1X_2 + 0.0008\,X_1X_3 - 0.002\,X_2X_3 \quad (3)$$

$$Y_2 = -682.5 + 4.670\,X_1 + 7.480\,X_2 + 35.19\,X_3 - 0.067\,X_1^2 - 0.583\,X_2^2 - 0.456\,X_3^2 + 0.0601\,X_1X_2 + 0.027\,X_1X_3 - 0.154\,X_2X_3. \quad (4)$$

Pareto chart analysis

The Pareto chart is a graph representing the importance of different variables in a phenomenon. In our study, it indicate the effects of three parameters; temperature, UAE extraction time, and liquid-solid ratio and their interactions on the content of water-soluble phenolic compounds as well as their DPPH scavenging activity. The vertical line shown in Figure 1 indicates that the effects were statistically significant. The length of each bar is proportional to the value of the calculated statistic for the associated effect (Wilkinson, 2006). All bars beyond the vertical line are statistically significant at the chosen significance level. In our case, there are three main parameters (A: temperature, B: UAE extraction time, and C: ratio liquid-solid) and three interactions (AB, AC, and BC). For the content of water-soluble phenolic compounds (Figure 1A), the values indicate that all independent linear factors are significant, while their interactions are non-significant. For the DPPH scavenging activity of the extract (Figure 1B), it is clearly shown that all linear and square interactions along with two-way interactions are statistically significant except for the interaction AC.

Extraction efficiency influenced by analytical factors

Multiple factors, including particle size, solvent type, temperature, and liquid-solid ratio, have an impact on the extraction efficiency of phenolic compounds assisted by ultrasonic (Elshreef et al., 2021). As a result, it is crucial to investigate how assorted variables influence target bioactive compound extraction. The ultrasonic-assisted extraction (UAE) is known for its simplicity, speed, efficacy, and ease of use (Wen et al., 2018). Among the multiple variables that have to be considered in the UAE process, the temperature, extraction time, and liquid-solid ratio are crucial and need to be precisely controlled since it affect the phenolic content of the extract as well as their antioxidant activities (Yusoff et al., 2022). Likewise, it is imperative to develop methodologies that contribute to enhance the phenolic content and preserving the bioactivity of target compounds.

The coefficients (β) of both answers [i.e., content of water-soluble phenolic compounds (Y_1) and their DPPH scavenging activity (Y_2)] are depicted in Table 3. The temperature and the extraction time affected negatively both responses as evidenced by the significance values of β_1 and $\beta_2$coefficients. As such, a rise

10.3389/fsufs.2023.1141207

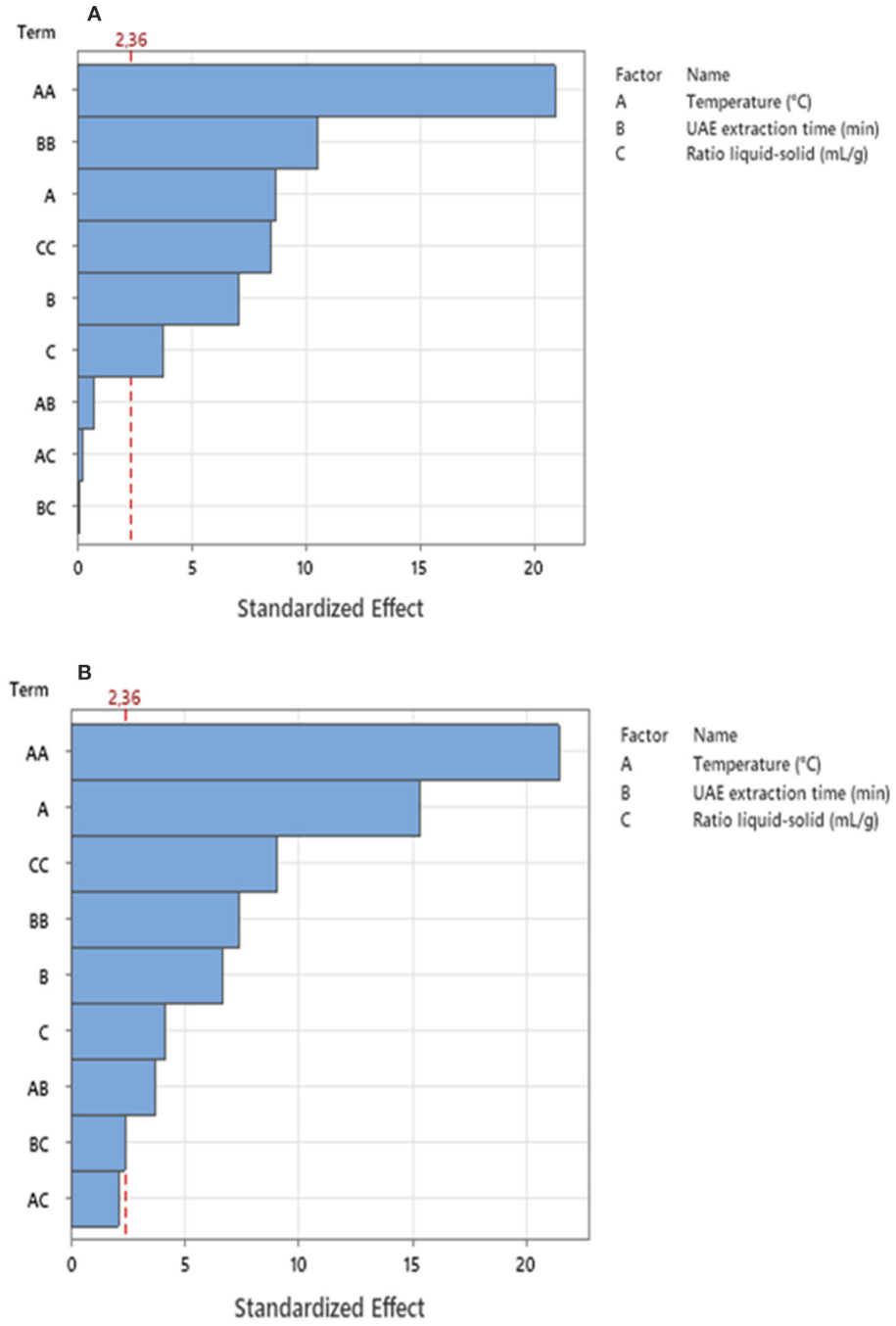

FIGURE 1
Pareto chart of the standardized effects ($\alpha = 0.05$) in samples **(A, B)** of *Polygonum equisetiforme* roots that influenced by several factors temperature, UAE extraction time and ration of liquid-solid.

in temperature and an expansion of the extraction time led to a decrease in the content of water-soluble phenolic compounds as well as a loss of their antioxidant activities. The combination of both factors demonstrated a positive and significant effect on the DPPH scavenging activity of the extract ($p = 0.008$) and a negative and non-significant effect on Y_1. The coefficient of liquid-solid ratio β_3 has shown to be the least significant on Y_1 and Y_2. In this case, the lower ratio should be used for industrial purposes.

Changing temperature influenced the DPPH scavenging activity

A maximum content of water-soluble phenolic compounds extracted by ultrasonic (45.248 mg GAE/g dry weight) was obtained at a temperature of 50°C, an UAE extraction time of 5 min, and a liquid-solid ratio of 40 mL/g (Table 4; Run 10). The results showed that the change in temperature from 30 to 70°C had influenced

TABLE 3 Coded regression coefficient of both responses.

Term	Coefficient (β)		p-value	
	Y_1	Y_2	Y_1	Y_2
Constant	45.260	120.16	0.000	0.000
β_1	−2.246	−14.062	0.000	0.000
β_2	−1.828	−6.110	0.000	0.000
β_3	−0.976	−3.802	0.007	0.004
β_1^2	−7.431	−27.05	0.000	0.000
β_2^2	−3.744	−9.33	0.000	0.000
β_3^2	−3.017	−11.42	0.000	0.000
$\beta_1\beta_2$	−0.263	4.80	0.494	0.008
$\beta_1\beta_3$	0.089	2.72	0.815	0.073
$\beta_2\beta_3$	−0.048	−3.09	0.899	0.048

the content and the DPPH scavenging activity of water-soluble phenolic compounds in a highly significant manner. An increase in temperature above 50°C leads to an increase in the phenolic content and antioxidant activity of the extract, since we registered the lowest phenolic content (29.324 mg GAE/g dry weight) and the lowest antioxidant activity (66.541 μmol Trolox/g dry weight) at a temperature of 70°C.

Some studies have proved that the increase in temperature would enhance the penetration of the solvent into plant cells and reinforce the release of phenolic compounds (Chew et al., 2011; Irakli et al., 2018). As well, it could enhance their solubility in the extraction solvent (Kaur P. et al., 2021). Saleem et al. (2021) noted that heat may improve the mass transfer of biomolecules and increase their surface tension, along with the reduction of the viscosity of the solvent. Furthermore, mild temperatures could weaken plant cells and make them softer, which intensifies their release (Ahangarpour et al., 2019). Kumar et al. (2021), reported that with increasing temperature, the UAE increased the yield of bioactive compounds due to the enhancement of desorption and solubility of the solute in the solvent. As an example, the increased yield observed from waste products of coffee grounds by UAE in temperature from 30 to 45°C and decreased yield reported beyond the 45°C (Al-Dhabi et al., 2017). Nonetheless, Chew et al. (2011) revealed a negative relationship between extraction temperature and antioxidant activity and a positive correlation between the increase of temperature and the content of phenolic compounds, inferring that raising the temperature above a certain point may result in the thermal destruction of the biomolecules (Bouaziz et al., 2020).

As illustrated in Figure 2, the maximum water-soluble phenolic content was attained at an UAE extraction temperature of 50°C and the same temperature pattern was observed for the DPPH scavenging activity of the extract. Consequently, an extraction temperature of 50°C was chosen as the best extraction condition. The water-soluble phenolic compounds obtained at these conditions were higher than those obtained by Demiray et al. (2009) in *Polygonum bistorta* roots. The reason for this difference may be due to the difference in species and the conditions of the extraction. Overall, the UAE was a reliable, effective, and feasible technique for the extraction of phenolic compounds compared with Soxhlet and maceration (Ali et al., 2018).

The ultrasound exposure time regulated the antioxidant potential

The ultrasound exposure time is critical for the UAE yield. As shown in Figures 2A–F, the content of water-soluble phenolic compounds as well as their DPPH scavenging activity were relevant for the first 6 min and then decreased gradually. The DPPH scavenging activity of the extract decreased proportionally with the decrease in the extraction time and the optimal scavenging activity was obtained at 5 min. Chew et al. (2011), noted that prolonged ultrasonic extraction might lead to the oxidation of phenolic compounds and a decrease in their antioxidant activity. At the initial stage of increasing sonication time, the cavitation enhanced, as a result, it facilitates hydration of plant tissue, followed by, fragmentation and creating pores and releasing more compounds. Prolonged exposure has been reported to cause structural injuries in solvent decreasing extraction yield (Nishad et al., 2019). Thus, selection of the best extraction time may improve the content and the antioxidant activity of target biomolecules, since the extension of time at a certain point will lead to more ultrasonic vibrations where the source of energy allowed the release of metabolites in the matrix complex. The main phenomena during sonication are the creation of cavities (more particularly the creation and collapse of these activities), friction, and the increase in broadcast rates (Rubino et al., 2020).

Liquid-solid ratio responsible for varying phenolic compounds content

The liquid-solid ratio had a highly significant effect on phenolic compounds content ($p = 0.007$) and their antioxidant activity ($p = 0.004$). As shown in Table 4, the antioxidant activity of the extract reaches its maximum at a ratio of 40 mL/g. As also depicted in Figures 2D–H, increasing the liquid-solid ratio from 35 to 40 mL/g leads to an increase in both responses. While an increase above 40 mL/g contributes to a decrease in Y_1 and Y_2. The higher liquid-solid ratios are attributed to higher cavitations and affect solute degradation and decrease yield (Samaram et al., 2015). As it was mentioned by Elshreef et al. (2021), a ratio of 40 mL/g had a highly significant effect on the antioxidant activity owning to the decrease in the mixture's density. Additionally, in the study of Quoc and Muoi (2016), it was mentioned that the best solvent/material ratio for the extraction of phenolic compounds from *Polygonum multiflorum* roots was 40 mL/g.

High anthocyanins, condensed tannins, and antioxidant capabilities were found in root extracts

Anthocyanins, condensed tannins content, FRAP, H_2O_2, and the ABTS scavenging activity of the extract were determined at the optimum conditions ($X_1 = 50$°C, $X_2 = 5$ min, and $X_3 = 40$

TABLE 4 Matrix of Box-Behnken design for three factors with water-soluble phenolic content and its DPPH scavenging activity.

Run	Independent variables			Responses	
	X1 (°C)	X2 (min)	X3 (mL/g)	Y1 (mg GAE/dry weight)	Y2 (μmol Trolox/g dry weight)
1	30	1	40	38.320	110.624
2	50	9	35	37.547	100.451
3	30	5	45	35.421	87.624
4	70	5	35	34.026	70.324
5	50	5	40	45.201	120.354
6	50	5	40	45.321	120.203
7	50	5	40	45.258	119.985
8	30	9	40	35.624	89.624
9	70	5	45	32.389	69.512
10	50	5	40	45.284	120.004
11	70	1	40	33.072	68.324
12	50	5	40	45.236	120.265
13	70	9	40	29.324	66.541
14	50	1	45	39.547	104.547
15	50	1	35	41.541	107.321
16	30	5	35	37.412	99.321
17	50	9	45	35.362	85.321

mL/g) (Table 5). Anthocyanins have been used in several fields, where their coloring, antioxidant, and biological capacities qualify them to be a crucial source in diverse domains (Chew et al., 2011). At optimal conditions, their content reached 4.468 mg Cy3G/L. Many studies have verified that the cytoplasmic membranes of Polygonum were rich in anthocyanin pigments (Kaur S. et al., 2021). Their intake in food has been linked to a variety of nutritional benefits, including anti-inflammatory and antioxidant effects (Dini et al., 2019). The condensed tannins content of the extract at optimal conditions was 57.023 mg CTE/g dry weight. Our findings were in accordance with those of Mahmoudi et al. (2021) where they reported that the roots of *P. maritimum* are rich in condensed tannins compared to those of other species. Apart from the difference among species, the variation in condensed tannins contents was proven to be according to the organ itself. Moreover, the choice of solvent plays a crucial role in the quantification of condensed tannins (Rhazi et al., 2019).

The antioxidant activity of the extract was evaluated through FRAP, H_2O_2, and ABTS scavenging activity. According to Albishi et al. (2013), since numerous mechanisms are involved in the testing of the antioxidant activity of an extract, at least two distinct antioxidant methods are recommended to confirm the antioxidant property of an extract. The ABTS scavenging activity of water-soluble phenolic compounds at optimum conditions was 424.325 μmol/g dry weight (Table 5). Our results were higher than that reported by Li et al. (2007), suggesting that the UAE extraction was more efficient than the maceration and decoction approaches, where the ABTS scavenging activity of *P. multifforum* roots for both extraction techniques was 256.7 and 257.9 μmol trolox/g dry weight, respectively. The ferric-reducing antioxidant power at optimal conditions was 361.530 μmol trolox/g dry weight, which is in accordance with the study of Wong et al. (2006), where the aqueous extract of *P. multifforum* roots showed a high antioxidant power that was higher than the extraction with methanol.

Evaluation of SEM-EDX image

As shown in Figure 3, SEM imaging reveals the shape of the fractured surface of phenolic compound walls. The morphological features of cell walls can be observed at a maximum diameter of 24.480 μm (Figure 3). The surface of the matrix was destroyed by the use of the UAE. The latter tends to form pits by exfoliating phenolic compounds. The ultrasonic probe illustrated that the cell membranes collapsed and the overall structure puffed up with numerous open holes. This revealed that the ultrasonic vibrations had an effect on cell walls due to the pressures caused by cavities (Vajić et al., 2015; Ali et al., 2018). As a result, the solvent will easily reach the inside compartment of the cell, increasing extraction efficiency and the antioxidant capacity of the extract (Kataoka, 2003; Ashokkumar et al., 2008; Patist and Bates, 2008). Besides, UAE vibrations resulted in the formation of bubbles within newly formed pores. Consequently, the collapses and oscillations created by the UAE generate internal pressure, resulting in structure expansion and additional erosion and dispersion of cavities and cracks (Han et al., 2018).

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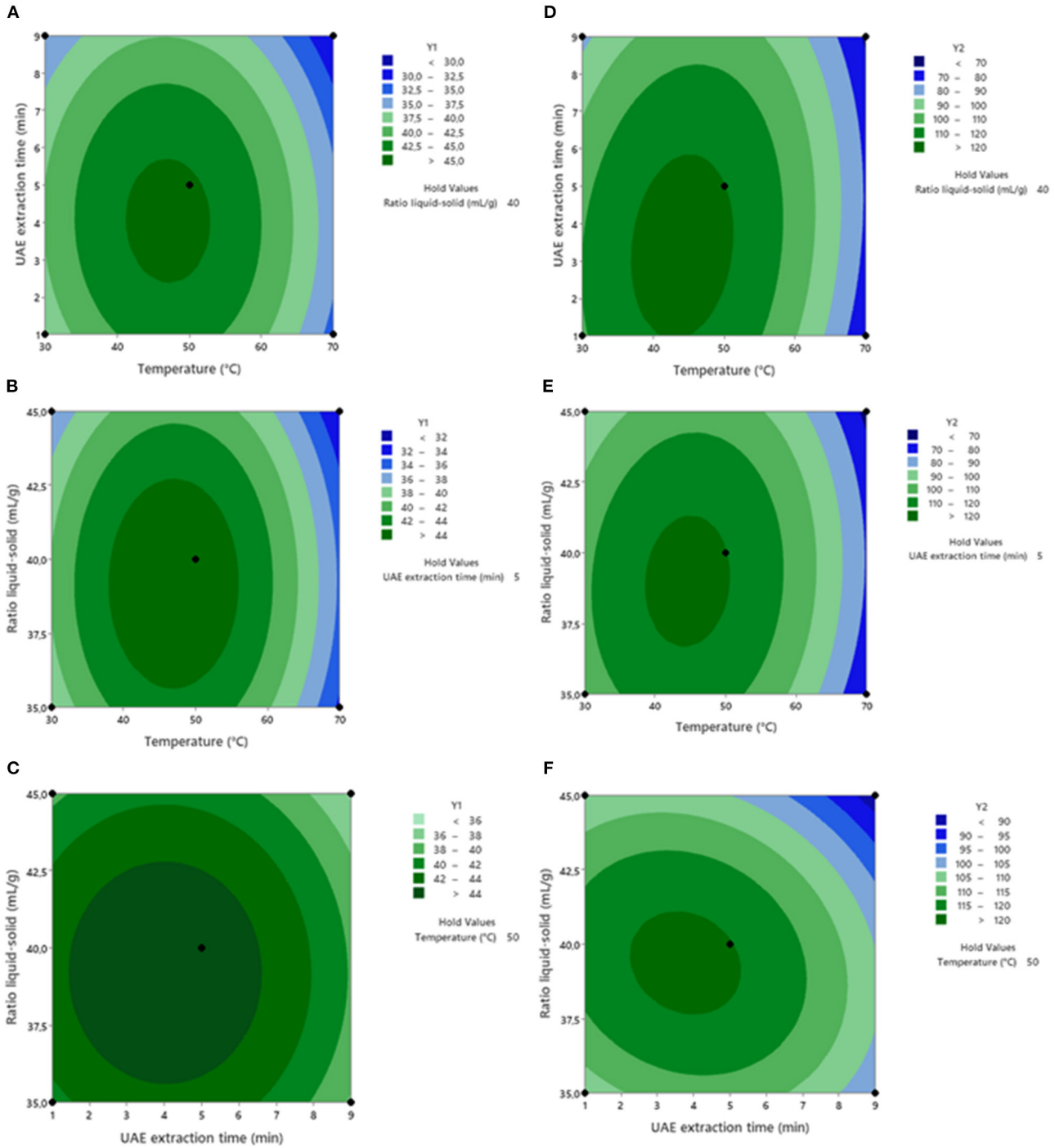

FIGURE 2
The effect of combined factors X_1: temperature, X_2: UAE extraction time, and X_3: ratio liquid-solid on the total content of phenolic compounds **(A–C)** and on the DPPH scavenging activity **(D–F)**.

The presence of functional groups was confirmed by FT-IR spectroscopy assay

The FT-IR spectroscopy was performed for the evaluation of functional groups in the extract due to the ease of sample preparation and analysis (Kwon et al., 2014; Song et al., 2016). In this study, the spectrum presented 18 peaks, revealing that the sample contains a complex compound. The spectrum showed severalmid-infrared groups (e.g., single bonds, double bonds, and fingerprints). The footprint showed peaks ranging from 457.05 to 3,874.2 cm^{-1} with an intense band at 3,289 cm^{-1} which belongs to the hydrogen group (Figure 4), and is considered a donor of the

TABLE 5 Anthocyanins, condensed tannin, and antioxidant screening of the extract ($n = 3$).

Analysis	Mean ± SD
Condensed tannins content (mg CTE/g dry weight)	57.023 ± 0.29
Anthocyanins (mg Cy3G/L)	4.236 ± 0.62
FRAP (μmol Trolox/g dry weight)	361.530 ± 5.24
ABTS (μmol Trolox/ g dry weight)	424.325 ± 0.30

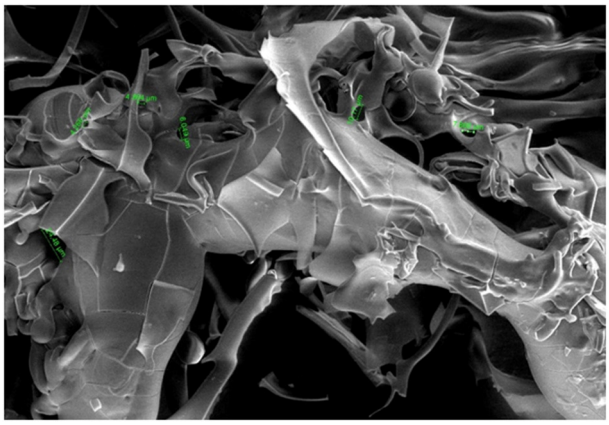

FIGURE 3
Scanning electron microscopy-energy dispersive X-ray Spectroscopy (SEM-EDX) image of water-soluble phenolic compounds extracted from *Polygonum equisetiforme* roots.

hydrogen atom (Silva et al., 2014; Hu et al., 2016). These molecules enhance the antioxidant activity of the extract (Vermerris and Nicholson, 2007). Bands in the region between 1,680 and 900 cm^{-1} were mainly associated with typical phenolic molecules (Diblan et al., 2018). The band at 1,604 cm^{-1} was characteristic of phenyl bands of caftaric acid (C=C). Bands at 1,519 and 1,324 cm^{-1} were characteristic of sinapic acid and p-coumaric acid (coupling between C=C and H-C=C bending of the phenolic ring at stretching mode) (Martin et al., 2017). The absorption peak of 1,020 cm^{-1} represents the presence of phenols (Satyavani et al., 2011).

The *P. equisetiforme* roots extract showed potential antibacterial activity

In this study, the antibacterial activity of water-soluble phenolic compounds from *P. equisetiforme* roots was assessed *In vitro* against two Gram-positive bacteria, namely *Staphylococcus aureus* and *Bacillus cereus*, and two Gram-negative bacteria, namely *Escherichia coli* and *Klebsiella pneumonia*. The inhibition diameter (cm) and the minimum inhibitory concentration (MIC) of root extract against several pathogenic bacteria are presented in Table 6. However, the disc diffusion data (50 μL/disc; 100 mg/mL dissolved in 5% DMSO) revealed that the water-soluble phenolic compounds from *P. equisetiforme roots* exhibit antibacterial activity against tested strains of *Escherichia coli*, *Bacillus cereus*, and *Staphylococcus aureus* with moderate inhibition zones of 16.50, 17.00, and 23.50 mm, respectively, while it not showed any antimicrobial activity *against Klebsiella pneumonia* (Table 6) With respect to all of the tested strains, the negative control (DMSO) did not display any inhibitory zones. The positive control, ampicillin, indicated an inhibition zone of 0, 13, 33, and 48 mm and against *Klebsiella pneumonia*, *Bacillus cereus*, *Escherichia coli*, and *Staphylococcus aureus*, respectively. While kanamycin exhibits an inhibition zone of 20 mm, 28 mm, against *Klebsiella pneumonia*, *Escherichia coli*, respectively, and 29 mm against *Bacillus cereus* and *Staphylococcus aureus*. Nature plants contain various useful compounds that linked to human health benefits (Islam M. et al., 2010; Islam S. et al., 2010; Akter et al., 2021), many of them exhibited antibacterial potential against disease causing bacteria (Islam et al., 2009; Rahman et al., 2009; Sheikh et al., 2010). In this current study, the antibacterial activity of root extract indicates the future prospects to use as therapeutic antimicrobial.

The minimum inhibitory concentration (MIC) of the extract showed high antibacterial activity against all strains between 0.076 and 0.625 mg/mL. Gram-positive strains were more sensitive compared to Gram-negative bacteria, since the latter are known to be less sensitive to bactericidal activity due to the richness of cell walls by polysaccharides, which restrict the penetration of bioactive compounds (Marques et al., 2017). *Staphylococcus aureus* showed to be the most susceptible strain, with a MIC of 0.076 mg/mL. The potency of the extract to inhibit the growth of studied pathogens evidenced in MIC indicated the water-soluble bioactive compounds were found to be more efficient against Gram-positive strains than Gram-negative strains. Our findings indicates the water-soluble phenolic compounds from *P. equisetiforme* roots can be promising source of new antibacterial agent for developing drugs to inhibit some human pathogenic bacteria. The overall findings of this present study on antioxidant, and antibacterial efficiencies of *P. equisetifome* can be useful to the food processing and pharmaceutical industries.

Conclusion

This study implies a Box-Behnken design based optimization of phenolic extractions process from *Polygonum equisetiforme* roots. The UAE extraction processes influence the extraction of water-soluble phenolic compounds from *P. equisetiforme* roots. This study further explored metabolic insights of *P. equisetiforme* roots extracts that exhibited promising antioxidant potentials, and antibacterial activities against several pathogenic bacteria (*Staphylococcus aureus*, *Klebsiella pneumonia),* wherein MIC potential was excellent. The overall findings associated with antioxidant and antibacterial efficiencies of *P. equisetifome* roots demonstrate that these compounds can be promising source of therapeutic antimicrobial agent for developing drugs to inhibit some human pathogenic bacteria.

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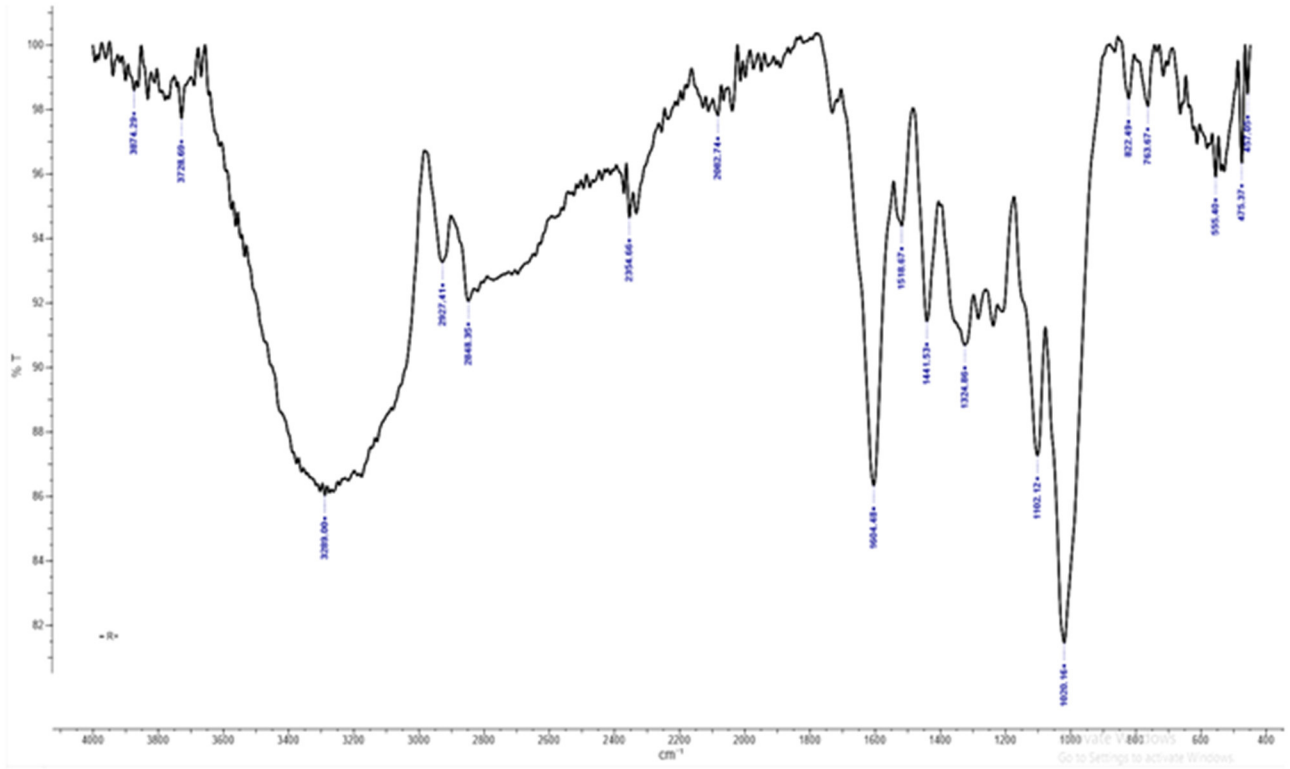

FIGURE 4
Fourier transform infrared spectroscopy (FT-IR) spectrum of water-soluble phenolic compounds from *P. equisetiforme* roots.

TABLE 6 Minimum inhibitory concentration (MIC) and inhibition diameter of aqueous extract of *Polygonum equisetiforme* roots.

	Gram-negative bacteria		Gram-positive bacteria	
	Escherichia coli	*Klebsiella pneumonia*	*Staphylococcus aureus*	*Bacillus cereus*
Component	**Inhibition diameter (mm)**			
Extract	16.50 ± 0.7^{a}	NA	23.50 ± 0.71^{a}	17.00 ± 1.41^{a}
Ampicillin	33.00 ± 4.24^{c}	0 ± 0.00^{a}	48 ± 0.00^{d}	13 ± 0.00^{a}
Kanamycin	28 ± 1.41^{d}	20 ± 0.00^{b}	29 ± 0.00^{e}	29 ± 0.00^{c}
DMSO	0.00 ± 0.00^{b}	0.00 ± 0.00^{a}	0.00 ± 0.00^{c}	0.00 ± 0.00^{b}
	MIC (mg/mL)			
Extract	0.156	0.625	0.076	0.156
Ampicillin	0.156	5	0.019	0.039
Kanamycin	0.039	0.039	0.009	0.009

Two results (Mean values ± SD, $n = 2$) read from the same column and marked with the same letter do not differ significantly at a threshold $\alpha = 5\%$ (Tow-way ANOVA; Tukey's test). NA, no activity.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

Author contributions

FE and AA: conceptualization and data curation. FE: formal analysis. CB and NK: funding acquisition and supervision. NK and AE: investigation. FE, AA, and NK: methodology. CB, NK, HS, and IV: resources. MA and AO: developed data analysis and critical

revision. MA, FE, and AA: software. MS, CB, NK, AO, and MR: visualization. AE, MS, and FE: writing, reviewing, and editing the original draft. CB, NK, AO, MA, MS, and AE: review and editing. CB, NK, and MR: editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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