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# Box-Behnken design optimization of the spray-drying process for yield and antioxidant activity of Koklan remedy extract powder

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## ABSTRACT

Koklan remedy is a traditional Thai herbal formulation used for the relief of muscle pain and inflammation. However, its decoction form presents limitations, including poor stability and low patient compliance. This study aimed to optimize the extraction and spray-drying conditions to convert Koklan remedy extract into a powder form with high yield and retained antioxidant activity. A Box-Behnken design was employed to investigate the effects of inlet temperature, feed rate, and decoction ratio on powder yield and ABTS radical scavenging activity. The results indicated that all three variables influenced the responses, with decoction ratio emerging as the most significant. The optimum condition for yield was found at 170˚C inlet temperature, 15% feed rate, and 3.71 decoction ratio. Validation experiments confirmed strong agreement in powder yield prediction but revealed some deviation in antioxidant activity due to model limitations. Overall, this study demonstrates the applicability of response surface methodology for optimizing herbal spray drying processes and supports the development of Koklan remedy powder as a more stable, scalable, and patient-friendly dosage form.

**Keywords:** Koklan remedy; spray drying; Box-Behnken design; process optimization; antioxidant activity

## 1. INTRODUCTION

Herbal remedies are complex formulations comprising multiple plant-based ingredients, traditionally used for the prevention, alleviation, or treatment of various illnesses, as well as for the general promotion of health. In Thailand, herbal remedies are extensively employed as part of traditional medicine, and many of these preparations are officially recognized and listed in the Herbal Product Division, Food and Drug Administration (2021). Among the various remedies documented, the Koklan remedy is particularly noted for its traditional use in relieving muscle pain and related musculoskeletal disorders. Three distinct Koklan remedy formulations, each featuring unique combinations of medicinal herbs, are included in the national list (Herbal Product Division, Food and Drug Administration, 2021). Of these, Koklan remedy formulation 3 has demonstrated superior pharmacological activity, particularly with respect to pain relief, anti-inflammatory action, and antioxidant properties, as reported in several pharmacological studies (Pongsaree et al., 2020; Maitnork & Konsue, 2019; Bumrungchaichana & Kamontham, 2020). Koklan remedy formulation 3 consists of six medicinal herbs: *Mallotus repandus* (Willd.) Mull. Arg., *Cryptolepis buchanani* Roem. & Schult., *Caesalpinia sappan* L., *Piper interruptum* Opiz, *Elephantopus scaber* L., and *Rhinacanthus nasutus* (L.) Kurz. The principal herb, *M. repandus* (Willd.) Mull. Arg., locally referred to as Koklan, has been reported to contain bergenin—a polyphenolic compound—as well as diterpenoids and triterpenoids. These phytochemicals are associated with notable antioxidant, anti-inflammatory, and analgesic effects (Hasan et al., 2014; Sriset et al., 2021). The remaining herbs in the formulation also contribute to its overall pharmacological efficacy, as they are abundant in various bioactive constituents, including flavonoids, alkaloids, phenolics, terpenoids, steroids, and anthraquinones. These compounds have also been shown to exert potent antioxidant and anti-inflammatory effects, further enhancing the synergistic potential of the Koklan remedy (Sharma et al., 2012; Rajput et al., 2022; Salleh et al., 2021; Junairiah et al., 2021; Hiradeve & Rangari, 2014; Brimson et al., 2020; Bukke et al., 2011). Traditionally, Koklan remedy formulation 3 is prepared via decoction, in which the herbal mixture is boiled in water until the volume is reduced from three parts to one. This extraction method isolates water-soluble active constituents and produces a concentrated herbal preparation. The recommended dosage of the decoction is 120–200 mL, administered orally three times per day (Herbal Product Division, Food and Drug Administration, 2021). However, despite its therapeutic advantages, the decoction form presents several limitations, including its strong and unpleasant taste, large volume requirement, poor patient compliance, difficulties in packaging and transportation, limited shelf life, and vulnerability to microbial contamination (Yang, 2010). To the best of our knowledge, the Koklan remedy is currently available primarily as a liquid decoction or in capsule form containing raw powdered herbs. The use of spray-dried Koklan extract in powder form has not yet been documented in the published literature. Therefore, the development of a stable, water-soluble, and patient-friendly powdered extract would constitute a significant advancement in the modernization of this traditional medicine.

Spray drying is a widely adopted technique in the pharmaceutical and food industries for converting liquid extracts into dry powders. This method involves atomizing a liquid into a stream of heated air, leading to rapid solvent evaporation and the formation of fine powder particles. Spray drying offers several advantages, including process simplicity, scalability, continuous operation, good reproducibility, and cost-effectiveness (Kriangkrai et al., 2021). Additionally, spray-dried powders often exhibit desirable physicochemical properties such as uniform particle size, spherical morphology, rapid solubility, and improved stability during storage. Compared to traditional liquid formulations, spray drying can also mask undesirable taste and reduce microbial contamination, thereby enhancing product acceptability (Sonsnik & Seremeta, 2015). However, the spray drying of herbal extracts is a complex process, influenced by parameters such as inlet temperature, feed rate, and extract concentration. These factors affect both powder yield and the retention of bioactive constituents, particularly heat-sensitive anti-oxidants. Therefore, optimizing spray-drying conditions is essential for producing high-quality herbal extract powders.

Response surface methodology (RSM), in conjunction with Box-Behnken design (BBD), is a robust statistical tool for process optimization. It enables evaluation of factor interactions and prediction of responses with a minimal number of experimental runs (Myers et al., 2016; Montgomery, 2017). This study aimed to optimize the extraction and spray-drying conditions for Koklan remedy formulation 3 using Box-Behnken design to maximize powder yield and preserve antioxidant activity. The effects of inlet temperature, feed rate, and decoction ratio were systematically investigated. The findings of this study are expected to support the development and scale-up of this traditional remedy into a modern dosage form.

## 2. MATERIALS AND METHODS

### 2.1 Herbal materials and Koklan remedy preparation

The dried herbal ingredients utilized in the Koklan remedy comprised *M. repandus* (Willd.) Mull. Arg., *C. buchanani* Roem. & Schult., *C. sappan* L., *P. interruptum* Opiz, *E. scaber* L., and *R. nasutus* (L.) Kurz. These herbs were sourced from and certified by Charoensuk Pharma Supply Co., Ltd., Nakhon Pathom, Thailand. They were then dried in a hot-air oven at 60°C and subsequently ground into a fine powder. The Koklan remedy was formulated according to the Herbal Product Division, Food and Drug Administration (2021). The composition included 20 g each of *M. repandus*, *C. buchanani*, *C. sappan*, and *P. interruptum*, as well as 10 g each of *E. scaber* and *R. nasutus*. The herbal mixture was decocted in water at an initial water-to-herb ratio of 20:1 and reduced to obtain the desired concentration. The decoction ratio was defined as the proportion between the initial water volume and the final extract volume. To prepare the evaporated dried extract, the decoction was concentrated using a rotary evaporator under reduced pressure to yield a solid, dry extract.

### 2.2 Spray drying process

The Koklan remedy extract was spray-dried using a Büchi B-290 mini-spray dryer (Buchi Labortechnik AG, Flawil, Switzerland). The extract was fed through a 0.7-mm nozzle, with an atomizing gas flow set at a height of 40 mm (equivalent to 473 L/h). The feed rate was maintained between 5–15% (corresponding to 2.5–5.0 mL/min). The inlet temperature ranged from 130 to 170 °C. The resulting spray-dried powder was collected in sealed bags and stored in a desiccator. The powder yield was calculated using the following equation:

$$\text{Yield (\%)} = \frac{\text{weight of spray-dried powder}}{\text{weight of herbal materials}} \times 100 \qquad (1)$$

where the weight of herbal materials refers to the total weight of raw dried herbs used to prepare the extract by decoction.

### 2.3 ABTS radical scavenging assay

The ABTS radical scavenging activity assay was adapted from the method described by Re et al. (1999). The ABTS radical cation ($ABTS^{\cdot +}$) was diluted with deionized (DI) water to achieve an absorbance of 0.70 ± 0.02 at 732 nm. A 20 µL aliquot of reconstituted Koklan remedy extract powder (0.01–1000 mg/mL) was mixed with 180 µL of the diluted $ABTS^{\cdot+}$ solution and incubated in the dark at room temperature for 6 minutes. The absorbance at 732 nm was subsequently measured using a microplate reader (BioTek Epoch with Gen 5 3.15 software, Agilent Technologies, Inc., California, USA). Antioxidant activity was calculated using the following equation:

$$ABTS^{\cdot+}\text{scavenging activity, (\%)} = \frac{Abs_{control} - (Abs_{sample} - Abs_{blank})}{Abs_{control}} \times 100 \qquad (2)$$

where $Abs_{control}$ represents the absorbance of the control, $Abs_{sample}$ is the absorbance of the Koklan remedy extract, and $Abs_{blank}$ is the absorbance of the blank. The half-maximal inhibitory concentration ($IC_{50}$) values of the Koklan remedy extract were determined by plotting the percentage of radical scavenging activity against the logarithm (log) of the final concentration of the sample (mg/mL).

### 2.4 Experimental design and optimization

The optimization of extraction and spray-drying conditions was carried out using the Box-Behnken experimental design in conjunction with RSM. The effects of the independent variables on powder yield and antioxidant activity were analyzed through analysis of variance (ANOVA). Data processing and regression model development were performed using Design-Expert version 11 software (Stat-Ease Inc., Minneapolis, USA). A three-factor, three-level Box-Behnken design was implemented, resulting in a total of 15 experimental runs (Table 1). The independent variables were inlet temperature (A), feed rate (B), and decoction ratio (C). All experimental runs were performed in triplicate to ensure reproducibility, and the average values of powder yield and ABTS $IC_{50}$ were used as response variables. The ranges of inlet temperature (130–170°C) and feed rate (5–15%) were selected based on preliminary studies aimed at producing spray-dried powder with favorable physical characteristics, acceptable yield, and retained antioxidant activity. The range of the decoction ratio (1.5–6.0) was chosen to reflect practical conditions in herbal preparation, encompassing both concentrated and diluted extracts, and to allow for the assessment of its effect on powder yield and antioxidant retention.

## 3. RESULTS AND DISCUSSION

The Koklan remedy was extracted using the decoction method, in accordance with traditional Thai preparation practices. The resulting extract was a clear, dark brown liquid with a distinctive herbal odor, characteristic of multi-herb formulations (Figure 1a). Following spray drying, the decoction was converted into a fine golden-brown powder (Figure 1b). This powder exhibited a noticeably milder aroma compared to the original decoction and reconstituted rapidly and completely upon contact with water, forming a clear brown solution. In contrast, the evaporated, dried Koklan remedy extract appeared as a dense, dark brown solid (Figure 1c), which required more time to dissolve in water than the spray-dried form. The transformation via spray drying not only enhanced the solubility and handling properties of the extract but also improved the overall product characteristics, potentially increasing patient compliance and acceptability.

(a) (b) (c)

**Figure 1.** Characteristics of Koklan remedy extract obtained by (a) the decoction method, (b) spray drying, and (c) evaporated drying

A Box-Behnken experimental design combined with RSM was employed to optimize the production process of Koklan remedy extract powder, with the objective of maximizing powder yield and preserving antioxidant activity. Three independent variables—inlet temperature, feed rate, and decoction ratio—were investigated for their effects on the two response variables. The experimental results were analyzed using ANOVA to assess the significance of each factor and to develop predictive models. Response surface plots were generated to visualize the interactions among the variables. The results and model validation are presented below, beginning with powder yield, followed by antioxidant activity, and concluding with the optimal conditions derived from the combined responses.

### 3.1 Optimization of yield

The experimental results in Table 1 show that the yield of Koklan remedy extract powder ranged from 5.92% to 11.41%, depending on inlet temperature, feed rate, and decoction ratio. The highest yield (11.41%) was achieved at a 170°C inlet temperature, a 5% feed rate, and a decoction ratio of 3.75. Conversely, the lowest yield (5.92%) occurred at a 150°C inlet temperature, a 15% feed rate, and a decoction ratio of 6.00. These results highlighted the strong influence of processing parameters on spray-drying efficiency.

**Table 1.** Box-Behnken experimental design matrix and results

| Run | Inlet temperature, A (°C) | Feed rate, B (%) | Decoction ratio (C) | Yield (%) | | ABTS $IC_{50}$ (µg/mL) | |
|---|---|---|---|---|---|---|---|
| | | | | Observed | Predicted | Observed | Predicted |
| 1 | 130 | 10 | 1.50 | 9.49 | 9.44 | 32.49 | 33.04 |
| 2 | 150 | 10 | 3.75 | 10.99 | 10.92 | 40.62 | 39.40 |
| 3 | 130 | 15 | 3.75 | 11.10 | 11.06 | 43.89 | 46.62 |
| 4 | 150 | 15 | 1.50 | 9.36 | 9.45 | 39.42 | 36.15 |
| 5 | 170 | 10 | 1.50 | 10.01 | 9.89 | 30.91 | 35.00 |
| 6 | 150 | 10 | 3.75 | 10.92 | 10.92 | 39.33 | 39.40 |
| 7 | 130 | 5 | 3.75 | 11.27 | 11.23 | 52.04 | 52.86 |
| 8 | 150 | 10 | 3.75 | 10.22 | 10.92 | 38.24 | 39.40 |
| 9 | 150 | 5 | 6.00 | 6.16 | 6.07 | 43.82 | 47.10 |
| 10 | 150 | 5 | 1.50 | 9.36 | 9.45 | 34.60 | 33.23 |
| 11 | 150 | 15 | 6.00 | 5.92 | 5.83 | 40.66 | 42.03 |
| 12 | 170 | 15 | 3.75 | 11.34 | 11.38 | 51.40 | 50.58 |
| 13 | 170 | 5 | 3.75 | 11.41 | 11.45 | 49.22 | 46.49 |
| 14 | 170 | 10 | 6.00 | 6.16 | 6.21 | 42.26 | 41.71 |
| 15 | 130 | 10 | 6.00 | 6.00 | 6.13 | 50.17 | 46.08 |
| Test1 | 170 | 15 | 3.71 | 12.04 | 11.41 | 45.09 | 50.55 |
| Test2 | 148 | 12 | 3.00 | 10.29 | 10.94 | 32.50 | 38.18 |

Regression analysis indicated that the quadratic model provided the best fit for predicting the yield of spray-dried Koklan extract. This model showed high predictive strength, with $R^2$ and adjusted $R^2$ values of 0.9933 and 0.9812, respectively—both higher than those of the linear, two-factor interaction, or cubic models. As noted by Gong et al. (2007), an $R^2$ value above 0.60 is sufficient to support the reliability of a predictive model. The polynomial equation for the response surface model describing yield is presented below:

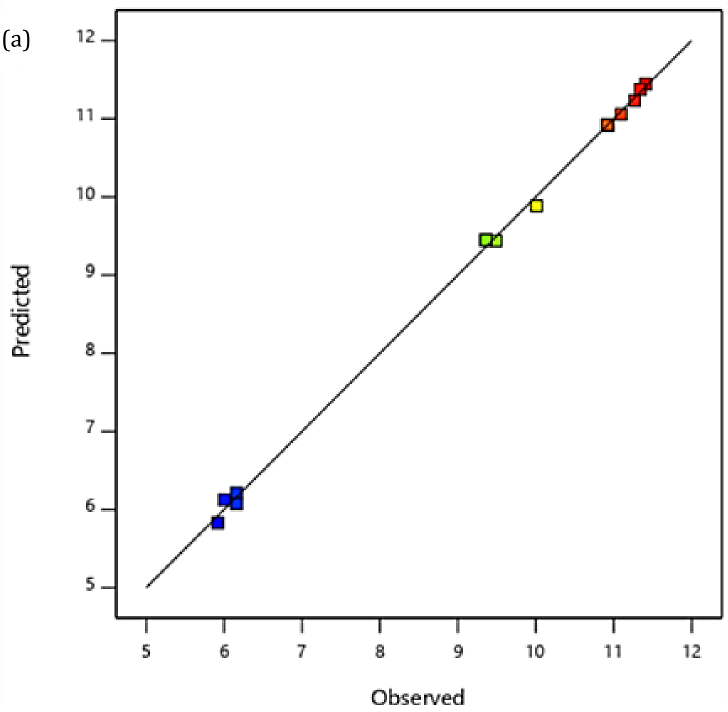
$$\text{Yield } (\%\ w/w) = 10.71+0.1328A-0.0606B-1.75C+0.0263AB-0.0906AC -0.0600BC+0.3922A^2+0.1766B^2-3.19C^2 \quad (3)$$

The ANOVA results in Table 2 confirmed that the regression model was statistically significant ($p$<0.001) for predicting yield. The lack-of-fit test, used to assess model validity, produced a $p$-value of 0.9331, indicating non-significance and thus supporting the model's adequacy. As shown in Table 1, observed values closely matched predicted ones, and the scatter plot of observed versus predicted yield (Figure 2a) displayed points tightly clustered along a straight line, further demonstrating the model's strong fit and predictive accuracy. Among the three independent variables examined, decoction ratio (C) had the most significant effect ($p$<0.001; Table 2). Yield increased with higher decoction ratios, peaking at approximately 3–4 (Figure 3b–c), after which it declined. This pattern may result from extended boiling at higher ratios: initially improving extraction of bioactive compounds but eventually causing thermal degradation, thereby reducing yield. The significance of the quadratic term $C^2$ ($p$<0.001) confirmed this nonlinear trend. Inlet temperature (A) showed no statistically significant effect on yield ($p$=0.2584), nor did feed rate (B) or the interaction terms (AB, AC, BC). However, the quadratic term for inlet temperature ($A^2$) was borderline significant ($p$=0.0508), suggesting a potential nonlinear effect and the existence of an optimum temperature range for maximizing yield. The three-dimensional response surface plots (Figure 3a–c) corroborated these findings, identifying decoction ratio as the most influential factor.

**Table 2.** ANOVA of the regression model for percentage yield of Koklan remedy extract powder

| Source | Coefficient estimate | Sum of squares | df | Standard error | Mean square | *F*-value | *P*-value |
|---|---|---|---|---|---|---|---|
| Model | 10.71 | 64.17 | 9 | 0.1701 | 7.13 | 82.12 | < 0.0001 |
| A-inlet temp | 0.1328 | 0.1411 | 1 | 0.1042 | 0.1411 | 1.63 | 0.2584 |
| B-feed rate | −0.0606 | 0.0294 | 1 | 0.1042 | 0.0294 | 0.3387 | 0.5859 |
| C-decoction | −1.75 | 24.42 | 1 | 0.1042 | 24.42 | 281.28 | < 0.0001 |
| AB | 0.0263 | 0.0028 | 1 | 0.1473 | 0.0028 | 0.0317 | 0.8656 |
| AC | −0.0906 | 0.0329 | 1 | 0.1473 | 0.0329 | 0.3784 | 0.5654 |
| BC | −0.0600 | 0.0144 | 1 | 0.1473 | 0.0144 | 0.1659 | 0.7007 |
| $A^2$ | 0.3922 | 0.5679 | 1 | 0.1533 | 0.5679 | 6.54 | 0.0508 |
| $B^2$ | 0.1766 | 0.1151 | 1 | 0.1533 | 0.1151 | 1.33 | 0.3016 |
| $C^2$ | −3.19 | 37.49 | 1 | 0.1533 | 37.49 | 431.83 | < 0.0001 |
| Residual | | 0.4341 | 5 | | 0.0868 | | |
| Lack of fit | | 0.0715 | 3 | | 0.0238 | 0.1315 | 0.9331 |
| Pure error | | 0.3626 | 2 | | 0.1813 | | |
| Cor total | | 64.61 | 14 | | | | |

(a)




(b)

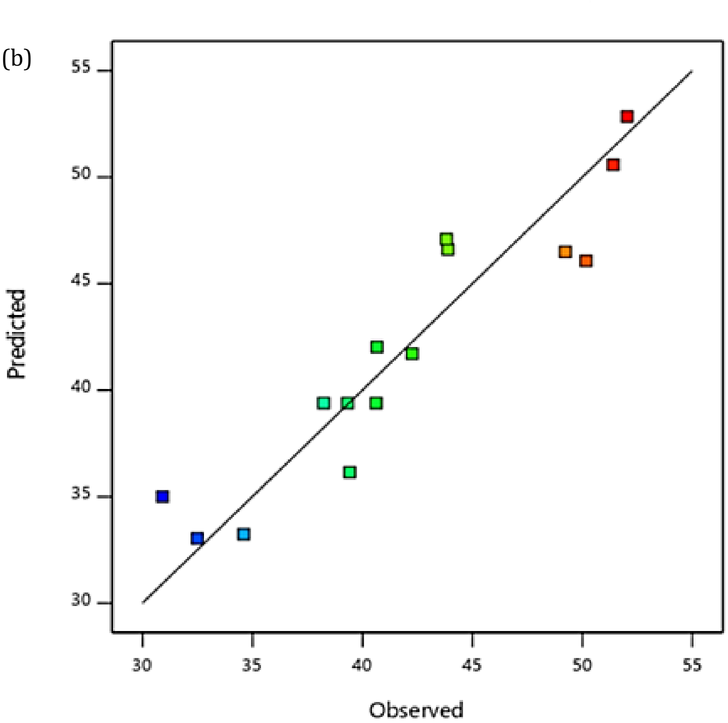



**Figure 2.** Correlation between observed and predicted values; (a) yield, (b) antioxidant activity (ABTS $IC_{50}$)

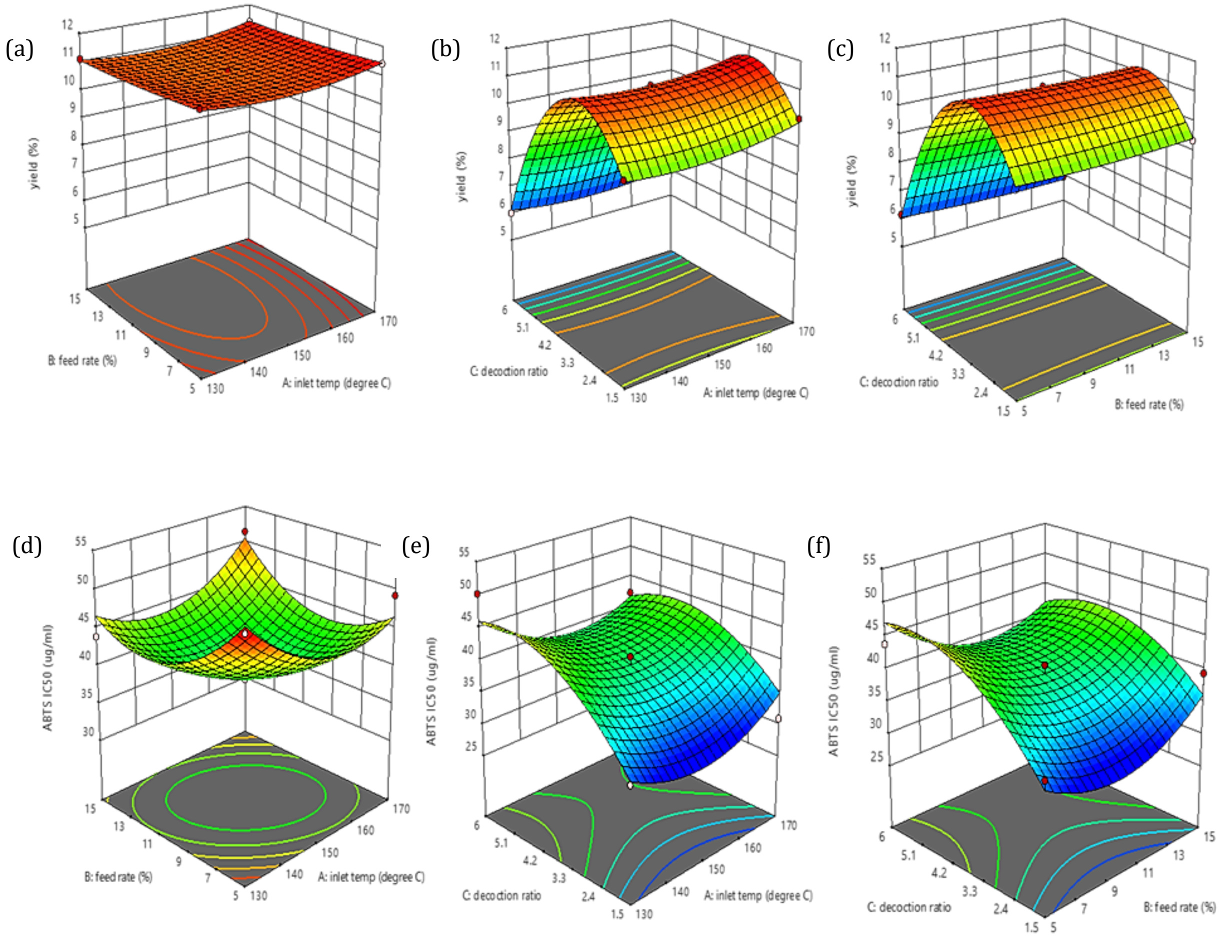



**Figure 3.** 3D surface plots represent the influence of factors on (a-c) the Koklan remedy extract powder yield and (d-f) the antioxidant activity (ABTS $IC_{50}$)
*Note*: The effect of inlet temperature (A) and feed rate (B) (a, c), the effect of inlet temperature (A) and decoction ratio (C) (b, e), and the effect of feed rate (B) and decoction ratio (C) (c, f).

## 3.2 Optimization of antioxidant activity

The antioxidant activity of Koklan remedy extract powder, determined by the ABTS radical scavenging assay and expressed as $IC_{50}$ values, was influenced by both decoction ratio and spray-drying conditions. $IC_{50}$ values ranged from 30.91 to 52.04 µg/mL, reflecting substantial variation in antioxidant capacity driven by processing parameters. The highest antioxidant activity (lowest $IC_{50}$, 30.91 µg/mL) was obtained under conditions of 170°C inlet temperature, 10% feed rate, and a 1.50 decoction ratio (Run 5). In contrast, the lowest antioxidant activity (highest $IC_{50}$, 52.04 µg/mL) occurred at a 130°C inlet temperature, a 5% feed rate, and a 3.75 decoction ratio (Run 7), as reported in Table 1. Among the regression models evaluated, the quadratic model provided the best fit for predicting antioxidant activity. This was supported by the coefficient of determination ($R^2$ = 0.8725) and adjusted $R^2$ (0.6431), indicating moderate performance in capturing variability in the response. The predictive model was expressed as a second-order polynomial equation:

$$ABTS\ IC_{50} = 39.40 - 0.6000A - 0.5387B + 4.94C + 2.58AB - 1.58AC - 2.00BC + 4.54A^2 + 5.20B^2 - 4.98C^2 \quad (4)$$

However, the overall model was not statistically significant ($p$=0.0777), suggesting that the independent variables did not exert a strong effect on antioxidant activity at the tested levels. Even so, the lack-of-fit test ($p$=0.0539) was also not significant, indicating that the model adequately represented the experimental data and was not missing key higher-order interactions (Table 3). This apparent contradiction implied that while the model reasonably approximated the observed data, additional factors or experimental variability may have contributed to the non-significant ANOVA outcome (Montgomery, 2017; Myers et al., 2016). The relatively low adjusted $R^2$ (0.6431) further indicated that some variability was not explained by the model. Whereas $R^2$ reflected overall fit, adjusted $R^2$ accounts for the number of predictors; a marked difference between them often signaled limited contribution of the included variables or omission of other influential factors (Montgomery, 2017). In herbal extracts, antioxidant activity is shaped by phytochemical stability, raw material variability, and sensitivity to environmental conditions such as heat, light, and oxidation. These biological complexities introduce variability that processing parameters alone cannot fully capture. Nonetheless, the selected factors remain scientifically meaningful and practical for process optimization.

As shown in Figure 2b, the deviation of data points from the straight line indicated a weak correlation between observed and predicted values, reinforcing the limited predictive capacity of the model for antioxidant activity. Among the tested variables, decoction ratio (C) exerted the most significant effect ($p$=0.0168), suggesting that higher decoction levels promoted the extraction of phenolic and flavonoid compounds. However, prolonged boiling or elevated inlet temperatures may cause thermal degradation of these bioactives. Notably, higher decoction ratios often improved antioxidant activity but reduced yield. This likely reflected the difference in measurement criteria: spray-dried yield depended on total solids (both active and inert compounds), whereas antioxidant activity was related to the retention of thermolabile constituents. Consequently, high antioxidant activity did not necessarily correspond to high yield. Statistical analysis further supported these findings. The quadratic terms $A^2$, $B^2$, and $C^2$ were not statistically significant ($p$-values 0.05–0.08), yet suggested possible nonlinear relationships between processing parameters and antioxidant activity (Table 3). The response surface plots (Figure 3d–f) showed that lower inlet temperatures favored better retention of antioxidant compounds. This observation is consistent with the heat sensitivity of many bioactive constituents, such as phenolics and flavonoids, which can degrade at excessively high temperatures (Shofinita et al., 2024). Conversely, very low temperatures may cause inefficient spray drying and reduce yield. Thus, identifying an optimum inlet temperature is critical for balancing antioxidant preservation with process efficiency.

**Table 3.** ANOVA of the regression model for the antioxidant activity of Koklan remedy extract powder

| Source | Coefficient estimate | Sum of squares | df | Standard error | Mean square | *F*-value | *P*-value |
|---|---|---|---|---|---|---|---|
| Model | 39.40 | 536.39 | 9 | 2.29 | 59.60 | 3.80 | 0.0777 |
| A-inlet temp | −0.6000 | 2.88 | 1 | 1.40 | 2.88 | 0.1838 | 0.6860 |
| B-feed rate | −0.5387 | 2.32 | 1 | 1.40 | 2.32 | 0.1482 | 0.7161 |
| C-decoction | 4.94 | 194.93 | 1 | 1.40 | 194.93 | 12.44 | 0.0168 |
| AB | 2.58 | 26.68 | 1 | 1.98 | 26.68 | 1.70 | 0.2488 |
| AC | −1.58 | 10.02 | 1 | 1.98 | 10.02 | 0.6392 | 0.4603 |
| BC | −2.00 | 15.92 | 1 | 1.98 | 15.92 | 1.02 | 0.3598 |
| $A^2$ | 4.54 | 75.99 | 1 | 2.06 | 75.99 | 4.85 | 0.0789 |
| $B^2$ | 5.20 | 100.00 | 1 | 2.06 | 100.00 | 6.38 | 0.0528 |
| $C^2$ | −4.98 | 91.42 | 1 | 2.06 | 91.42 | 5.83 | 0.0605 |
| Residual | | 78.36 | 5 | | 15.67 | | |
| Lack of fit | | 75.52 | 3 | | 25.17 | 17.73 | 0.0539 |
| Pure error | | 2.84 | 2 | | 1.42 | | |
| Cor total | | 614.74 | 14 | | | | |

## 3.3 Optimum condition

The optimization study showed that both yield and antioxidant activity of Koklan remedy extract powder were influenced by inlet temperature, feed rate, and decoction ratio. However, as indicated in Table 3, antioxidant activity was not well captured by the regression model, limiting its reliability for predicting this response. To assess predictive performance, a confirmation experiment (Test 1) was carried out under the conditions expected to maximize powder yield: decoction ratio 3.71, inlet temperature 170°C, and feed rate 15% (Table 1). The observed yield was 12.04%, with a prediction error of only 5.52%, demonstrating good model accuracy. In contrast, antioxidant activity showed a larger deviation, with a prediction error of 10.80%, confirming the weaker predictive power of the model for this parameter. A second validation experiment (Test 2) was then performed under a compromise condition balancing yield and antioxidant activity: inlet temperature 148°C, feed rate 12%, and decoction ratio 3.00 (Table 1). The observed yield (10.29%) and antioxidant activity (ABTS $IC_{50}$ = 32.50 µg/mL) corresponded to prediction errors of 5.90% and 14.88%, respectively. Overall, these results confirmed that the regression model was reasonably accurate for predicting powder yield, as both validation runs yielded errors below 10%. In contrast, the greater prediction error observed for antioxidant activity suggested that the model was not sufficiently robust for reliable prediction of this response. This limitation may be attributed to either unmodeled variability within the experimental process or inherent fluctuations in the raw materials used. Herbal ingredients can vary in their phytochemical composition due to differences in geographical origin, cultivation methods, harvest timing, and post-harvest handling. Although the herbs were sourced from a certified supplier, such natural variability could still influence the antioxidant content of the final product. Furthermore, the findings supported the notion that, while increasing the decoction ratio can enhance antioxidant activity—likely due to improved extraction of bioactive constituents—it may also reduce the final yield because of prolonged boiling and potential degradation of thermolabile compounds. Therefore, the careful selection of an appropriate decoction ratio is essential to achieve a balance between maximizing yield and preserving bioactivity in the final product. Nevertheless, despite the limited predictive accuracy for antioxidant activity, the model remains a useful tool for guiding initial process development. The identified conditions provide a rational foundation for further optimization, formulation refinement, and future scale-up of Koklan remedy extract production.

## 4. CONCLUSION

This study successfully applied Box-Behnken design and RSM to optimize the production process of Koklan remedy extract powder. The results demonstrated that decoction ratio, inlet temperature, and feed rate influenced the powder yield and antioxidant activity. Among these, decoction ratio showed the strongest effect on both responses. The optimum condition identified was 170°C inlet temperature, 15% feed rate, and 3.71 decoction ratio, which provided a maximized yield. Validation experiments confirmed the model's accuracy in predicting powder yield but demonstrated lower reliability for antioxidant activity, likely due to variability in the quality of herbal materials. Nevertheless, the optimized spray-drying conditions enhanced the feasibility of producing the Koklan remedy in powder form. This research supports the practical application of RSM for process optimization and contributes to the development and standardization of traditional herbal remedies in modern pharmaceutical formulations.

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