CarakaTani
Journal of Sustainable Agriculture
ISSN 2613-9456 (Print) 2599-2570 (Online)

Caraka Tani: Journal of Sustainable Agriculture, 41(3), 374-391, 2026
URL: https://jurnal.uns.ac.id/carakatani/article/view/119421
DOI: http://dx.doi.org/10.20961/carakatani.v41i3.119421

Advanced Hybrid RSM-ANN-GA Modeling for Efficient Ultrasound-Assisted Hot-Water Extraction of Polyphenol-Rich Bioactives from Pilangkasa Fruit

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Abstract

Pilangkasa (*Ardisia elliptica* Thunb.) is a source of natural antioxidants with potential applications. Ultrasound-assisted extraction (UAE) has been proposed as a sustainable alternative to conventional extraction methods, but extraction efficiency highly depends on processing conditions. Therefore, the present study was carried out to optimize the UAE of phytochemicals from polyphenol-rich fruit using Response Surface Methodology (RSM) and Artificial Neural Network-Genetic Algorithm (ANN-GA) modeling. A Box-Behnken design was used to study the effects of extraction temperature (50 to 70 °C), time (10 to 30 minutes), and ultrasonic power (50 to 70%) on the total phenolic content (TPC), total flavonoid content (TFC), and antioxidant activities (DPPH and FRAP). The RSM models were highly predictive with coefficients of determination ranging from 85.52 to 98.71%. Among all the responses, extraction time was found to be the most influential factor. Results indicated that cavitation-enhanced mass transfer was the main factor influencing TPC and TFC, whereas antioxidant activity was greatly influenced by structural stability and the sonochemical degradation of polyphenols. The hybrid RSM-ANN-GA predicted the optimal conditions to be 60.2 °C, 22.45 minutes, and 60.34% ultrasonic power, resulting in TPC of 92.24 mg GAE g^{-1}, TFC of 175.35 mg QE g^{-1}, DPPH of 81.27%, and FRAP of 1.61 mg TE g^{-1}. The ANN-GA model showed better prediction than RSM, with high correlation and slightly improved predicted optimal conditions. These results illustrate the potential of hybrid modeling approaches for optimizing extraction processes and provide insights into the physicochemical mechanisms underlying polyphenol recovery.

Keywords: ANN-GA; *Ardisia elliptica*; polyphenols; response surface methodology; ultrasound-assisted extraction

Cite this as: Mansamut, C., Vinh, B. T., & Loan, L. T. K. (2026). Advanced Hybrid RSM-ANN-GA Modeling for Efficient Ultrasound-Assisted Hot-Water Extraction of Polyphenol-Rich Bioactives from Pilangkasa Fruit. *Caraka Tani: Journal of Sustainable Agriculture*, *41*(3), 374-391. doi: http://dx.doi.org/10.20961/carakatani.v41i3.119421

INTRODUCTION

Polyphenol compounds are an important group of plant secondary metabolites and are present in many fruits, vegetables, and grains (Simsek and Whitney, 2024). They include many types such as phenolic acids, flavonoids, tannins, and anthocyanins, which are characterized by high biological activities (Simsek and Whitney, 2024). Polyphenols have also been shown to play a major role in decreasing the risk of chronic diseases such as cardiovascular disease, diabetes, and certain cancers (Shanmugam, 2025). The high polyphenol content in fruits is increasingly being

* *Received for publication May 20, 2026*
Accepted after corrections July 7, 2026

considered as a potential source of raw materials for the production of functional foods (Fernandes et al., 2023; Van Tai et al., 2023; Thuy et al., 2025). Specifically, pilangkasa (*Ardisia elliptica* Thunb.) has been found to be rich in anthocyanins and other bioactive compounds (Yukongphan et al., 2013; Vinh et al., 2026). However, the use of this raw material in value-added products remains limited.

Bioactive compounds of this fruit can be extracted from the fruit tissue (Rifna et al., 2023). However, the extraction method employed is a major determinant of the efficiency of polyphenol compounds extraction from the plant material (Rifna et al., 2023). Conventional extraction techniques such as maceration or Soxhlet extraction are generally characterized by long extraction times, high solvent and energy usage, and degradation of heat-sensitive compounds (Osorio-Tobón, 2020; Rifna et al., 2023).

Recently, extractive techniques have been developed to improve extraction efficiency and to reduce solvent consumption and processing time. Ultrasound-assisted extraction (UAE) is one of the most effective and environmentally friendly extraction technologies (Vilkhu et al., 2008; Osorio-Tobón, 2020). The main mechanism of UAE is acoustic cavitation, which leads to the formation and collapse of microbubbles in the solvent, generating microjets and high mechanical shear forces (Vilkhu et al., 2008). These effects can destroy the structure of the plant cell wall and increase the contact area between the solvent and plant tissue, as well as the mass transfer of bioactive compounds into the solvent (Awad et al., 2021). This has led to the extensive use of UAE for the extraction of polyphenols from various plant sources, such as some berries (Castro-López et al., 2017; Skenderidis et al., 2017; Weremfo et al., 2022).

Weremfo et al. (2022) studied different UAE conditions for extracting bioactive compounds from turkey berry, including temperature (40 to 80 °C), time (3 to 25 minutes), ethanol concentration (20 to 80%), and liquid-to-solid ratio (10 to 50 ml g^{-1}). In another study on goji berries, various temperatures ranging from 40 to 80 °C combined with different sonication powers were used to extract antioxidant compounds. This study found that the optimum temperature was 60 °C, which resulted in maximum yield. However, the efficiency of the UAE process depends on several technological parameters, including temperature, extraction time, and ultrasonic power (Rifna et al., 2023). These factors can interact among themselves in nonlinear ways, necessitating the optimization of extraction conditions, in order to achieve maximum efficiency in polyphenols recovery while limiting the degradation of sensitive bioactive compounds.

In food technology, process optimization research commonly employs statistical methods such as Response Surface Methodology (RSM). In particular, the Box-Behnken design (BBD) enables the evaluation of linear, quadratic, and interaction effects among technological variables using a relatively small number of experiments (Thuy et al., 2025). RSM is a good tool for modeling technological processes. However, polynomial regression models sometimes fail to capture the complex nonlinear relationships between the input variables and biological responses.

In recent years, artificial intelligence methods such as Artificial Neural Network (ANN) have been extensively used in modeling food processes due to their ability to predict nonlinear relationships without pre-assuming the functional form of the model (Nguyen et al., 2026a). ANN-GA models, which integrate an ANN with a Genetic Algorithm (GA), an optimization algorithm based on the principles of biological evolution, can effectively determine the global optimal conditions of a process (Pappu and Gummadi, 2017; Nguyen et al., 2026d). Hybrid ANN-GA models have been reported to offer greater predictive capacity and optimization performance than conventional RSM models (Gürgen et al., 2026; Nguyen et al., 2026b; Nguyen et al., 2026c).

Although the UAE has been widely used for extracting polyphenols from various plant sources, studies combining RSM and ANN-GA to model and optimize the extraction of bioactive compounds from polyphenol-rich fruits such as Pilangkasa remain limited. Therefore, this study aimed to: (i) evaluate the effects of ultrasonic extraction parameters, including temperature, extraction time, and ultrasonic power, on total phenolic content (TPC), total flavonoid (TFC), and antioxidant activity (DPPH and FRAP); and (ii) develop models to predict and determine the optimal extraction conditions using RSM with a BBD in combination with ANN-GA. The results of this study provide a scientific basis for applying advanced modeling methods to optimize the extraction of polyphenols from bioactive fruit sources.

MATERIALS AND METHOD

Materials

Pilangkasa fruit samples were collected from local markets and transported to the laboratory under refrigerated conditions to minimize the degradation of bioactive compounds. To minimize biological variability, all fruits were harvested at the commercial-ripe stage from a single cultivar grown in the same orchard in Samut Prakan Province in one harvesting season. After collection, samples were sorted for uniform size and color to remove damaged fruits, then washed with distilled water to remove surface impurities and allowed to dry at room temperature. The samples were then ground in a high-speed grinder to obtain a homogeneous puree. The puree was kept frozen at -20 °C in airtight polyethylene bags until the extraction experiment. Frozen puree samples were thawed at room temperature in a natural way and thoroughly mixed to obtain a homogeneous sample before each experiment. Storing samples as frozen puree helps limit enzymatic activity and oxidation, and maintain the content of anthocyanins and phenolic compounds, as reported in studies on the preservation of anthocyanin-rich materials (Syamaladevi et al., 2012).

UAE procedure

The UAE was used for the extraction of bioactive compounds. The sample was mixed with 60% ethanol solvent (food grade) at a solvent-to-sample ratio (20 ml g^{-1}). The mixture was then treated in a bath-type ultrasonic device at a frequency of about 60 kHz. Preliminary experiments were performed to choose the extraction parameters for the optimization study, including extraction temperature (50 to 70 °C), extraction time (10 to 30 minutes), and ultrasonic power (50 to 70%). During extraction, the temperature was maintained using ice with regular monitoring. The extract mixture was centrifuged at 6,000 rpm for 15 minutes to separate the solid phase and then cooled to room temperature. Before chemical analysis, the extract was filtered through filter paper or a membrane filter (0.45 μm).

Determination of TPC, TFC, and antioxidant activities

TPC was determined by the Folin-Ciocalteu method according to the procedure described by Wanyo et al. (2014) with some minor adjustments. The mixture was incubated in the dark at room temperature for 30 minutes, then the absorbance was measured at 765 nm using a UV-Vis spectrophotometer. Results were expressed as mg gallic acid equivalent per g sample (mg GAE g^{-1}).

TFC was determined using the $AlCl_3$ colorimetric assay as described by Wang et al. (2013). Absorbance was measured at 415 nm using a UV-Vis spectrophotometer (Shimadzu 1800, Japan). Flavonoid content was calculated based on the quercetin standard curve and expressed as mg quercetin equivalent per g sample (mg QE g^{-1}).

Free radical scavenging activity (DPPH) was evaluated using the DPPH assay as described by Tabaraki and Nateghi (2011). The absorbance of the reaction mixture was measured at 517 nm. The free radical scavenging capacity was expressed as the percentage of DPPH inhibition (%).

Ferric reducing antioxidant power (FRAP) was determined using the FRAP assay according to the procedure of Tabaraki and Nateghi (2011). The FRAP reagent was prepared by mixing TPTZ solution, $FeCl_3$, and acetate buffer. The extract was mixed with FRAP reagent and incubated at 37 °C for 10 minutes, then the absorbance was measured at 593 nm. Results were expressed as μmol Trolox equivalent per g sample (μmol TE g^{-1}).

Experimental design and data analysis

The experimental design was based on the BBD to evaluate and optimize the effects of ultrasonic extraction parameters on the antioxidant properties of the sample. Three independent variables were selected: extraction temperature (A, °C), extraction time (B, minutes), and ultrasonic power (C, %). Each variable was investigated at 3 coded levels: −1, 0, and +1, corresponding to the following actual values: temperature 50, 60, and 70 °C; extraction time 10, 20, and 30 minutes; ultrasonic power 50%, 60%, and 70%. The three-factor BBD consisted of 18 experimental runs with 6 center points and was performed in triplicate. The responses included TPC, TFC, DPPH, and FRAP.

Experimental data obtained from the BBD were analyzed using multivariate regression to construct a quadratic polynomial model. The model fit was assessed using analysis of variance (ANOVA), the coefficient of determination R^2, the adjusted coefficient of determination (R^2_{adj}), and the lack-of-fit test. Three-dimensional (3D) response surface plots and contour lines were used to represent the influence of independent variables on each response, thereby determining the optimal

conditions for the extraction process. Multi-response optimization was performed using a desirability function with equal weight factors to find the most suitable combination of technological conditions that simultaneously maximizes TPC, TFC, DPPH, and FRAP.

ANN-GA optimization

Prediction and optimization of biological compound extraction using UAE via an ANN model combined with GA. The ANN-GA method was used because it can better describe the complex nonlinear relationships between technological variables and biological responses than traditional regression models (Aung et al., 2022).

ANN modeling

ANN models were developed using a feed-forward multilayer perceptron (MLP) structure with an input layer, one or more hidden layers, and an output layer. The network had 3 input variables: (1) extraction temperature (°C), (2) extraction time (minutes), and (3) ultrasonic power (%). The corresponding output variables were the responses obtained from the experiment: (1) TPC, (2) TFC, (3) DPPH, and (4) FRAP. Experimental data from the BBD were used to train the ANN. The dataset was divided into 3 parts: a training set (70%), a validation set (15%), and a testing set (15%) to evaluate the model's accuracy. A back-propagation algorithm was used to adjust the network weights to minimize the error between predicted and experimental values. An early-stopping criterion based on the validation performance was used to terminate the model training.

To improve model generalization and reduce overfitting, the experimental dataset was randomly partitioned into training, validation, and testing subsets. The final network architecture was selected based on the lowest prediction error and the highest correlation coefficient. The quality of an ANN model was evaluated based on statistical indicators such as the coefficient of determination (R^2) and root mean square error (RMSE). An ANN model has high accuracy when the R^2 value is close to 1 and the RMSE is low.

GA optimization

The trained and validated ANN model was coupled with GA to search for the optimal combination of input variables for maximizing the desired responses. GA is an optimization algorithm inspired by biological evolution. The major steps of GA include population initialization, selection, crossover, mutation, and generational replacement (Van Tai et al., 2024). The individual fitness function was calculated from the predicted values of the ANN model. The evolutionary algorithm was iterated until the convergence condition or the maximum number of generations was reached. The ANN-GA optimization process was used to determine optimal extraction conditions to simultaneously maximize TPC, TFC, DPPH, and FRAP responses. The validation test was conducted to compare the actual values with the predicted values from each model.

RESULTS AND DISCUSSION

Effect of extraction conditions on the yield of polyphenol

The research results showed that extraction conditions, such as temperature, time, and ultrasonic power, significantly affected the TPC of the extract. The ANOVA (Table 1) indicated that all 3 factors were statistically significant ($p < 0.001$). Extraction time was the most influential factor, followed by the temperature and ultrasonic power. This suggests that mass transfer kinetics play a decisive role in the release of polyphenols from the plant matrix. In addition, ultrasonic waves could help promote mass transfer and cell destruction, thus improving the efficiency of the extraction process. The quadratic regression model constructed for the TPC yield is presented in Equation 1.

With a high R^2 of 0.9871 and an adjusted R^2 of 0.9826, the model demonstrated good predictive ability within the surveyed range. The lack-of-fit value was not significant ($p = 0.3249$), confirming that the model adequately fitted the empirical data.

TPC increased sharply with the increasing temperature from 50 to 60–62 °C and time from 10 to 20–25 minutes (Figure 1). This tendency can be explained by the cavitation mechanism of UAE, in which the collapse of microbubbles generates a strong mechanical shear force that disrupts the cell wall structure and enhances the transfer of polyphenols into the solvent (Chemat et al., 2017). Moreover, solvent viscosity decreases with increasing temperature, thereby

$$TPC = -735.993 + 12.1652A + 3.78839B + 13.2844C - 0.0932447A^2 - 0.0287347AB - 0.00120286AC - 0.0671497B^2 + 0.0191217BC - 0.111167C^2 \quad (1)$$

Table 1. ANOVA for TPC

Source	Sum of squares	F-ratio	*p*-value
A: Extraction temperature (°C)	173.196	113.37	0.0000
B: Extraction time (minutes)	442.048	289.36	0.0000
C: Sonication power (%)	103.726	67.90	0.0000
A^2	758.8	496.70	0.0000
AB	66.0546	43.24	0.0001
AC	0.11575	0.08	0.7887
B^2	393.52	257.59	0.0000
BC	29.2513	19.15	0.0014
C^2	1,078.52	705.99	0.0000
Lack-of-fit	30.7382	1.34	0.3249

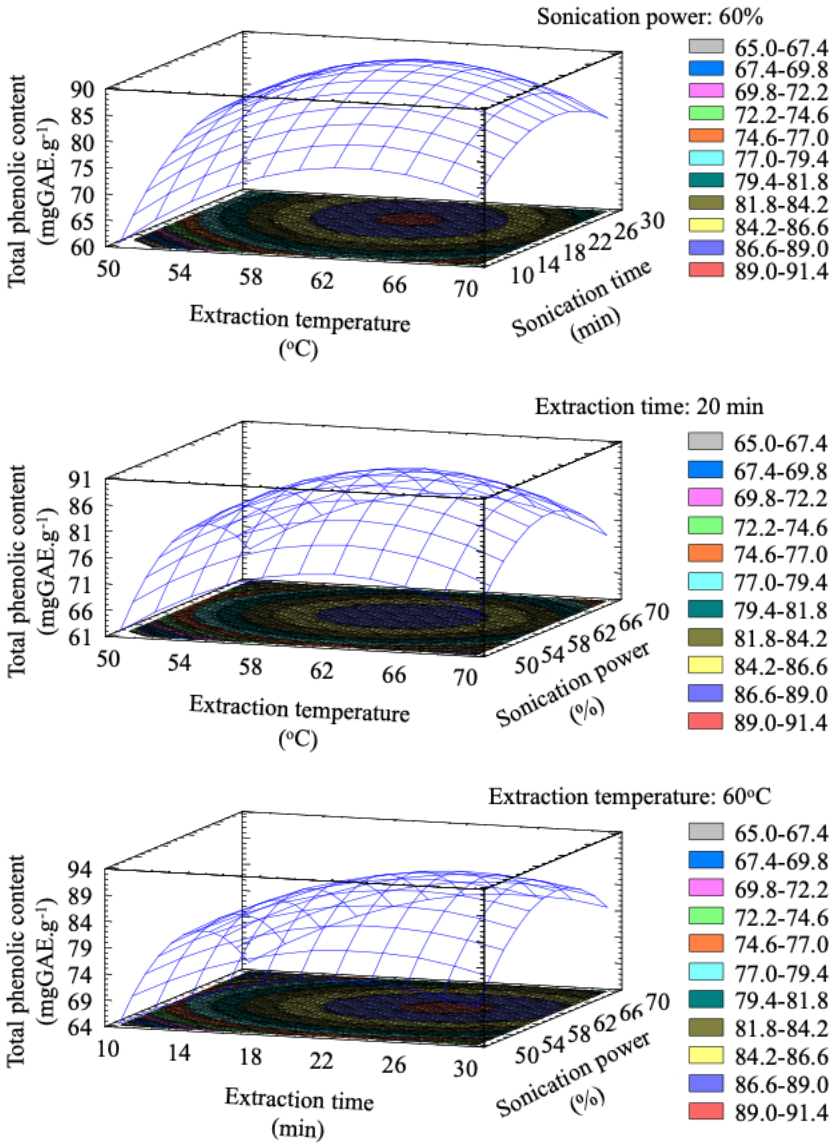

Figure 1. RSM 3D plots for the effect of extraction conditions on TPC content of the extract

increasing the diffusion coefficient and enhancing extraction efficiency (Bitwell et al., 2023; Loan et al., 2023).

However, TPC decreased slightly when the extraction parameters were out of the optimal range. The very significant quadratic coefficients indicate clearly the presence of a kinetic maximum. High ultrasonic power and prolonged time can produce intense cavitation zones that lead to the formation of free radicals and

temperature zones, which can cause oxidation or degradation of polyphenols (Gil-Martín et al., 2022; Shehzadi et al., 2026).

Moreover, a significant interaction between temperature and time (AB) was found, indicating a synergistic effect on extraction efficiency. However, the interaction between temperature and ultrasonic power (AC) was not significant (p = 0.7887), which indicated that the 2 factors had relatively independent effects within the studied range. The interaction between time and power (BC) was significant, indicating the role of time in the accumulation of cavitation energy. The extraction yield typically increases with increasing cavitation time, allowing for greater energy accumulation and longer interaction times between cavitation bubbles and the substrate. In the UAE of β-glucans from barley, longer sonication times resulted in higher extraction yields, although the molecular weight decreased due to prolonged exposure to cavitation energy (Benito-Román et al., 2013).

The optimum conditions for the highest TPC were a temperature of 61.16 °C, time of 23.88 minutes, and ultrasonic power of 61.47%, with a predicted TPC value of 89.54 mg GAE g^{-1}. This is observed in the intermediate range of the variables studied, which is consistent with studies on raw materials rich in polyphenols such as berries and hibiscus, where the highest extraction efficiency is reported to occur when there is a balance between increased mass transfer and reduced biodegradation (Chew et al., 2021; Teixeira et al., 2024). The results suggest that the UAE process is controlled by a complex interplay between mass transfer and sonochemical reactions, in which time and ultrasonic power are more influential than temperature in the extraction of polyphenols from Pilangkasa.

Effect of extraction conditions on the total yield of flavonoid

ANOVA results indicated a good fit of the quadratic regression model for TFC (Table 2), with R^2 = 0.9492 and adjusted R^2 = 0.9317. The lack-of-fit was not statistically significant (p = 0.9989), confirming that the model fitted the experimental data in the studied range. All 3 linear factors, temperature, time, and ultrasonic power, on TFC were significant, with the strongest effect for extraction time, followed by ultrasonic power and temperature. This order of influence differs from that of TPC. For TFC, ultrasonic power plays an almost equivalent role to temperature and becomes a crucial factor in unlocking the linked flavonoid structure, rather than merely supporting general mass transfer. The quadratic regression model for TFC was established and presented as Equation 2.

The positive linear coefficients of A, B, and C in Equation 2 indicated that increasing temperature, time, and power in the initial phase all increased TFC. However, the negative quadratic coefficient of B^2 was significantly larger than those of A^2 and C^2, suggesting that time was the most pronounced factor in curving the TFC response. In other words, TFC had an optimal time interval: sonication was long enough to release flavonoids, but when prolonged excessively, the accumulation of energy reduces recovery efficiency due to oxidation, degradation, or structural transformation of flavonoids.

The response surface graph showed that TFC increased sharply as the extraction time increased from 10 to approximately 25 minutes, especially in the high ultrasonic power range. The decrease in TFC at longer sonication times may be attributed to structural changes or oxidation of flavonoids due to prolonged ultrasonic irradiation. Although no compound-specific analysis was conducted in the present study, similar trends have also been reported in the UAE of polyphenol-rich materials (Chemat et al., 2017). Further high-performance liquid chromatography (HPLC) or liquid chromatography-mass spectrometry (LC-MS) characterization is needed to confirm the degradation pathways of single flavonoids.

This pattern differs from TPC, for which the optimal value was reached at a medium power of about 61%. For TFC, optimal conditions were achieved at 60.84 °C, 25.44 minutes, and 70% ultrasonic power, with a predicted value of 174.88 mg QE g^{-1} (Figure 2). The fact that the optimal power lies at the upper edge of the investigated domain suggests that the flavonoid compounds in the sample may require higher cavitation intensity to be efficiently released from the cell matrix. This mechanism may be related to flavonoids existing as glycosides or being bound to the cell wall, making them less readily released at lower energies compared to some simple phenolics (Alara et al., 2021; Hu et al., 2025). However,

$$TFC = -408.082 + 8.96651A + 6.1959B + 6.31116C - 0.0441203A^2 - 0.0272821AB - 0.0414826AC - 0.103843B^2 + 0.0106667BC - 0.0268474C^2 \quad (2)$$

Table 2. ANOVA for TFC

Source	Sum of squares	F-ratio	*p*-value
A: Extraction temperature (°C)	650.21	30.37	0.0003
B: Extraction time (minutes)	1,748.04	81.65	0.0000
C: Sonication power (%)	1,059.79	49.50	0.0000
A^2	169.885	7.94	0.0183
AB	59.5452	2.78	0.1263
AC	137.665	6.43	0.0296
B^2	941.101	43.96	0.0001
BC	9.10234	0.43	0.5291
C^2	62.9045	2.94	0.1173
Lack-of-fit	54.0103	0.17	0.9989

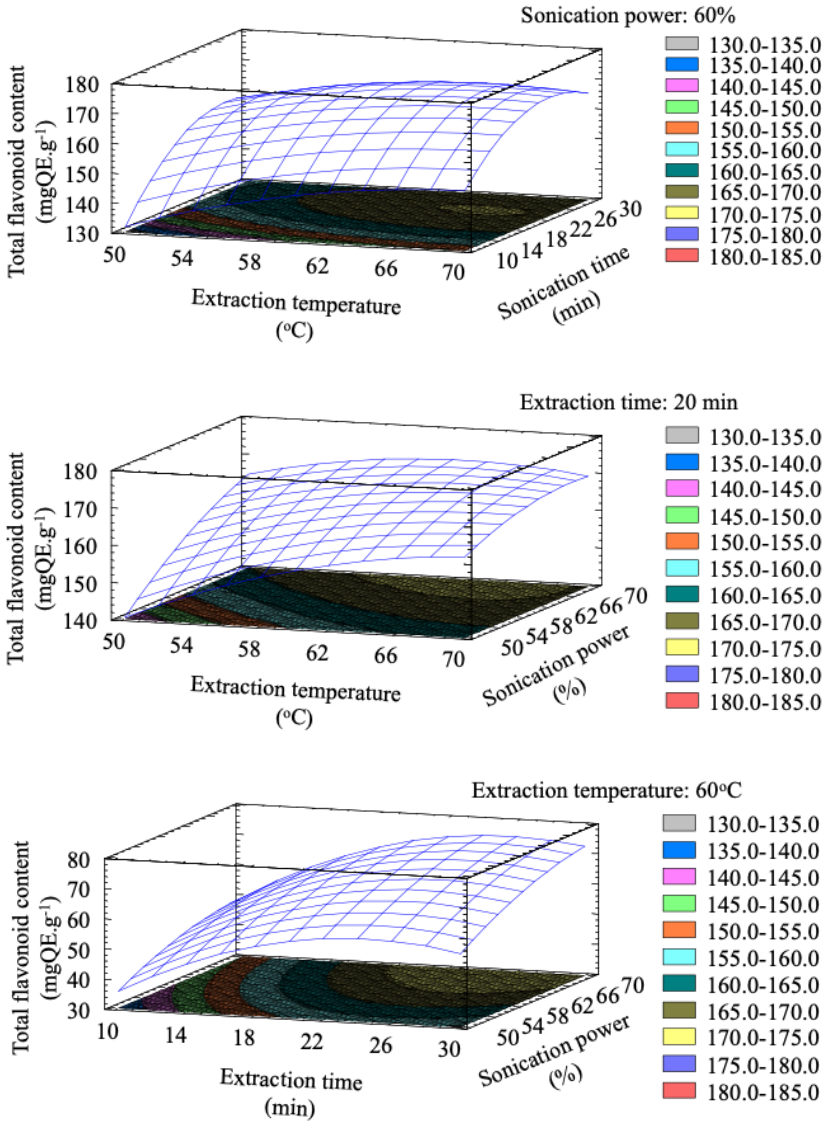

Figure 2. RSM 3D plots for the effect of extraction conditions on TFC content of the extract

the optimization was restricted to the defined experimental domain, and further research is required to establish optimal conditions for extracting flavonoid compounds, including studies at ultrasound powers above 70%.

Cavitation damaged the tissue and increased solvent penetration into cell cavities and intercellular spaces. As ultrasonic power increased, the density of cavitation bubbles increased, generating more microjets and shear

forces, thereby loosening the cell wall structure and releasing flavonoids trapped within the polysaccharide network (Chemat et al., 2017). This explains the reason ultrasonic power has a strong linear effect on TFC (F = 49.50).

This trend suggested that TFC did not simply depend on the amount of soluble polyphenols but strongly depended on the ability to disrupt the physical structure of the tissue material. The interaction between temperature and ultrasonic power was statistically significant, while the interactions between temperature-time and time-power were not. This shows that for TFC, the efficiency of ultrasonic power was significantly dependent on the temperature used. The increase in temperature reduced the solvent's viscosity and increased cell wall permeability, thereby improving the transfer of cavitation energy into the extraction system (Chemat et al., 2017; Bitwell et al., 2023; Teixeira et al., 2024). Thus, temperature not only increased diffusion but also amplified the mechanical efficiency of sonication. This is a key difference from TPC, where the AC interaction was negligible, suggesting that TPC is less dependent on coordination between heat and power than flavonoids.

Although high ultrasonic power was advantageous for TFC, the strongly significant B^2 coefficient (F = 43.96; p = 0.0001) indicated that time remained the primary limiting factor of the process. The released flavonoids remained under high-energy conditions during sonication, increasing the likelihood of oxidation/structural changes (Vilkhu et al., 2008; Bitwell et al., 2023). Critically, some flavonoids might be sensitive to heat, pH, and free radicals generated during cavitation (Teixeira et al., 2024). Thus, the long-term decrease does not necessarily indicate a decrease in total flavonoid solubility, but may reflect changes in flavonoid structures that can complicate the reaction assay used in TFC measurement. This is consistent with the fact that flavonoids generally have their own optimal extraction regions, which do not fully coincide with TPC (Teixeira et al., 2024; Shehzadi et al., 2026).

In many polyphenol-rich fruit systems, TFC usually needs more mechanical energy for the liberation of bound flavonoids. Alternatively, the TPC may peak earlier due to the easy solubility of simple phenolics (Khoddami et al., 2013; Md Yusof et al., 2025; Kumar et al., 2026). In general, TFC had a more specific mechanism in which cavitation intensity determined the amount of bound flavonoids released, and extraction time determined the boundary between the release and degradation. Therefore, optimizing TFC required prioritizing sufficiently high ultrasonic power to disrupt the cell matrix, while limiting sonication time to an optimal range to maintain flavonoid structure and reactivity in quantitative measurements.

Effect of extraction conditions on DPPH free-radical scavenging ability

As shown in Table 3, the ANOVA showed that all 3 factors (temperature (A), time (B), and ultrasonic power (C)) had statistically significant effects (p < 0.001), with time being the most dominant factor (F = 130.19), followed by temperature (F = 58.60) and power (F = 23.31). Unlike TPC and TFC, all two-factor interactions (AB, AC, BC) were significant, suggesting that the DPPH activity is highly dependent on the simultaneous coordination of extraction parameters rather than on the individual effect of each factor.

The response surface plots indicated that DPPH increased rapidly with increasing temperature and time at the initial stage, especially in the medium-high power region. This is attributed to increased polyphenol compounds with free-radical-scavenging capacity, resulting from the cavitation mechanism, which liberates active hydroxyl groups (Chemat et al., 2017). However, the increase in DPPH was not directly proportional to polyphenol content and depended on the molecular structure and preservation of active functional groups (Dung et al., 2026). Therefore, the variation in DPPH under the influence of UAE reflected not only the release of compounds but also the chemical transformation of polyphenols in the sonication environment. The regression model was established and is presented as Equation 3.

A significant characteristic of the model was the very large quadratic coefficients for time (B^2, F = 123.31) and power (C^2, F = 40.90), demonstrating that DPPH is extremely sensitive to the accumulation of sonication energy. An increase in time or power causes cavitation to

$$\text{DPPH} = -373.518 + 6.62349A + 3.02575B + 6.52761C - 0.0342128A^2 - 0.0234085AB - 0.0276584AC - 0.0766577B^2 + 0.0337799BC - 0.0441462C^2 \quad (3)$$

$$R^2 = 0.9122;\ R^2 \text{ (adjusted for d.f.)} = 0.8818$$

Table 3. ANOVA for DPPH

Source	Sum of squares	F-ratio	*p*-value
A: Extraction temperature (°C)	243.715	58.60	0.0000
B: Extraction time (minutes)	541.449	130.19	0.0000
C: Sonication power (%)	96.955	23.31	0.0007
A^2	102.154	24.56	0.0006
AB	43.8367	10.54	0.0088
AC	61.1989	14.72	0.0033
B^2	512.85	123.31	0.0000
BC	91.2865	21.95	0.0009
C^2	170.085	40.90	0.0001
Lack-of-fit	152.135	2.44	0.0792

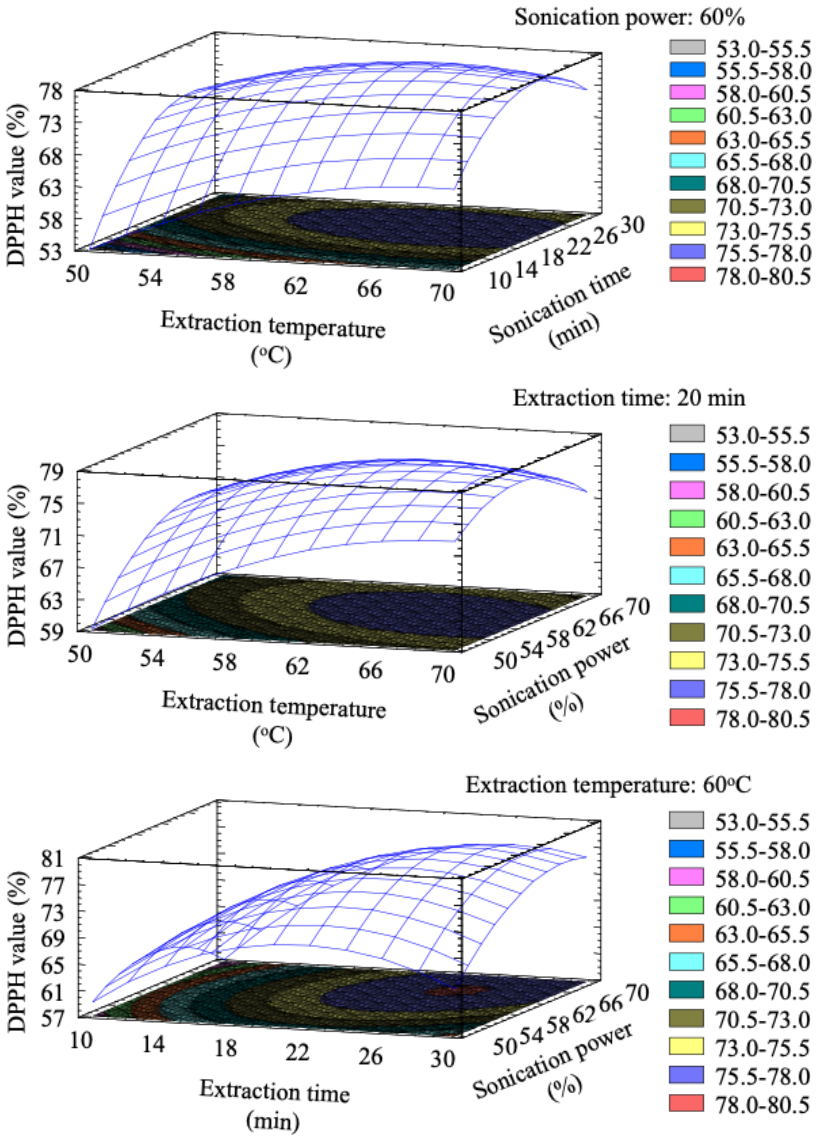

Figure 3. RSM 3D plots for the effect of extraction conditions on DPPH free-radical scavenging ability of the extract

not only release the compound but also to produce free radicals (•OH, •H), leading to secondary oxidation reactions (Hoo et al., 2022). Such reactions can modify flavonoid or phenolic structures, especially the B-ring of flavonoids, which controls the electron-donating potential, and hence decrease DPPH activity (Hoo et al., 2022).

The optimum extraction conditions predicted for DPPH (62.9 °C, 24.1 minutes, and 63.5%

ultrasonic power) were located in the central region of the experimental design (Figure 3), indicating that excessive extraction severity was not conducive to radical-scavenging activity. This result further supports the hypothesis that antioxidant activity depends on preserving the structural integrity of redox-active polyphenols while optimizing extraction efficiency. Therefore, the response surface suggests a balance between the cavitation-enhanced release and the sonochemical degradation of antioxidant compounds. A higher increase in energy can cause the degradation rate to exceed the release rate, leading to a loss of antioxidant activity.

All interactions (AB, AC, BC) were significant, indicating that DPPH was the most complex response among the 4 parameters. This is because antioxidant capacity is affected by the amount of the substance and also by the kinetic interactions among heat, cavitation energy, and contact time (Syamaladevi et al., 2012; Castro-López et al., 2017). TPC and TFC were mostly associated with polyphenol content; DPPH activity was determined not only by polyphenol content but also by the electron or hydrogen-donation capacity of particular molecular structures (Baliyan et al., 2022). Thus, DPPH was simultaneously influenced by extraction efficiency, compound stability, and potential interactions among phenolic constituents.

Temperature-modified solvent diffusivity and cavitation intensity, sonication power governed bubble collapse and cell disruption, whereas extraction time determined the cumulative energy input. The simultaneous influence of these variables explains the significant interaction terms observed in the quadratic model. These interactions indicate that antioxidant activity depends on the combined balance between enhanced mass transfer and the preservation of antioxidant-active molecular structures, rather than on any single extraction factor.

Effect of extraction conditions on FRAP value

FRAP is based on a different mechanism of antioxidant activity from DPPH, involving the reduction of Fe^{3+} ions to Fe^{2+}, and is therefore directly dependent on the redox potential of polyphenol compounds (Gulcin and Alwasel, 2025). This makes the FRAP value a more sensitive indicator of the chemical state and degree of oxidation of the phenolic system than the total amount of polyphenols. The ANOVA results indicated that the effects of time and temperature were significant ($p < 0.05$), while the effect of ultrasonic power was not ($p = 0.0599$) (Table 4). Interestingly, none of the two-factor interactions were statistically significant, unlike in the DPPH model. This indicates that the combined effect of variables had little influence on FRAP, and that the FRAP was mainly dependent on the individual effect of each factor, especially the extraction time.

The highest term in the model was the quadratic term of time, indicating that FRAP was highly sensitive to sonication time. FRAP initially increased with increasing time due to the release of strongly reducing compounds. However, the FRAP value decreased faster than DPPH as time increased. This implies that compounds capable of reducing Fe^{3+} are easily oxidized or structurally changed, and hence easily deactivated under cavitation. The regression model is expressed as Equation 4.

Figure 4 shows that the optimal conditions for FRAP (62.4 °C, 22.3 minutes, 64.5%) tended to favor a shorter time than those for TFC and DPPH. This reflects that the compounds contributing to FRAP degrade more rapidly with prolonged exposure to high-energy environments. This mechanism is consistent with previous studies, in which FRAP was considered the most sensitive indicator of secondary oxidation in UAE (Santos et al., 2019). Furthermore, FRAP did not completely follow the trend for TPC or TFC. While TPC may remain high or continue to increase, FRAP may decrease due to changes in the molecular structure of polyphenols.

Pearson's analysis showed that antioxidant content (TPC, TFC) and antioxidant activity (FRAP and DPPH) were all significantly and positively correlated ($r > 0.9$). Although both DPPH and FRAP evaluate antioxidant capacity, they rely on fundamentally different reaction mechanisms. The DPPH assay measures the donation of a hydrogen atom and an electron to a stable organic radical. It is highly sensitive to both the concentration and structural features of antioxidant compounds (Baliyan et al., 2022).

$$FRAP = -10.7375 + 0.225293A + 0.116921B + 0.122743C - 0.00168824A^2 + 0.000228199AB - 0.000303293AC - 0.00326544B^2 + 0.000226504BC - 0.000843769C^2 \quad (4)$$

$R^2 = 0.8552$; R^2 (adjusted for d.f.) = 0.8052

Table 4. ANOVA for FRAP

Source	Sum of squares	F-ratio	*p*-value
A: Extraction temperature (°C)	0.131635	6.05	0.0337
B: Extraction time (minutes)	0.29533	13.57	0.0042
C: Sonication power (%)	0.0979323	4.50	0.0599
A^2	0.248742	11.43	0.0070
AB	0.00416598	0.19	0.6711
AC	0.00735892	0.34	0.5738
B^2	0.930596	42.75	0.0001
BC	0.00410431	0.19	0.6734
C^2	0.0621335	2.85	0.1220
Lack-of-fit	0.116927	0.36	0.9644

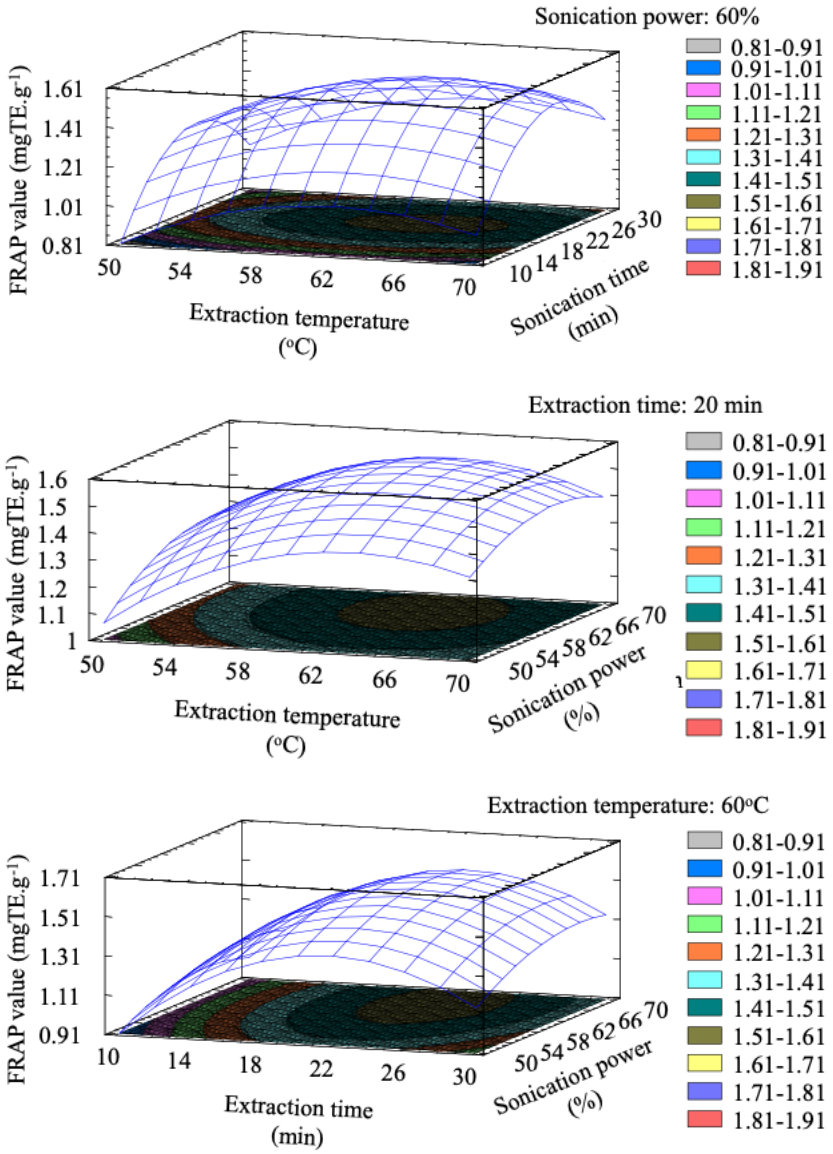

Figure 4. RSM 3D plots for the effect of extraction conditions on the FRAP value of the extract

Thus, the radical-scavenging activity may be affected by concurrent changes in extraction temperature, sonication power, and extraction time, which may have important interaction effects. On the other hand, the FRAP assay detects the reducing potential of antioxidants towards Fe^{3+} ions under acidic conditions (Gulcin and Alwasel, 2025). The reaction is mostly influenced

by the reducing potential of the extracted compounds and thus less by the interactions among the extraction variables.

The FRAP was predominantly governed by the individual effects of extraction time and temperature, whereas DPPH presented more effective synergistic responses to the combination of extraction conditions. This suggests that FRAP reflects the chemical quality of the phenolic system. Overall, FRAP is the most sensitive indicator of sonochemical degradation during the UAE process. Therefore, optimizing FRAP requires tight control of extraction time to avoid exceeding the energy threshold that degrades reduction activity.

Multi-response optimization and overall mechanistic interpretation

The desirability function method was employed to establish the optimal extraction conditions that simultaneously maximize biological responses. The results showed a maximum desirability value of 0.957, which indicates a very high agreement between the predictive model and the multivariate optimization target. The best conditions were obtained at 62.27 °C, 23.22 minutes, and 62.69% ultrasonic power, with the corresponding predicted values: TPC of 89.24 mg GAE g^{-1}, TFC of 171.34 mg QE g^{-1}, DPPH of 78.27%, and FRAP of 1.55 mg TE g^{-1}. The composite

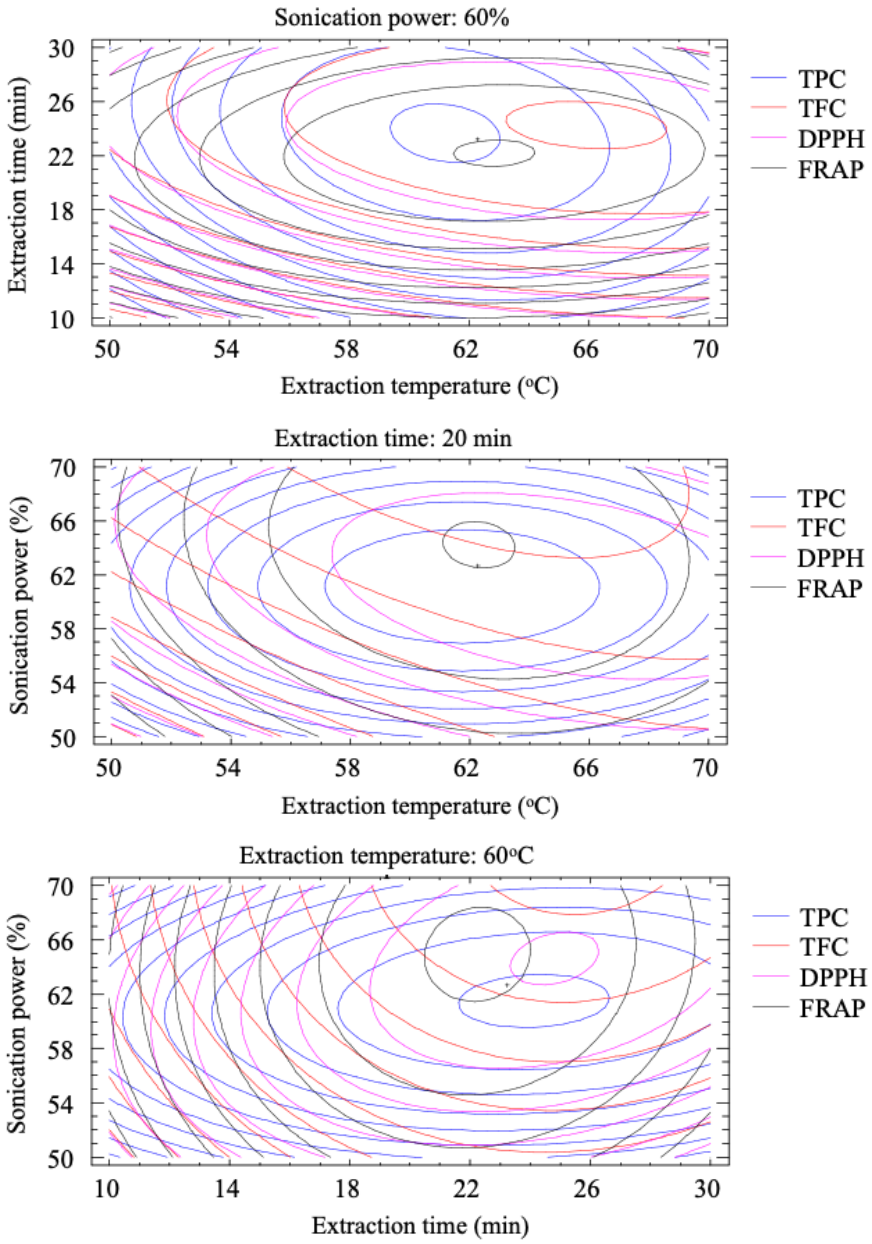

Figure 5. Overlay plots for the effect of extraction conditions on the antioxidant quality of the extract

contour plot (Figure 5) reveals that the optimum region is clearly clustered around the average conditions. This suggests that all responses peaked in a relatively narrow range of conditions, indicating an optimum balance between the physical and chemical mechanisms in the UAE process.

The optimal conditions for TPC, TFC, and DPPH mechanistically suggested that these responses were mainly influenced by the efficiency of polyphenol release by cavitation. In this first stage, cavitation damages the cell structure and releases phenolic compounds from cells, simultaneously increasing both polyphenol content and the antioxidant activity (Chemat et al., 2017). However, as energy accumulates over a prolonged duration or at high power, the process transitions to a second stage in which sonochemical and oxidative reactions begin to dominate, resulting in a gradual decrease in the content of antioxidant compounds (Shehzadi et al., 2026).

It is important to note that FRAP reached optimal conditions in less time than TPC and TFC, indicating that this parameter is more sensitive to the structural changes of polyphenols. This is because FRAP is very sensitive to the chemical state and electron-donating capacity of the phenolic compounds rather than to their total amount. Recent studies have demonstrated that optimal conditions are generally achieved at moderate temperatures (50 to 65 °C) and intermediate times (Aung et al., 2022; Thuy et al., 2025; Shehzadi et al., 2026). This supports the hypothesis that the UAE is a process controlled by a balance between cavitation-enhanced mass transfer and sonochemical degradation. The multi-response optimization results reveal that UAE is a suitable technology for the extraction of polyphenol compounds and antioxidant activity from plant materials. However, for optimal performance, it is essential to tightly control technological parameters to balance enhanced mass transfer with the stability of bioactive compounds.

ANN-GA model development and optimization

The experimental data from RSM were used for ANN model development. Each neuron in the hidden and output layers has a bias value and is linked to neurons in the preceding layer via interconnections with specific weights. The ANN model was developed with bias (b) and weight (w) values for the hidden layer (1) and output layer (2), as shown in Equations 5-8.

Figure 6 also presents the model performance. It can be seen that the coefficient of determination (R^2) values were nearly 1. The R^2 values for training, testing, validation, and overall were 0.99964, 0.99989, 0.99988, and 0.9997, respectively. The architecture of the ANN comprised 3 layers: an input layer with 3 neurons, a hidden layer with 10 neurons, and an output layer consisting of 4 neurons. The number of neurons in the hidden layer was determined through iterative trial and error by adjusting the neuron count until optimal regression (R) and minimal mean squared error (MSE) were achieved, thereby preventing overfitting. By integrating GA optimization with the developed ANN model, the generalization ability of the ANN was significantly enhanced. This is attributed to the universal approximation property, which allows them to model any form of non-linearity or nonlinear process behavior. However, RSM only considers the quadratic nonlinear relationships, which require a deep understanding of the defined ranges for each

$$b_1 = \begin{bmatrix} 2.0552 \\ -3.4131 \\ -1.6480 \\ 1.2551 \\ 0.4468 \\ 0.9143 \\ -2.6219 \\ 1.3391 \\ -2.3596 \\ 3.6121 \end{bmatrix} \quad (5) \qquad w_1 = \begin{bmatrix} -2.3077 & -2.5841 & 1.6869 \\ 1.7087 & -0.3718 & 1.5365 \\ 2.7518 & 1.3026 & -1.4768 \\ -1.0355 & -3.5074 & 1.0159 \\ -2.0600 & -0.1999 & 2.2781 \\ 1.3284 & 2.7682 & 0.1955 \\ -1.8969 & -2.1122 & 0.05827 \\ 0.8584 & -0.5890 & 2.9361 \\ -1.3149 & 2.16856 & 2.3131 \\ 1.7243 & -1.4714 & -1.4288 \end{bmatrix} \quad (6)$$

$$b_2 = \begin{bmatrix} -0.9108 & -0.8094 & 0.3625 & -0.1651 \end{bmatrix} \quad (7)$$

$$w_2 = \begin{bmatrix} -0.2001 & -0.6977 & -0.9226 & -0.1439 & -0.3289 & 0.5591 & -0.3771 & 0.4450 & -0.6545 & -1.1551 \\ -0.7217 & 0.0658 & -0.3456 & 0.4774 & 0.0252 & 0.4239 & -0.5339 & 0.2846 & 0.6152 & 1.0857 \\ -0.6263 & 0.1294 & -0.8327 & 0.6069 & -0.6522 & 0.9586 & 0.0496 & 0.2594 & 0.3140 & -0.3808 \\ -1.2570 & 0.4199 & -1.1541 & 0.8801 & -0.3039 & 0.9288 & -0.0322 & 0.1447 & 0.3337 & 0.2812 \end{bmatrix} \quad (8)$$

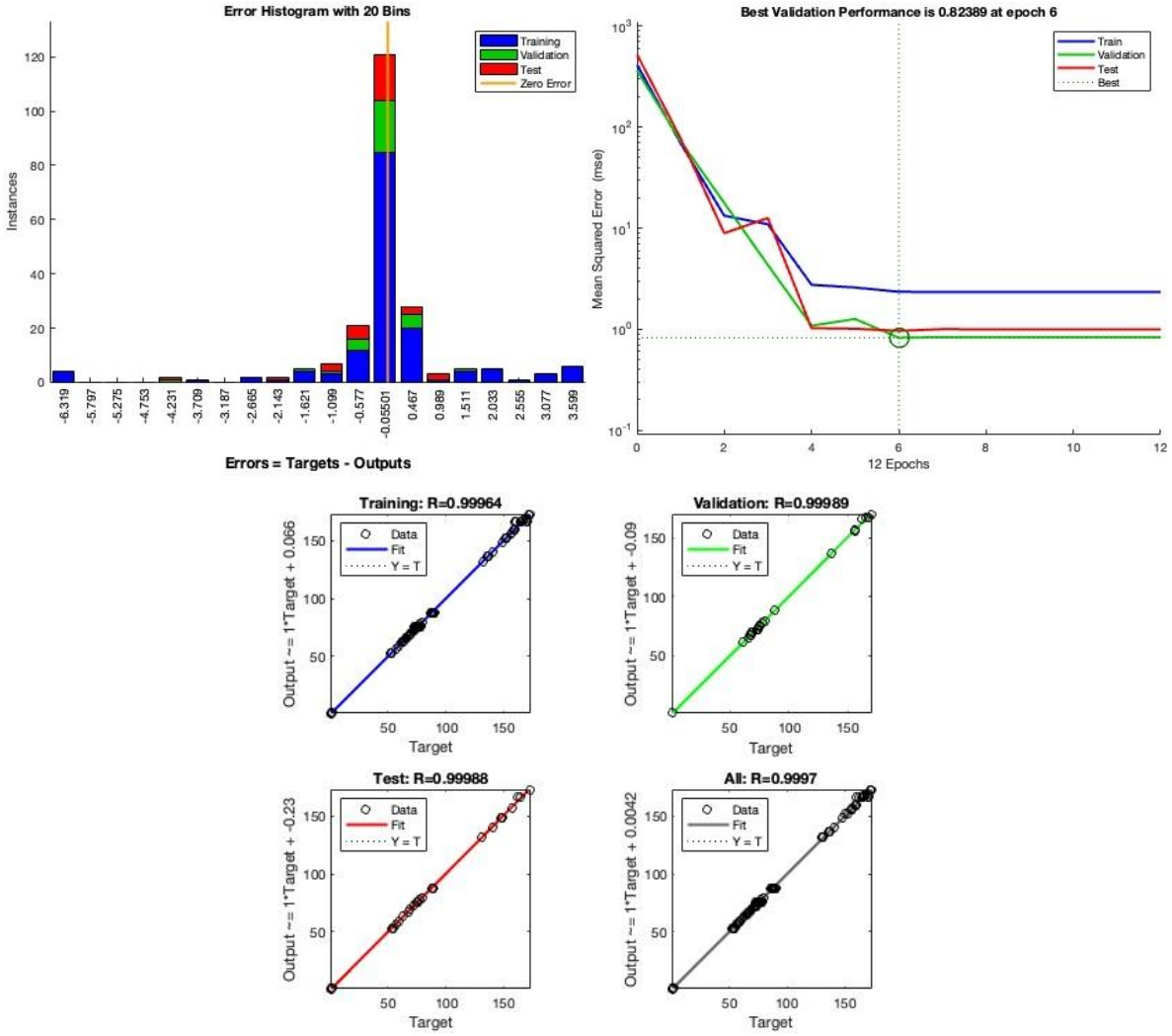

Figure 6. ANN model performance

independent variable (Giang et al., 2025; Loan et al., 2025).

Hybrid RSM-ANN-GA indicated that the optimal settings were an ultrasonic duration of 22.45 minutes, a temperature of 60.2 °C, and an ultrasound power of 60.34%. Under these conditions, the extract obtained had a TPC of 92.24 mg GAE g^{-1}, a TFC of 175.35 mg QE g^{-1}, a DPPH of 81.27%, and a FRAP of 1.61 mg TE g^{-1}. The values were empirically evaluated, revealing a deviation of less than 1% between the expected and actual results from ANN-GA; the prediction error from RSM was approximately 5%. In comparison to RSM, the ANN model exhibited greater precision and markedly improved accuracy in fitting experimental data. The results showed the ANN model achieved the minimum deviation with uniform residuals, whereas the RSM model exhibited large differences between the predicted and actual values of the target responses (Gopan et al., 2018; Al Hasan et al., 2025). However, the present study is limited to the spectrophotometric determination of phytochemicals and antioxidant activities. No compound-specific characterization (e.g., HPLC-DAD or LC-MS) was performed to confirm changes in individual phenolic or anthocyanin compounds during extraction.

CONCLUSIONS

The present study showed that UAE is an effective method for recovering polyphenolic compounds and antioxidant activity from polyphenol-rich fruit materials, with the performance governed by the complex interplay among temperature, time, and ultrasonic power. The RSM results showed that the responses of TPC, TFC, DPPH, and FRAP were optimal in a specific region, reflecting a balance between the enhancement of mass transfer due to cavitation and attenuation due to the sonochemical reactions. The optimal multi-response conditions obtained by RSM were 62.27 °C, 23.22 minutes, and

62.69% power, indicating the potential for optimization of multiple targets simultaneously. In addition, the ANN-GA model had a higher accuracy than RSM, highlighting the potential of artificial intelligence methods for modeling complex nonlinear processes in food technology. Future work should focus on the stability of each bioactive compound, validation of the models in pilot/industrial scale processing, and the economic feasibility of the optimized extraction process, to enable industrial application.

ACKNOWLEDGEMENT

The authors would like to thank Dhonburi Rajabhat University, Tien Giang University, and Mekong University for facilitating the completion of this study, and the three anonymous reviewers for their insightful suggestions and careful reading of the manuscript.

DECLARATION OF GENERATIVE AI USE

During the preparation of this work, the authors used ChatGPT and Grammarly as search aids and language assistants. No scientific content, interpretations, or figures were generated by AI. After using these tools/services, all authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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