**Optimization of ultrasound-assisted extraction of bioactive compounds from *Carthamus caeruleus* L. rhizome: Integrating central composite design, Gaussian process regression, and multi-objective Grey Wolf optimization approaches.**

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**ABSTRACT**

The prediction of ultrasound-assisted extraction (UAE) for total phenolic content (TPC) and total flavonoid content (TFC) from *Carthamus caeruleus* L. rhizomes was conducted using a Gaussian process regression model (GPR) with a multi-objective Grey Wolf optimization approach (MOGWO). A central composite design (CCD) was employed first, examining ethanol concentration, temperature, time, and solvent-to-solid ratio as independent variables. TPC and TFC responses were analyzed under various conditions, revealing significant quadratic and interaction effects (p *<* 0.05). The GPR was then utilized to predict TPC and TFC, showing high accuracy with correlation coefficients near 1 and minimal root mean square error (RMSE) values. To simultaneously maximize TPC and TFC, the MOGWO was used in a multi-objective framework. Validation through CCD and GPR high- lighted GPR’s superior predictive accuracy. Optimal conditions (10% ethanol, 40°C, 20minutes sonication, and 50 mL g-1 solvent to solid ratio) showed significant discrepancies in CCD predictions but high accuracy in GPR predictions. An interactive tool predicts TPC and TFC using CCD and GPR models. Users input extraction parameters and receive predictions, with a GWO-based optimization module for optimal conditions. The interface enables model comparison, improves process understanding, and optimizes bioactive compound extraction.

1. Introduction

*Carthamus caeruleus L.* (Asteraceae), commonly known in Algeria as “Mers’gousse,” is a native plant of the Barbary region and is widely found in North Africa and southern European countries such as Spain, Greece, and Italy. In Algeria, *C. caeruleus* L. thrives in fields and uncultivated areas [1]. Traditionally, the rhizome of this plant has been used in Algerian medicine for accelerating wound healing and promoting hair growth. These therapeutic properties are attributed to its rich content of tannins, flavonoids, anthocyanins, leucoanthocyanins, sennosides, free quinones, saponins, glycosides, mucilage, coumarins, sesquiterpenes, and fatty acids, which exhibit diverse biological activities [2,3]. In recent years, green extraction techniques for bioactive compounds have gained prominence in various industrial sectors, including food and pharmaceuticals. Methods such as ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE), ultrasound-microwave-assisted extraction (UMAE), pressurized liquid extraction (PLE), and supercritical fluid extraction (SFE) are favored for their reduced energy costs, lower residual solvent impurities, and higher extraction efficiencies [4]. UAE and MAE, in particular, have demonstrated significant potential in accelerating extraction processes and enhancing the leaching of phenolic molecules from natural sources [5].

The extraction of bioactive compounds from medicinal plants is a complex, multifactorial process with significant challenges in terms of time, energy, and cost, particularly for the food and pharmaceutical industries. To address these challenges, the design of experiments (DoE) has long been utilized across various fields as an effective chemometric method. DoE involves planning, designing, and analyzing experiments to improve product quality and optimize extraction factors efficiently [6,7]. Among the various DoE methodologies, the central composite design (CCD) is frequently employed to study the relationships between input and output variables [8-12]. CCD is particularly suitable for response surface methods due to its capability for rapid screening and optimization across a wide range of extraction conditions. This design effectively identifies the role and behavior of each variable with a limited number of experiments, thereby enhancing process clarity [13]. CCD has been used successfully in various studies, such as optimizing ultra-high pressure extraction of polyphenols from green tea [14], microwave-assisted extraction of total polyphenolic compounds from *Aronia melanocarpa* [15], and ultrasound-assisted extraction of diarylheptanoid phytoestrogens from *Curcuma comosa* rhizomes [[16]](#bookmark77).

Furthermore, Gaussian process regression (GPR) is a modern machine learning algorithm rooted in Bayesian and statistical theories. Known for its robust adaptability and strong generalization capabilities, GPR has emerged as a versatile tool for addressing intricate regression challenges. Consequently, it has found widespread application across various domains, leveraging its ability to handle complex datasets effectively, while preventing over-fitting; also, it aims at making predictions that quantify the uncertainty due to limitations in the quantity and quality of the data. [17,18]. Additionally, the Multi-Objective Grey Wolf Optimizer (GWO), introduced by Mirjalili et al., [19], represents another effective metaheuristic algorithm. Inspired by the hierarchical leadership and group hunting behavior observed in grey wolves, GWO offers distinct advantages in multi-objective optimization tasks. Compared to other metaheuristic algorithms like particle swarm optimization, evolutionary algorithms, and differential evolution, GWO has demonstrated superior accuracy and convergence rates [19,20]. This makes GWO particularly well-suited for efficiently solving complex optimization problems where multiple objectives need to be optimized simultaneously.

To the best of the authors’ knowledge, there is a significant gap in the literature regarding the application of GPR and GWO to predict multiple responses, including total phenolic compounds (TPC) and total flavonoid content (TFC), from *Carthamus caeruleus* L. rhizomes. While studies have explored various extraction techniques and optimization methods for bioactive compounds from medicinal plants, the integration of GPR and GWO specifically for optimizing TPC and TFC extraction from *C. caeruleus* L. rhizomes remains underexplored. This research aims to fill this gap by UAE optimizing TPC and TFC from *C. caeruleus* L. rhizome. The process began with the use of CCD to model the complex relationship between independent variables such as ethanol-water concentration, temperature, sonication time, solid/solvent ratio, and response variables including TPC and TFC. Subsequently, GPR was employed to establish robust predictive models. These models were crucial for predicting experimental values of TPC and TFC based on experimental conditions, providing a solid foundation for further optimization. Multi-objective optimization was carried out using GWO, chosen for its effectiveness in handling multi-objective optimization problems, aiming to maximize both TPC and TFC simultaneously. The optimization results were validated through extensive laboratory experiments, confirming the relevance and accuracy of the predicted optimal conditions. A detailed comparison between CCD and GPR model predictions and actual experimental results was conducted to evaluate the performance of each prediction method, demonstrating the reliability of the developed predictive models in accurately forecasting TPC and TFC levels under different experimental conditions. Finally, to facilitate the use and application of CCD and GPR models as well as GWO-based optimization, a user-friendly interface was developed. This interface allows users to easily input specific experimental conditions and instantly obtain accurate predictions for TPC and TFC. It also offers advanced analysis tools to compare experimental results with model predictions, thereby facilitating informed decision-making.

The novelty of this study lies in its integration of UAE for optimizing TPC and TFC from *C. caeruleus* L. rhizomes. This method not only employs CCD to model complex relationships among extraction variables but also enhances predictive accuracy through GPR. The introduction of multi-objective optimization using GWO further distinguishes this work by simultaneously maximizing TPC and TFC under varied experimental conditions. Rigorous validation against extensive laboratory experiments underscores the reliability of the optimized extraction parameters predicted. Moreover, the development of a user-friendly interface facilitates practical implementation and comparison of model predictions with experimental results, promoting informed decision-making in research and application contexts.

1. Materials and methods
   1. **Reagents**

Ethanol absolute, and methanol were purchased from Merck Millipore (Co.,3050 Spruce, St. Louis, MO 63103 USA 314-771-5765, Product of Denmark). Folin-Ciocalteu’s reagent and sodium carbonate (Na2Co3), Aluminum chloride reagent (AlCl3.6H2o), Folin-Ciocalteu’s reagent, Gallic acid, and Quercetin were purchased from SIGMA- ALDRICH (Co.,3050 Spruce, St. Louis, MO 63103 USA 314-771-5765, product of Denmark). All chemical reagents used in these experiments were analytical grade.

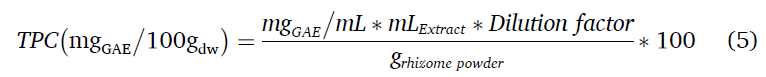
* 1. Ultrasound-assisted extraction of phenolic and flavonoid compounds

The rhizome of *C. caeruleus* L., identified by a taxonomist at the National School of Agronomy, Algeria ([https://gdebelair.com/boi/boi5.](https://gdebelair.com/boi/boi5.html) [html](https://gdebelair.com/boi/boi5.html)), was collected from Ain Bessem, Bouira province, Algeria (latitude 36.381707; longitude 3.711553; altitude 798 m) in February 2019. The oven drying (Venticell) method at 40 ◦C was applied for drying a high amount of water until constant weight after cleaning the whole rhizomes with distilled water the large impurities and cut into small parts with 1 mm of thickness. The dried rhizome was milled using an electric grinder (High Star, AR-1045). The rhizome powder was sieved to obtain a powder with a diameter inferior to 500 gm and was stored in airtight bags until use.

The extraction of phenolic and flavonoid compounds from *C. caeruleus’* rhizome was realized under sonication effect using the ultrasound water bath (J.P. SELECTA, s.a*,* Spain, 40 kHz, Power generator 120 W, Power heater 75W, SN. 3000865) with cavity dimensions of 15 cm x 24 cm x 14 cm (height/width/depth). Briefly, 1g rhizome powder was mixed with different volumes of ethanol-water mixture as extraction solvent based on the single-factor approach and experimental design (Tables 2 and 3). The ultrasound-assisted extraction of TPC and TFC was performed at different sonication times (3.4-40 min) and extraction temperatures (18-50 ◦C). The temperature was controlled using a thermostatic water bath. The final ethanol-water extracts were adjusted to equal volume and separated from solids powder using centrifugation (EZ swing 3 K) (10 min, 1000 rpm) followed by filter paper (Nr.4). The final ethanol-water extracts were stored in the refrigerator (◦C) until used for determination of TPC, TFC.

* 1. Total phenolic and flavonoid compounds determination

The colorimetric method of Hamid et al., [[21]](#bookmark80) was employed. In concisely, 125 μL of diluted ethanol extracts of *C. caeruleus* L. rhizome was added to 625 μL water-diluted Folin-Ciocalteu’s reagent (1/10), after 2 min of incubation at room temperature in the dark, 500 μL of sodium carbonate 7.5 % were added. The absorbance was measured using a UV-vis spectrophotometer (Optizen pop, Korea, and No.5U4605-118117-00) at 760 nm after 15 min of incubation at 50 ◦C and then cooled in a water-ice bath to stop the reaction. The results were calculated based on the equation ([Eq. 5](#bookmark23)) and expressed as mgGAE*/*100gdw according to the Gallic acid’s linear equation *y* = 12*.*089*X* +0*.*0034 with R2= 0.9998.



The flavonoid content of the rhizome extracts was estimated by the Alcl3 method. Briefly, 1 mL of extract solution was added to 1 mL of 2 % methanolic AlCl3.6H2o. The absorbance was measured at 430 nm after 10 min of incubation at room temperature, then was calculated by the equation (Eq. 6) and expressed mgQE*/*100 gdw according to the quercetin’s linear equation *y* = 38*.*43*X* +0*.*0037 with R2= 0.998 (Fig. A.1**)** [22,23].



* 1. Modeling the UAE of TPC and TFC from C. caeruleus L. rhizome
     1. Central composite design

The experimental design was divided into two major steps. Firstly, the single-factor design was carried out to study the effect of each factor including; *x*1: ethanol-water concentration, *x*2: temperature, *x*3: sonication time, *x*4: solvent to solid ratio on TPC, and TFC extraction from *C. caeruleus* L. rhizome by maintaining the other variables at a constant value. The single-factor design was carried out to choose the experimental range of UAE parameters to be used in the central composite design (Table A.1).

Based on the results of the single factor design, the central composite design with five levels was employed for optimization and studying the effect of the extraction parameter on TPC and TFC from *C. caeruleus* L. rhizome powder. Four independent variables including *x*1 : concentration of ethanol in water, *x*2 : temperature, *x*3 : sonication time, and *x*4 : solvent to solid ratio were studied, (Table 1). The analyses were carried out in triplicate and the mean ± SD of TPC and TFC was taken as the responses. The independent variables were labeled as *xi*, based on Eq. 1:

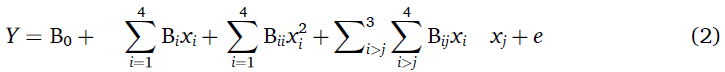


***Table 1-*** *Coded variables employed for central composite design.*

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Where *xi* is the coded values (- *a*, -1, 0,1, *a*) of independent variables,  is the real value of an independent variable at the center point, Δ *Xi* is the step of change value. All the variables with their coded and natural values used are represented in Table 1. A second-order polynomial equation was used to express the dependent variable (Y) as a function of independent variables, and also was used to generate 3D surface plots based on its estimated coefficients (2):

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Where B0, Bi Bii, Bij are the estimated coefficients of the predicted model, which B0 is a constant coefficient and Bi Bii, Bij are the co­efficients of the linear, quadratic, and interactive terms, respectively, for *xi* and *xj* are the coded independent variables of the model, and e is the error.

* 1. Gaussian process regression (GPR)

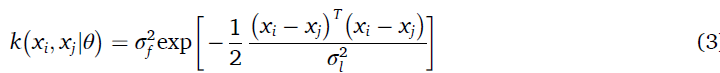
GPR is a non-parametric statistical method used for modeling and predicting uncertain data [24]. Unlike traditional regression techniques, which assume a specific functional form for the relationship between independent and dependent variables, GPR uses a distribution of stochastic processes to model this relationship [25]. This allows for greater flexibility and better handling of uncertainties [26]. A Gaussian process is defined by a mean and a covariance function [27]. The mean function represents the central tendency of the process, often assumed to be zero for simplicity, while the covariance function, or kernel, describes the spatial or temporal dependence between data points [28]. The choice of the kernel is crucial as it controls the smoothness and properties of the modeled function [29].

Learning in GPR involves adjusting the hyperparameters of the kernel by maximizing the likelihood of the observed data. Once the model is fitted, it can provide predictions for new data by calculating the conditional distribution of the predictive values, which includes not only an estimate of the mean value but also a measure of uncertainty (variance) [30]. GPR is particularly useful in situations where data are scarce or expensive to obtain, such as in climate modeling, engineering, and spatial data exploration. However, one of the main challenges of GPR is its computational complexity, which grows cubically with the size of the dataset, limiting its application to moderately sized datasets [31]. Dimensionality reduction and approximation techniques are often used to mitigate this issue. In summary, GPR offers a robust and flexible approach to modeling uncertain data, with the unique ability to provide predictions accompanied by measures of uncertainty [30].

In this study, GPR was used for predicting TPC and TFC. The database, created using the CCD, was reused. The variables studied were: X1: ethanol-water concentration, X2: temperature, X3: sonication time, X4: solid/solvent ratio, for the extraction of TPC and TFC from the rhizome of *C. caeruleus L*. The database was normalized to the range of [-1, +1] and then split into two sets: 70 % for training and 30 % for validation (Fig. 1).

To find the most performant model, ten kernel functions were optimized: exponential, exponential squared, matern32, matern52, quadratic rational, ard exponential, ard exponential squared, ard matern32, ard matern52, and ard quadratic rational. The optimization process involved exploring various basis functions (constant, linear, PureQuadratic, and zero) and fine-tuning the parameters (Kernel Scale [sigmaM, sigmaF] and sigma) of each kernel function (Fig. 1). The following ten karnel functions were used in this work [[30]](#bookmark88):

**Squared Exponential Kernel**



Where *σl* σl is the characteristic length scale, and σ*t* is the signal standard deviation.

**Exponential Kernel**

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***Figure 1.*** *Organization chart for the development and optimization of the GPR.*

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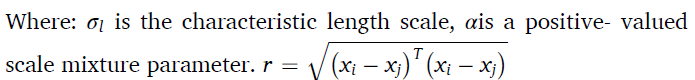
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**Rational Quadratic Kernel**

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**ARD Squared Exponential Kernel**

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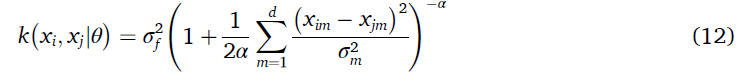
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**ARD Rational Quadratic Kernel**

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* 1. Statistical analyses

In this research, the CCD’s quality was evaluated using analysis of variance (ANOVA). The model’s fit was determined by examining the correlation coefficients R2 and adjusted R2. Statistical significance was assessed using the calculated F-value (Fisher’s variation ratio) and P- value (probability). The significance of individual factors and their interactions was analyzed through the P-value for each term. Additionally, the relationship between the response and the variables was illustrated with 2D and 3D plots using the Root Mean Square Error (RMSE) [31-33].

The performance of each GPR model was also evaluated using various metrics, including the correlation coefficient (R) and RMSE [33-38].

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Where *N* is the number of data samples, *K* is the number of variables (inputs), *y*exp and *ypred* are the experimental and the predicted values respectively, and are respectively the average values of the experimental and the predicted values.

1. Results and discussion
   1. CCD model fitting

The central composite design was applied to optimize total phenolic compounds and flavonoid content from *C. caeruleus* L. rhizome using UAE. Firstly, analysis of variance (ANOVA) indicated a significant model with *p*-value *<* 0.0001, which confirmed that the model was significant and explained the variation in the response and there is a good agreement between the experimental and predicted values (Tables 2 and 3). A non-significant lack of fit (*p*-value = 0.1457) for TPC as a response indicated that the model is adequate to describe the experimental data ([Table 3](#bookmark44))**.** Moreover, *R*2 and *R*2 adjusted of the TPC model with 0.93 and 0.86 respectively confirmed that a high proportion of explained variation fitted the regression model ([Table 3](#bookmark44)). Concerning the model of total flavonoid content also significant (*p*-value *<* 0.0001) with a non- significant lack of fit (*p*-value = 0.220) which means there is a good relationship between the response and predictors, and 98 % of all variability of the response data fitted the model (Table 3). The Coefficient of variation is a descriptive parameter that was calculated as the ratio of RMSE to the mean of response, smaller values of C.V as observed for TPC (3.65 %) and TFC (9.5 %) indicate that the model fitted well and the predictors and observed values are close to each other (Table 3).

The mathematical Eqs. 15 and 16 represent the correlation between the recovery of TPC, TFC, and the independent variables respectively; the final equations were obtained after excluding insignificant factors as mentioned below:

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***Table 2 -*** *Central composite design’s matrix used for the optimization of UAE of TPC, and TFC.*

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* 1. Effect of extraction parameters on TPC

The independent variables are significant on the TPC and TFC at 95 % of a confidence interval. The results showed that all the linear factors including temperature, solvent to solid ratio, sonication time, and concentration of solvent significantly affected the extraction of total phenolic compounds with p-values p *<* 0.0001, p *<* 0.0001, p = 0.0009, and p = 0.0077 respectively (Table 3). Their estimated coefficients emphasized that the temperature, sonication time, and solid-to-solvent ratio had a positive effect, while the ethanol concentration had a negative effect (Table 3). In addition, ultrasonic extraction of TPC was also affected significantly by interaction and quadratic terms including *x*2*x*3 (p = 0.0143), and *x*21 (p = 0.0150) (Table 3).

***Table 3 -*** *Regression coefficients and analysis of variance of CCD model.*

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**TPC;** Total phenolic compounds, **TSC;** Total saponin content, **EC;** Estimated coefficient, **RMSE;** Root Mean Square Error, **C.V;** Coefficient of variance, **p-value a;** statistically significant**, p-value b;** statistically not significant; **RMSEa** of TPC is expressed in mgGAE*/*100gdw; **RMSEb** of TFC is expressed in mgqE*/*100gdw

The 3D response surface plots of the interactive effects of ethanol concentration, sonication time, temperature, and solid-to-solvent ratio on the UAE of total phenolic compounds were plotted based on regression coefficients of the TPC model (Eq.15). Fig. 2d and e show the interactive effects of temperature and sonication time, temperature and liquid-to-solid ratio when the third and fourth independent variables were kept constant at its zero levels as shown in the response surface plots. The results on TPC increased when the extraction temperature increased from 20 to 40 ◦C, and the highest TPC yield was observed at 40 ◦ C with extended extraction time from 5 min to 20 min, and a higher solid-to-solvent ratio (50 mL g-1).

Many reports suggested that the intensification and faster extraction of TPC obtained at higher temperatures due to the higher number of cavitational nucleus, and could enhance the solubility of TPC and decrease of viscosity and density of extract [39,40]. However, the lower yield of TPC was observed at a higher temperature because of the high losses of ethanol changing the solid-to-solvent ratio, this phenomenon could explain by the fact that a higher extraction temperature above boiling point leads to the acceleration of solvent volatilization and production of free radical that increase the oxidation of phenolic compounds [41,42]. Furthermore, the effect of sonication time showed a positive interactive effect with ethanol concentration, temperature, and solid-to-solvent ratio ([Table 3](#bookmark44)). The maximum TPC extraction was related to the longer sonication time at 20 min (Figs. 2b, 2d and 2f), because of increasing the contact time of the solvent with solids, and additional disruption of cell walls leading to improve diffusion of the compounds [[39,43]](#bookmark91). However, Dahmoune et al., [[44]](#bookmark93) showed that the degradation of phenolic compounds phenomena was the consequence of higher extended sonication time of UAE which 15 min of sonication time was optimal for recovery of phenolic compounds from *Citrus limon* residues.

A solvent to solid ratio was also considered as the most significant parameter that showed an impact on TPC extraction, where a higher amount of solvent to solid ratio leads to an increase in TPC yield. In this study, the solid-to-solvent ratio of 50 mL g-1 was the optimal condition for the extraction of phenolic compounds (Fig. 2c, e, and f). A similar tendency of solid-to-solvent ratio effect was also acquired for the phenolic compounds from defatted hemp, flax, and canola seed cakes, and *Sorghum bicolor L,* where, found that the best solvent volume that yielded the highest phenolic content was 50 mL [45,46]. A higher solid-to-solvent ratio could dissolve the phenolic compounds more effectively leading to an enhanced mass transfer rate and increasing the extraction yield [39].

While lower TPC yield of rhizome of *C. caeruleus* L. was observed with the lower aqueous ethanol volume in the extraction medium. The reason could be the higher amount of bioactive compounds, which led to the rise of viscosity, and so inhibited diffusion of phenolic compounds through the extraction medium [47]. On the other hand, the presence of a large amount of raw material involved in the attenuation of the ultrasonic waves and the active part was limited to a zone located in the region of the ultrasonic emitter [47]. The optimal solvent mixture’s concentration in ultrasound-assisted extraction offered the best vapor pressure, viscosity, and surface tension for efficient acoustic extraction resulting in the best extraction of bioactive compounds [48]. Figs. 2a, 2b, and 2c reflect the interactive effects of ethanol-water concentration and temperature, ethanol concentration and time, ethanol-water con­centration, and solid-to-solvent ratio on TPC extraction respectively.

From all these plots, ethanol concentration showed the same impact as the other extraction parameters, where, TPC yield was gradually increased with an increase in ethanol concentration from 10 % to 27 %, after that TPC yield decreased when ethanol concentration was exceeded 27 %. The maximum yield of total phenolic compounds was noticed at 27 % ethanol-water concentration and high temperature, extended extraction time, and high amount of solvent to solid ratio. These findings fit the results of Dent et al.,[49], who found that 30 % of aqueous ethanol or aqueous acetone was the most efficient for the extraction of polyphenols from dry sage leaves. As well as, Zhou et al., [50], mentioned that the antioxidant activity values of Mung Bean reached their maximum value around 35 % of ethanol-water concentration. Furthermore, Uma, Ho and Wan Aida [51] claimed that by adding the proportion of water to alcohols, the solvent mixture can recover phenolic compounds including high and low polarity substances, as well as those of moderate polarity.

* 1. Effect of extraction parameters on TFC

The statistical results from Table 3 demonstrate that almost all the linear factors affected significantly the extraction of TFC including the concentration of solvent effect (p *<* 0.0001), time **(**p *<* 0.0001) and ratio (p *<* 0.0001) except temperature with p-value *>* 0.05 did not affect flavonoids’ extraction. In addition to the linear effect, the interaction and quadratic terms suchas *x*1*x*3, *x*1*x*4, *x*1*x*2, and *x*21, *x*23, and *x*22 showed smaller *p*-values (p *<*0.05), which significantly affect the recovery of total flavonoids content ([Eq. 3, and Eq](#bookmark33). 16).

To study deeply the effect of factors on TFC extraction, the 3D response surface profilers were carried out, Fig. 3a-f explains the vari­ation of total flavonoid content caused by UAE factors. Fig. 3a-c shows the response surface plots of the effect of ethanol-water concentration and temperature, ethanol-water concentration and sonication time, ethanol-water concentration, and solid-to-solvent ratio on the TFC extraction respectively, with the third and fourth variable fixed at constant level. It can be observed that the effect of ethanol-water con­centration showed a similar trend with the other variables. The TFC yield increased at first and then decreased with the increase of ethanol- water concentration from 10 % to 30 % when the temperature varied from 20 to 40 ◦C, sonication time varied from 5 to 20 min, and solid to- solvent ratio 30-50 mL g-1. The results of Huang et al., [[52]](#bookmark100) confirmed that the increase of ethanol proportion from 25 % to 40 % led to enhanced flavonoid extraction. Moreover, the better recovery of flavonoids was affected by the polarity of the solvent where the highest values were achieved at a low ethanol concentration, on the other hand, the presence of water in the solvent system increased the contact surface area between the plant matrix and solvent [[52-54]](#bookmark100).

***Figure 2 :*** *Response surface plots illustrate the variation of total phenolic compounds (mg GAE/ 100 g) was caused by several ultrasound-assisted extraction factors. (a) effects of Ethanol concentration and temperature; (b) effect of Ethanol concentration and time; (c) Effect of concentration of solvent and ratio; (d) effect of temperature and time; (e) effect of temperature and ratio; (f) effect of time and ratio.*

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***Figure3:*** *Response surface plots illustrate the variation of total flavonoid content (mg QE/ 100 g dw) was caused by several ultrasound-assisted extraction factors. (a) effects of ethanol concentration and temperature; (b) effect of Ethanol concentration and time; (c) Effect of concentration of solvent and ratio; (d) effect of temperature and time; (e) effect of temperature and ratio; (f) effect of time and ratio.*

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Furthermore, the sonication time and solid-to-solvent ratio were the extraction parameters that have been studied, and their impact on the extraction of TFC was similar to the effect of sonication time and solid- to-solvent on TFC extraction from *C. caeruleus* L. rhizome. It was clear that sonication time and solid-to-solvent ratio showed a positive relationship with TFC yield; it could achieve a maximum level of flavonoids at higher levels of sonication time and solid-to-solvent ratio (Fig. 4. b-f). Yang and Zhang [55] reported that an increase in extraction yield of rutin and quercetin could be observed with the increase in the extraction time for the first 30 min with an increase of the solid to-solvent ratio, especially when this ratio was increased from 20 to 40 mL g-1. These results are explained by the fact that prolonged extraction time provides more chances to ultrasound produce the rupture of plant cells based on the potential of micro-jets liberated by collapsing the acoustic cavitation. On the other hand, a suitable solid-to-aqueous ethanol ratio fully makes flavonoids dissolve from plants by increasing the contact area between the material and solvent [56].

UAE Temperature may improve the yield of bioactive compounds based on different properties such as viscosity, diffusivity, solubility, and surface tension [41]. The combined effect of temperature and time, temperature and solid-to-solvent ratio on the extraction of TFC were shown in Figs. 3d, and [4](#bookmark47)e, where the reaction temperature plays a major role in affecting TFC extraction when the sonication time and solid-to-solvent ratio were determined numerical values, the changing in temperature affects the TFC yield.

The temperature hurt TFC yield when the temperature was 20-30 ◦C TFC declined and increased afterward when the temperature was beyond 30 ◦C. Moreover, Xu et al., [57] also demonstrated that temperatures from 30 ◦C to 40 ◦C enhanced the activity of antioxidants. The higher temperature could improve the flavonoid extraction phenomena by increasing the molecular movement, increasing the flavonoid solubility [56,58]. In addition, Ghasemzadeh et al., [59] mentioned that decreasing the flavonoid yield at high UAE temperatures could be related to the degradation of these compounds at higher temperatures ( *>* 56° C).

* 1. Gaussian process regression (GPR)

After optimizing ten kernel functions and the base function, the most efficient kernel function was chosen based on statistical criteria. The outcomes of this selection process are presented in Table 4, detailing the optimal model and its corresponding parameters (kernel scale and sigma).

The table also evaluates the model’s performance using diverse statistical measures (R, RMSE) across three phases (training, validation, and overall data), alongside the kernel parameters. Furthermore, the table outlines the preferred kernel function, the resulting base functions, and the best model achieved. Table 4 demonstrates strong correlation, determination, and adjustment coefficients, almost reaching 1, across all three phases, as indicated by the results. Conversely, the statistical co­efficients obtained by the model for the three phases were notably low, confirming the model’s precision. These results are visually presented in [Fig. 4](#bookmark47), providing a graphical representation of the findings.

The results from the best GPR models for predicting TPC and TFC show significant performance based on the kernel configurations used. For TPC, the R reached 0.9929 for training, 0.9988 for validation, and 0.9944 overall, indicating a strong correlation between the model pre- dictions and actual data. The RMSE was measured at 1.5744 for training, 0.4058 for validation, and 1.0881 overall, demonstrating better precision of the model on validation data compared to training. For TFC, the correlation coefficients were even higher with values of 0.9970 for training, 0.9999 for validation, and 0.9979 overall. The RMSE values for TFC were 1.0460 for training, 0.0138 for validation, and 0.8752 overall, indicating exceptional precision of the model particularly during validation. These results highlight that specific kernel configurations enabled the GPR models to achieve high accuracy in predicting TPC and TFC concentrations, with remarkable adaptability to new data and overall satisfactory performance.

***Figure 4.*** *Relationship between the experimental and the GPR model predicted values: (a) TPC, (b) TFC.*

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***Table 4 -*** *Performances of the GPR model.*

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* 1. Optimization and Validation of the optimum conditions

The Grey Wolf Optimizer (GWO) is a metaheuristic algorithm created by Mirjalili et al., [19] and introduced in Matlab on May 22, 2018 [60]. It offers a novel approach for tackling global optimization problems [61,62]. The algorithm is inspired by the social structure and hunting tactics of grey wolves, utilizing these behaviors to form its optimization strategy [63]. By imitating the leadership dynamics and cooperative hunting practices observed in wolf packs, GWO efficiently searches for global optima in a variety of optimization scenarios. It applies to both single-objective and multi-objective optimization problems [64]. The GWO algorithm has proven its effectiveness and versatility across a wide range of optimization tasks [30].

The multi-objective optimization method based on GWO (MOGWO) was utilized to optimize the independent parameters for obtaining both maximum TPC and TFC. The optimization results were subsequently validated through laboratory experiments using CCD and GPR. Table 5 shows a comparison between the predicted values and the experimental results, along with the corresponding errors. The table provides a detailed comparison of the performance of the CCD and GPR models in predicting TPC and TFC under specific experimental conditions (X1 = 10, X2 = 40, X3 = 20, and X4 = 50).

For the CCD model, the experimental values for TPC, and TFC, were 356.9300, 50.7200, respectively. The predicted values, however, were 364.5340 for TPC, and 41.2400 for TFC, resulting in notable prediction errors of 7.6040 for TPC, and 9.4800 for TFC. These significant discrepancies indicate that the CCD model’s predictions diverge substantially from the actual experimental data, highlighting its limitations in accurately modeling the relationships between the independent vari­ables and the response variables.

In stark contrast, the GPR model exhibits exceptional accuracy. The experimental values for TPC, TFC, and TPC + TFC were 356.9300, 50.7200, and 407.6500, closely matched by the predicted values of 356.9298 for TPC, 50.7197 for TFC, and 407.6495 for TPC + TFC. The resulting errors are minimal, with 0.0002 for TPC, 0.0003 for TFC, and 0.0005 for TPC + TFC. This demonstrates the GPR model’s high precision and its capability to almost perfectly predict the experimental values.

The stark contrast in errors between the CCD and GPR models underscores the superior performance of the GPR model. While the CCD model struggles with larger prediction errors, the GPR model achieves nearly perfect accuracy, making it a far more reliable and effective tool for predicting TPC and TFC. The minimal errors of the GPR model reflect its robustness and precision, highlighting its significant advantage in applications requiring high predictive accuracy. These findings emphasize the effectiveness of GPR in modeling complex relationships and provide compelling evidence for its use over traditional methods like CCD in achieving superior predictive performance.

* 1. Interface for optimization and prediction

In this study, an application was developed to predict TPC and TFC using models derived from CCD and GPR (Fig. 5). The application allows users to input specific experimental conditions such as ethanol-water concentration, temperature, sonication time, and solid/solvent ratio to obtain predictions for TPC and TFC (Fig. 5).

Additionally, the application features a multi-objective optimization module based on the GWO, which identifies the optimal conditions for maximizing both TPC and TFC. The GWO algorithm efficiently searches for the best experimental conditions within a specified range, providing users with the highest predicted values for TPC and TFC using CCD and GPR models. This optimization process is validated through experimental data to ensure practical applicability.

The user-friendly interface displays predicted values, optimal conditions, and error metrics, enabling users to compare the performance of CCD and GPR models and understand the relationship between input conditions and outcomes (Fig. 5). This application serves as a valuable tool for researchers and industry professionals in optimizing bioactive compound extraction processes and can also be used as an educational resource to demonstrate experimental design, predictive modeling, and optimization algorithms.

***Table 5 -*** *Comparison between actual and predicted responses at optimum conditions.*

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1. Conclusion

In this study, ultrasound-assisted extraction (UAE) of total phenolic compounds (TPC) and total flavonoid content (TFC) from *C. caeruleus* L. rhizome was optimized using a combination of central composite design (CCD), Gaussian process regression (GPR), and Grey Wolf optimize (GWO). The primary objective was to maximize the extraction efficiency of these bioactive compounds known for their antioxidant properties. The application of CCD revealed significant quadratic and interaction effects of ethanol concentration, extraction temperature, sonication time, and solid-to-solvent ratio on both TPC and TFC extraction yields. However, the predictive accuracy of CCD models was overshadowed by notable discrepancies when compared to experimental data, under- scoring its limitations in accurately capturing the complex relationships within the extraction process.

In contrast, GPR demonstrated exceptional precision in predicting TPC and TFC, with correlation coefficients nearing unity and negligible root mean square errors (RMSE). This highlights GPR’s robust capability to model and predict bioactive compound extraction outcomes with high accuracy, making it a superior alternative to traditional CCD methods. Furthermore, the application of GWO in a multi-objective optimization framework (MOGWO) successfully identified optimal extraction conditions that maximized both TPC and TFC. Validation through experimental data reaffirmed the efficacy of GPR over CCD, as evidenced by minimal errors in predicted versus experimental values under optimal conditions. The development of an interactive application for predicting TPC and TFC using GPR and CCD models enhances accessibility and usability in optimizing bioactive compound extraction processes. This tool not only facilitates predictive modeling but also empowers researchers and industry professionals to efficiently identify and implement optimal extraction parameters. Overall, this study underscores the importance of advanced statistical techniques like GPR and metaheuristic optimization algorithms such as GWO in enhancing the efficiency and reliability of bioactive compound extraction from natural sources. Future research could explore further refinements in modeling techniques and optimization algorithms to address specific challenges and expand the application of these methodologies in the field of natural product extraction and pharmaceutical development.

***Figure 5.*** *MATLAB interface for multi-objective optimization analysis based on the GWO and prediction of TPC and TFC using CCD and GPR.*

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Description générée automatiquement

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CRediT authorship contribution statement

**Sabrina Lekmine:** Software, Resources, Methodology. **Farid Dahmoune:** Supervision, Project administration, Funding acquisition. **Hamza Moussa:** Writing - review & editing, Writing - original draft, Validation, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Abdeltif Amrane:** Validation, Supervision. **Jie Zhang:** Supervision. **Nassim Moula:** Supervision, Methodology. **Nourelimane Benzitoune:** Writing - review & editing, Visualization. **Sarah Hamid:** Writing - review & editing, Writing - original draft, Formal analysis. **Hichem Tahraoui:** Writing - review & editing, Vali­dation, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Amal Mameri:** Methodology, Formal analysis, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.procbio.2024.10.009](https://doi.org/10.1016/j.procbio.2024.10.009).

**Data availability**

Data will be made available on request.

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