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D-Optimal Mixture Design in Sonication-Maceration Solvent Extraction of Total Phenolic and Antibacterial Activity from *Acanthus ilicifolius* Leaves

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ABSTRACT

Acanthus ilicifolius is a widely recognized traditional medical herb in Indonesia. The objective of this study is to determine the optimal combination of solvents (water, ethanol, and acetone) for the extraction yield, total phenolic content, and antibacterial activity from *A. ilicifolius* leaves. The sonication-maceration solvent extraction was employed to acquire *Acanthus ilicifolius* leaves extract yield, phenolic content and antibacterial activity. Total phenolic content (TPC) was calculated using the Folin–Ciocalteu colorimetric method. The agar disk diffusion method was used to test the extracts for antibacterial activity against *Staphylococcus aureus*. The extraction method was optimized, the experimental data was modeled, and the design of experiments were all carried out using a D-optimal mixture design. The maximum extraction yield (4.10%) was reached by water-acetone extract. The ethanol-acetone, water-ethanol, water-acetone, and water-ethanol-acetone (41.67-16.66-41.67%) extracts were the highest TPC with values of 10.09, 10.13, 10.42 and 10.42 mg GAE/g dry weight, respectively. Finally, the optimum zone inhibition against *S. aureus* (2.25 mm) was showed by water-ethanol-acetone (16.67-66.66-16.67%) extract. The ideal conditions based on D-optimal mixture design were highly accurate at 61% attractiveness with a mixed solvent of water (49.52%) and ethanol (50.48%), predicting extraction yield, TPC, and antibacterial activity of 2.67%, 7.86 mg GAE/g DW, and 1.49 mm, respectively. Results showed the water-ethanol mixture were the best solvent in the sonication-maceration extraction for antibacterial properties of phenolic compounds, and extraction yield from *A. ilicifolius* leaves.

Keywords: *Acanthus ilicifolius*, antibacterial activity, extraction, maceration, solvents, sonication, total phenolic content

Introduction

Acanthus ilicifolius, also referred to as "jeruju" in Indonesia, is a widely recognized traditional medicinal herb in Indonesia. Historically, this botanical specimen has been employed for its medicinal properties in the treatment of several ailments, including coughs, bloating, stomach ache, rheumatism, hypertension, pruritus, dental pain and gingivitis, hepatic disorders, toxicosis, menstrual disorders, and seborrheic dermatitis.[1] Pharmacological investigations have additionally demonstrated the considerable potential of the plant as a therapeutic agent. According to reports, the aqueous extract of the plant has been found to possess antioxidant effects due to the presence of polysaccharides.[2] The utilization of in silico methodologies has demonstrated that the constituents present in *A. ilicifolius* possess the ability to operate as antibacterial agents against multidrug-resistant bacteria.[3]

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The antimicrobial capabilities of methanol and chloroform extracts were demonstrated through in vitro investigations, indicating its potential as antibacterial agents. [4,5] There are several additional pharmacological features associated with the substance, including its hepatoprotective, anticancer, and antidiabetic effects, which are believed to be mediated through its mechanism as a glucosidase inhibitor.[6–9]

Significant amounts of bioactive chemicals can be extracted from *A. ilicifolius*.[6,10] It is composed of phenolic compounds like coumaric acids, for example.[11] Phenolic compounds are widely recognized in the food sector for their bio preservation properties, which encompass both antibacterial and antioxidant activities.[12] Moreover, they are increasingly being explored as a viable substitute for synthetic additives.[13,14] The extraction of these chemicals from food is an essential process in the isolation and purification of bioactive constituents. Nonetheless, the process is subject to various factors such as the choice of extraction solvents, the ratio of sample to solvent, the duration and method of extraction, as well as the physical and chemical characteristics of the sample matrix.[15–17]

The existing research does not present a consensus regarding a singular, effective standard extraction procedure or the optimal extraction solvent. Multiple studies have found that solid-liquid extraction employing various solvents is the most efficient method, with solvents of higher polarity often exhibiting enhanced solubility of polyphenols in the extraction process.[18] In a variety of extraction techniques, isolated solvents are employed, which have been found to have suboptimal extraction outcomes. In instances of this nature, the utilization of solvent mixes is advantageous, including a range of

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compositions including binary, ternary, and multi-component combinations.[19] In addition, the utilization of a mixed solvent provides the advantage of varying polarity, hence facilitating the extraction of phenolic compounds with varying degrees of polarity.[20] Extensive research has been conducted on the impact of solvent type on the extraction efficiency of antibacterial phenolic compounds from various source materials. One of the approaches to optimize the mixed solvent for extraction is the D-optimal design. This mathematical methodology was used to optimize the mixture, which reduced the number of formulas by maximizing the determinant of the information matrix. The advantages of using a D-optimal design in optimized solvent extraction are a smaller number of runs and not require a long time.[21] D-optimal mixture design has been conducted in optimization of functional drink that enriched with *Moringa oleifera* leaves and formulation of hard candy with antiviral herbal extracts.[22,23] However, there is a limited amount of research available on the extraction of antibacterial phenolic compounds from *A. ilicifolius*. To the best of current knowledge, there is a lack of research conducted on the extraction of antibacterial phenolic compounds from *A. ilicifolius* using solvents. Limited research has been conducted on the specific extraction of antibacterial activity from this raw material utilizing the soxhlet extraction method.[4,5]

Based on the authors' understanding, there is a lack of research pertaining to the utilization of mathematical methodologies in optimizing solvent combinations for the purpose of producing phenolic-rich extracts with antibacterial properties from *A. ilicifolius*. Therefore, the objective of this study is to determine the optimal combination of solvents (water, ethanol, and acetone) for the extraction yield, total phenolic content, and antibacterial activity from *A. ilicifolius* leaves using D-optimal mixture design.

Materials and Methods

Plant preparation

The *A. ilicifolius* leaves (BMK0270102016) were collected from Tropical Biopharmaca Research Center, IPB University, Bogor, Indonesia in July 2023. Leaves were cleaned using flowing water. Subsequently, the samples underwent a drying process in an oven for a duration of two days at a temperature of 40°C, until a stable weight was achieved. Following this, the samples were subjected to milling to obtain a powdered form (80 mesh), in preparation for the extraction process.

D-Optimal design and extraction

As indicated in Table 1, the solvent extraction process utilized a D-optimal design that involved combinations of water, ethanol pro analysis (Merck, Germany), and acetone pro analysis (Merck, Germany). These combinations were developed using the Design-Expert tool, specifically version 11.0. The examination of all components in the combination spanned from 0% to 100%, and the most suitable model was chosen for each response. The data answers were subsequently subjected to statistical analysis using Design-Expert software version 11.0 (Stat-Ease Inc., Minneapolis, USA). The extraction of samples was conducted using sonication-maceration techniques, using previously established methodologies with minor adjustments.[15] To provide a concise overview, the experimental procedure involved the mixing of 30 g of the sample with 150 mL of solvent, as specified in Table 1. The combination underwent sonication (Decon F5 Major, Decon Laboratories, US) for a duration of 30 minutes, followed by maceration for a period of 3 h in a water bath shaker (DAIHAN WiseBath, South Korea) maintained at a temperature of 30°C. Subsequently, the solution underwent filtration and concentration via a rotary evaporator (specifically, the Hahnvapor HS-2005V model manufactured by Hahnshin Scientific). The determination of the extract yield was conducted, followed by the utilization of the extract for the analysis of total phenolics and assessment of its antibacterial activity.

Measurement of total phenolic content (TPC)

The analysis of total phenolic content (TPC) was conducted using the methodology established by Calvindi *et al.* [24] with several changes. Furthermore, a volume of 20 µL of the sample extract with a concentration of 1000 ppm was introduced into a 96-well microplate. Subsequently, 120 µL of Folin–Ciocalteu reagent (Merck, Germany) with a concentration of 10% was added to the microplate. The microplate was then transferred to a dark room and left undisturbed for a duration of 5 min. Subsequently, a volume of 80 µL of a sodium carbonate (Na_2CO_3) (Merck, Germany) solution with a concentration of 10% was introduced into the sample. The resulting combination was then subjected to another incubation period of 30 min under the same conditions. The measurement of absorbance was conducted using a microplate reader (Epoch BioTek, USA) at a specific wavelength of 750 nm. The measurement of TPC in a sample was expressed in milligrams of gallic acid equivalent (GAE) per gram of dry weight (DW) using a gallic acid standard (SRL Ltd., India) variation ranging from 7.81 to 1000 ppm. Each sample necessitates triplicate analysis.

Measurement of antibacterial activity

The agar-disc diffusion experiment was employed to assess the antibacterial property.[25] The bacterial inoculum of *Staphylococcus aureus* (SAeureus AtCC 6538) was introduced into the tryptic soy agar (TSA) medium using a loop needle. Subsequently, sterile paper discs with a diameter of 6 mm, impregnated with extract samples (10 µL) at a concentration of 15% (v/v) in DMSO 20%, were placed on the surface of the inoculated agar. Following a 24-hour incubation period at a temperature of 37°C, the diameter of the zone of inhibition (excluding the diameter of the discs) was measured. Chloramphenicol (KalbeFarma, Indonesia) was used as a positive control, and DMSO was used as a negative control using the same procedure.

Statistical analysis

In order to design and analyze the results of the experiments, we used the Design-Expert application (11.0 edition, State-Ease Inc., MN, USA), including analysis of variance (ANOVA), mathematical model selection, contour plot, and optimization formula. The PerformanceAnalytics package in R Studio was used to generate the Pearson correlation coefficients.

Results and Discussion

Table 1 displays the observed responses of extraction yield (EY), total phenolic content (TPC), and inhibition zone (IZ) against *S. aureus* for each solvent mixture used in the D-optimal mixture design experiment.

Table 2 shows the ANOVA results for the EY, TPC, and IZ. The best mathematical model for determining the parameters of interest (EY, TPC, and IZ) was chosen through analysis of variance with 95% confidence.[26] The ANOVA results presented in Table 2 enabled the generation of a trancing plot contour (Figure 1) that depicted the EY, TPC, and IZ values as a function of solvent properties. Contour plot vertices represent the response value, and triangle edges indicate concentration, which represent individual components and their binary and ternary mixtures, respectively.[27] The results show no significance for the model in all responses studied ($p > 0.05$). However, the R^2 value of the three models indicates that the data distribution can be trusted, with a value above 0.60.[28–30] To evaluate the sufficiency of the experimental and theoretical outcomes, adjusted R^2 was used.[31] Adjusted R^2 compared with R^2 value is not compatible in all responses studied, since the difference was calculated as > 0.2. Since the computed dissimilarity between adjusted R^2 and R^2 value is > 0.2, they are incompatible in all investigated responses.[32]

Extraction yields

The results obtained for the yield extracted from *A. ilicifolius* using various solvents ranged from 1.30% to 4.10% (Table 1). The contour plot depicted in Figure 1A illustrates that the mixture of solvents, especially water-acetone and ethanol-acetone, has a greater capacity for extracting yield compared to the isolated solvent.

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Table 1: Solvent mixtures used in the D-optimal design and their corresponding results obtained for extraction yield, total phenolic content, and inhibition zones of *A. ilicifolius*

Run	Solvent mixtures (%)			Responses		
	A: Water	B: Ethanol	C: Acetone	EY	TPC	IZ
1	16.67	16.67	66.66	1.30	2.77	1.00
2	0.00	0.00	100.00	1.70	1.79	0.00
3	0.00	100.00	0.00	2.20	2.76	1.59
4	0.00	50.00	50.00	3.30	10.09	0.00
5	16.67	66.66	16.67	1.50	4.59	2.25
6	0.00	50.00	50.00	2.30	5.28	0.00
7	41.67	41.67	16.66	1.80	4.43	0.53
8	50.00	50.00	0.00	1.80	6.38	1.61
9	50.00	50.00	0.00	3.60	10.13	1.30
10	0.00	100.00	0.00	1.90	3.05	1.20
11	50.00	0.00	50.00	4.10	10.42	0.33
12	100.00	0.00	0.00	2.90	4.81	0.46
13	41.67	16.66	41.67	3.10	10.42	0.00
14	0.00	0.00	100.00	1.70	3.47	0.00
15	66.66	16.67	16.67	2.10	4.03	0.96
16	100.00	0.00	0.00	2.60	3.48	0.07

Note = EY, extraction yield (%); TPC, total phenolic content (mg GAE/g DW); IZ, inhibition zone of extract againt *S. aureus* (mm).

Table 2: Analysis of variance results for extraction yield (EY), total phenolic content (TPC), and inhibition zone against *S. aureus* (IZ)

	EY	TPC	IZ
	Special cubic	Special cubic	Special quartic
F	2.28	2.39	2.95
P	0.13	0.12	0.08
R^2	0.60	0.61	0.77
Adjusted R^2	0.34	0.36	0.51

The mathematical equation for extraction yield was presented in Equation 1. The equation demonstrates that the combination of water and acetone contributes significantly to achieving high extract yields. The findings shown here are inconsistent with prior studies that demonstrated the inferior extract yields of the water-acetone solvent in comparison to water, water-ethanol, and water-methanol solvents when applied to *Tamarix aphylla* plants.[33] Variations in outcomes may still arise as a result of the sampling of different plant species.

Extraction yield (%) = 2.73A + 2.04B + 1.61C + 1.12AB + 7.87AC + 3.36BC – 54.32ABC(1)
Where, A = water, B = ethanol, and C = acetone.

Extraction of TPC
The results obtained for total phenolic content (TPC) extracted from *A. ilicifolius* using various solvents exhibited a range of 1.79 to 10.42 mg GAE/g DW, as presented in Table 1. The contour map presented in Figure 1B demonstrates that the solvent mixture yielded elevated concentrations of phenolic chemicals in comparison to the single solvent. The mathematical representation, denoted as Equation 2, elucidates the hierarchical arrangement of solvent effectiveness for TPC extraction, with water-acetone exhibiting the highest efficacy (30.56), followed by ethanol-acetone (18.75), water-ethanol (17.69), water (3.94), ethanol (2.95), and acetone (2.34). The quantities utilized were optimized, consisting of an equal ratio of 50% water and 50% acetone. The observed results are consistent with the findings of [27,34], which indicate that a mixture of 50% acetone and water is an appropriate solvent for extracting phenolic chemicals from date palm and black tea. Additionally, in the study conducted on strawberry extracts,[21] it was shown that the extraction solutions consisting of acetone/water (50/50, v/v) and (70/30, v/v) yielded the highest TPC.

$$TPC = 3.94A + 2.95B + 2.34C + 17.69\,AB + 30.56AC + 18.75B - 162.64\,ABC \quad (2)$$
Where, A = water, B = ethanol, and C = acetone.

Antibacterial activity againts S. aureus
The antibacterial efficacy of the *A. ilicifolius* leaves extract against *S. aureus* based on the D-optimal design formula ranges from 0.00 – 2.25 mm (Table 1). The research findings indicate that the water-ethanol-acetone mixture (16.67:66.66:16.67, v/v) exhibits much higher antibacterial activity compared to the individual solvents (water, ethanol, and acetone). This conclusion is supported by Equation 3 and Figure 1C. Additionally, the water-ethanol (1.61 mm) and ethanol (1.59 mm) extracts also demonstrate notable antibacterial properties. The obtained outcome exhibits a lower value compared to the extracts of ethanol (18 mm), butanol (8 mm), and chloroform (21 mm) from *A. ilicifolius* leaves that were extracted by the Soxhlet extraction method.[35] The data presented in this study demonstrate that the Soxhlet extraction approach exhibits more efficacy in extracting antibacterial chemicals when compared to the sonication-maceration method employed in this investigation. The data collected indicates a lack of association between phenolic content and antibacterial activity. There exists a potential for the presence of additional chemicals that contribute to the antibacterial properties exhibited by this plant. Prior studies have demonstrated the existence of several chemicals, namely alkaloid, acanthicifoline, 2-benzoxazolinone, and glycosides, within the ethanol extract derived from this particular plant.[11]

$$IZ = 0.35A + 1.43B + 0.01C + 2.40AB + 0.98AC - 2.56BC - 78.46A^2BC + 70.16AB^2C + 40.24ABC^2 \quad (3)$$
Where, IZ = inhibitor zone against *S. aureus*, A = water, B = ethanol, and C = acetone.

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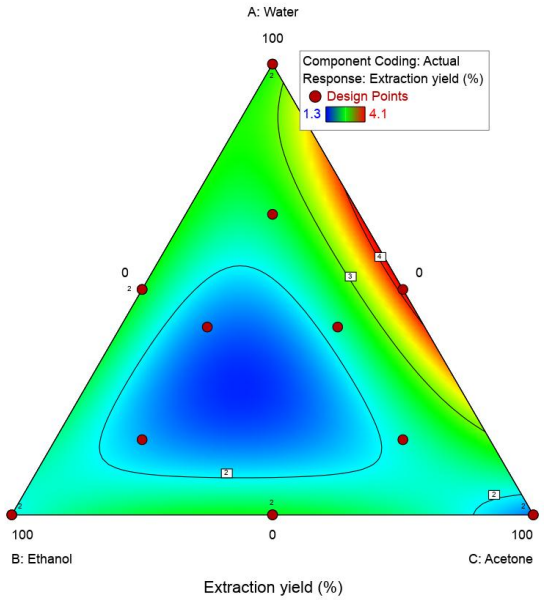
A)



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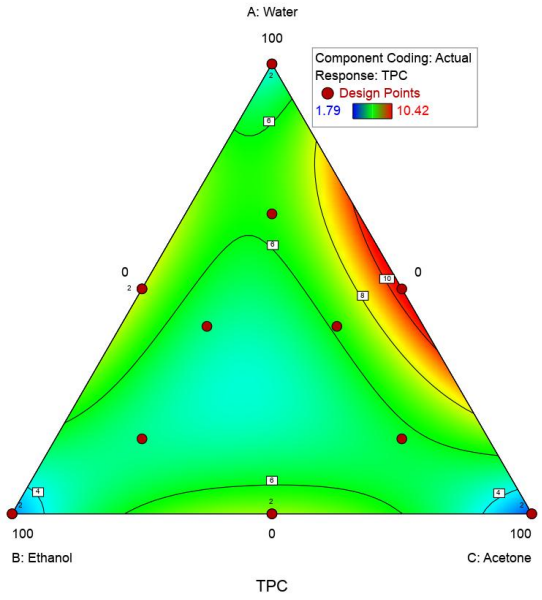

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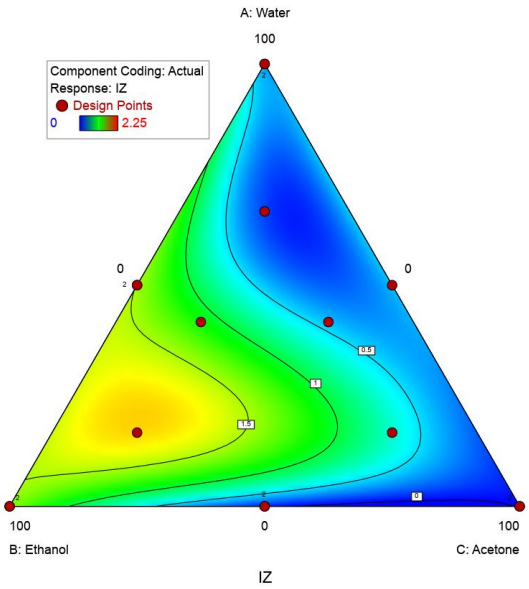

Optimization solution of extraction yield, total phenolic content and antibacterial activity

The selection of variables for the experimental set was mostly focused on their desirability, with a maximum score of 1.00.[36] The best solution was achieved by utilizing a mixture of 50% water and 50% ethanol as extraction solvents, resulting in a desirability value of 0.61 (61%). The solution exhibited anticipated extraction yield, TPC and IZ values of 2.66%, 7.87 mg GAE/g DW, and 1.49 mm, respectively.

Correlation between extraction yield, total phenolic content, and antibacterial activity of A. ilicifolius

Figure 2 shows the results of the Pearson correlation between the responses studied, namely extraction yield (EY), phenolic content (TPC), and antibacterial activity (IZ). EY showed a significant positive correlation with TPC ($p < 0.001$, $r = 0.83$), whereas with IZ, the negative correlation was not significant ($p > 0.05$, $r = -0.33$). In addition, a non-significant negative correlation was also found between IZ and TPC ($p>0.05$, $r = -0.16$). In this study, the correlation coefficient between EY and TPC was higher than that between EY and IZ. This shows that the higher the EY value, the higher the TPC. In addition, the antibacterial activity of *A. ilicifolius* leaves was not influenced by extraction yield or phenolic content. This result aligns with the findings of Tomás-Menor *et al*.[37], who stated that there was no completely correlation between the inhibition of *S. aureus* and the phenolic content in various Spanish cistus. This suggests that phenolic content is not the primary compound responsible for the antibacterial activity of *A. ilicifolius*.

Conclusion

The utilization of the D-Optimal design proved to be effective in optimizing the extraction yield as well as the extraction of phenolic and antibacterial chemicals from A. ilicifolius leaves. The solution utilized in the optimization of extraction yield, phenolic content, and antibacterial activity in *A. ilicifolius* leaves consisted of a binary mixture of 50% water and 50% ethanol. The software analysis yielded a desirability value of 0.61 for this particular solution. Future study for the characterization of phenolic and antibacterial compounds from *A. icifolius* leaves from the optimum formula can be explored to characterize the primary compounds responsible for the antibacterial activity of *A. ilicifolius* leaves.

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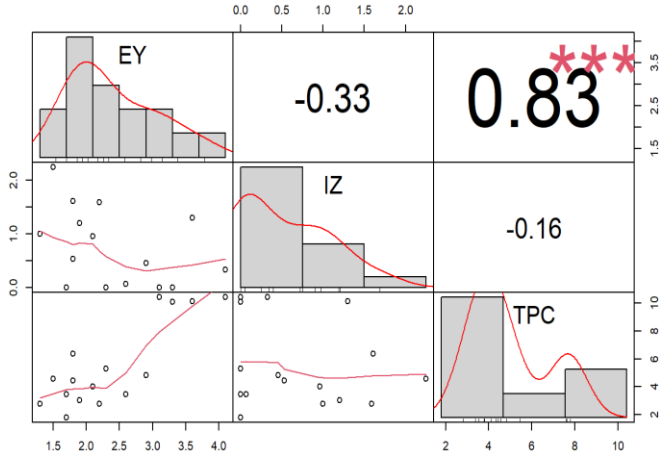

Figure 2: The correlation for extraction yield (EY), inhibition zone against *S. aureus* (IZ), total phenolic content (TPC). *** showed significant level with p-value of 0.001. The figure showed the variable on the diagonal, the bivariate scatter plots with a fitted line on the bottom of the diagonal, and the value of the correlation with the significance level on the top of the diagonal.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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