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Development of a predictive model for antioxidant recovery yield from Cẩm leaves using sustainable green extraction methods

Desarrollo de un modelo predictivo para el rendimiento de recuperación de antioxidantes de las hojas de Cẩm utilizando métodos de extracción verde sostenibles

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Abstract

This research aimed to enhance the extraction process of antioxidant compounds from *Peristrophe bivalvis* L. Merr leaves utilizing hot water and ultrasound, employing two prediction modeling and optimization approaches: Response Surface Methodology (RSM) and an Artificial Neural Network integrated with a Genetic Algorithm (ANN-GA). The findings indicated that ultrasound intensity and extraction temperature were the primary factors influencing the recovery efficiency of polyphenols, anthocyanins, and antioxidant activity (DPPH), whereas the duration required necessitated optimal adjustment to minimize the degradation of sensitive compounds. The RSM model indicated optimal conditions at 45 min, 60% ultrasound intensity, and a temperature of 68°C, resulting in a total phenolic content (TPC) of 224.13 mgGAE/g, anthocyanin concentration of 50.25 mg/g, and a DPPH inhibition of 84.63%. The ANN-GA model demonstrated superior predictive accuracy, achieving an error margin below 2%. It resulted in TPC of 236.07 mgGAE/g, anthocyanin content of 50.46 mg/g, and DPPH inhibition of 85.45% under optimal conditions of 42.86 min, 60% sonication power, and a temperature of 62°C. The experimental results validated the accuracy of the ANN-GA model and demonstrated its significant application potential in the green extraction and optimization of plant-based food technology.

Keywords: ultrasound-assisted extraction; Peristrophe bivalvis; antioxidants; Response Surface Methodology; Artificial Neural Network – Genetic Algorithm.

Resumen

Esta investigación tuvo como objetivo mejorar el proceso de extracción de compuestos antioxidantes de las hojas de Peristrophe bivalvis L. Merr utilizando agua caliente y ultrasonido, empleando dos enfoques de modelado y optimización: la Metodología de Superficie de Respuesta (RSM) y una Red Neuronal Artificial integrada con un Algoritmo Genético (ANN-GA). Los hallazgos indicaron que la intensidad del ultrasonido y la temperatura de extracción fueron los factores principales que influyeron en la eficiencia de recuperación de polifenoles, antocianinas y actividad antioxidante (DPPH), mientras que la duración requerida necesitó un ajuste óptimo para minimizar la degradación de compuestos sensibles. El modelo RSM indicó condiciones óptimas a 45 minutos, 60% de intensidad ultrasónica y una temperatura de 68°C, resultando en un contenido fenólico total (TPC) de 224.13 mgGAE/g, una concentración de antocianinas de 50.25 mg/g y una inhibición de DPPH del 84.63%. El modelo ANN-GA demostró una precisión predictiva superior, logrando un margen de error por debajo del 2%. Resultó en un TPC de 236.07 mgGAE/g, un contenido de antocianinas de 50.46 mg/g y una inhibición de DPPH del 85.45% bajo condiciones óptimas de 42.86 min, 60% de potencia de sonicación y una temperatura de 62°C. Los resultados experimentales validaron la precisión del modelo ANN-GA y demostraron su significativo potencial de aplicación en la extracción verde y optimización de la tecnología de alimentos de origen vegetal.

Palabras clave: extracción asistida por ultrasonido; Peristrophe bivalvis; antioxidantes; Metodología de Superficie de Respuesta; Red Neuronal Artificial – Algoritmo Genético.

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1 Introduction

Purple "Cẩm" leaves is known by the synonym *Peristrophe bivalvis* (L.) Merr, which is indigenous to East, Southeast, and South Asia, spanning from southern Assam to Sri Lanka and extending eastward to mainland Southeast Asia, Java, southern China, and Taiwan (Hang *et al*., 2024). This is a herbaceous plant primarily found in Southeast Asia. The northern provinces of Vietnam are home to the most abundant purple leaf plant. Subsequently, the southern provinces of Vietnam and the delta regions are also capable of cultivating it (Le *et al*., 2023). Purple "Cẩm" leaves are extracted in Vietnam to create traditional culinary preparations. It characterized by their brilliant hue, serve as a natural culinary colorant in various food products, including sticky rice, bread, and noodles (Thuy *et al*., 2022). Recent research has demonstrated the potential of bioactive compounds and the antioxidant activity of purple "Cẩm" leaves. Purple "Cẩm" foliage possesses elevated concentrations of anthocyanins (Le *et al*., 2023; Thuy *et al*., 2022). Furthermore, researchers have demonstrated that "Cẩm" leaves have antioxidant properties and cytotoxic effects on zebrafish embryos (Hang *et al*., 2024; Le *et al*., 2023). It has been confirmed that purple "Cẩm" leaf extracts can be safely utilized in food products (Hang *et al*., 2024). Food coloring not only captivates consumers, but the utilization of natural components can enhance the quality and nutritional value of food products.

A common simple method employed by households in Vietnam for extracting color components from purple leaves involves the use of boiling water for extraction. Common polyphenol components are susceptible to temperature; elevated temperatures can result in a reduction of phenolic content and diminish antioxidant activity (Molaveisi *et al*., 2019). Consequently, it is essential to examine auxiliary ways to enhance the effectiveness of the extraction process while adhering to the principles of simplicity and cleanliness. A prevalent method currently employed is ultrasonication (Bhargava *et al*., 2021; Loan *et al*., 2024). Ultrasound has been extensively utilized in the extraction of biological components from many raw materials, including essential oil from rosemary (Rosmarinus officinalis L.) leaves (Chen *et al*., 2024), polyphenols from papaya leaves (Wani & Uppaluri, 2023), antioxidants from coffee leaves (Ji *et al*., 2022). This approach is regarded as a green technology that is currently garnering interest (Bhargava *et al*., 2021; Bonto *et al*., 2020; Loan *et al*., 2023). The rise of numerous ailments and shifts in contemporary lifestyles have led to an escalating consumer desire for functional foods that confer health advantages (Baker *et al*., 2022). Plant-based foods provide an abundant supply of bioactive chemicals at a low cost, offering significant promise as nutritional supplements (Xue & Yin, 2024). Nevertheless, to properly capitalize on natural edible plant resources, they remain underdeveloped. Extraction is an essential process for obtaining bioactive compounds from botanical sources (Sasidharan *et al*., 2011). A proficient extraction technique is required to provide optimal yield with a high concentration of target chemicals. Polyphenols may be adversely impacted by light, heat, acids, and alkalis as previous mentioned (Brglez Mojzer *et al*., 2016). Consequently, to obtain the optimal quantity of polyphenols and other beneficial compounds without degradation, it is essential to use an extraction method that minimizes harm to bioactive compounds. Nonetheless, extraction using organic solvents poses the drawback of hazardous solvent residues remaining in the final extract, hence restricting its applicability (Chemat *et al*., 2019). Water is perhaps the optimal medium for extracting water-soluble polyphenol compounds for culinary applications (Plaskova & Mlcek, 2023). Moreover, response surface methodology (RSM) is regarded as an effective instrument for optimizing experimental circumstances, facilitating the concurrent enhancement of many output parameters (Weremfo *et al*., 2023). Response Surface Methodology (RSM) is widely used for the optimization of multifactorial processes in food processing. It is a statistical and mathematical technique that helps design experiments, build models, and evaluate the effects of multiple factors on process outcomes (Gopan *et al*., 2018; Van Tai *et al*., 2024). RSM has been applied to optimize various food processing operations, including enzymatic hydrolysis, extraction processes, machine design, and food formulation (Gopan *et al*., 2018; Lau *et al*., 2023; Weremfo *et al*., 2023). Recently, a novel method known as ANN-GA has emerged, which employs data gathered from RSM to construct a model while concurrently identifying the optimal point efficiently, precisely, and rapidly. Artificial Neural Networks (ANNs) are computational tools that can model complex, nonlinear relationships in food processing systems (Figueroa-Garcia *et al*., 2021; Lau *et al*., 2023; Thuy *et al*., 2025; Van Tai & Luangsakul, 2025). ANNs have been used for modeling and predicting outcomes in various food processing operations, such as juice quality prediction, extraction optimization, and machine performance modeling. When combined with Genetic Algorithms (GA), the resulting ANN-GA hybrid models are particularly effective for global optimization and can handle large search spaces and nonlinear interactions (Gopan *et al*., 2018; Lau *et al*., 2023; Loan *et al*., 2025; Susaimanickam *et al*., 2023). Moreover, it can be utilized in industrial systems to enhance production scale (Susaimanickam *et al*., 2023). Both RSM and ANN/ANN-GA are valuable tools in food processing optimization. RSM is preferred for its interpretability and efficiency in experimental design, while ANN and ANN-GA excel in predictive accuracy and handling complex, nonlinear systems. Therefore, this study aimed to optimize the extraction process of biological chemicals from "Cẩm" leaves in hot water via ultrasound, employing novel statistical techniques such as Response Surface Methodology (RSM) and Artificial Neural Network-Genetic Algorithm (ANN-GA) for analysis and description.

2 Materials and methods

2.1 Sample collection

Purple "Cẩm" leaves were gathered consistently from a garden in Tien Giang Province, Vietnam. Subsequent to collecting, purple leaves were dried at 60°C for 7 hours until the moisture content fell below 5%, then meticulously crushed and sieved through an 80 mesh. The samples were thereafter placed in a dark, vacuum-sealed bag and stored at low temperatures in anticipation of the extraction process.

2.2 Experimental design

Statistical software (Statgraphic Centurion XV.I) was utilized in the experimental design. The RSM model was employed and based on the test results of each component influencing extraction efficiency, three parameters were identified: extraction temperature (°C), extraction duration (min), and ultrasonic power (%). The ideal experimental design employed the Box–Behnken Design (BBD) to construct the runs. The experiment was structured to incorporate six center points and three replications. Consequently, the total number of runs will amount to 18, while the overall number of compiled data sets will comprise 54 datasets. The gathered data were utilized in quadratic polynomial modeling to forecast the output parameters, including total polyphenol concentration, anthocyanin content, and antioxidant activity. Analysis of Variance (ANOVA) was employed to assess the goodness of fit and reliability of the RSM fitting model, consequently evaluating the statistical significance of each component term within the model (Weremfo *et al*., 2023). Simultaneously, a multi-factor optimization method was employed to determine the ideal conditions for extracting the highest activity antioxidant compounds based on the RSM model.

2.3 Artificial Neural Network coupled Genetic Algorithm optimization

Simultaneously, the data from RSM were processed by the ANN model utilizing the Neural Network Toolbox^{TM} in MATLAB R2023b software. The ANN model was developed using extraction temperature, extraction duration, and ultrasonic power as input components, whereas total polyphenols content, anthocyanin content, and antioxidant activity served as output factors. According to the findings from published documents, and to prevent overfitting, the dataset was randomly partitioned into three segments: 70% for training and the remaining 30% allocated equally for testing and validation. A hidden layer with 10 neurons was chosen to construct the ANN model (Gopan *et al*., 2018). The Levenberg–Marquardt algorithm was chosen for its efficacy in error minimization (Lau *et al*., 2023). The ideal ANN model was determined by the minimal MSE value and the maximal correlation coefficient (R value), while the ANN model utilized the Genetic Algorithm (GA) for optimization (Gopan *et al*., 2018; Lau *et al*., 2023; Thuy *et al*., 2024). Genetic Algorithm optimization with the solver function "gamultiobj", involving processes such as crossover fraction (0.8), population size (500), max generations (1000) and function tolerance (0.0001), was subsequently utilized to refine the model parameters for improved performance.

The samples were precisely measured, and three parallel experiments were conducted based on the optimal extraction parameters forecasted by RSM and ANN-GA. The relative errors between the actual and projected extraction rates of "Cẩm" leaves were computed. The differences between the actual extraction yields of "Cẩm" leaves and the model predictions were measured as relative errors, providing an assessment of the models' predictive accuracy.

2.3 Analysis of total phenolic compounds

The total polyphenol content was assessed through the reaction of the extract (0.2 μL) with 10% Folin-Ciocalteu solution (1.5 μL) and 7.5% sodium carbonate solution (1.5 μL). Following 90 minutes of reaction in the absence of light, the absorbance of the solution was assessed at 765 nm using a microplate reader (Kasapoğlu *et al*., 2022). A standard curve for gallic acid was established, and the total phenolic content in the solution was quantified and represented as mg GAE/mL.

2.4 Analysis of total anthocyanin content

The anthocyanin content was measured using the pH differential technique. Buffer solutions with pH 1 and pH 4.5 were formulated using method of Kasapoğlu *et al*. (2022). The extract was combined with the prepared pH buffer solutions at a ratio of 0.1 μL of extract to 1.5 μL of buffer solution. Following a 30-minute reaction period, the absorbance of the reaction solution was assessed at 500 and 750 nm wavelengths prior to quantifying the anthocyanin content in the extract. The anthocyanin concentration in the extract was quantified as mg/g.

2.5 Antioxidant activity

A 0.1 mL sample solution was combined with 3.9 mL of a 95% ethanol solution of DPPH (25 mg/L, stock solution), reacted in darkness for 30 minutes, and then the absorbance was measured at 517 nm (Chen *et al.*, 2024). The inhibition capacity of DPPH is expressed as antioxidant activity (%).

2.6 Statistical analysis

The results of the experiments were expressed as the mean and standard deviation (mean ± SD). The Statgraphic Centurion XV.I and Neural Network Toolbox^{TM} in MATLAB R2023b were employed for RSM and ANN-GA analysis, respectively.

3 Results and discussion

3.1 RSM model development and effect of extraction conditions on quality of extract

3.1.1 Total phenolic content

Total polyphenol content (TPC) from "Cấm" leaves significantly increased with higher ultrasound intensity and extraction temperature; however, prolonged extraction time tended to reduce TPC due to compound decomposition. Specifically, increasing ultrasound power (50–60%) enhanced polyphenol recovery by approximately 20% relative to lower ultrasound levels (20%), while increased temperature (from 50 to 70°C) also significantly led to higher value of TPC.

Ultrasound waves induce a cavitation effect that disrupts the architecture of plant cell tissue, facilitating enhanced solvent penetration and the release of additional polyphenols (Mehta *et al.*, 2022; Wani & Uppaluri, 2023). Consequently, ultrasound assistance enhanced the extraction efficiency of TPC, which could be seen from the contour plot in Figure 1. This trend aligns with several research; for instance, ultrasound treatment has been demonstrated to markedly increase the polyphenol and antioxidant levels in papaya leaves (Wani & Uppaluri, 2023). Under optimal conditions, ultrasonic extraction can produce approximately 1.8 times greater phenolic content than traditional methods (Wani & Uppaluri, 2023), demonstrating strong concordance with existing literature. Moreover, rising temperatures enhance molecule kinetic energy and decrease solvent viscosity, therefore expediting the dissolution and diffusion of polyphenols into the extraction solution (Hu *et al.*, 2022). Simultaneously, heat facilitated the softening of plant tissue, thereby enhancing the release of polyphenols (Fraterrigo Garofalo *et al.*, 2024; Hiranpradith *et al.*, 2025). Experiments demonstrate that when the temperature raised from 50 to around 70°C, TPC remarkably increased. Specifically, polyphenols in "Cấm" leaves demonstrated considerable thermal stability within the examined temperature range; thus, high-temperature extraction for a reasonable duration does not diminish

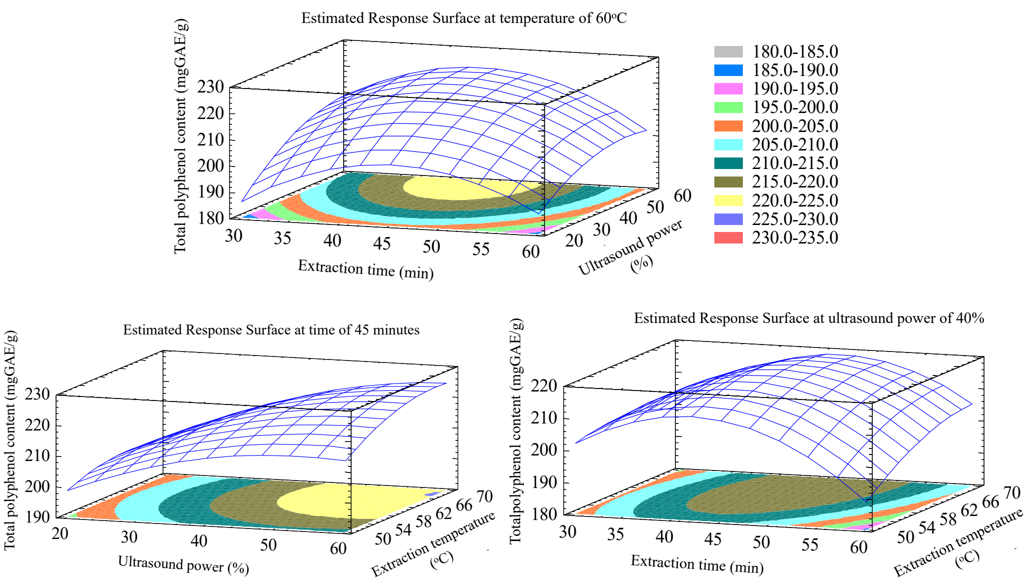

Figure 1. Contour plots of effect of extraction conditions on polyphenols content in extract.

TPC obtained. This trend quite differed from certain other materials; for instance, polyphenols are frequently susceptible to high temperatures, resulting in decomposition, which diminishes both their content and antioxidant efficacy (Antony & Farid, 2022). Nevertheless, within the temperature range of 70°C and below, our findings align with studies indicating that numerous polyphenols can endure higher temperatures provided the duration of heating is not excessive.

Extending the initial extraction duration facilitates more diffusion of polyphenols into the solvent. Nonetheless, if the time of extraction extended, TPC content may diminish due to the oxidation or hydrolysis of the compounds over time (Gil-Martín *et al*., 2022). This study observed that prolonged exposure to heat and ultrasonic partially destroyed the polyphenols, leading to a reduction in TPC measured in the extract. Additional research has indicated a comparable pattern: polyphenol extraction yields frequently reached a peak after an optimal duration, subsequently stabilizing or experiencing a slight decline due to equilibrium or compound degradation (Gil-Martín *et al*., 2022; Hiranpradith *et al*., 2025). Consequently, selecting the ideal extraction duration is crucial for achieving elevated total phenolic content (TPC) without sacrificing the extract's quality.

The ANOVA results indicated that the three main factors – extraction time (A), ultrasonic power (B), and extraction temperature (C) – significantly influenced polyphenol content in the obtained extracts, with P-values of 0.0456, 0.0000, and 0.0003, respectively. Ultrasonic power (F = 172.58) and temperature (F = 21.82) were identified as the two factors exerting the most significant effects. The interactions AC (time × temperature) and BC (ultrasonic power × temperature) were significant ($P < 0.05$), suggesting that extraction efficiency improved with optimal factor combinations. This clearly demonstrated the synergistic role of physical factors in polyphenol extraction. The regression model (Equation 1) demonstrated high accuracy, with R^2 = 89.18% and adjusted R^2 = 86.97%, signifying that it accounted for nearly 90% of the variation in the data. The P-value for the lack-of-fit test is 0.0691, which, while near the 0.05 threshold, remains adequate to affirm the model's appropriateness. The polyphenol content rose with prolonged extraction time, peaking at approximately 40–50 min, after which a slight decline was observed with additional time. The observed phenomenon may result from the diffusion process achieving saturation, leading to the decomposition of sensitive compounds under extended exposure to heat and ultrasound as previous explaination. Increasing the temperature from 50°C to 70°C significantly enhanced the polyphenol content, attributed to the softening of plant tissue and increased solubility, particularly when combined with ultrasound at medium to high power levels (50–60%). The optimized conditions determined through response surface methodology for maximizing polyphenol content were a duration of 45.04 min, ultrasonic power set at 60%, and a temperature of 68.05°C, resulting in a total phenolic content of approximately 224.13 mg GAE/g. The optimized method, which incorporates ultrasonic techniques and optimal modeling, yielded nearly four times the total phenolic content compared to the traditional method (extraction in boiling water for 30 min, TPC = 56.34 mg GAE/g), thereby highlighting its superiority.

$$TPC = -11.91 + 4.71A + 1.26B + 2.72C - 0.072A^2 - 0.008AB + 0.033AC - 0.014B^2 + 0.0118BC - 0.036C^2 \quad [R^2 = 89.18\%,\ R^2(adjusted) = 86.97\%] \tag{1}$$

Tabe 1. Analysis of Variance for TPC.

Source	Sum of Squares	F-Ratio	P-Value
A: Time (min)	62.5083	4.75	0.0456
B: Ultrasound power (%)	2268.97	172.58	0.0000
C: Temperature (°C)	286.84	21.82	0.0003
A^2	3474.01	264.24	0.0000
AB	64.9268	4.94	0.0421
AC	301.415	22.93	0.0002
B^2	424.116	32.26	0.0000
BC	67.2736	5.12	0.0390
C^2	172.082	13.09	0.0025
blocks	67.458	2.57	0.1101
Lack-of-fit	740.083	2.08	0.0691
Pure error	197.208		
Total (corr.)	8662.06		

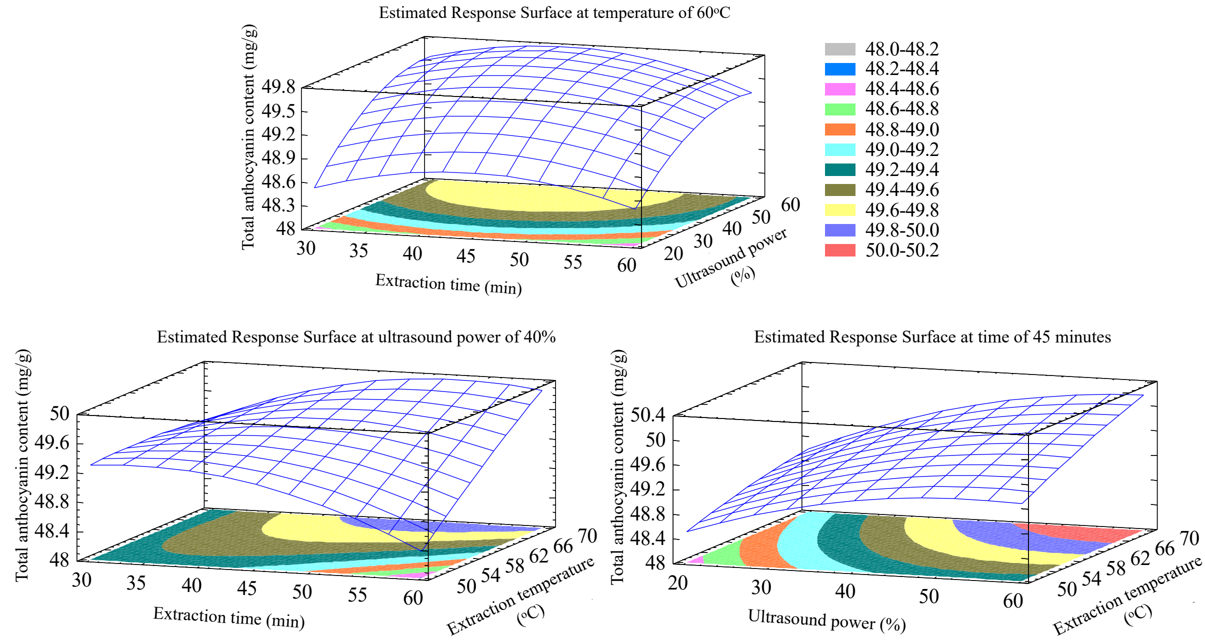

Figure 2. Contour plots of effect of extraction conditions on total anthocyanin content in extract.

3.1.2 *Anthocyanin content*

The overall anthocyanin concentration in "Cẩm" leaf extract is influenced by comparable factors; however, anthocyanin, as a pigment, exhibits more sensitivity to heat than polyphenols in general (Xue *et al*., 2024). Experimental findings indicated that anthocyanin concentration rose with increased temperature and ultrasonic intensity; nevertheless, too severe conditions (high temperature or prolonged exposure) may result in pigment degradation, hence diminishing the yield of anthocyanin (Figure 2). The utilization of ultrasonic facilitates the release of anthocyanin from plant cells via the cavitation effect, akin to that of polyphenols. The rupture of the cell wall facilitates direct contact between the solvent and the color particles, enhancing extraction efficiency (Loan *et al*., 2023; Mehta *et al*., 2022). The research findings indicated that high ultrasound levels markedly enhanced anthocyanin content in comparison to the absence of ultrasound (Ji *et al*., 2022). This tendency is corroborated by previous studies; several publications indicated that ultrasonic extraction yields a greater quantity of anthocyanin compared to traditional procedures, owing to the effective release of color components from plant tissues (Bhargava *et al*., 2021; Loan *et al*., 2023). Given the sensitivity of anthocyanins, it is essential to optimize the ultrasound energy level; our findings align with the prevailing trend that ultrasound enhances the extraction efficiency of anthocyanins, provided the intensity is regulated to prevent the degradation of the color component (Ji *et al*., 2022). Temperature exerts a dual influence on anthocyanins. On one side, elevating the temperature enhances the extraction rate of anthocyanins (similar to polyphenols) by improving solubility and facilitating the destruction of tissue structure (Wani & Uppaluri, 2023). Experiments demonstrated that elevating the temperature to approximately 70°C resulted in an increased yield of anthocyanins, suggesting that elevated temperatures facilitate the release of more anthocyanins during a short extraction period. Conversely, anthocyanins exhibit instability at elevated temperatures; prolonged exposure may alter or disintegrate the anthocyanin structure (flavylium), hence diminishing its concentration (de Moura *et al*., 2024). In this work, the optimized extraction duration resulted in a negligible reduction of anthocyanins at 70°C. The findings align with those of Thuy *et al.* (2022), where the extraction of purple leaves via the conventional method at 88°C for approximately 27 min yielded a substantial anthocyanin concentration of 25.61 mg/g dry matter. This indicates that anthocyanin may endure elevated temperatures shortly to enhance extraction efficiency. Nonetheless, prolonged elevation in temperature will result in a significant loss of anthocyanins. Thuy *et al.* (2022) documented that anthocyanin in purple leaf extract exhibits a half-life of around 19 days at 28°C, in contrast to 221 days at -9°C, indicating a significant rise in the breakdown rate with rising temperature. Consequently, alternative research frequently selects mild temperatures to optimize the equilibrium between efficiency and anthocyanin stability. For instance, anthocyanin extraction from purple maize was most effective at approximately 70°C for about 25 minutes, however for more delicate materials like red cabbage, the ideal temperature was merely at 15°C when employing ultrasonic to prevent color degradation (Muangrat, 2023). This comparison indicated that the pattern seen in our work as anthocyanin increases with temperature to an optimum, that aligned with recent literatures; however, the optimum temperature may differ based on the material and the stability of the specific anthocyanin.

The extraction duration of anthocyanins required careful optimization. An extended initial duration would yield a greater extraction of anthocyanins owing to the elevated concentration gradient and residual pigment within the tissue. Nonetheless, anthocyanins may progressively deteriorate when subjected to heat and light (Oancea, 2021). Consequently, prolonging the duration after most anthocyanins have been extracted would be led to a reduction in content due to the breakdown of the color molecules (Ngoc Nhon *et al*., 2022). Our findings indicate that there exists an ideal duration for achieving maximum anthocyanin content; extending this period results in no further rise and a modest decline in anthocyanin levels. This aligns with research on anthocyanin extraction kinetics: typically, after around 20–30 min of extraction (with ultrasonic assist), the anthocyanin concentration peaks and subsequently declines due to color deterioration. The findings of this study align with established theory and literature, indicating that sufficient time is required for the release of anthocyanins, whereas excessive duration may lead to the degradation of color components (Enaru *et al*., 2021).

ANOVA analysis results indicated that the anthocyanin content was strongly influenced by the extraction parameters, particularly temperature and ultrasonic power (Table 2). The ultrasonic power (factor B) and extraction temperature (factor C) exerted a highly significant statistical influence on anthocyanin content ($P < 0.001$), with F-ratios of 61.37 and 35.54, respectively. The primary effect of extraction time (factor A) was not significant ($F = 1.40$, $P = 0.2548$), indicating that varying the time within the range of 30–60 min did not substantially alter the quantity of anthocyanin extracted. The quadratic time component (A^2) was statistically significant ($P = 0.0015$), suggesting that anthocyanin content peaked at an ideal duration before experiencing a minor decline with further time extension. Likewise, the quadratic aspect of ultrasound power (B^2) was significant ($P = 0.0045$), indicating that the enhancing impact of ultrasound does not rise linearly but rather approaches saturation at elevated power levels. Simultaneously, the quadratic term of temperature (C^2) proved to be insignificant ($P = 0.5338$), suggesting a predominantly linear correlation with temperature within the examined range of 50–70°C. Concerning the interactions among components, only the interaction between time and temperature (AC) was statistically significant ($F = 20.16$, $P = 0.0004$). The impact of time extension is contingent upon temperature: at elevated temperatures, prolonged duration enhanced anthocyanin extraction, but at lower temperatures, the increase in time yielded diminished improvements in yield. The interactions between time and ultrasound (AB) ($P = 0.5885$) and between ultrasound and temperature (BC) ($P = 0.2458$) were not significant, indicating that the influence of ultrasound power was mostly independent of time and temperature within the experimental parameters. Among the three parameters, ultrasonic power exerted the most significant influence, followed by temperature, but time had a comparatively minor impact on anthocyanin output. The adequacy of the quadratic regression model (RSM) was assessed using statistical metrics (Equation 2). The coefficient of determination (R^2) was approximately 82.08%, indicating that the model accounted for roughly 82% of the variation in anthocyanin content. The lack-of-fit test yielded statistically insignificant findings ($P = 0.8198 > 0.05$), suggesting that the model adequately encompassed all relevant variables and effectively represented the experimental data at the 95% confidence level. The derived RSM model exhibited a strong fit and good statistical characteristic, enabling it to study the impact of variables and forecast anthocyanin content based on extraction circumstances. The change in anthocyanin content based on extraction parameters can be elucidated by the model's regression coefficients. The substantial positive coefficient of ultrasound power (+0.055) signifies that anthocyanin yield markedly increases with heightened ultrasound intensity. This aligns with the process by which ultrasonic induces cavitation to disrupt tissue structures, hence enhancing anthocyanin release efficiency. The negative coefficient of temperature (–0.04) indicates that excessively high temperatures may marginally diminish anthocyanin yield, potentially due to partial thermal breakdown of the molecule. Nonetheless, the influence of temperature is not wholly detrimental: the positive correlation between time and temperature (+0.0026) indicates that at elevated temperatures, anthocyanin production continues to increase significantly with adequate time extension. In the temperature range of 50–70°C, elevated temperatures expedite the extraction process; nonetheless, they necessitate precise time management to prevent future degradation of anthocyanins. The tiny and statistically negligible negative linear coefficient indicates that extending the duration from 30 to 60 min does not substantially alter the anthocyanin content. The extraction efficiency diminishes only when the duration beyond the ideal range (about 50 min), as indicated by the negative quadratic effect (A^2).

Table 2. Analysis of Variance for total anthocyanin content.

Source	Sum of Squares	F-Ratio	P-Value
A: Time (min)	0.126428	1.40	0.2548
B: Ultrasound power (%)	5.53302	61.37	0.0000
C: Temperature (°C)	3.20471	35.54	0.0000
A^2	1.35344	15.01	0.0015
AB	0.027554	0.31	0.5885
AC	1.81745	20.16	0.0004
B^2	1.00705	11.17	0.0045
BC	0.131555	1.46	0.2458
C^2	0.0365675	0.41	0.5338
blocks	0.101953	0.57	0.5798
Lack-of-fit	1.63952	0.67	0.8198
Pure error	1.35244		
Total (corr.)	16.6983		

In summary, the anthocyanin content significantly increases with higher ultrasonic power and elevated extraction temperatures within the examined range, while the extraction duration requires optimization to achieve an appropriate level. The study results indicate that elevating the ultrasonic power from 20% to 60% markedly enhances anthocyanin content, while raising the temperature from 50°C to 70°C also boosts anthocyanin extraction efficiency; however, it is essential to avoid extending the duration at high temperatures to mitigate compound decomposition. The best circumstances for maximizing anthocyanin content, as estimated by RSM, are roughly 51.2 min, 70°C, and 60% ultrasonic power, with a predicted anthocyanin concentration of around 50.25 mg/g. This represents the ideal level within the testing range, yielding the maximum anthocyanin content. This outcome establishes a scientific foundation for determining optimal extraction conditions to enhance the anthocyanin yield from “Cẩm” leaves in practical applications.

$$\text{Total anthocyanin content (mg/g)} = 48.7 - 0.0255A + 0.055B - 0.04C - 0.00142A^2 - 0.00016AB + 0.0026AC - 0.0007B^2 + 0.0005BC - 0.0005C^2 \quad [R^2 = 82.1\%,\ R^2(adjusted) = 78.4\%] \tag{2}$$

3.1.3 Antioxidant activity (DPPH)

The antioxidant activity, quantified by DPPH, indicates the overall quantity of chemicals capable of donating electrons or protons, primarily polyphenols and anthocyanins, present in the extract (Chen *et al*., 2024; de Moura *et al*., 2024). Consequently, the determinants influencing DPPH are predominantly analogous to those impacting TPC and anthocyanins (Loan *et al*., 2023; Molaveisi *et al*., 2019). The findings indicated that high ultrasound intensity and temperature enhanced the DPPH inhibition percentage of the extract, achieving an optimal value exceeding 84% at approximately 58% ultrasound power, 68°C, and 45 min (Figure 3). Ultrasound enhances the release of antioxidants into the solution, resulting in improved DPPH radical scavenging capacity. This study demonstrated that ultrasound exerted the most substantial effect on DPPH activity, as indicated in Figure 2, with elevated ultrasound power resulting in markedly enhanced antioxidant activity. Wani and Uppaluri (2023) demonstrated that ultrasonic extraction from papaya leaves produced an extract with a DPPH reduction capability of around 88.5%, much surpassing that achieved using conventional extraction methods. The primary mechanism remains the cell disruption impact of ultrasound, which facilitates the extraction of antioxidant chemicals (such as polyphenols and flavonoids), thus elevating the concentration of reducing agents in the solution. This tendency is well-documented, affirming the correlation between the findings of this study and recent studies regarding the advantages of ultrasound technology in augmenting the antioxidant activity of extracts (Bhargava *et al*., 2021; Fraterrigo Garofalo *et al*., 2024; Molaveisi *et al*., 2019).

High temperatures up to an optimal level facilitated the extraction of more antioxidant molecules, hence enhancing the DPPH activity of the extract with increasing temperature. This rise is mostly attributable to the increased levels of polyphenols and anthocyanins that are soluble at high temperatures, as noted for TPC and anthocyanins previously mentioned. However, if the temperature is excessively elevated or maintained for prolonged periods, certain antioxidants may degrade, hence diminishing the DPPH-scavenging capacity. Experiments on purple leaves indicated that antioxidant activity progressively increased within the temperature range of 50–70°C, peaking at approximately 68°C, following which a little decline may occur with additional temperature elevation due to the initiation of decomposition.

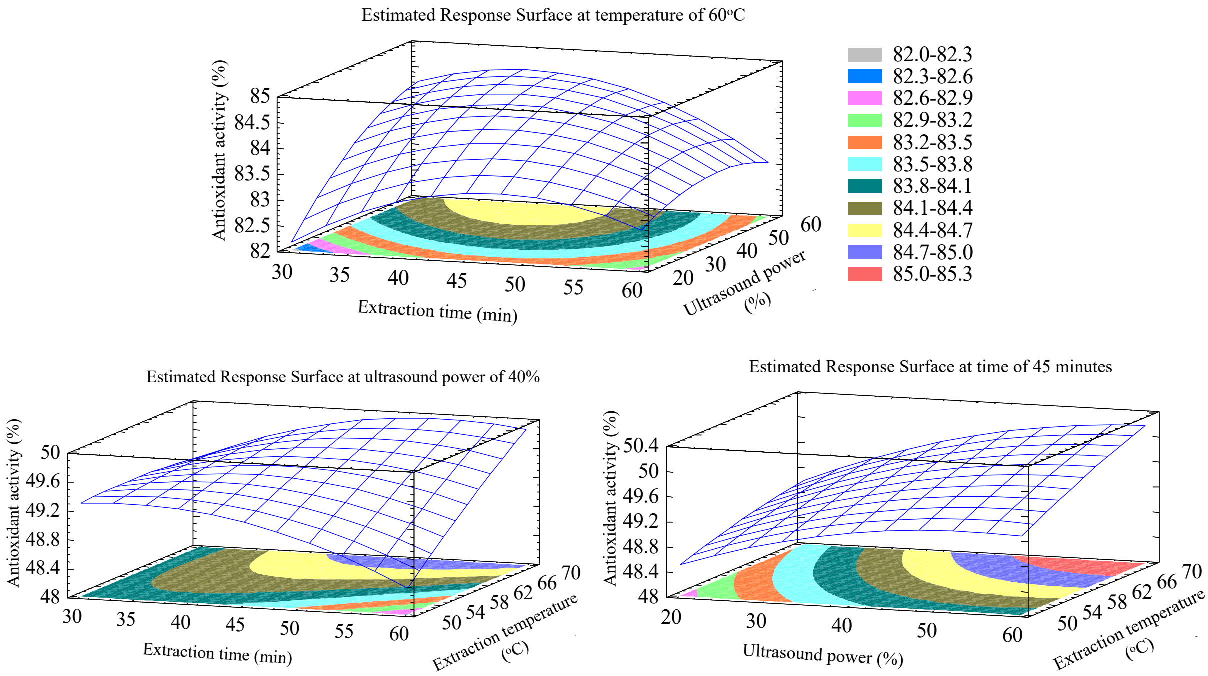

Figure 3. Contour plots of effect of extraction conditions on antioxidant activity in extract.

This outcome aligns with the prevailing notion that moderate temperatures enhance antioxidant extraction, but excessively high temperatures yield the contrary effect. Molaveisi *et al*. (2019) observed that extended heating decreased the phenolic content and DPPH activity in honey samples. Likewise, extending the initial extraction duration facilitates the release of more antioxidants, resulting in an increase in % DPPH. However, as saturation approaches, extending the duration would be not substantially enhanced the activity and may even lead to a minor decline due to the degradation of chemicals. The ideal outcome of around 45 min indicates that extending the duration to 60 min does not enhance DPPH activity and may even lead to a reduction relative to the optimal threshold. This parallels the trend of TPC/anthocyanin and aligns with earlier research indicating that the antioxidant activity of the extract reaches a peak before diminishing with prolonged extraction time (Luangsakul *et al*., 2025; Van Tai *et al*., 2021). Consequently, to achieve optimal antioxidant capacity, it is essential to employ an extraction duration that adequately retrieves all antioxidants while preventing excessive extension. This performance level is exceptional, indicating that the synergy of heat and ultrasound might augment the biological value of the extract from "Cẩm" leaves.

ANOVA analysis of the DPPH index indicated that ultrasound power (B) and extraction temperature (C) exerted a statistically significant influence ($P < 0.01$), with F-ratios of 32.65 and 9.50, respectively, underscoring the critical importance of these factors in augmenting the DPPH free radical scavenging capacity of the extract (Table 3). The quadratic term of time (A^2) and the interaction between time and temperature (AC) had a significant impact ($P < 0.01$), indicating that the antioxidant effect did not perpetually escalate with prolonged time, but rather reached an optimal maximum that required optimization. Additional interactions, such as AB and B^2, also exhibited P-values less than 0.05, signifying that the ultrasonic power level required suitable adjustment rather than merely raising to the maximum. Simultaneously, the singular extraction duration (A) did not yield a statistically significant impact ($P = 0.1676$), indicating that merely altering the extraction time within the 30–60 min interval was insufficient to substantially affect antioxidant capacity, provided that other variables remained constant. The quadratic linear regression model (Equation 3) effectively captured the fluctuation of DPPH in relation to the extraction circumstances, with $R^2 = 84.18\%$ and modified $R^2 = 80.94\%$, signifying that the model accounted for almost 80% of the data variation. The P value of the Lack-of-fit test is 0.9806, indicating that the model is well-fitted and does not omit a significant variable. The Durbin–Watson value of 2.85777 ($P = 0.9988$) negated the likelihood of autocorrelation in the residuals, hence affirming the reliability of the regression results. Consequently, this is a reliable and robust Response Surface Methodology model for DPPH optimization research. Regression analysis indicated that the positive coefficients of ultrasonic power (+0.14) and temperature (+0.11) were the primary factors contributing to the enhancement of antioxidant capacity.

Table 3. Analysis of Variance for DPPH.

Source	Sum of Squares	F-Ratio	P-Value
A:Time	0.548058	2.10	0.1676
B:Ultrasound	8.50746	32.65	0.0000
C:Temp	2.47511	9.50	0.0076
AA	8.92382	34.24	0.0000
AB	2.43311	9.34	0.0080
AC	8.05035	30.89	0.0001
BB	1.66625	6.39	0.0232
BC	0.0953973	0.37	0.5542
CC	1.05898	4.06	0.0621
blocks	0.250687	0.48	0.6274
Lack-of-fit	2.83921	0.40	0.9806
Pure error	3.9089		
Total (corr.)	42.6554		

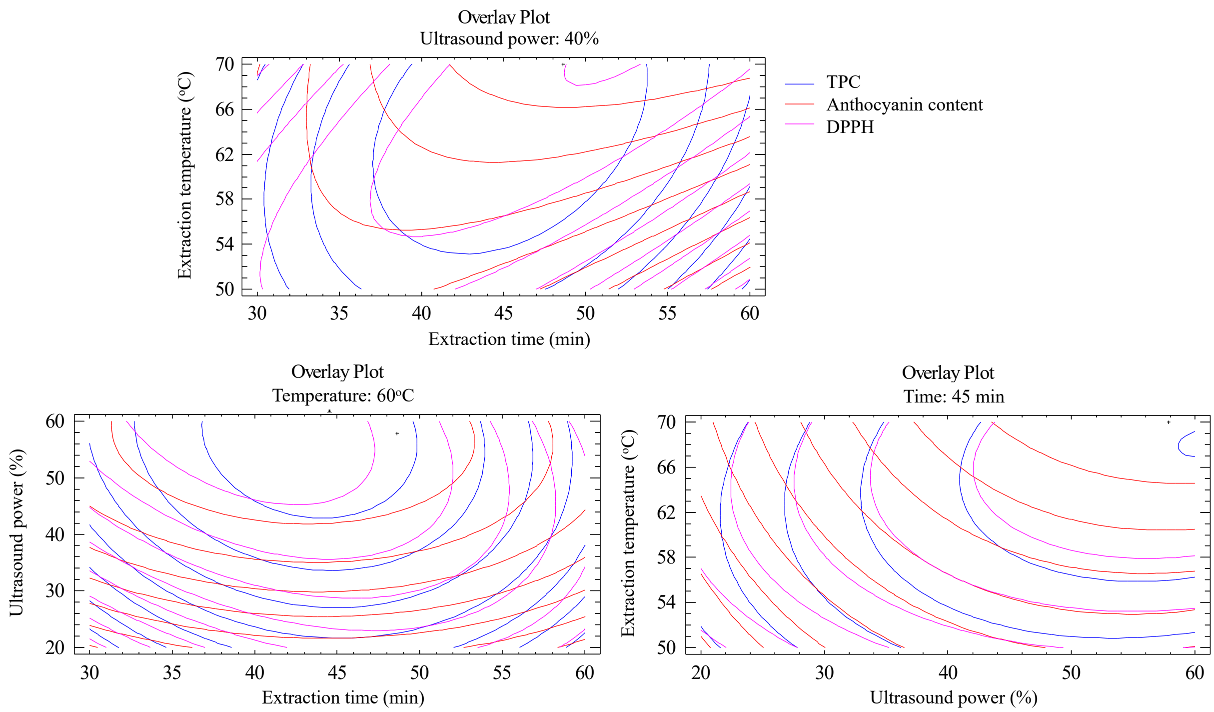

Figure 4. Overlay plots for multi-objective optimization by RSM.

This aligns with the mechanism of phenolic chemical release resulting from agitation, cellular disturbance, and thermal activation. The negative coefficients of the second-order components for all three parameters (A^2, B^2, C^2) indicate that exceeding the threshold may diminish efficiency due to the breakdown of heat-sensitive chemicals or reverse oxidation.

$$DPPH(\%) = 75.6 + 0.05A + 0.142B + 0.11C - 0.0037A^2 - 0.0015AB + 0.005AC - 0.0009B^2 + 0.0004BC - 0.0028C^2 \quad [R^2 = 84.18\%,\ R^2(adjusted) = 80.94\%] \tag{3}$$

The overlay graphic illustrates the intersection of distinct optimization regions for three quality indicators: TPC, anthocyanin content, and antioxidant capacity (DPPH) (Figure 4). This graphic is designed to identify the range of extraction conditions in which all three indicators attain elevated values, hence facilitating the selection of suitable technological parameters for the purple leaf extraction process. The findings indicate that the comprehensive optimization parameters are defined by an extraction time of approximately 48.6 minutes, ultrasonic power of roughly 58%, and a temperature of 70°C. Under these conditions, the model forecasts a total phenolic content of around 224.13 mg GAE/g, anthocyanin levels of 50.23 mg/g, and a DPPH inhibition of 84.63%. The response level for all three variables is consistently strong, yielding an overall attractiveness value of 0.933. Analysis of the overlay diagram indicates that the intersection zone of the best conditions for each parameter is notably constrained, particularly owing to the sensitivity of anthocyanins to temperature and duration. Anthocyanins possess flavylium structures that exhibit instability at extreme conditions, but polyphenols and other antioxidant chemicals demonstrate greater heat resistance within the examined range. Consequently, the synthetic optimization zone is primarily established near the upper boundary of the anthocyanin optimization zone and resides inside the safe zone of TPC and DPPH. The selection of synthetic optimization parameters aligns with the focus of prior research on optimizing the extraction process through multi-objective response surface modeling. Luangsakul *et al*. (2025) highlighted the significance of the overlay contour technique in identifying the efficient crossover zone among various biological responses in ultrasonic extraction. The research by Susaimanickam *et al*. (2023) also investigated for the utilization of overlay charts in conjunction with desirability functions to optimize the efficiency and stability of chemicals inside intricate extraction processes. Based on the optimal conditions was found, the actual test for RSM as follow ultrasonic power (58%) and an extraction temperature of 70°C for 49 min was conducted. It found that the obtained extract from acutall test had phenolic content of 212.13±0.3 mg GAE/g, anthocyanin levels of 49.13±0.9 mg/g, and a DPPH inhibition of 82.63±0.8%. The difference between predicted and actual value were found about 5.35%, 2.19% and 2.36%, respectively.

3.2 ANN-GA model development and optimization

The experimental design established extraction time, sonication power, and temperature ranges of 30-60 minutes, 20-60%, and 50-70°C, respectively. The experimental data (TPC, anthocyanin content, antioxidant activity) were acquired through extraction following the BBB method and utilized for ANN modeling. The best ANN model was established by repeatedly training the network with the goal that the model has good performance in all three datasets, that is, minimum Mean Squared Error (MSE) and maximum R (Kumar *et al*., 2024). The optimal ANN model, characterized by a topology of 3-10-3, is defined by the connection weights and bias values across the layers, as illustrated in Equations 4-6. Figure 5 presents a regression analysis that assesses the alignment of predicted values with actual values through R values across the training, validation, test, and overall data sets. The results indicate a strong correlation between the actual values and the predicted values of TPC,

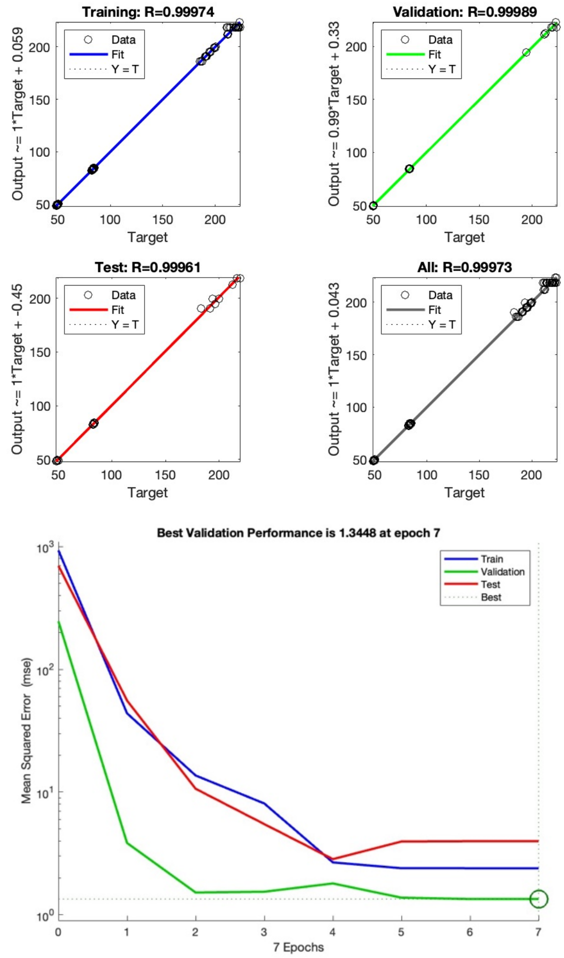

Figure 5. Regression analysis of the ANN model.

anthocyanin content, antioxidant activity generated by the ANN model, thereby affirming the model's reliability and predictive accuracy. Figure 5 presents the performance evaluation results of the MSE as the number of epochs increases during training, validation, and testing. The developed ANN model completed training after seven epochs, yielding MSE values of 2.396, 1.344, and 3.976 for the training, validation, and test sets, respectively. The results indicate that the constructed ANN prediction model demonstrates strong performance.

The genetic algorithm (GA) is a widely utilized approach for addressing optimization problems, characterized by its global search capabilities and adaptive control features (Sgarro *et al*., 2024). Upon full training of the ANN model, which accurately reflects the extraction process, the ANN-GA can be utilized to optimize the three extraction factors (extraction time, ultrasound power, temperature) to achieve maximum total phenolic content, anthocyanin content, and antioxidant activity. Following ANN-GA optimization, the fitness function reached convergence, yielding peak predicted values of TPC, anthocyanin content, and antioxidant activity at 236.07 mgGAE/g, 50.46 mg/g, and 85.45%, respectively.

The optimized conditions derived from ANN-GA were identified as a temperature of 61.59°C, an extraction time of 42.86 min, and an ultrasound power of 59.99%. The extraction conditions were adjusted for the experimental work as follows: extraction temperature of 62°C, extraction duration of 42.86 min, and ultrasound power set at 60%. The TPC, anthocyanin content, and antioxidant activity obtained under the specified extraction conditions in the experimental work were 235.3±0.2 mgGAE/g, 49.9±0.1 mg/g, and 85.2±0.9%, respectively. The percentage difference compared to the predicted values is less than 2%. As presented in the study of Thuy *et al.* (2022), "Cẩm" leaves was extracted by water with assist of microwave, which have reached 30.6 mg/g of anthocyanin. Therfore, it could be presented the possible to enhance the extraction recovery by sonication. Moreover,The prediction results indicate that the proposed ANN model demonstrates satisfactory predictive capability for estimating TPC, anthocyanin content, antioxidant activity based on the specified extraction conditions. The advantage of ANN-GA lies in its capacity to model complex nonlinear relationships among variables, thereby addressing the constraints of the quadratic regression function utilized in RSM (Huang *et al.*, 2017). ANN is recognized as a viable alternative to RSM, owing to its capacity for self-learning in multivariate modeling, which enhances predictive performance in multifactor optimization processes (Huang *et al.*, 2017; Luong & Poeaim, 2024; Qayyum Khan *et al.*, 2023). The ANN-GA model effectively identifies optimal extraction conditions for enhanced antioxidant content, whereas the RSM model may inadequately capture the system's nonlinearity (Fernandez-Avalos *et al.*, 2025; Luangsakul *et al.*, 2025; Luong & Poeaim, 2024).

Conclusions

This study demonstrated that ultrasonic-assisted hot water extraction is an effective and environmentally sustainable method for recovering antioxidant compounds from "Cẩm" leaves. The use of water as a green solvent combined with ultrasonic energy enhances extraction efficiency while minimizing environmental impact. Predictive modeling using Response Surface Methodology (RSM) and Artificial Neural Network–Genetic Algorithm (ANN-GA) showed strong predictive performance, with the ANN-GA model providing superior accuracy due to its ability to capture complex nonlinear relationships among extraction variables. The combined use of both models improved the reliability of the optimization process. Despite these promising results, the study was conducted at laboratory scale, and factors relevant to industrial applications, such as ultrasonic energy distribution and raw material variability, were not investigated. Furthermore, antioxidant evaluation was limited to total indices without identification of individual bioactive compounds. Future studies should focus on process scale-up, compound identification using advanced analytical techniques, and evaluation of biological activities to further support the utilization of "Cẩm" leaves as a sustainable source of natural antioxidants for functional foods and natural colorants.

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