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Research Article

Optimization of Ultrasonic-Assisted Extraction of Phenolics and Terpenoids from Sweet Basil Leaves Using Natural Deep Eutectic Solvents

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This investigation focused on assessing and enhancing ultrasound-assisted extraction (UAE) using natural deep eutectic solvents (NADES) to extract phenolics and terpenoids from sweet basil leaves. The initial stage involved evaluating the extraction performance of twelve NADES and ethanol. A NADES comprising lactic acid and glucose with a 2 : 1 molar ratio and 20% water content (WC) obtained the highest total phenolic content (TPC) and total terpenoid content (TTC). Single-factor experiments systematically examined the impact of liquid-to-solid ratio (LSR), water content in NADES (WC), ultrasound power, temperature, and exposure time on the extraction yield. Optimization using Box–Behnken Design (BBD) models for the lactic acid and glucose-based UAE revealed the optimal conditions to be 80 ml/g LSR, 30% water, 300 W, 50°C temperature, and a 15-minute exposure time. Under these optimized parameters, the extraction achieved the highest TPC and TTC at 69.88 mg GAE/g and 110.71 mg UA/g, respectively. This study presents an environmentally friendly and sustainable extraction protocol for the extraction of phenolic compounds and terpenoids from sweet basil leaves.

1. Introduction

Free radicals are molecules with unpaired electrons and unstable chemical structures [1]. They encompass reactive oxygen and nitrogen species, which arise from cellular processes (such as mitochondrial energy conversion) and environmental factors [2]. While reactive oxygen species play vital roles in biological signal transduction cascades, their excessive production can lead to the oxidation of lipids, DNA, and proteins, resulting in protein denaturation, DNA fragmentation, and lipid polymerization, ultimately disrupting cellular physiological processes [3, 4]. Current research highlights the potential of antioxidants, including phenolics and terpenoids found in food, to mitigate the detrimental effects of free radicals on cells [5]. Furthermore, terpenoids, known as secondary metabolites, exhibit antioxidant, antimicrobial, and anti-inflammatory properties, contributing to disease resistance and serving as sources of vitamins A, E, K, and coenzyme Q10 [6]. Various plant strains have demonstrated antioxidant activity, and sweet basil (*Ocimum basilicum*), a widely cultivated herb in Asian countries, is no exception [5]. In traditional medicine, sweet basil is employed to treat ailments such as cancer, toothaches, gout, and nausea. Sweet basil leaves are rich in phenolics and terpenoids, which offer protection against oxidative processes, inflammation, and cancer [7]. According to Jayasinghe et al., the primary phenolic compound in sweet basil is rosmarinic acid, which exhibits a capacity to capture 1.52 radicals per molecule and synergizes positively with vitamin E (α-tocopherol) [8]. Numerous terpenoids, including eucalyptol, linalool, and eugenol, have also been identified in basil leaves [9]. Thus,

harnessing the phenolic and terpenoid contents from sweet basil presents a promising avenue for creating natural antioxidant compounds for food preservation and fortification.

Conventional methods for extracting phenolics and terpenoids from plants, such as maceration, mechanical pressing, and Soxhlet extraction, are associated with various drawbacks. Maceration and Soxhlet extraction are characterized by high consumption of organic solvents and time, whereas mechanical pressing yields a low extraction [10–12]. In contrast, ultrasonic-assisted extraction (UAE) offers several advantages over traditional techniques, operating at lower temperatures, utilizing less energy, reducing extraction duration, and preserving the quality of extracts [13]. Consequently, UAE emerges as an environmentally friendly approach for the recovery of plant-derived bioactive matter.

NADES represents a subtype of ionic liquids formed through the complexation of a natural acceptor (HBA) and hydrogen bond donor (HBD) in certain molar ratios, inducing charge delocalization and thereby reducing the mixture's melting point in comparison to individual components [14]. Recognized for their eco-friendly attributes, including low cost, biodegradability, low toxicity, nonvolatility, and biocompatibility, NADES has emerged as a viable alternative to organic solvents [14, 15]. Their growing popularity spans various applications, notably in the extraction and separation of bioactive compounds such as flavonoids, phenolics, and terpenoids, as well as in biocatalysis involving enzymes such as lipase [16–18]. The enhanced extraction efficiency of NADES with bioactive compounds is attributed to the establishment of extensive hydrogen bond networks among its constituents [17]. The synergistic utilization of NADES and ultrasound-assisted extraction (UAE) have demonstrated further improvements in the extraction yield of bioactive compounds in recent studies, including the recovery of crocin from gardenia fruits, phenolics from olive leaves, flavonoids from rhizomes of *Polygonatum odoratum*, flavonoids from two fruits of Rubia strains, and anthocyanin from *Aronia melanocarpa* [19–22]. Extensive research has been dedicated to investigating the chemical composition of basil over the years. In a study by Lee and Scagel, the essential oil profiles of basil leaves were scrutinized through gas chromatography/mass spectrometry (GC/MS), revealing linalool and estragole as major components [23]. Another investigation by Carolina Aloisio et al. utilized an ultrasonic probe for the extraction of phenolic matter from the leaves of *Ocimum basilicum*, employing ethanol as the solvent. The study identified the optimal parameters for the ultrasound-assisted extraction (UAE) process, including a 50% ethanol concentration, 200 W of ultrasonic power, and a 5-minute duration [19]. Despite the enhanced cell wall destruction capability of ultrasonic probes compared to baths, a drawback lies in the uneven power distribution of probes relative to baths [13]. Notably, there is a dearth of research employing natural deep eutectic solvents NADES-based UAE for the simultaneous extraction of phenolics and terpenoids from sweet basil leaves, and the optimization of five critical factors in the NADES-based UAE process remains unexplored.

Response surface methodology (RSM) is frequently utilized for outlining experimentation and determining the optimal parameters of food and pharmaceutical processes [20]. The impact of introduced parameters and their interplays on the responses can be examined by constructing the polynomial regression models [21]. In RSM, Box–Behnken design (BBD) and central composite design (CCD) models were usually employed to find the optimized parameters of the ultrasonic-assisted extraction process. The drawback of CCD compared to BBD is the extreme points; thus, it possesses more experiments than BBD [22]. Nipornram et al. used the BBD model to optimize the low-power UAE process to achieve the highest extraction efficiency of phenolics from Mandarin. The highest phenolics were acquired at ultrasonic power of 56.71 W, extraction time of 40 min, and 48°C [24]. The BBD models were also employed to find the optimal parameters of UAE processes to recover the highest extraction yield of phenolics from olive pomace, coffee leaves, mulberry, and *Arbutus unedo* L. fruits [22].

This study aimed to employ NADES-based UAE to acquire phenolics and terpenoids from sweet basil leaves. The investigation involved assessing the extraction yield of each NADES in extracting phenolics and terpenoids from basil leaves. NADES with different polarities were produced to investigate the effect of their polarity on the extraction yield of phenolics and terpenoids from sweet basil leaves. This investigation indicated the polar range of these bioactive compounds. Various conditions of UAE based on NADES, namely, water content of NADES (WC), LSR, sonication power, time, and temperature, were systematically examined to understand their effects on the extraction efficiency of phenolics and terpenoids. The optimization of NADES-based UAE conditions was carried out deploying response surface methodology (RSM) with a Box–Behnken design (BBD) model. Notably, the BBD model was chosen due to its absence of extreme experimental points, requiring fewer runs compared to the central composite design, and its advantage in handling three-level designs by selecting runs from these parameters [22].

2. Materials and Methods

2.1. Materials. Sweet basil was procured from GO supermarket in Ho Chi Minh City, Vietnam. The leaves were isolated and subsequently dried at 45°C for 50 hours to achieve a moisture content of 4%. The dried leaves were pulverized with sweet basil leaf powder (SBLP) using a milling machine (model: 3600H, Makita, Emin Corporation, Singapore). Various chemicals, including the Folin–Ciocalteu reagent (2.1 N), absolute ethanol, gallic acid monohydrate, perchloride acid, acetic acid, and vanillin, were sourced from Sigma-Aldrich Chemical Co., Ltd., Singapore. Additionally, chemicals for preparing NADES were bought from Xilong Scientific Co., Ltd., Guangdong, China.

2.2. Preparation of NADES and Screening. NADES underwent heating at 85°C utilizing a heating machine (model: C–MAG HS 7, IKA Industrie, Germany). The heating was

terminated upon achieving a state where the HBD and HBA mixture transformed into a homogeneous and transparent liquid. The formation of NADES was confirmed by the absence of crystal formation in the clear liquid at ambient temperature. Table 1 detail the acronyms and molar ratios of the NADES generated in the process. The NADES composition in Table 1 was selected from our previous works and Ramón et al. [25, 26].

2.3. One-Factor Experiments. The sweet basil leaf powder was weighed 0.5000 ± 0.0010 g, and 10 ml of natural deep eutectic solvents (NADES) was introduced into an amber glass bottle. The resulting mixture underwent ultrasound treatment (model: RS22L 40 kHz, Rama Viet Nam Joint Stock Company, Vietnam) at 30°C with an ultrasonic power of 300 W for 10 minutes. Subsequently, the mixture was subjected to centrifugation (DM0412, DLAB Scientific Co., Ltd., China) at 2100 g and 30°C for 10 minutes, yielding a supernatant. The obtained supernatants were then analyzed for TPC and TTC.

SBLP was introduced into an amber glass bottle, followed by the addition of 10 ml of natural deep eutectic solvents (NADES). The ensuing mixture underwent processing in an ultrasonic bath under varying conditions, including different liquid-to-solid ratios (LSR, ranging from 1 : 10 to 1 : 100 g/ml), WC (10–50%, g/g), ultrasonic power levels (0, 150, 300, 450, 600, 750, and 900 W), and temperatures (30–70°C) for extraction times ranging from 5 to 30 minutes with intervals of 5 minutes. The amber glass bottles containing SBLP were arranged in two rows at the center of the ultrasonic bath, and the distance of each sample was 1 cm. After treatment, the mixture underwent centrifugation at 2100 g and 30°C for 10 minutes to remove the solid part, after which the TPC and TTC of the resulting homogeneous liquid extracts were quantified Table 2.

2.4. Experimental Design. RSM was utilized to optimize conditions for terpenoid and phenolic extraction. Building on the findings from one-factor experiments, a BBD model was implemented, featuring five independent factors (x_1: LSR, x_2: WC, x_3: ultrasonic power, x_4: temperature, and x_5: time) each at three levels (−1, 0, +1). The responses evaluated were TPC, denoted as y_1, and TTC from SBLP, denoted as y_2. The correlation between the independent factors and the responses was captured by a polynomial equation.

Table 1: NADES prepared in the present research.

No.	HBD	HBA	Abbreviation	Molar ratio
1	Acetic acid	Choline chloride	AA-Iso	2 : 1
2	Acetic acid	Isopropyl alcohol	AA-Cho	2 : 1
3	Acetic acid	Glycerine	AA-Gly	2 : 1
4	Acetic acid	Glucose	AA-Glu	2 : 1
5	Lactic acid	Choline chloride	Lac-Iso	2 : 1
6	Lactic acid	Isopropyl alcohol	Lac-Chol	2 : 1
7	Lactic acid	Glycerine	Lac-Gly	2 : 1
8	Lactic acid	Glucose	Lac-Glu	2 : 1
9	Citric acid	Choline chloride	Ci-Iso	2 : 1
10	Citric acid	Isopropyl alcohol	Ci-Cho	2 : 1
11	Citric acid	Glycerine	Ci-Gly	2 : 1
12	Citric acid	Glucose	Ci-Glu	2 : 1
13	Ethanol			

$$Y = d_0 + \sum_{i=1}^{n} d_i x_i + \sum_{j<j}^{n} d_{ij} x_i x_j + \sum_{i=1}^{n} d_{ii} x_i^2. \quad (1)$$

In this equation, b_0 represents the intercept, while d_i, d_{ij}, and d_{ij} denote the linear, interactive, and quadratic coefficients, respectively. Variables x_i and x_j signify the independent factors ($n = 5$), and TPC and TTC represent the responses. The statistical significance of the regression model was assessed using analysis of variance (ANOVA), and the p values were employed to ascertain the interactive effects of the independent factors.

The prediction error (%) between predicted values and experimental values was calculated by the following equation [27]:

$$\text{Prediction error} = \frac{|\text{the mean of measured value} - \text{predicted values}|}{\text{the mean of measured value}} * 100. \quad (2)$$

2.5. Measuring Total Phenolic and Total Terpenoid Contents. TPC and TTC were determined through colorimetric methods using a UV-vis spectrophotometer (Hach DR/2010, LabWrench, Canada). TPC was assessed employing the Folin–Ciocalteu reagent and expressed as milligrams of gallic acid equivalent per gram of dried basis (mg GAE/g DB). Meanwhile, TTC was assessed using the Biswajit Biswas method and presented as milligrams of ursolic acid per gram of dried basis (mg UA/g DB) [28, 29].

2.6. Statistical Analysis. All experiments were conducted in triplicate, and the results were reported as the mean ± standard deviation (SD). Statistical analyses, including ANOVA with a significance level (α) of 5%, and post hoc multiple-range tests were carried out using Minitab 19 (Minitab, Inc, USA). Graphical representations were generated using Origin Pro (Origin Lab, USA). The Box–Behnken design (BBD) model was established using Design-Expert v.13 software (Stat-Ease Inc., USA).

Table 2: The experimentation for one-factor experiments.

Number 1	UAE	
	Factors	Fixed conditions
1	LSR: 10–100 ml/g; interval: 10 ml/g	Water content: 20%; ultrasonic power: 300 W, temperature: 30°C; time: 5 min
2	Water content: 10–50%; interval: 10%	LSR: the result of 1; ultrasonic power: 300 W, temperature: 30°C; time: 5 min
3	Ultrasonic power: 0–900 W; interval: 150 W	LSR: the result of 1; water content: the result of 2; temperature: 30°C; time: 5 min
4	Temperature: 30–70°C; interval: 10°C	LSR: the result of 1; water content: the result of 2; ultrasonic power: the result of 3; time: 5 min
5	Time: 5–30 min; interval: 5 min	LSR: the result of 1; water content: the result of 2; ultrasonic power: the result of 3; temperature: the result of 4

3. Results and Discussion

3.1. Selection of NADES as Extraction Solvent. The composition of NADES significantly impacts their viscosity, polarity, ability to extract substances, and solvation properties when it comes to phenolics and terpenoids [14]. These NADES were prepared using twelve different combinations, each containing 20% water, consisting of four HBA components: isopropyl alcohol, choline chloride, glucose, and glycerol, and three HBD components: acetic acid, lactic acid, and citric acid. The choice of HBA and HBD components was based on their varying polarities, which play a crucial role in determining the efficiency of these solvents in extracting bioactive compounds. To identify the most effective extractants for phenolics and terpenoids from SBLP, the extractability of NADES was compared, and the results are illustrated in Figure 1(a). When subjected to sonication, nearly all NADES, apart from Lac-Gly, yielded more phenolics than ethanol, reaching 5.45 ± 0.27 mg GAE/g DB. Lac-Glu, Lac-Cho, and Ace-Cho demonstrated the highest phenolic extraction yields, while Lac-Gly had the lowest. The highest recovery of terpenoids, measured as total terpenoid content (TTC), was achieved with Lac-Glu, at 67.28 ± 0.74 mg UA/g DB, followed by Lac-Iso and Lac-Cho. The superior extraction performance of Lac-Glu can be accounted for its similarity in polarity with terpenoids and phenolics in SBLP [3, 4]. Additionally, the strong solubility of Lac-Glu can result from the generation of robust hydrogen bond networks with phenolics and terpenoids [5]. However, Lac-Cho, Lac-Iso, and Lac-Gly exhibited lower terpenoid extraction yields compared to Lac-Glu, possibly due to the lower polarity of glycerol, isopropyl alcohol, and choline chloride compared to [6, 30, 31]. Among the tested solvents, the NADES prepared with Lac-Glu exhibited the highest total phenolic content (TPC) and TTC and was thus chosen as the environmentally friendly solvent for subsequent experiments.

3.2. Single-Factor Experiments

3.2.1. Effect of Liquid-to-Solid Ratio. This investigation delved into how the LSR impacted the extraction efficiency of phenolics and terpenoids using NADES-based UAE under fixed conditions: 20% WC, 300 W ultrasonic power, and 30°C for 5 minutes. The outcomes are depicted in Figure 1(b), which illustrates an enhancement in the extraction yield of phenolics and terpenoids as the LSR increased from 10 to 80 ml/g. As the LSR rose, it led to an improvement in the cavitation effect and the contact area between the solvent and the material, ultimately resulting in increased analyte extraction [32]. Mass transfer can face obstacles when the difference in levels between the dispersed and liquid phases is not significant [13]. Nevertheless, when the LSR surpassed 80 ml/g, the TPC and TTC declined by 1.08 and 1.63 times, respectively, attributable to the excessive cavitation negatively affecting the stability of terpenoids and phenolics [32]. In a prior study, an LSR of 35 ml/g, utilizing NADES, yielded high concentrations of polyphenols from *Rosa damascene* Mill. [15]. Conversely, in the case of extracting phenolics from *Asparagopsis taxiformis*, a lower LSR of 20 ml/g was effective when using betaine-levulinic acid as a DES [33]. Consequently, an LSR of 80 ml/g was determined to be suitable for extracting phenolics and terpenoids from SBLP.

3.2.2. Effect of Water Content in NADES. The impact of varying WC within the NADES on the extraction efficiency of terpenoids and phenolics was investigated under consistent conditions: 80 ml/g LSR, 300 W ultrasonic power, and 30°C for 5 minutes, and the results are represented in Figure 1(c). When the WC was increased to 30%, there was a notable 2.1-fold increase in TPC and a 1.4-fold increase in TTC. The addition of water reduced the viscosity of NADES, leading to enhanced mass transfer rates and, consequently, improved extraction yields [32]. These findings align with the research conducted by Wu et al. [29], who also observed the positive influence of increasing WC on the extraction yields of phenolics from *Moringa oleifera* L. leaves. However, a further increase in WC to 30–50% resulted in a decline in extraction yield. This decrease could be attributed to the disruption of the supramolecular structure of NADES at excessive WC, which could reduce the interactions among NADES, phenolics, and terpenoids, impacting the extraction yield [34]. As a result, NADES composed of Lac-Glu with 30% WC was chosen as the intermediate level for subsequent optimization using RSM.

3.2.3. Effect of Ultrasonic Power. The impact of ultrasonic power on the extraction of TPC and TTC was investigated under constant conditions: 80 ml/g LSR, 30% WC, and 30°C for 5 minutes, and the experimental findings are displayed in Figure 1(d). As the ultrasonic power increased from 0 to 450 W, there was a significant enhancement in the extraction yield of phenolics and terpenoids. This effect was attributed to the enlargement of cavitation bubbles with increasing ultrasonic power, resulting in more forceful bubble collapse. The more vigorously collapsing bubbles led to greater sonoporation, shearing force, and fragmentation, improving the breakdown of rigid cell walls with limited permeability [35]. These results were consistent with the findings of Altemimi et al. [35], who also observed an increase in the extraction yield of phenolics when power was raised from 30% to 44.66% during the extraction of phenolic compounds from peaches and pumpkins. However, TPC and TTC declined when the ultrasonic power was further increased to 900 W. The elevated ultrasonic power leads to a greater number of cavitation bubbles, which results in bubble coalescence, deformation, and nonspherical implosion, diminishing their disruptive effect on plant cell walls. Additionally, the high levels of free radicals generated during the collapse of bubbles could deteriorate phenolics and terpenoids, thus reducing the extraction yield [13]. Based on these findings, an ultrasonic power of 300 W was selected as the proper output power.

3.2.4. Effect of Temperature. The impact of temperature on the recovery of phenolics and terpenoids was examined while keeping other parameters constant: 80 ml/g LSR, 30%

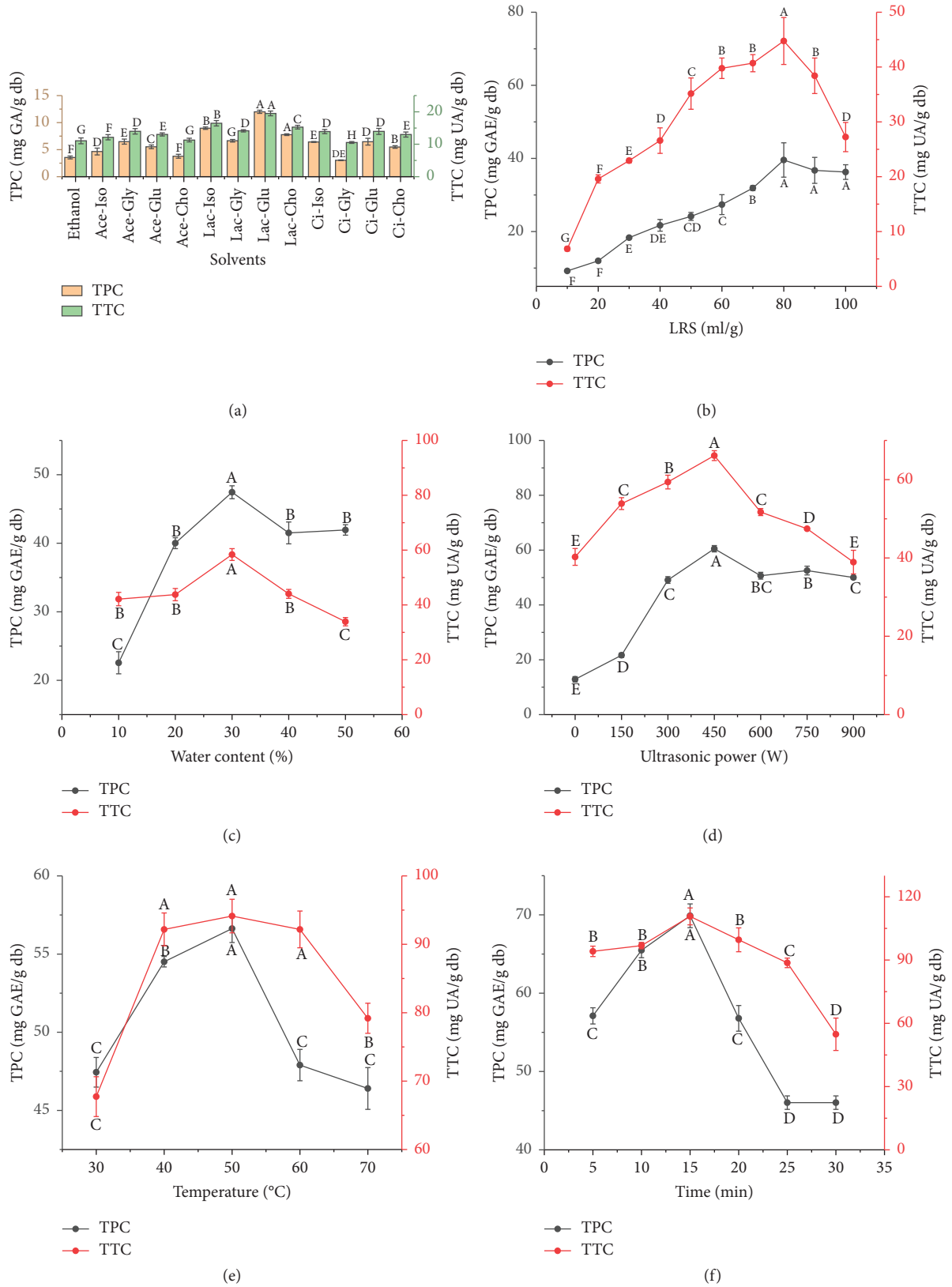


Figure 1: The effect of solvents and UAE conditions on the extraction yield of phenolics and terpenoids: (a) the effect of solvents on the extraction yield of phenolics and terpenoids; (b) the effect of LSR on the extraction yield of phenolics and terpenoids; (c) the effect of WC on the extraction yield of phenolics and terpenoids; (d) the effect of ultrasonic power on the extraction yield of phenolics and terpenoids; (e) the effect of temperature on the extraction yield of phenolics and terpenoids; (f) the effect of time on the extraction yield of phenolics and terpenoids. Different characters express the significance of statistics.

WC, and 450 W of ultrasonic power for 5 minutes. As illustrated in Figure 1(e), the TPC and TTC rose as the temperature rose from 30 to 50°C. This moderate temperature increase facilitated the raw material's softening and swelling, enhancing the target analytes' solubility and desorption capacity while declining the NADES viscosity [36]. Consequently, the mass transfer of phenolics from SBLP was more efficient at higher temperatures. This trend aligns with previous research that examined the impact of various parameters on the extraction yields of polyphenols [37–39]. Conversely, when the temperature was further elevated to 70°C, TPC and TTC decreased to 56.63 ± 0.89 mg GAE/g DB and 94.13 ± 2.45 mg UA/g DB. Excessively high temperatures can accelerate the degradation of terpenoids and phenolics, leading to a decline in extraction yield [13]. Additionally, the excessively high temperature can significantly decline the cavitation threshold, generating numerous small cavitation bubbles. This effect can reduce the devastating effect of the cavitation effect, alleviating the movement of bioactive compounds from plant cells into the extraction medium [13]. Therefore, an extraction temperature of 50°C was selected for subsequent optimization.

3.2.5. Effect of Time. The influence of sonication time on the extraction of phenolics and terpenoids was investigated under constant conditions: 80 ml/g LSR, 30% WC, 450W ultrasonic power, and 50°C. As depicted in Figure 1(f), the levels of all studied components exhibited a significant increase with prolonged extraction time, up to 15 minutes. However, further extending the extraction time led to degradation. This observation aligns with findings from various studies by Cvjetko Bubalo et al. [40] and Upadhyay [41], respectively, who reported similar trends during the UAE of polyphenols from winemaking waste, polysaccharides from *Ziziphus jujuba* Mill., phenolic compounds from grape marc, phenolics from grape skin, and flavonoids and phenolics from *Ocimum tenuiflorum* leave, respectively. Increasing the ultrasonic time initially promotes better exposure of materials to ultrasound, facilitating the breakdown of plant cell walls and enhancing the extraction yield [36]. However, prolonged sonication can result in excessive thermal damage to the target analytes, reducing the extraction yield of phenolics and terpenoids [36]. A sonication time of 15 minutes was chosen as the optimal duration for extracting phenolics and terpenoids from SBLP.

3.3. Optimizing Ultrasonic-Assisted Extraction of Terpenoids and Phenolics. The response surface methodology, specifically the BBD model, was employed to optimize the conditions for UAE in order to maximize the extraction yield of bioactive components. Each independent variable was set at three levels (−1, 0, 1), with the optimal conditions determined from single-factor experiments being set at level 0. Table 3 presents the experimental design with five factors based on the BBD model and the recorded values for TPC and TTC from a total of forty-five runs. Under the conditions where all variables were set to 0, the highest values were achieved for TPC (69.88 mg GAE/g DB) and TTC (110.71 mg UA/g DB). Conversely, the lowest TPC value (27.95 mg GAE/g DB) was obtained when the WC was increased to 40% (+1 level), and the extraction time was reduced to 10 minutes (−1 level). Similarly, the lowest amount of TTC (24.18 mg UA/g) was observed when the liquid-to-solid ratio (LSR) was decreased to 70 ml/g (−1 level), and the temperature was lowered to 40°C (−1 level).

Table 4 presents the results of the ANOVA and the associated regression coefficients for the utilized BBD models. ANOVA results were utilized to assess the significance of the regression coefficients in each model, offering insights into how the independent and response variables interact. According to the information in Table 3, the model is remarkably significant ($p < 0.0001$) for both response variables. The determination coefficient (R^2) of the model was above 0.9, and the adjusted R^2 exceeded 0.8 for both response variables, which signifies that the model is a strong fit. These outcomes affirm that the models for both response variables are well matched with the experimental data and are suitable for making predictions within the tested range of experimental variables. Equations (3) and (4) depict how the independent variables relate to the dependent responses: TPC (y_1) and TTC (y_2).

$$y_1 = 69.88 + 3.86\,x_2x_5 - 3.71\,x_3x_4 - 17.22\,x_1^2 - 14.11\,x_2^2 - 15.69\,x_3^2 - 10.31\,x_4^2 - 19.36\,x_5^2, \tag{3}$$

$$y_2 = 110.71 + 10.62\,x_1 - 4.74\,x_2 - 16.10\,x_1x_2 + 9.18\,x_1x_3 - 8.36\,x_1x_5 - 34.03\,x_1^2 - 27.90\,x_2^2 - 30.00\,x_3^2 - 44.22\,x_4^2 - 25.35\,x_5^2. \tag{4}$$

Table 4 indicates that the linear interaction had a minimal impact on TPC, but LSR and extraction time had a substantial impact on TTC. Furthermore, the combined influence of WC and time interval had a positive and significant effect on TPC, while the interaction between ultrasonic power and temperature had a negative effect. Regarding TTC, the combined impact of LSR with time and WC had a negative effect, whereas LSR and ultrasonic power had the opposite effect.

3D response surface graphics (Figure 2) were drawn to depict the significant interactive effect on TPC and TTC. Figure 2(a) shows that the increase in both water content and extraction time (x_2x_5) accelerated the extraction of phenolics at a liquid-to-solid ratio of 80 mL/g, power at 300 W,

Table 3: The experimental results of BBD models.

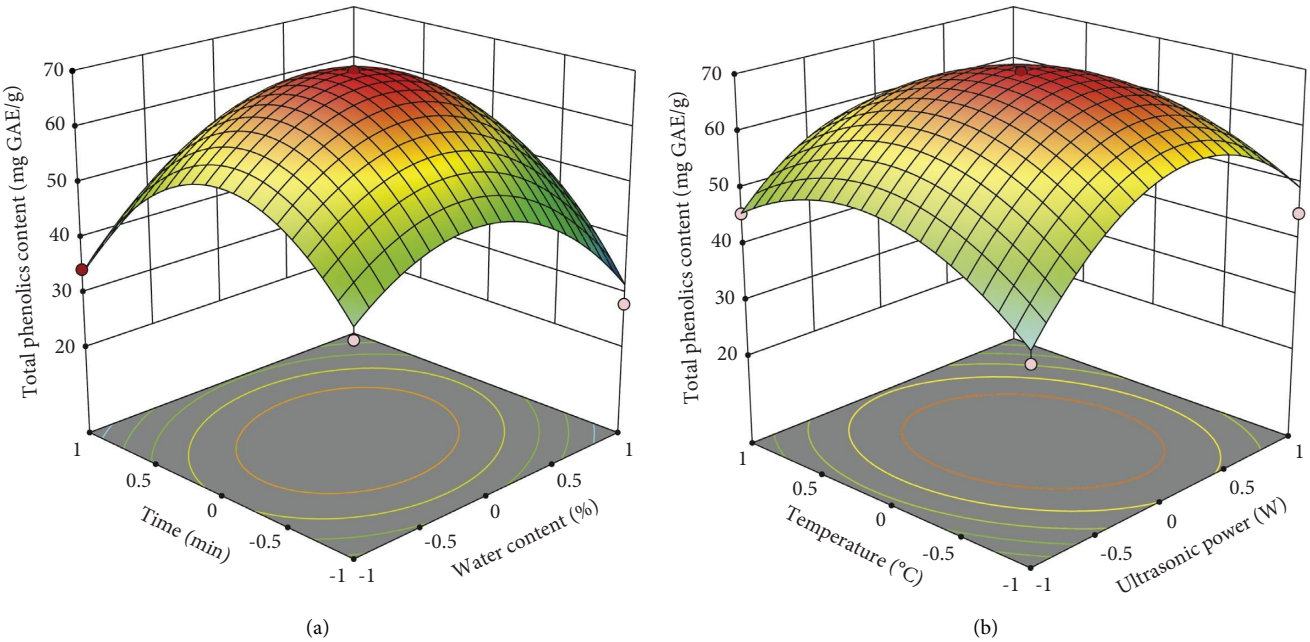
STT	LSR (x_1)	WC (x_2)	Ultrasonic power (x_3)	Temperature (x_4)	Time (x_5)	Phenolics	Terpenoids
1	0	−1	0	0	−1	40.48 ± 4.75	63.72 ± 8.13
2	0	−1	−1	0	0	40.17 ± 4.60	53.12 ± 1.00
3	1	z	0	0	1	30.57 ± 4.23	50.58 ± 0.50
4	−1	−1	0	0	0	43.42 ± 5.79	33.53 ± 2.84
5	−1	1	0	0	0	33.51 ± 5.42	49.57 ± 6.03
6	0	0	0	−1	−1	37.02 ± 2.67	41.23 ± 5.02
7	0	0	0	1	1	33.51 ± 2.83	29.98 ± 8.54
8	−1	0	0	0	−1	37.18 ± 5.27	31.40 ± 6.53
9	0	1	−1	0	0	34.56 ± 0.67	48.45 ± 4.73
10	1	0	1	0	0	40.22 ± 7.34	62.76 ± 8.54
11	0	1	0	1	0	45.41 ± 0.30	25.00 ± 4.52
12	0	0	0	0	0	69.88 ± 5.82	110.71 ± 7.43
13	1	−1	0	0	0	39.38 ± 1.11	89.71 ± 6.53
14	0	0	0	0	0	69.88 ± 5.82	110.71 ± 7.43
15	0	−1	1	0	0	38.02 ± 2.45	61.68 ± 8.54
16	−1	0	−1	0	0	38.70 ± 2.67	36.75 ± 7.43
17	0	0	1	0	−1	42.21 ± 5.27	63.01 ± 1.00
18	0	−1	0	0	1	34.40 ± 0.74	57.32 ± 2.05
19	0	1	0	−1	0	45.20 ± 2.23	32.11 ± 1.55
20	0	0	0	0	0	69.88 ± 5.82	110.71 ± 7.43
21	0	1	0	0	1	37.28 ± 0.67	55.55 ± 6.53
22	0	0	1	1	0	38.17 ± 2.37	43.45 ± 4.56
23	0	−1	0	−1	0	50.40 ± 3.49	37.79 ± 3.78
24	0	0	0	0	0	69.88 ± 5.82	110.71 ± 7.43
25	0	0	0	0	0	69.88 ± 5.82	110.71 ± 7.43
26	0	0	−1	1	0	45.73 ± 4.60	38.5 ± 0.50
27	0	0	1	0	1	42.21 ± 6.68	54.43 ± 7.08
28	0	0	1	−1	0	44.78 ± 0.30	34.95 ± 0.50
29	−1	0	0	0	1	31.51 ± 1.41	40.63 ± 4.52
30	−1	0	1	0	0	28.73 ± 10.98	32.46 ± 5.02
31	0	0	0	0	0	69.88 ± 5.82	110.71 ± 7.43
32	−1	0	0	1	0	38.38 ± 3.71	25.00 ± 1.51
33	0	0	−1	−1	0	37.49 ± 3.78	44.89 ± 4.52
34	1	1	0	0	0	37.02 ± 0.45	41.34 ± 5.53
35	0	0	0	−1	1	41.43 ± 1.34	40.69 ± 5.53
36	1	0	0	1	0	44.94 ± 3.46	42.00 ± 2.51
37	1	0	0	−1	0	46.36 ± 2.97	52.00 ± 1.51
38	0	1	1	0	0	46.51 ± 2.60	47.29 ± 0.5
39	1	0	0	0	−1	30.99 ± 4.38	74.78 ± 4.93
40	0	1	0	0	−1	27.95 ± 4.23	58.03 ± 8.08
41	−1	0	0	−1	0	46.51 ± 0.67	24.18 ± 1.58
42	1	0	−1	0	0	37.34 ± 4.15	30.33 ± 5.02
43	0	0	−1	0	−1	35.45 ± 1.78	53.77 ± 4.12
44	0	0	−1	0	1	32.93 ± 2.82	59.46 ± 8.04
45	0	−1	0	1	0	48.40 ± 1.11	36.37 ± 1.51

and temperature at 50°C. However, the extraction yield decreased beyond 30% of water content in Lac-Glu and 15 min of extraction time. The water content enhances the solubilizing capacity of the target analyte in solvents and reduces the medium's viscosity. This effect can facilitate Lac-Glu in the basil leaf matrix, increasing the extraction rate [14]. Additionally, excessive water can break the supramolecular complex of Lac-Glu, reducing hydrogen bond formation capacity between the target analyte and solvents, which decreases extraction [40]. From Figure 2(b), the extraction yield of phenolics reached its peak by simultaneously increasing the temperature and ultrasonic power (x_3x_4) to 50°C and 300 W power. The temperature can decrease the extraction medium's viscosity, which reduces the cavitation threshold, producing more cavitation bubbles [14]. Furthermore, power ultrasound induces acoustic streaming, and cavitation produces intense agitation and mass transfer enhancement, resulting in higher yields of extracted compounds [14]. However, the verification examination to validate the reliability of BBD models was conducted and is shown in Table 4. The predicted optimal extraction yield was 69.92 mg GAE/g DB of TPC and 111.13 mg UA/g DB of TTC under the following conditions: 81.79 ml/g, 27.59% water, 297.73 W, 48.76°C, and 14.77 min, which was close to the experimental extraction yield (72.86 ± 1.91 mg GAE/g DB and 108.36 ± 3.12 mg UA/g DB,

Table 4: Regression coefficients and ANOVA of BBD models.

Regression coefficients	Phenolics	F value	p value	Terpenoids	F value	p value
d_0	69.88	23.44	<0.0001*	110.71	36.77	<0.0001*
d_1	0.55	0.39	0.5364	10.62	46.43	<0.0001*
d_2	−1.70	3.71	0.0660	−4.74	9.26	0.0056*
d_3	1.15	1.71	0.2038	2.17	1.94	0.1763
d_4	−0.67	0.51	0.4840	−1.31	0.6261	0.4366
d_5	−0.72	0.59	0.4513	−2.74	2.75	0.1100
d_{12}	1.89	1.14	0.2957	−16.10	26.67	<0.0001*
d_{13}	3.21	3.31	0.0815	9.18	8.67	0.0071*
d_{14}	1.68	0.90	0.3515	−2.70	0.7517	0.3945
d_{15}	1.31	0.55	0.4651	−8.36	7.19	0.0131*
d_{23}	3.53	3.99	0.0573	−2.43	0.6075	0.4433
d_{24}	0.55	0.10	0.7579	−1.42	0.2076	0.6528
d_{25}	3.86	4.76	0.0391*	0.98	0.0981	0.7568
d_{34}	−3.71	4.41	0.0463*	3.72	1.43	0.2442
d_{35}	0.62	0.12	0.7302	−3.57	1.31	0.2641
d_{45}	−3.72	2.96	0.0982	−4.02	1.11	0.3030
d_{11}	−17.22	205.75	<0.0001*	−34.03	257.89	<0.0001*
d_{22}	−14.11	138.10	<0.0001*	−27.90	173.35	<0.0001*
d_{33}	−15.69	170.72	<0.0001*	−30.00	200.52	<0.0001*
d_{44}	−10.31	69.51	<0.0001*	−44.22	410.78	<0.0001*
d_{55}	−19.36	245.38	<0.0001*	−25.35	135.00	<0.0001*
R^2	0.91			0.97		
Adjusted R^2	0.84			0.94		
Predicted R^2	0.65			0.87		

Note. *Significant statistical differences ($p < 0.05$).



(a) (b)

Figure 2: Continued.

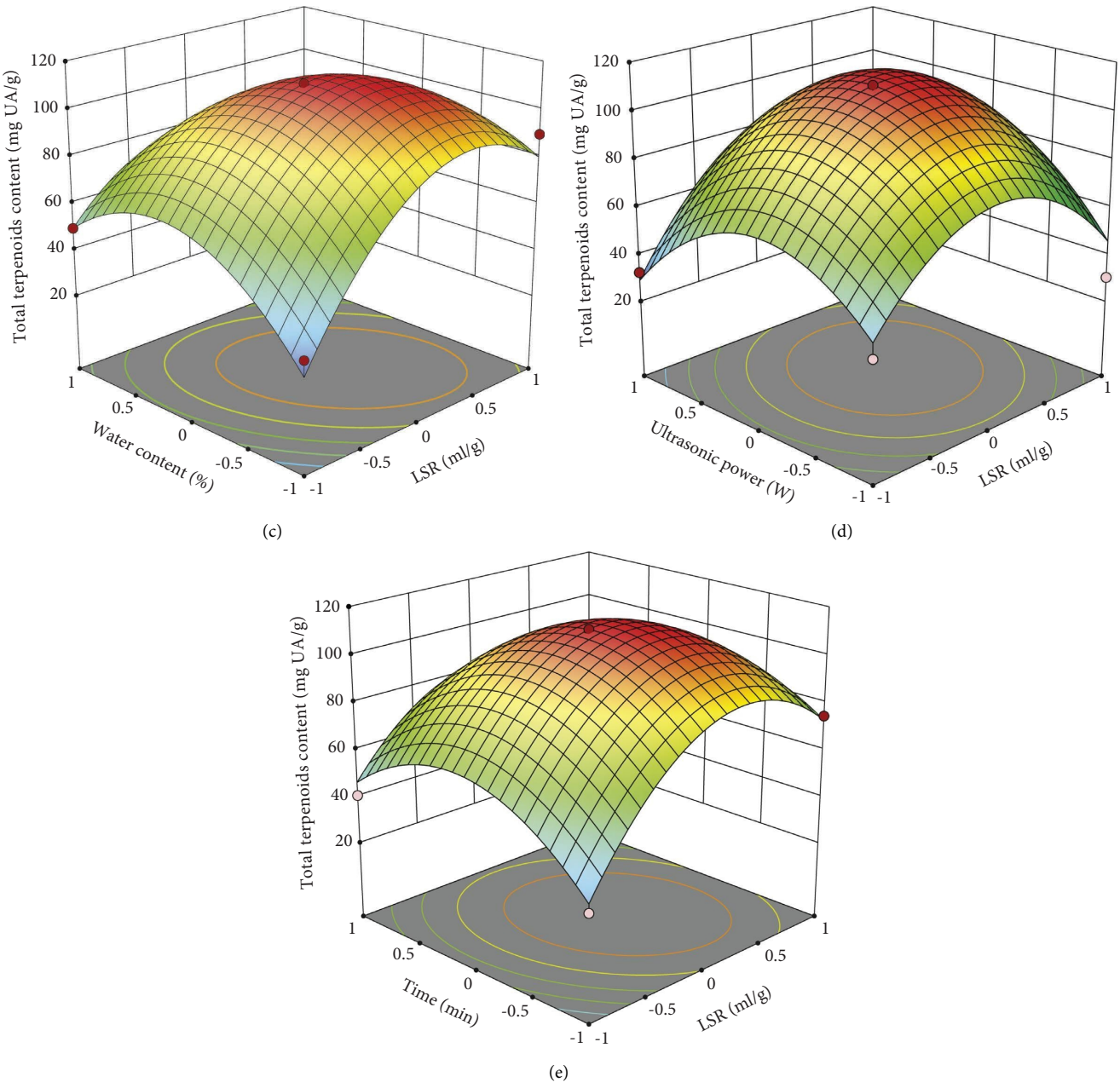


Figure 2: 3D reply surface graphics illustrating the interaction influence of independent variables on TPC (a, b) and TTC (c)–(e).

respectively) under actual operating conditions (80 ml/g, 30% water, 300 W, 50°C, and 15 min). The actual data showed the fit of the polynomial regression models and the precision of optimal results within a certain range of process conditions.

It should be noted that the thermally sensitive phenolics can deteriorate at certain temperatures or ultrasonic power values, causing a decline in the extracted yield.

Figure 2(c) describes the interaction effects of LSR and water content (X_1X_2) while other variables were fixed. The effect of LSR on terpenoid yield displayed a linear increase, while the effect of water content slighter rose. A similar trend is also seen in Figure 2(d), showing the mutual effect of LSR and power ultrasound (X_1X_3) on the terpenoid yield, with the highest value obtained at 80 ml/g and 300 W power. As shown in Figure 2(e), an increase in the LSR and exposure time resulted in a higher amount of TTC, but the beyond values of 80 ml/g and 15 min exhibited a downward trend. This trend can be explained by the acoustic value equation, which is directly proportional to the exposure time (t), proposed by Patis and Bates [42]:

$$P_a = P_{a,\max} \times \sin(2\pi f t). \quad (5)$$

In terms of LSR, a large ratio can generate a higher gradient concentration of terpenoids between NADES and SBLP, as well as lower the viscosity of the medium. However, a large ratio leads to complex posttreatment procedures [43].

Table 5: The experimental values and biological activities at the optimal conditions of the UAE operation.

Criteria	UAE conditions	TPC (mg GAE/g DB)		TTC (mg UA/g DB)	
		Predicted values from BBD models	Experimental values	Predicted values from BBD models	Experimental values
LSR (ml/g)	81.79				
WC (%)	27.59				
Ultrasound power (W)	297.73	69.92a	72.16 ± 1.91a	111.13a	108.33 ± 3.12a
Temperature (°C)	48.76				
Time (min)	14.77				
Anticipated errors %		3.05		2.58	
Predicted R^2		0.7957		0.8686	

Note. The same characters depict the insignificant statistical analysis, and Student's *t*-test was used to analyze the difference between observed and predicted results with 95% confidence.

Therefore, the optimized conditions for the UAE of terpenoids and phenolics were 300 W of ultrasonic power, 80 ml/g of LSR, 50°C, 15 min, and 30% WC in NADES (Lac-Glu), in which TPC and TTC were 69.9 mg GAE/g DB and 110.7 mg UA/g DB, respectively.

3.4. Model Validation. A verification test was conducted to confirm the reliability of the BBD models, and the results are presented in Table 5. The predicted optimal extraction yields were 69.92 mg GAE/g DB for TPC and 111.13 mg UA/g DB for TTC. These predictions were made under the following conditions: 81.79 ml/g for LSR, 27.59% for WC, 297.73 W for ultrasonic power, 48.76°C for temperature, and 14.77 minutes for extraction time. These predicted values were very close to the experimental extraction yields, which were measured at 72.86 ± 1.91 mg GAE/g DB for TPC and 108.36 ± 3.12 mg UA/g DB for TTC, respectively, under the actual operating conditions of 80 ml/g LSR, 30% WC, 300 W ultrasonic power, 50°C temperature, and 15 minutes of extraction time. These actual results demonstrate the accuracy of the polynomial regression models and the precision of the optimal extraction conditions within a specific range of process variables.

4. Conclusion

In this study, RSM was effectively applied to optimize the UAE process for phenolic compounds from sweet basil leaves using lactic acid-glucose as a natural deep eutectic solvent NADES. The optimal extraction conditions, yielding a maximum of 69.88 mg GAE/g for phenolics and 110.71 mg UA/g for terpenoids, were determined as follows: LSR of 80 mL/g, WC of 30%, ultrasonic power of 300 W, temperature of 50°C, and extraction time of 15 minutes. The UAE-NADES process exhibited a significantly higher TPC compared to conventional ethanol extraction (26.60 mg GAE/g DB) of the same plant species and UAE-ethanol procedure (9.41 mg GAE/g DB) for holy basil (*Ocimum tenuiflorum*). However, the lactic-glycine solvent with UAE showed a higher TPC for mint (109.67 mg GAE/g DB) than UAE-NADES. The literature on terpenoid extraction through the combination of UAE and NADES remains limited. This study proposes an advanced and sustainable extraction technique utilizing a nontoxic, renewable, and efficient solvent for the simultaneous extraction of phenolics and terpenoids.

Data Availability

All data generated or analyzed during this study are included within this published article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Tan Phat Vo conceptualized, visualized, and investigated the study, developed methodology and software, performed formal analysis, contributed to data curation, wrote the original draft, and reviewed and edited the article. Thuy Han Phan investigated the study, performed formal analysis, and wrote the original draft. Nguyen Thuc Doan Luu, Thi Bich Xuong Tran, Nhat Quyen Pham, Thai Anh Thi Ho, Nguyen Minh Huy Ha, and Minh Thu Nguyen performed formal analysis and investigated the study. Dinh Quan Nguyen visualized and supervised the study and wrote, reviewed, and edited the article.

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