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Optimization of Solvent Mixtures and Maceration Method Using Simplex Centroid Design for Phenolic Extraction and Radical Scavenging Activity in *Amomum compactum* Fruit

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ABSTRACT

Phenolic compounds are valued for their antioxidant, anti-inflammatory, and antimicrobial properties, making them crucial in food, pharmaceutical, and nutraceutical industries. This study aimed to optimize phenolic antioxidant extraction from *Amomum compactum* fruit using a simplex-centroid design with water, methanol, ethanol, and ethyl acetate as solvents. The maceration process, applied to 15 solvent combinations, yielded total phenolic content (TPC) values ranging from 0.045 to 0.346 mg GAE/g DW and DPPH radical scavenging activities from 0.001 to 0.197 µmol TE/g DW. The optimal solvent mixture, achieving a desirability score of 0.933, was a 50:50 mixture of water and methanol, resulting in a TPC of 0.333 mg GAE/g DW and DPPH antioxidant activity of 0.179 µmol TE/g DW. The high polarity of methanol, particularly in combination with water, enhances the extraction of phenolic and antioxidant compounds. In contrast, ethyl acetate demonstrated a lower efficiency, with the lowest TPC (0.045 mg GAE/g DW) and DPPH activity (0.001 µmol TE/g DW) observed in combinations containing this solvent. These findings underscore the critical role of solvent polarity and interactions in optimizing the extraction of bioactive compounds, providing valuable insights for applications in food and pharmaceutical industries.

Keywords: *Amomum compactum*, Phenolic extraction, Solvent optimization, Radical-scavenging activity, Maceration method.

Introduction

Extraction of bioactive compounds from plant materials, particularly phenolics, is critical because of their well-established antioxidant, anti-inflammatory, and antimicrobial properties. These properties make phenolics valuable across various industries, including food, pharmaceuticals, and nutraceuticals.[1] Phenolic compounds, recognized for their radical scavenging activity, possess hydroxyl groups that enhance their ability to neutralize free radicals.[2,3] The efficiency of phenolic extraction is primarily influenced by the selection of solvent and extraction methodology.[4–6] Among the various extraction methodologies, solvent-based maceration is widely utilized for its simplicity and efficacy, particularly in the extraction of thermolabile compounds.[7] Nevertheless, the identification of the optimal solvent or solvent combination for the extraction of phenolic compounds from specific plant species, such as *Amomum compactum* fruit, remains a significant challenge.

A. compactum, commonly known as Java cardamom, is a member of the Zingiberaceae family and is notable for its diverse phytochemical composition and pharmacological activities. This species contains a range of bioactive compounds, including phenolics, flavonoids, terpenoids, and essential oils, which contribute to its antioxidant, anti-inflammatory, and antimicrobial properties.[8] For instance, research has demonstrated that aqueous extraction of *A. compactum* yields substantial quantities of phenolic and flavonoid compounds, which are correlated with high antioxidant activity.[9] Its diverse bioactive profile of *A. compactum* demonstrates its potential for pharmaceutical and nutraceutical applications; however, optimizing its extraction methods remains critical to fully utilize these properties.

Polar solvents such as methanol and ethanol have been frequently reported to enhance phenolic extraction due to their ability to dissolve polar bioactive compounds.[10] Combining these solvents with water further improves the solubility and yield of phenolics, as shown in previous studies.[11] Conversely, less polar solvents, like ethyl acetate, have been found less effective at solubilizing phenolic compounds, making them suboptimal for extraction.[12] Despite progress in solvent use, the optimal solvent mixture for extracting phenolics from *A. compactum* has yet to be thoroughly investigated, highlighting a critical gap in optimizing extraction for this underutilized plant.

Recent advancements in extraction techniques have focused on the optimization of solvent mixtures through statistical methodologies such as the Simplex Centroid Design (SCD). This approach systematically evaluates various solvent combinations to identify the optimal ratios for maximizing phenolic content and antioxidant activity.[13] Research has demonstrated the efficacy of SCD across diverse plant systems. For instance, Aazza (2021) optimized polyphenol extraction from *Cannabis sativa* waste utilizing ethanol, methanol, and water mixtures, attaining high total phenolic content (TPC) and antioxidant activity with a combination of 75% ethanol, 12.5% methanol, and 12.5% water.[14] Similarly, Nurcholis et al. (2023) optimized solvents for extracting

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phenolic antioxidants from *Curcuma xanthorrhiza*, identifying a ternary combination of water, acetone, and methanol (40.9:30.7:28.4%) as the most efficacious.[15] Additional applications, such as those involving *Lavandula stoechas*, have demonstrated that ternary solvent combinations enhance both phenolic and flavonoid content.[16] For *A. compactum*, the utilization of SCD in conjunction with maceration presents a promising methodology for refining solvent mixtures and enhancing extraction efficiency. The statistical approach of SCD facilitates detailed interaction analysis between solvents, as demonstrated in *Justicia gendarussa* and Jambolan fruit (*Syzygium cumini*).[17,18] Nevertheless, the application of this design to *A. compactum* remains limited, presenting an opportunity for further investigation to optimize phenolic yields and antioxidant properties.

This investigation seeks to address this research gap by optimizing solvent mixtures for the extraction of phenolic compounds from *A. compactum* fruit utilizing maceration and the SCD. The primary objective is to identify the optimal combination of water, methanol, ethanol, and ethyl acetate that maximizes total phenolic content (TPC) and radical scavenging activity. Achieving this optimization not only enhances extraction efficiency but also provides valuable insights into solvent selection for phenolic extraction, which may have broader applications in the food, pharmaceutical, and nutraceutical industries.

Materials and Methods

Sample Preparation and Extraction of Cardamom Fruits

Cardamom fruit, dried and sized to 50 mesh, was obtained from the Tropical Biopharmaca Research Center, IPB University, Bogor, Indonesia. A total of 300 g of dried powder was divided into 15 portions. Extraction was conducted via maceration utilizing ethanol, methanol, and ethyl acetate as solvents, based on a modified method from.[13] The solvent combinations utilized for extraction are delineated in Table 1. A total of 15 distinct extraction combinations were evaluated. Each 20 g aliquot of powdered sample underwent extraction with 100 mL of solvent and was subjected to maceration in a dark environment for 48 hours. Subsequently, the filtrates were passed through filter paper, and the solvents were removed via rotary evaporation (Model G3, Heidolph Instruments, Germany). The resultant dried extracts were weighed and stored in sealed containers for subsequent analyses, encompassing total phenol content and antioxidant activity.

Determination of Total Phenolic Content

The total phenolic content of the extracts was determined utilizing a spectrophotometric assay based on the Folin-Ciocalteu reagent.[19] The test sample was dissolved in ethanol to create a 1 mg/mL solution. In each well of a 96-well microplate, 10 µL of the sample was combined with 160 µL of distilled water. The mixture was subsequently supplemented with 10 µL of 10% Folin-Ciocalteu reagent and 20 µL of 10% sodium carbonate. Following incubation at room temperature for 30 minutes, the absorbance was measured at 750 nm utilizing a microplate reader (SPECTROstar Nano, BMG LABTECH, Ortenberg, Germany). A gallic acid standard curve was employed to quantify the total phenolic content, with results expressed as milligrams of gallic acid equivalents per gram of dry weight (mg GAE/g DW).

Antioxidant Activity Assay Using DPPH

Antioxidant activity was evaluated utilizing the DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging assay, in accordance with the methodology delineated by Seno et al. (2022), with modifications.[2] To conduct the assay, each extract (10 mg) was dissolved in dimethyl sulfoxide (DMSO) (1000 µL). A microplate received 200 µL of the extract solution, followed by 100 µL of 125 µM DPPH in ethanol. Following homogenization, the mixture was incubated for 30 minutes at 37°C. Trolox served as the positive control, with concentrations ranging from 20–120 µmol/L, while ethanol functioned as the negative control. A microplate reader (SPECTROstar Nano, BMG LABTECH, Ortenberg, Germany) measured absorbance at 517 nm. The antioxidant activity was expressed as µmol Trolox equivalents per gram of dry weight (µmol TE/g DW).

Data Analysis

Design-Expert software version 23.1.4 (Stat-Ease, Inc., Minneapolis, MN, USA, 2023) was used to develop solvent combinations, analyze data, fit models, and optimize solvent ratios, resulting in predictive equations. The optimal extraction conditions were chosen based on the highest desirability score.

Results and Discussion

Influence of solvent maceration on the total phenolic content (TPC)

The extraction of phenolic compounds from *A. compactum* fruit was optimized using different solvent mixtures based on a simplex-centroid design (Table 1). Phenolic compounds, abundant in plants and valued for their antioxidant, anti-inflammatory, and antimicrobial properties, have hydroxyl groups attached to aromatic rings, necessitating efficient extraction for health-related uses.[1] The TPC in this study varied from 0.045 to 0.346 mg GAE/g DW, with the highest yield (0.346 mg GAE/g DW) achieved using a 50:50 methanol-ethanol mixture (Run 6), highlighting the synergistic effect. Methanol, with a higher dielectric constant (32.7) than ethanol (24.3), is more effective at dissolving highly polar phenolic compounds due to its greater polarity.[10] Conversely, ethyl acetate's lower polarity constrains its capacity to extract phenolics efficiently, as evidenced by the lowest TPC value of 0.045 mg GAE/g DW observed in Run 11.[12] Similarly, it was found that less polar solvents, like ethyl acetate, are less efficient than polar solvents, such as methanol and ethanol, which yield higher total phenolic content and antioxidant activity.[20,21] Methanol alone (Run 5) also exhibited significant extraction efficiency, yielding 0.223 mg GAE/g DW, further corroborating the efficacy of highly polar solvents in maximizing phenolic extraction. This aligns with the findings of Galanakis et al. (2013), who note the limitations of using less polar solvents like ethyl acetate.[22] The mechanism of phenolic extraction involves solvents disrupting hydrogen bonds in plant cell walls, thereby facilitating the release of phenolic compounds into the solvent.[23] This investigation demonstrates that solvent polarity plays a critical role in optimizing phenolic extraction from *A. compactum*, with methanol-ethanol mixtures yielding superior extraction outcomes, which aligns with previous research findings and indicates their potential utility in food, pharmaceutical, and nutraceutical applications.

Influence of solvent maceration on the radical scavenging activity

The DPPH assay revealed significant variations in the radical scavenging activity of *A. compactum* extracts across different solvent combinations, with values ranging from 0.001 to 0.197 µmol TE/g DW, as presented in Table 1. The highest antioxidant activity (0.197 µmol TE/g DW) was observed in Run 7, which utilized an equimolar mixture of water and ethanol. This finding suggests that the balanced polarity of these solvents facilitates the extraction of compounds with antioxidant properties. These results are consistent with previous research demonstrating that solvents with polar characteristics, such as water and ethanol, enhance the extraction of phenolics and flavonoids, which are known to contribute to antioxidant activity.[11] Conversely, Run 4, which utilized a combination of water, ethanol, and ethyl acetate, yielded the minimum DPPH value of 0.001 µmol TE/g DW. The incorporation of ethyl acetate, a solvent with lower polarity, likely reduced the extraction's efficacy, as this solvent generally exhibits diminished capacity for dissolving phenolic compounds.[22] Run 6, which utilized a 1:1 blend of methanol and ethanol, also demonstrated significant antioxidant properties (0.182 µmol TE/g DW). This observation supports the hypothesis that combining polar solvents enhances the extraction of phenolic compounds, as both methanol and ethanol possess the capacity to disrupt plant cell walls and facilitate the release of bioactive substances.[23] These findings are consistent with research conducted by Meneses et al. (2013),[20] which demonstrated that polar solvent mixtures enhance the extraction of antioxidant phenolics. The findings elucidate the significance of solvent polarity in optimizing the

extraction of antioxidants from *A. compactum*. Mixtures of water-ethanol and methanol-ethanol exhibited the highest efficacy, whereas the incorporation of solvents with lower polarity, such as ethyl acetate, resulted in a diminished antioxidant yie

Table 1: Solvent mixture from simplex-centroid design and results for total phenolic content and radical scavenging activity responses

Run	Solvents				Responses	
	(A) Water	(B) Ethyl acetate	(C) Methanol	(D) Ethanol	TPC (mg GAE/g DW)	DPPH (µmol TE/g DW)
1	25	25	25	25	0.249	0.065
2	-	50	-	50	0.086	0.051
3	-	33.3	33.3	33.3	0.142	0.089
4	33.3	33.3	-	33.3	0.192	0.001
5	-	-	100	-	0.223	0.091
6	50	-	50	-	0.346	0.182
7	50	-	-	50	0.267	0.197
8	-	-	-	100	0.109	0.111
9	100	-	-	-	0.184	0.075
10	-	50	50	-	0.194	0.024
11	-	-	50	50	0.045	0.028
12	33.3	-	33.3	33.3	0.241	0.087
13	50	50	-	-	0.154	0.089
14	-	100	-	-	0.048	0.134
15	33.3	33.3	33.3	-	0.191	0.024

Model fitting for TPC and DPPH antioxidant activity

Statistical analysis utilizing Analysis of Variance (ANOVA) was conducted on Total Phenolic Content (TPC) and DPPH radical scavenging activity, employing a quadratic model for TPC and a special cubic model for DPPH, as presented in Table 2. The TPC quadratic model demonstrated statistical significance, with an F-value of 7.89 and a p-value of 0.0175, indicating its capacity to account for 93.42% of TPC variation, as evidenced by the R^2 value. The adjusted R^2 of 0.8159 further corroborates the model's reliability for generating accurate predictions. Conversely, the DPPH special cubic model exhibited a lower F-value of 2.95 and a non-significant p-value of 0.4299, suggesting its inadequacy in elucidating the observed antioxidant activity variation. Despite a high R^2 value of 0.9745, the adjusted R^2 of 0.6437 indicates potential model overfitting, underscoring the necessity for further optimization to enhance its predictive accuracy for DPPH radical scavenging activity in *A. compactum* extracts. In conclusion, while the TPC quadratic model demonstrates robustness, the DPPH model requires refinement to improve its performance.

To evaluate the impact of various solvents (water, methanol, ethanol, and ethyl acetate) on the total phenolic content (TPC) in fruit extracts of *A. compactum*, a quadratic model was constructed. The model's coded equation is presented in Equation 1:

$$TPC = 0.1852A + 0.0462B + 0.2216C + 0.1019D + 0.0960AB + 0.5146AC + 0.5275AD + 0.2277BC + 0.1266BD - 0.3884CD \quad (1)$$

Where A = water, B = ethyl acetate, C = methanol, and D = ethanol.

The quadratic model demonstrated that methanol exhibited the strongest positive influence (+0.2216) on phenolic extraction, followed by water (+0.1852) and ethanol (+0.1019). Ethyl acetate displayed the least impact (+0.0462), indicating its limited efficacy in TPC extraction. Significant positive interactions were observed between methanol and water (AC, +0.5146) and ethanol and water (AD, +0.5275), highlighting the effectiveness of polar solvent combinations for extracting phenolic compounds. In contrast, methanol and ethanol exhibited negative interaction effects (CD, -0.3884), suggesting their combination did not enhance phenolic extraction. The contour plot (Figure 1) elucidated these solvent interactions, illustrating that higher proportions of methanol and water yielded the highest TPC values, while the less polar ethyl acetate resulted in lower TPC values. This observation confirms the preference of polar solvents for extracting predominantly polar phenolic compounds. The quadratic model underscores the significance of solvent polarity and combinations in maximizing phenolic extraction from *A. compactum* fruit.

The special cubic model was employed by researchers to assess the effects of water, methanol, ethanol, and ethyl acetate on the DPPH radical scavenging activity in *A. compactum* extracts. Equation 2 represents the coded equation of this model:

$$DPPH = 0.0755A + 0.1346B + 0.0913C + 0.1118D - 0.0763AB + 0.3819AC + 0.3989AD - 0.3671BC - 0.3009BD - 0.3075CD - 1.61ABC - 2.65ABD - 1.29ACD + 2.57BCD \quad (2)$$

Where A = water, B = ethyl acetate, C = methanol, and D = ethanol.

The special cubic model revealed that ethanol exhibited the strongest positive linear impact on DPPH activity (+0.1118), with ethyl acetate (+0.1346) and methanol (+0.0913) following subsequently. Synergistic effects were observed in the interactions between water and ethanol (AD, +0.3989) and water and methanol (AC, +0.3819), enhancing antioxidant extraction. A notable cubic interaction among ethanol, ethyl acetate, and methanol (BCD, +2.57) indicated a substantial synergistic effect when these solvents were combined. However, certain solvent pairings, such as methanol with ethyl acetate (BC, -0.3671) and ethanol with methanol (CD, -0.3075), demonstrated negative interactions, reducing antioxidant extraction efficiency. The special cubic interactions (ABC, ABD, and ACD) also showed negative contributions, suggesting a decrease in DPPH radical scavenging activity when water, ethyl acetate, and methanol were utilized in combination.

Table 2: ANOVA results for TPC and DPPH responses

	TPC	DPPH
	Quadratic model	Special Cubic model
F	7.89	2.95
p	0.0175	0.4299
R^2	0.9342	0.9745
Adjusted R^2	0.8159	0.6437

F = F-value; p = p-value; R^2 = Coefficient of determination; Adjusted R^2 = Adjusted coefficient of determination; TPC = total phenolic content; DPPH = 2,2-diphenyl-1-picrylhydrazyl

Figure 2, a contour plot, visually corroborated these findings by depicting the impact of various solvent mixtures on DPPH radical scavenging activity. The highest DPPH values were associated with greater proportions of ethanol and ethyl acetate, while water played a moderately positive role. Conversely, lower DPPH values were linked to solvent combinations involving methanol and ethyl acetate, underscoring their negative interaction. Despite its lower polarity, ethyl acetate demonstrated a significant positive effect on antioxidant activity, potentially due to its capacity to extract specific bioactive compounds that contribute to radical scavenging.

The special cubic model emphasized the significance of solvent interactions in maximizing the extraction of antioxidant compounds from *A. compactum* fruit. Ethanol, utilized alone or in combination with water or ethyl acetate, proved most effective in enhancing DPPH radical scavenging activity. Conversely, combinations involving methanol and ethyl acetate were found to be less efficacious.

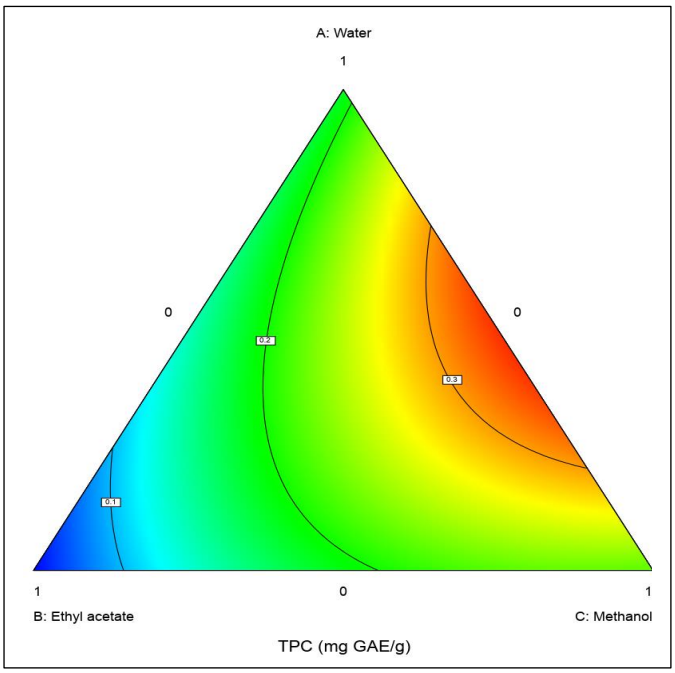

Figure 1: Contour graph showing the predicted total phenolic content (TPC) for maceration using solvent optimization with simplex-centroid design for *A. compactum* fruit. D, ethanol.

Optimization Solution for Total Phenolic Content (TPC) and DPPH Antioxidant Activity in A. compactum Fruit

Research on optimizing solvent mixtures for extracting total phenolic content (TPC) and DPPH antioxidant activity from Amomum compactum fruit demonstrated that methanol-water combinations were most efficacious. The highest desirability score of 0.933 was achieved using a water-methanol mixture, resulting in a predicted TPC of 0.333 mg GAE/g DW and DPPH activity of 0.179 µmol TE/g DW. These findings are congruent with previous studies, including Rajauria et al. (2013),[24] who ascertained that a 60% methanol extract from *Irish brown* seaweed yielded the highest phenolic content and antioxidant activity, and Moayyed et al. (2023),[25] who identified a 50:50 methanol-water mixture as optimal for phenolic extraction in burdock root. The efficacy of methanol can be attributed to its polarity, which enhances phenolic solubilization. This is further corroborated by Sarikurkcu et al. (2015) and Namvar et al. (2018),[26,27] who observed strong correlations between phenolic content and antioxidant activity in methanol extracts of *Clinopodium vulgare*. Additional comparative studies, such as those conducted by Li et al. (2009) and Chua et al. (2014),[28,29] demonstrate methanol's superiority, with methanol extracts exhibiting significantly higher phenolic content and antioxidant activity compared to water extracts. These results underscore the significance of methanol-water mixtures in maximizing TPC and DPPH activity, highlighting the crucial role of solvent selection in the extraction of phenolic compounds.

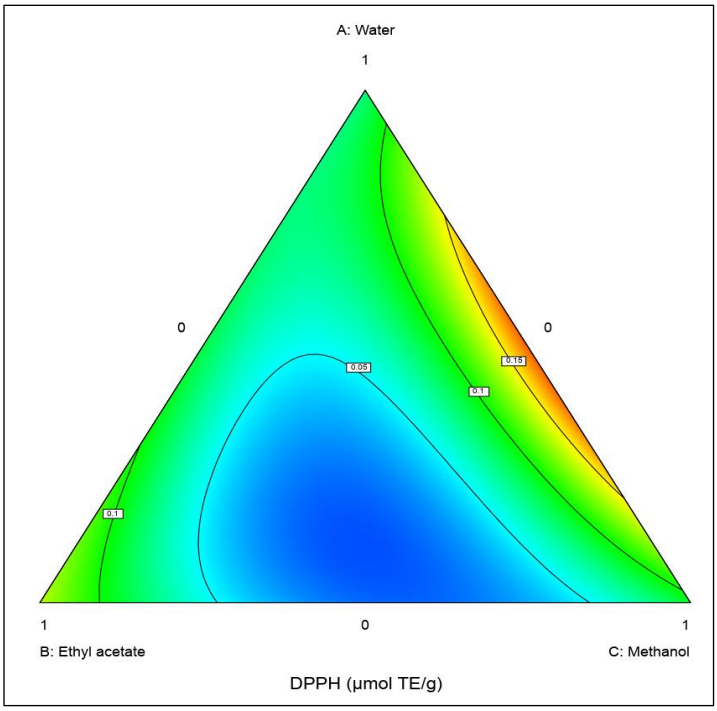

Figure 2: Contour graph depicting the predicted antioxidant DPPH maceration in solvents, optimized using a simplex-centroid design for *A. compactum* fruit. D, ethanol.

Conclusions

The investigation demonstrates the significant potential of *A. compactum* fruit as a substantial source of phenolic compounds and antioxidants, with optimal extraction outcomes achieved utilizing an equimolar mixture of water and methanol. These findings underscore the critical importance of solvent polarity and synergistic effects in enhancing total phenolic content and antioxidant activity, providing valuable insights for applications in food, pharmaceutical, and nutraceutical industries. Further research should explore the scale-up of the extraction process and examine additional bioactive compounds in *A. compactum* to fully elucidate its therapeutic properties. Furthermore, the incorporation of advanced extraction methodologies, such as ultrasound-assisted or supercritical fluid extraction, in conjunction with the simplex-centroid design, could enhance the optimization process and increase yield and efficiency, establishing a foundation for industrial applications.

Conflicts of Interest

The investigators affirm the absence of any potential conflicts of interest pertaining to this research.

Authors' Declaration

The authors hereby certify that the research presented in this manuscript is original and has not been disseminated in any other publication. Additionally, they explicitly acknowledge their complete accountability for any potential claims stemming from the content contained within this article.

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