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# OPTIMIZATION OF MICROWAVE-ASSISTED EXTRACTION OF PHENOLIC COMPOUNDS FROM *INULA BRITANNICA* L. USING THE BOX-BEHNKEN DESIGN

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A closed-vessel microwave-assisted extraction (MAE) of phenolic compounds from the aerial parts of *Inula britannica* L. using single-factor experiments and the Box-Behnken design with four independent variables (liquid-to-solid ratio, ethanol concentration, extraction time, and temperature) was investigated. The ANOVA results showed that the obtained model was significant at a 95 % confidence level. The extraction parameters for the maximal total phenolic content (46.19 mg GAE/g DM) were determined to be 15.13 ml/g liquid-to-solid ratio, 55.95 % EtOH, 73.74 ºC, and 5.73 min. Compared with classical maceration, the proposed MAE of phenolic compounds from *I. britannica* saves a lot of time and gives a high extraction yield.

**Keywords:** *Inula britannica* L.; phenolic compounds; microwave-assisted extraction; Box-Behnken design

## ОПТИМИЗАЦИЈА НА МИКРОБРАНОВО ПОМОГНАТА ЕКСТРАКЦИЈА НА ФЕНОЛНИ СОЕДИНЕНИЈА ОД *INULA BRITANNICA* L. СО ПРИМЕНА НА МЕТОДОЛОГИЈАТА НА BOX-BEHNKEN

Извршено е испитување на микробраново помогната екстракција (MAE) во затворен сад на фенолни соединенија од надземните делови на *Inula britannica* L. со примена на еднофакторни експерименти и методологија на Box-Behnken со четири независни променливи (однос течна/цврста фаза, концентрација на етанол, време на екстракција и температура). Резултатите од ANOVA покажуваат дека добиениот модел беше значаен со ниво на сигурност од 95 %. Параметрите за екстракција за максимална содржина на фенолни соединенија (46,19 mg GAE/g DM) изнесуваа 15,13 ml/g за однос на течна/цврста фаза, 55,95 % EtOH, 73,74 ºC и 5,73 min. Споредено со класична мацерација, предложената MAE на фенолни соединенија од *I. britannica* носи заштеда во време и дава висок принос.

**Клучни зборови:** *Inula britannica* L.; фенолни соединенија; микробраново помогната екстракција; методологија на Box-Behnken

## 1. INTRODUCTION

Phenolic compounds are broadly distributed in the plant kingdom and are the most abundant secondary metabolites of plants.[1,2] Plant polyphenols have drawn increasing attention and have become a major area of health- and medical-related research due to their potent antioxidant properties and their marked effects in the prevention of various oxidative stress associated diseases, such as cancer, cardiovascular, and neurodegenerative diseases.[3,4] Phenolic compounds can be obtained from the plant material by different conventional (Soxhlet, maceration, and soaking) and unconventional (ultrasound-assisted, pressurized-assisted, supercritical fluid, microwave-assisted, etc.) methods.[5,6] Among these methods, microwave-assisted extraction (MAE) is mostly employed due to its

simplicity, cost effectiveness, reduction in time of recovering phenolic compounds from plant materials, and reduction in solvent consumption.[7–9] MAE is affected by different factors, namely, microwave power, temperature, irradiation time, solvent concentration, and liquid-to-solid ratio. In order to optimize these factors, the response surface methodology (RSM) is being used as a statistical method to generate the predictive mathematical model that considers the possible interactions between the different factors.[10] The Box-Behnken design (BBD) is one of the most efficient types of RSM because it permits the estimation of the parameters of the quadratic model, building of sequential designs, detection of lack of fit of the model, and use of blocks.[11]

*Inula britannica* L. is an important plant species used in Traditional Chinese Medicine (TCM) and Kampo Medicines as antibacterial, carminative, diuretic, laxative, stomach, and tonic remedies and for treating asthma, hepatitis, and tumors.[12] *I. britannica* L. possesses various biological activities – anti-inflammatory, antitumor, antibacterial, antitussive, antiproliferative, antioxidant, hepatoprotective, etc.[12–15] A phytochemical study of the Bulgarian accessions of the species revealed the presence of sesquiterpene lactones, triterpenoids, flavonoids, and mono- and dicaffeoyl esters of quinic acid (chlorogenic, 1,5-, 3,5-, 4,5-, and 3,4-dicaffeoylquinic acids).[16,17] Recently, it has been determined that there is a significant variability in the amount of total phenolics, total flavonoids, and individual compounds within the different populations of *I. britannica* in Bulgaria, which is also reflected in their antioxidant capacity. The samples containing the highest amounts of phenolics and flavonoids were the best DPPH (2,2-diphenyl-1-picrylhydrazyl) and ABTS (2,2'-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) radical scavengers.[17] These results prompted us to continue the investigations on *I. britannica* and to develop an effective method for the extraction of total phenolics by MAE. Single-factor experiments and the Box–Behnken design were used to obtain the optimal conditions for the extraction of phenolic compounds from the aerial parts of *I. britannica*.

## 2. MATERIALS AND METHODS

### 2.1. *Plant material*

The aerial parts of wild growing *Inula britannica* L. were collected in the full flowering stage in July 2020 from the Northern Balkan Region in Bulgaria. The plant was identified by Assoc. Prof. Dr Ina Aneva, and a voucher specimen was deposited in the Herbarium of the Institute of Biodiversity and Ecosystem Research, Bulgarian Academy of Sciences. The plant material was air-dried, powdered, and kept in a dry place.

### 2.2. *Microwave-assisted extraction (MAE)*

#### 2.2.1. *Single-factor experiments*

MAE was performed using a closed vessel microwave apparatus (Microwave 3000, Anton Paar, Austria) equipped with a power sensor and a temperature sensor. The extraction was performed at a constant microwave power of 300 W. The aerial parts of *I. britannica* at the desired weight were placed into the 100 ml PTFE (polytetrafluoroethylene) extraction vessel with a constant solvent volume of 20 ml and heated to the desired temperature in 1 min and then held at a certain temperatures for a certain time period according to the experimental design. The temperature of the system was monitored by a reference vessel with an immersion temperature probe in the rotor and controlled by an external infrared sensor. After microwave heating, the mixture in the extraction vessel was allowed to cool down to room temperature (in ca. 10 min) and centrifuged for 10 min, and the supernatant was filtered through a Whatman filter. Water and ethanol (99.9 %, Supelco) at different proportions were chosen as the extraction solvents (ethanol concentration varied from 0 to 100 %, v/v). The time of microwave extraction (2–11 min), liquid-to-solid ratio (10–40 ml/g), and temperature (30–75 °C) were the other factors in the extraction study of total phenolic content. The maximum values used for the temperature and the irradiation time were selected according to the microwave power limitation.

#### 2.2.2. *Box-Behnken design*

The Box-Behnken design (BBD) was employed to statistically optimize the parameters and evaluate the main effects, interaction effects, and quadratic effects of the ingredients on the extraction yields of polyphenols. Based on the single-factor experiments, a BBD with four factors (liquid-to-solid ratio $X_1$ (A), ethanol concentration $X_2$ (B), extraction time $X_3$ (C), and temperature $X_4$ (D)) and three levels (–1, 0, +1) including 27 experimental runs was used to evaluate the combined effects on the total phenolic content (Table S1). A second order polynomial mathematical model was

developed by measuring the relationship between the independent variables and the response values:

$$Y = \beta_0 + \sum_{i=1}^{4} \beta_i X_i + \sum_{i=1}^{4} \beta_{ii} X_i^2 + \sum_{i=1}^{3} \sum_{j=i+1}^{4} \beta_{ij} X_i X_j$$

where $Y$ is the response variable (TPC), $X_i$ and $X_j$ are independent variables ($i \neq j$), and $\beta_0$, $\beta_i$, $\beta_{ii}$, and $\beta_{ij}$ are the regression coefficients of variables for the intercept, linear, quadratic, and interaction terms, respectively.

The design of the experiments, analysis of the results, and prediction of the responses were carried out using the Design-Expert software (Version 11). The models were predicted through statistical analysis and regression analysis (ANOVA), and the fitness of the polynomial model equation was expressed by the coefficient of determination $R^2$. Models and regression coefficients were considered significant when *p*-values were lower than 0.05.

### 2.3. *Total phenolic content (TPC) determination*

TPC was measured using the Folin–Ciocalteu's method.[18] Gallic acid was employed as a calibration standard, and the results were expressed as mg gallic acid equivalents per g of dry plant material (mg GAE/g DM).

### 2.4. *Conventional extraction procedures*

Air-dried and powdered plant material (1 g) was extracted with 20 ml of aqueous ethanol (50 %, v/v) a) at room temperature (23–25 ºC) for 24 h (maceration); b) under reflux for 30 min (reflux); c) in an ultrasonic bath (SIEL, Bulgaria) at 50 ºC for 30 min (UAE). The samples were centrifuged for 10 min, and the supernatant was filtered through a Whatman filter and analyzed for TPC.

## 3. RESULTS AND DISCUSSION

### 3.1. *Single-factor experimental analysis*

The solvent is one of the most important factors in an extraction process, particularly in a microwave environment. In general, a higher dielectric constant and dielectric loss results in a higher capacity of the solvent to absorb microwave energy, which can lead to a faster rate of heating of the solvent with respect to the plant material.[19] An aqueous ethanol solution is the most common extraction solvent used for the extraction of natural products due to its high-efficiency and eco-friendly and recyclable characteristics.[9,20] The effect of the ethanol (EtOH) concentration (25–100 %, v/v) on the extraction yield of total phenolics was evaluated when controlling for other variables (temperature 60 ºC, time 8 min, and liquid-to-solid ratio - 20 ml/g). As shown in Figure 1A, the highest total phenolic content (31.12 mg GAE/g DM) was obtained with 75 % EtOH. The increase in ethanol concentration to 100 % significantly decreased the total phenolic content.

The liquid-to-solid ratio has a significant role in the mass transfer of extracts between the materials and extraction solvents, and a higher liquid-to-solid ratio increases the recovery due to an increase in the concentration gradient between the solvent and the solid, which drives mass transfer [21]. To optimize the liquid-to-solid ratio, in this work, the liquid-to-solid ratio was set at 10–40 ml/g, keeping other variables constant (EtOH concentration 75 %, extraction temperature 60 ºC, and extraction time 8 min). In this experiment (Fig. 1B), a higher liquid-to-solid ratio resulted in lower recoveries. This behavior can probably be explained by the excessive swelling of the material by water when a larger liquid-to-solid ratio is used, thus reducing the release of the target compounds.[22] This phenomenon has been shown by several research groups who used the MAE technique for the extraction of polyphenols.[23–25] As can be seen from Fig. 1B, the optimal liquid-to-solid ratio was determined to be 20 ml/g, giving 31.12 mg GAE/g DM of total phenolics.

Time is a significant factor influencing the extraction yield of total phenolics. A reasonable extraction time can help shorten the production cycle, reduce energy consumption, and improve yield. However, an extraction time that is too long will result in the decomposition of the target compounds.[23,25] To optimize the extraction time, the extraction time was set at 2, 5, 8, and 11 min, keeping other variables constant (ethanol concentration 75 %, extraction temperature 60 ºC, and liquid-to-solid ratio 20 ml/g). Figure 1C shows that the extraction yields increased with time and reached the highest values when the extraction time was 5 min, and after this point in time, the extraction yield started to slightly decrease.

Temperature can be considered a physical parameter that exerts positive effects on the extraction process due to the fact that molecules move faster at higher temperatures, leading to enhanced diffusion and permeation behaviours. In addition, in a closed microwave vessel, the temperature of the solvent could increase above the boiling point

temperature.[7] This could improve the polyphenol extraction yields in a shorter extraction time but also can cause degradation of the heat-sensitive components.[5] To improve the extraction yield, extraction temperatures in the range of 25–75 ºC were studied when controlling for other factors (EtOH concentration 75 %, extraction time 8 min, and liquid-to-solid ratio 20 ml/g). Figure 1D shows that the extraction yield of total phenolics increased in the range of 45–75 ºC.

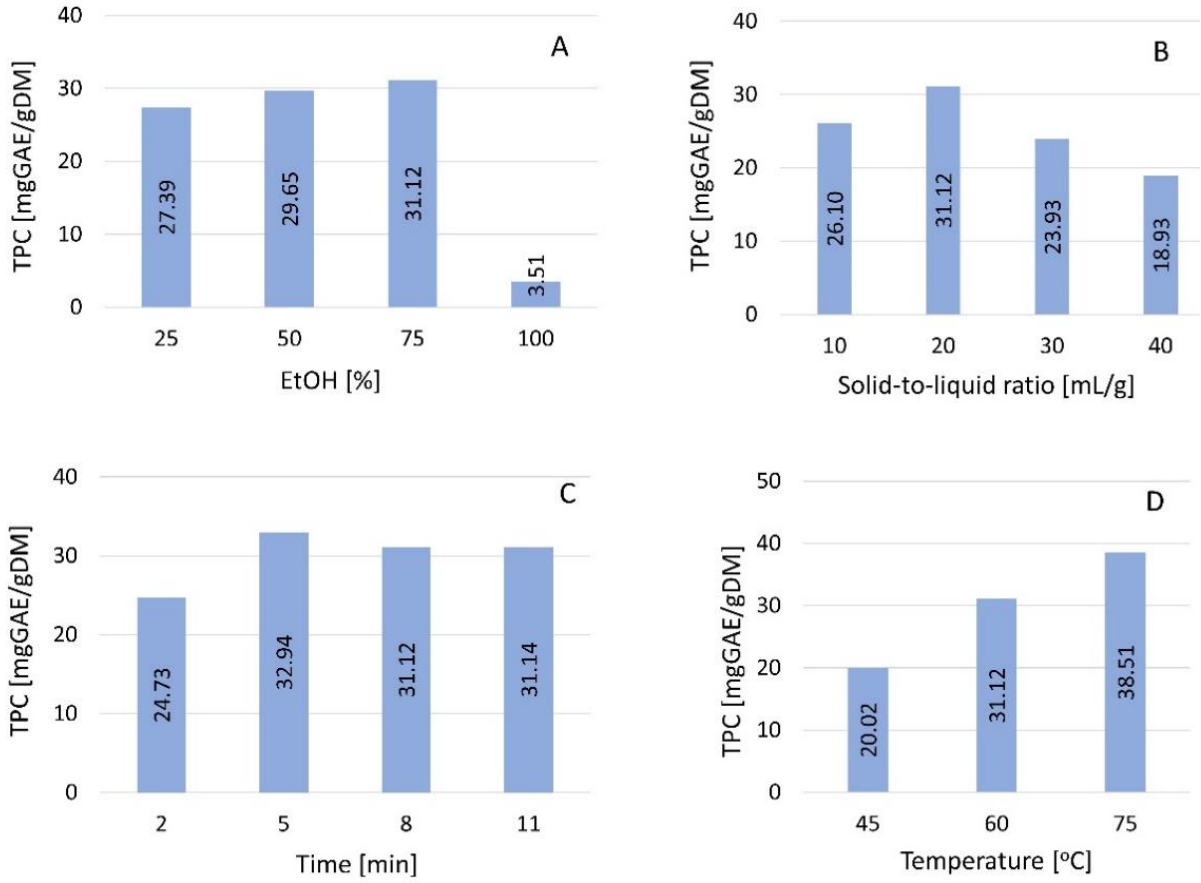


**Fig. 1.** Effects of ethanol concentration (**A**), liquid-to-solid ratio (**B**), time (**C**), and temperature (**D**) on the extraction yield of total phenolics (TPC).

### 3.2. *Optimization of the extraction of phenolic compounds from I. britannica L.*

After determining the preliminary range of the parameters by a single-factor experiment, the BBD was carried out to study the influence of the interaction between the main four variables (liquid-to-solid ratio (A), EtOH concentration (B), extraction time (C), and extraction temperature (D)) on the extraction yield of TPC. The detailed experimental design and results are summarized in Table S1.

ANOVA for the TPC was carried out in order to test the model significance and suitability (Table 1). The regression coefficient of the obtained models, such as the intercept, linear, quadratic, and interaction terms, was evaluated and subjected to a significance test. A $p$-value < 0.05 indicates that the model term is significant, while $p$-values greater than 0.1000 indicate that the model term is not significant. Thus, the obtained $F$-value of 90.89 for TPC implies that the model is significant. The adjusted coefficient (adj. $R^2 = 0.9481$) was close to the $R^2$ (0.9798), which meant that the experimental values fitted well with the predicted values. Moreover, a low value of coefficient of the variation (CV = 7.81 %) indicated a high degree of precision and a good deal of reliability of the experimental values. The linear coefficients (B, C, and D), cross product coefficient (BD), and quadratic coefficients ($A^2$, $B^2$, and $C^2$) were significant model terms ($p < 0.05$). By applying multiple regression analysis on the experimental data, the response variable (TPC) and the test variables were related by the following second-order polynomial equation:

$$Y = +31.76 - 1.23*A - 13.03*B + 3.67*C + 7.79*D - 0.5289*AB + 0.4879*AC - 1.71*AD - 1.04*BC - 4.21*BD + 0.1852*CD*A^2 - 10.41*B^2 - 6.79*C^2 - 0.4172*D^2$$

The ANOVA statistical results indicated the reliability of the obtained model, and this model can be used to make predictions about the response for given levels of each factor.

T a b l e 1

*ANOVA of MAE process optimization for total phenolic content*

| Source | Sum of squares | df | Mean square | *F*-value | *p*-value |
|---|---|---|---|---|---|
| **Model** | 3777.80 | 14 | 269.84 | 90.89 | < **0.0001** |
| **A – Solid-to-liquid ratio** | 18.24 | 1 | 18.24 | 6.15 | 0.0290 |
| **B – EtOH concentration** | 2036.66 | 1 | 2036.66 | 686.02 | < **0.0001** |
| **C – Time** | 161.56 | 1 | 161.56 | 54.42 | < **0.0001** |
| **D – Temperature** | 728.06 | 1 | 728.06 | 245.24 | < **0.0001** |
| **AB** | 1.12 | 1 | 1.12 | 0.3769 | 0.5507 |
| **AC** | 0.9520 | 1 | 0.9520 | 0.3207 | 0.5816 |
| **AD** | 11.63 | 1 | 11.63 | 3.92 | 0.0711 |
| **BC** | 4.36 | 1 | 4.36 | 1.47 | 0.2486 |
| **BD** | 70.88 | 1 | 70.88 | 23.87 | **0.0004** |
| **CD** | 0.1372 | 1 | 0.1372 | 0.0462 | 0.8334 |
| **$A^2$** | 94.87 | 1 | 94.87 | 31.95 | **0.0001** |
| **$B^2$** | 578.47 | 1 | 578.47 | 194.85 | < **0.0001** |
| **$C^2$** | 245.75 | 1 | 245.75 | 82.78 | < **0.0001** |
| **$D^2$** | 0.9283 | 1 | 0.9283 | 0.3127 | 0.5863 |
| **Coefficient $R^2$** | 0.9798 | | | | |
| **Adj. $R^2$** | 0.9481 | | | | |

In order to provide a better visual representation of the effects of interactions between the independent variables on the response value, three-dimensional response surface plots drawn by the BBD are shown in Figure 2a–f. For each figure, TPC was gained by changing two variables while the other two variables remained unchanged. The depicted response (Fig. 2a) showed that TPC increased at a higher temperature (75 ºC) and lower ethanol concentration (50 % EtOH) at a constant liquid-to-solid ratio (A, 20 ml/g) and extraction time (C, 5 min) and reached the highest value (45.81 mg GAE/g DM). TPC decreased (Fig. 2b) at higher EtOH concentrations and increased with the extraction time up to 5 min and then stayed almost constant up to 8 min at a constant liquid-to-solid ratio (A, 20 ml/g) and temperature (D, 75 ºC). TPC (Fig. 2c) was more sensitive to the extraction temperature than the extraction time at a fixed EtOH concentration (50 %) and liquid-to-solid ratio (20 ml/g). The liquid-to-solid ratio exhibited a weaker effect on TPC (Fig. 2d, e, and f).

The results from the optimization of TPC using the Design Expert software showed that the maximum TPC can be achieved when the liquid-to-solid ratio, EtOH concentration, extraction temperature, and extraction time were 15.13 ml/g, 55.95 %, 73.74 ºC, and 5.73 min. At these specific conditions, the maximum predicted yield of total phenolics was 46.19 mg GAE/g DM.

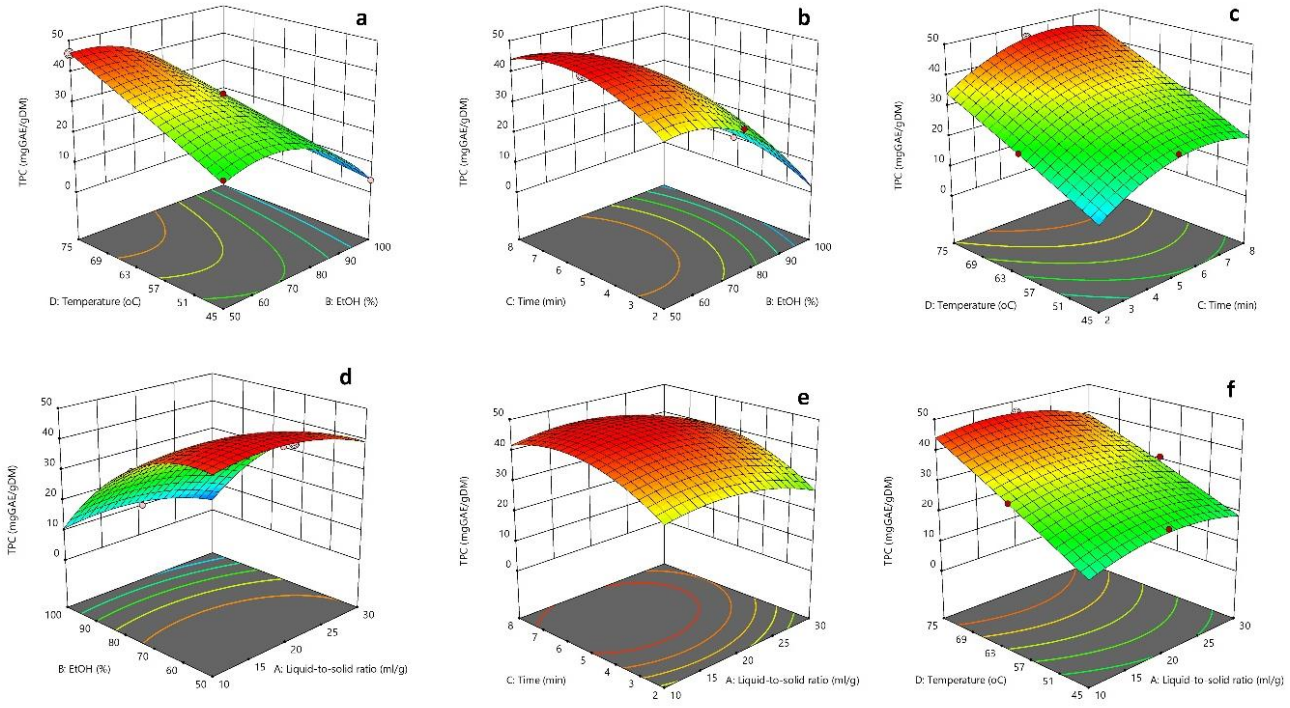


**Figure 2.** Response surface plots showing the effects of variables on the extraction yield of total phenolics: interaction of EtOH concentration and extraction temperature (a), interaction of EtOH concentration and extraction time (b), interaction of extraction temperature and extraction time (c), interaction of EtOH concentration and liquid-to-solid ratio (d), interaction of extraction time and liquid-to-solid ratio (e), and interaction of extraction temperature and liquid-to-solid ratio (f)

### 3.3. *Comparison with conventional extraction methods*

Maceration at room temperature, reflux extraction, as well as ultrasound-assisted extraction were carried out in order to compare MAE with the most frequently used extraction methods (Table 2). The liquid-to-solid ratio and EtOH concertation in all experiments were 20 ml/g and 50 % EtOH, respectively. The obtained results clearly showed that in the conditions of microwave extraction, higher amounts of phenolic compounds can be extracted in a very short time.

T a b l e 2

*Comparison of extraction methods*

| Method | A*: [ml/g] | B: [%] | C: [min] | D: [ºC] | TPC [mg GAE/g DM] |
|---|---|---|---|---|---|
| **Maceration** | 20 | 50 | 24 h | 23–25 | 36.63 |
| **Reflux** | 20 | 50 | 30 | Reflux | 40.70 |
| **UAE** | 20 | 50 | 30 | 50 | 35.10 |
| **MAE** | 20 | 50 | 5 | 75 | 45.81 |

* Liquid-to-solid ratio (A), EtOH concentration (B), extraction time (C), extraction temperature (D), and total phenolic content (TPC)

## 4. CONCLUSION

An efficient process of MAE was developed for the extraction of polyphenols from the aerial parts of *I. britannica* with enhanced yield. The BBD was successfully employed to optimize the extraction parameters in this work. Compared to the conventionally used maceration, reflux, and ultrasound-assisted extractions, the proposed MAE is a more efficient method that provides a higher yield in a shorter amount of time.

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