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RESEARCH ARTICLE

Optimization of Ultrasound-Assisted Extraction of Total Extractive Substances from *Galium verum* L.

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Abstract

Ultrasound-assisted extraction (US-AE) of total extractive substances from the herb Lady`s Bedstraw (Galium verum L.) is useful extraction method for its application in food manufacturing. The effect of different temperatures (T) and solvent-to-solid ratios (S) on the US-AE extraction yield was studied in this paper. The influence and optimum of the operating parameters (T and S) was investigated using response surface methodology (RSM). The T and S had impact on extraction yield. RSM showed that the optimal extraction parameters, which gave a maximum extraction yield of 18.7%, were T of 40 °C and S of 30 kg kg^{-1}. Using modeled optimized conditions, detected relative difference between predicted and experimental yield was 3.3 %. RSM successfully predicted optimal parameters and proved as useful tool for standardization of extraction conditions for bioactive components from plants important for food industry.

Keywords

Galium verum L., Optimization, Response surface methodology, Ultrasound-assisted extraction

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1 Introduction

Serbian flora represents an abundant resource of interesting plants, including genus *Galium* (Rubiaceae), represented with 37 species [1, 2]. Among them the herb Lady`s Bedstraw (*Galium verum* L.) is the most frequently used in traditional medicine [3] and food manufacturing [4]. The *G. verum* is widely used to coagulate milk and, in Scotland, the plant is still used as a dye and in cheese manufacturing [4]. Chemical composition and biological activity is what makes this plant very interesting [5-12].

Recently, improved methods have been developed to extract bioactive compounds from *Galium* species [13-16]. Compared with conventional solvent extraction methods, the use of ultrasound-assisted extraction (US-AE) for extraction of bioactive compounds has been reported as faster, more efficient, and solvent-saving technique [15, 17, 18]. Ultrasonic waves generate a cavitation effect in the solvent, resulting in faster movement of molecules and higher penetration of the solvent into the target material [19, 20].

Rebirth of research that occurred lately demonstrated the implementation of modeling tools in order to simulate US-AE of bioactive compounds from different sources [18, 21, 22]. Modeling followed by optimization of US-AE contributed to its further improvement by increasing the extraction yield for *Galium* species [13, 15, 16]. When yield of extractive substances from plant is influenced by several parameters response surface methodology (RSM) is the most commonly used for development, improvement and optimization of extraction processes [22-25]. Therefore, the objectives of this study were to estimate the influence and combined effects of important extraction parameters such as temperature (T) and solvent-to-solid ratio (S), as well as to optimize operational parameters of US-AE using RSM in order to obtain a maximal possible extraction yield from *G. verum*.

2 Materials and Methods

2.1 Sample collection and plant extraction

Aerial parts of white lady's bedstraw (*G. verum* L.) were collected during the blooming (Vlasina locality, southeast region of Serbia). The specimen of this plant is conserved at the Herbarium of the University of Belgrade – BEOU under the number 17071. The plant was dried in a shadow and grounded immediately prior to extraction (average plant particle size: 0.75 mm).

2.2 Extraction equipment and procedures

An ultrasonic bath (Sonic, Niš, Serbia, power 120 W, frequency 40 kHz) was used for indirect ultrasonication. Water was circulated through the ultrasonic bath by a pump from a thermostated water bath, which was kept at a constant temperature. The ultrasonic power input was 7.3 ± 0.3 W [15].

The grounded plant material was mixed with 96% (v/v) ethanol in an Erlenmeyer flask, equipped with a reflux condenser. The ultrasound-assisted extraction was performed for 80 min at 20, 28, 34 and 40 °C and *S* varied between 5 and 40 kg kg^{-1}. After 80 min, the suspension of plant particles in solvent was cooled to the room temperature, taken from the flask and filtered under vacuum to separate the liquid extract from the solid residue. The solvent was then evaporated in a rotary vacuum evaporator until a half-solid residue was obtained, which was then dried at 60 °C to constant weight. The masse extracted from dry plant material defines the yield of total extractive substances known as resinoid (*y*) in %. Each experiment was performed in triplicate.

2.3 Optimization of the extraction procedure using RSM model

The optimization of extraction parameters of resinoid from *G. verum* in order to obtain the maximum yield was carried out by RSM. The independent process variables were extraction temperature (*T*) and solvent-to-solid ratio (*S*). RSM models were developed in the form of a second-order polynomial equation:

$$y = b_0 + b_1 \times T + b_2 \times S + b_{12} \times T \times S + b_{11} \times T^2 + b_{22} \times S^2 \qquad (1)$$

where *y* is the resinoid yield, *T* is extraction temperature, *S* solvent-to-solid ratio, b_i and b_{ij} (*i*=0, 1, 2 and *j*=1, 2) are the parameters of equation (1) obtained by the multiple nonlinear regression method.

The performance of developed models was assessed with various statistical criteria such as: the coefficient of determination (R^2), the coefficient of variation (*CV*), the adequate precision (*Adec. Prec.*) and the mean relative percentage deviation (*MRPD*) [26]. Adequate precision is a signal to noise ratio. It compares the range of the predicted values at the design points to the average prediction error. Ratios greater than 4 indicate adequate model discrimination. The mean relative percentage deviation (*MRPD*), calculated according to the following equation:

$$MRPD = \frac{100}{n} \times \sum_{1}^{n} \left| \frac{y_{p,i} - y_{a,i}}{y_{a,i}} \right| \qquad (2)$$

where $y_{p,i}$ and $y_{a,i}$ are the predicted and actual values and *n* is the number of experimental runs. Another way to evaluate model suitability is the lack-of-fit test. The statistical significance of the models as well as independent variables and their interactions was estimated by the ANOVA. Using developed models, the maximum predicted resinoid yields and the optimal extraction conditions were determined through the optimization with the target goal "maximum" using the Design-Expert 7.0.0 Trial software (Stat-Ease Inc., Minneapolis, MN).

3 Results and discussion

3.1 Influence of extraction parameters on the extraction yield

As can be seen from Fig. 1, the extraction yield from *G. verum* obtained by US-AE depends on the extraction conditions. The results indicate that the extraction yield increased with the increase of *T* and the highest resinoid yield was obtained at 40 °C at different *S* (Fig. 1). The highest extraction yield obtained at 40 °C under the US power is in accordance with earlier reports which confirmed the positive effects of *T* on extraction efficiency of *G. mollugo* [13–16]. Now, it is confirmed that extraction temperature also has significant impact on extraction yield from *G. verum* obtained using US-AE. Generally, temperature increase can accelerate the softening of the raw materials and improve the solubility of extracted compounds [27].

In this work, second variable influencing the resinoid yield from *G. verum* was *S*. Results indicate that the resinoid yield increased with the increase of *S* at different *T*. This result is in accordance with earlier report which confirmed the positive effects of *S* on extraction efficiency of bioactive components from grape seeds at different *T* [28]. In our case, increasing the solvent proportion in the system improved the extraction yields and thus led to a more efficient extraction (Fig. 1), which is in agreement with the previous studies [23, 28, 29]. Fig. 1 shows that the extraction yield of *G. verum* was mainly achieved over *S* of 20 kg kg^{-1}. However, there was no significant difference ($P < 0.05$) of resinoid yield obtained at *S* of 30 and 40 kg kg^{-1}. Actually, the increase of *S* over 30 kg kg^{-1} did not show significant influence on resinoid yield from *Galium* species.

With increased *T* and *S* the extraction yields varied from 6.4 to 18.1%. Different levels of resinoid yield of *G. verum* reported in this and other studies [6, 30, 31] could be ascribed to several factors, including environmental factors, cultivars, harvest time, as well as the solvent type used, extraction method, temperature and time [25].

3.2 Response surface methodology - RSM model

The RSM model based on second-order polynomial equation was applied to correlate changes in the resinoid yield with *T* and *S*. The changes in the resinoid yield (*y*) along with two operating variables (*T* and *S*) were analyzed using multiple nonlinear regression models. The second-order polynomial equation

(Eq. (1)) was used to fit experimental data. The obtained result presents the resinoid yield (y) as a function of values of extraction temperature (T), and solvent-to-solid ratio (S) as follows:

$$y = 1.85 + 6.68\times10^{-1}\times T + 1.08\times10^{-2}\times S + 4.04\times10^{-3}\times T\times S + 8.55\times10^{-3}\times T^2 + 5.61\times10^{-3}\times S^2 \quad (3)$$

The statistical significance of the equation model, the operating variables, their interactions and the validity of the fitting, all analyzed using ANOVA, are shown in Table 1. The $p < 0.05$ values indicate that model terms are significant. Two operating variables (T and S), their interaction and two square values (T^2 and S^2) had significant impact on y.

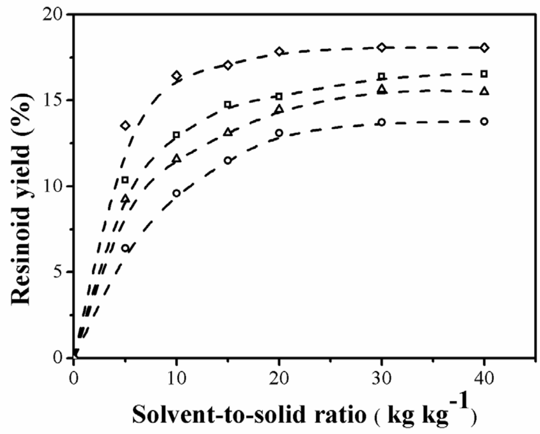

Fig. 1 The extraction yield (y) from aerial part of *G. verum* as function of solvent-to-solid ratio (S) at different temperatures (T): 20 (◊), 28 (□), 34 (Δ) and 40 (○) °C.

Table 1 Analysis of variance for the second-order polynomial model.

Source of variance	Sum of squares	Degrees of freedom	Mean square	F-value	p-Value
Model	447.05	5	89.41	140.35	< 0.0001
T	212.40	1	212.40	333.41	< 0.0001
S	172.12	1	172.12	270.18	< 0.0001
TS	6.79	1	6.79	10.66	0.0022
T^2	37.90	1	37.90	59.49	< 0.0001
S^2	7.06	1	7.06	11.09	0.0018
Residual	26.75	42	0.63		
Lack of Fit	14.77	18	0.82	1.65	0.1267*
Pure Error	11.98	24	0.49		
The total correc.	473.80	47			
R^2	0.979				
CV	3.33				
Adeq Precision	71.09				
MRPD	± 2.8%				

T - temperature; S - solvent-to-solid ratio; R^2 - coefficient of determination; *CV* - coefficient of variation; *MRPD* - mean relative percentage deviation.
*Statistically not significant at the confidence level of 95%.

Work was focused our attention onto statistical criteria indicating the adequacy, reliability and precision of the developed RSM model (Table 1 and Fig. 2). The statistical significance of the RSM model was estimated based on difference between calculated and tabulated F value ($F_{tab} = 2.63$), along with the p-value less than 0.05. RSM model was statistically significant at the confidence level of 95%. Another way to evaluate model suitability is the lack-of-fit test. The R^2 values (Table 1) approximately equal to one proved a good fit by the second-order polynomial equation. Relatively low values of the *CV* (Table 1) indicated the remarkable precision and reliability of the model. The values of *Adeq. Precision* which measures the signal to noise ratio, are much greater than 4, so the model can be used to navigate the design space. The low values (± 2.8%), also implied the reliability and accuracy of the developed model. There was no significance in the lack of fit ($p > 0.05$) which indicated that the model could be used to predict the responses.

Diagnostic plots are shown in Fig. 2. The residuals were close to the straight line and evenly distributed around it, confirming the normal distribution of residuals and validating the ANOVA results (Fig. 2A). The values of Cook's distance, shown in Fig. 2B, were far below the limit of 0.8, indicating that there were no outliers in the experimental data sets. Random scattering of dots around diagonal could be observed by comparing the predicted and actual values of y (Fig. 2C).

RSM was used to explain the effect of T and S on resinoid yield extracted from the *G. verum* (Table 1). The resinoid yield as a function of T and S is shown in the form of Eq. (3). The resinoid yield increased with T and S increasing which promoted the solubility and mass transfer rate of resinoid (Fig. 1). Also, viscosity and surface tension of the extracting solvent were reduced at higher T, which facilitated the penetration of the solvent into the plant particles, improving the extraction yield [26]. While, on the other hand, increasing the amount of solvent favorably modifies the final equilibrium state and increases the driving force for the mass transfer, i.e. the concentration difference between the solid and the liquid phase [32, 33].

The RSM model proved the impact of extraction techniques, time and temperature on extraction yield of *Galium* species [15]. In this work, we used RSM model to examine the effect of S on the yield of *Galium* species. The solvent-to-solid ratio was also a vital factor for increasing the yield of bioactive components, since increased solvent-to-solid ratio could facilitate the access of the solute to the solvent [18]. In addition, cavitation is known to produce a series of mechanical effects, such as particle collisions and cell wall disruption [34], which promote penetration of the solvent into the sample matrix and increase rates of mass transfer for bioactive components [35].

In fact, an RSM study is a very important tool for delineation of the process, which provides the knowledge about effects of process variables such as solvent-to-solid ratio and temperature on the extraction yield. These parameters are then used to predict extraction process and, in this way, to estimate the viability of the process on an industrial scale.

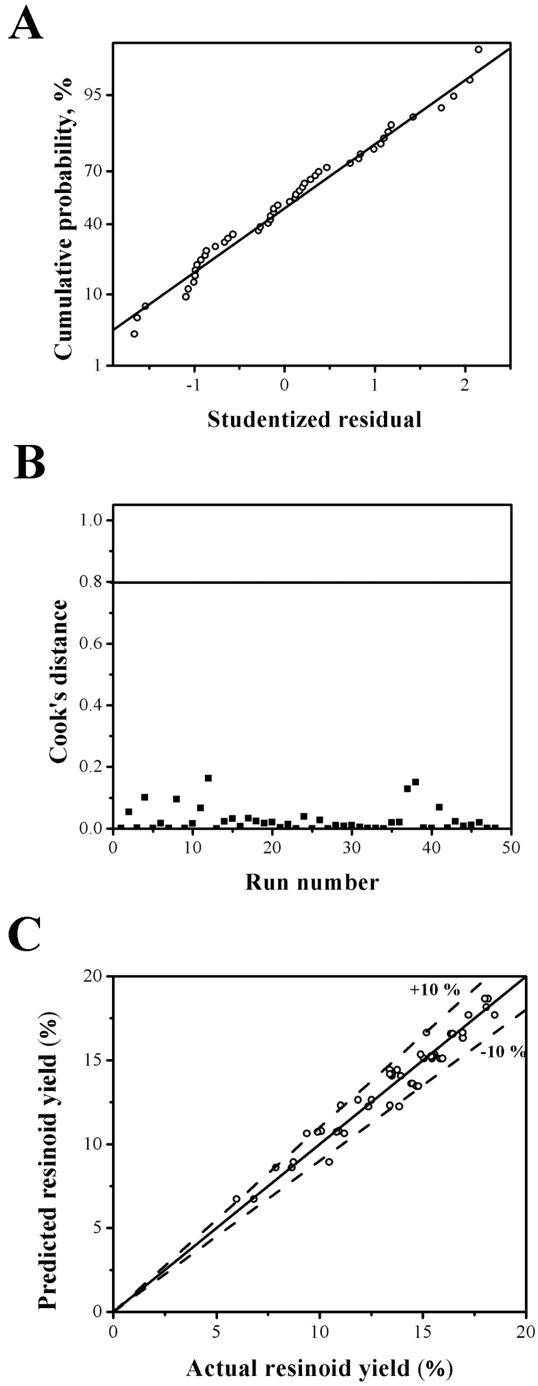

Fig. 2 Diagnostic plots: normal probability plot of residuals (A), Cook's distance (B) and predicted and actual values of retinoid yield (C).

3.3 Optimization the ultrasound assistant extraction (US-AE) by RSM model

The maximum predicted value of the resinoid yield was found through the optimization by the RSM model. The maximum predicted y, corresponding to T of 40 °C and S of 30 kg kg^{-1}, was 18.7%. This value was in accordance with the resinoid yield (18.1%) obtained at 40 °C and 30 kg kg^{-1} thus verifying the developed model. The relative deviation between predicted and experimentally obtained values of resinoid yield at the optimal model conditions is ±3.3%. The confirmed validity of the RSM under optimal conditions is in agreement with the previous studies [15, 25, 36].

In this work, for the first time, the resinoid extraction from *G. verum* was studied using a statistical method based on the RSM model in order to identify and quantify the variables able to maximize the relative US extraction efficiency. Hence, US-AE is being widely used in the extraction of bioactive compounds from natural sources for use in food industry [37]. Furthermore, use of ultrasound reduces the use of toxic solvents, which is desirable for extracting bioactive compounds for human consumption [18]. Milić and coworkers [15] reached better extraction yield from *Galium* species with RSM model using the ethanol aqueous solution for US-AE. However, a better extraction yield does not necessarily mean a higher content of desired components, since ballast substances present in higher percentage reduce the portion of bioactive components [38]. Importance of this study, as well, is the fact that we use effective solvent, such as ethanol, for solid–liquid US extraction, in order to minimize impact on human health. The current food industry adopts US technique and focuses on extracting and recovering valuable active compounds from different plant materials [18, 21, 33, 39]. Therefore, our research suggests combined use of numerical modeling and ultrasound in extraction of active components from *G. verum* for traditionally food manufacturing in order to improve productivity and reduce operational cost.

4 Conclusion

The response surface methodology (RSM) optimization methods employed in the present work have not been earlier used for optimizing the extraction of total extractive substances from *G. verum* by ultrasound-assisted extraction (US-AE). In this work, RSM has been employed for the first time for evaluating the effects of the extraction process variables such as temperature (T) and solvent-to-solid ratio (S) on total extractive substances from *G. verum* in the presence of ultrasound; as well as to optimize operational parameters of US-AE in order to obtain a maximal possible extraction yield from *G. verum*. The obtained experimental data was adequately fitted into second-order polynomial models with coefficient of determination (R^2) of 0.979. The RSM model pointed out the impact of S and T on extraction yield of *G. verum*. Also, RSM was successfully applied to obtain set of optimal parameters for increasing the US-AE efficiency from *G. verum.* RSM showed that the optimal extraction parameters, which gave a maximum extraction yield of 18.7%, were obtained for 40 °C (T) and 30 kg kg^{-1} (S). Using the modeled optimized conditions, the detected relative difference between predicted and experimental yield was ±3.3%. Results of this work showed that RSM proved as useful and new tool for optimizing the extraction of total extractive substances from *G. verum*.

The RSM as numerical modeling offers an affordable, fast and efficient means to characterize and optimize US processes [15, 22]. A numerical modeling must be a mathematical tool that reflects the physical behavior of the actual structure and experimental observations [40]. Methodologies that are not standardized and control parameters are the main reasons why in food industry numerical modeling cannot be widely applied in research yet. The RSM model was proved as easy, acceptable, accurate and useful tool for the standardization of extraction conditions for bioactive component from important food industry plants. Numerical modeling can for instance be utilized to simplify explanation of phenomena, optimize extraction processes, reduce operational cost and improve productivity [15, 21].

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