EXTRACTION AND OPTIMIZATION OF PHYTOCHEMICALS FROM

Curcuma xanthorrhiza Roxb.

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EXTRACTION AND OPTIMIZATION OF PHYTOCHEMICALS FROM *Curcuma xanthorrhiza* Roxb.

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ABSTRACT

Curcuma xanthorrhiza belongs to the Zingiberaceae family is a rich source of phenolics and terpenoids with various bioactivities. The essential oil from the rhizomes was obtained by hydro-distillation and analyzed by gas chromatography (GC) and gas chromatography-mass spectrometry (GC-MS). Xanthorrhizol **(1)**, ar-curcumene **(4)**, and α-cedrene **(18)** were found as the most abundant constituents in the essential oil. Optimization of the ultrasound-assisted extraction (UAE) of the extract from the rhizomes of *C. xanthorrhiza* was carried out via response surface methodology (RSM). Seventeen experiments were developed with Box-Behnken design (BBD) using three variables which are extraction time (5, 12.50, 20 min), temperature (30, 40, 50°C), and liquid-solid ratio (6, 8, 10 mL/g), respectively. The effect of parameters on the responses of extraction yield, quantification of xanthorrhizol **(1)**, and curcumin **(2)** was determined. In the extracts, xanthorrhizol **(1)** and curcumin **(2)** were quantified using reversed-phase high-performance liquid chromatography (RP HPLC) combined with a photodiode array detector. The highest percentage of yield (72.20%) and the concentration of xanthorrhizol **(1)** (85.68% w/w) were found at the extraction temperature of 50°C, time of 20 minutes and 8 mL/g liquid-solid ratio. The highest concentration of curcumin **(2)** (39.73% w/w) was found at the extraction temperature of 30°C, time of 12.50 minutes, and 10 mL/g liquid-solid ratio. Experimental values are closely agreed with the predicted values. The determination coefficient (R^2) of extraction yield, xanthorrhizol **(1)**, and curcumin **(2)** are 0.9960, 0.9983, and 0.9990, respectively. The variance analysis (ANOVA) showed good quadratic model. The numerical data suggested the success of the RSM method in optimizing the phytochemicals extraction parameters from the rhizomes of *C. xanthorrhiza*.

ABSTRAK

Curcuma xanthorrhiza yang tergolong dalam keluarga Zingiberaceae merupakan sumber yang kaya dengan kumpulan fenolik dan terpenoid dengan pelbagai bioaktiviti. Minyak pati daripada rizom diperolehi secara penyulingan hidro dan telah dianalisis menggunakan kromatografi gas (KG) dan kromatografi gas-spektrometri jisim (KG-SJ). Xanthorrizol **(1),** ar-kurkumena **(4)**, and α-cedrene **(18)** telah dikenalpasti hadir dalam komposisi yang banyak di dalam minyak ini. Pengoptimuman pengekstrakan berbantukan ultrasonik (UAE) bagi ekstrak *C. xanthorrhiza* telah dijalankan melalui metodologi gerak balas permukaan (RSM). Sebanyak 17 eksperimen telah dirangka menggunakan reka bentuk Box-Behnken (BBD) menggunakan tiga pembolehubah iaitu masa pengekstrakan (5, 12.50, 20 min), suhu (30, 40, 50°C), dan nisbah cecair-pepejal (6, 8, 10 mL/g). Kesan parameter-ini terhadap gerak balas hasil pengekstrakan dan kuantiti xanthorrizol (**1**) dan kurkumin (**2**) telah ditentukan. Di dalam ekstrak ini, kuantiti xanthorrizol (**1**) dan kurkumin (**2**) telah ditentukan dengan menggunakan kromatografi cecair berprestasi tinggi fasa terbalik yang berganding dengan pengesan fotodiod. Peratusan tertinggi hasil (72.20%) dan kepekatan xanthorrizol (**1**) (85.68% w/w) telah didapati pada suhu pengekstrakan 50°C, masa 20 minit dan nisbah cecair-pepejal 8 mL/g. Kepekatan tertinggi bagi kurkumin (**2**) (39.73% w/w) pula dikenalpasti pada suhu pengekstrakan 30°C, masa 12.50 minit dan nisbah cecair-pepejal 10 mL/g. Nilai-nilai eksperimen adalah menghampiri nilai ramalan. Penentuan pekali (R^2) bagi hasil pengekstrakan, kepekatan xanthorrizol (**1**) dan curcumin (**2**) masing-masing adalah 0.9960, 0.9983 dan 0.9990. Analisis varians (ANOVA) menunjukkan model kuadratik yang baik. Data kajian ini menunjukkan kaedah RSM Berjaya mengoptimumkan parameter bagi pengekstrakan fitokimia daripada rizom *C. xanthorrhiza*.

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LIST OF ABBREVIATIONS

ANOVA	-	Analysis variance
BBD	-	Box-Behnken design
CCD	-	Central Composite Design
F-value	-	Fisher value
ICH	-	The International Conference on Harmonization of Technical Requirements for Pharmaceuticals for Human Use
LOD	-	Limit of detection
LOQ	-	Limit of quantification
MAE	-	Microwave assisted extraction
MeOH	-	Methanol
NA	-	Not available
OFAT	-	One factor at a time
OVAT	-	One variable at a time
PRESS	-	Predicted residual sum of squares
min	-	Minutes
-OH		Hydroxyl
PDA	-	Photo Diode array
P-value	-	Probability value
R^2	-	Correlation coefficient
R^2 adj	-	Correlation coefficient adjusted
RP HPLC-PDA	-	Reversed-phase High-Performance Liquid Chromatography with photodiode array
RSD	-	Relative standard deviation
RSM	-	Response surface methodology
SD	-	Standard deviation
SFE	-	Supercritical fluid extraction
SPE	-	Solid-phase extraction
TP	-	Total polyphenols
TPC	-	Total phenolic content
UAE	-	Ultrasound-assisted extraction

2D	-	Contour plot
2FI	-	Two factorial interactions
3D	-	Response surface plot
w/w	-	Weight per weight
WHO	-	World Health Organization
CUR	-	Curcumin
DMC	-	Demethoxycurcumin
BDMC	-	Bisdemethoxycurcumin
MCF-7 cells	-	Michigan Cancer Foundation-7 cells
1H- NMR	-	Proton- Nuclear Magnetic Resonance
2D-NMR	-	Two-dimensional Nuclear Magnetic Resonance
1D-NMR	-	One-dimensional Nuclear Magnetic Resonance
MS	-	Mass Spectrometry
IR	-	Infrared
CE	-	Convection Extraction
DF	-	Desirability Function
GC	-	Gas Chromatography
GC-MS	-	Gas Chromatography-Mass Spectrometry
Ar	-	Aromatic
EO	-	Essential oil
HD	-	Hydro-Distillation
FAMES	-	Fatty Acids Methyl Esters
NIST	-	National Institute of Standards and Technology
UV-Vis	-	Ultra Violet Visible
FID	-	Flame Ionization Detector
HP-1 MS.M	-	High quality, 100% dimethylpolysiloxane
UTM	-	Universiti Teknologi Malaysia
XNT	-	Xanthorrhizol
US	-	United States

LIST OF SYMBOLS

cm	-	Centimetre
°C	-	Degree Celsius
dm	-	Dry mass
μL	-	Microliter
μm	-	Micrometre
mg	-	Milligram
mL	-	Milliliter
ppm	-	Part per million
x	-	Concentration
y	-	Peak area
σ	-	Standard deviation
Σ	-	Standard Deviation of Response
α	-	Alpha
β	-	Beta
Hz	-	Hertz
C	-	y-intercept
S	-	Slope
Kg	-	Kilogram
W	-	Watt
kHz	-	Kilohertz
$	-	Dollar
&	-	And

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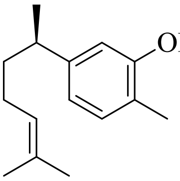
CHAPTER 1

INTRODUCTION

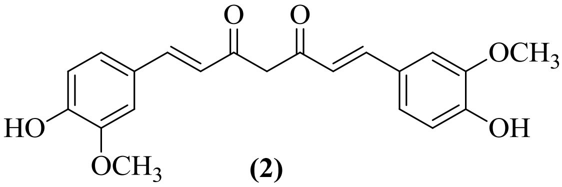
1.1 Background of the Study

Curcuma xanthorrhiza Roxb. belongs to the Zingiberaceae family (ginger family) and originated plants of Indonesia. It is cultivated in Sri Lanka, Malaysia, the Philippines, and Thailand (Theresia *et al*., 2019). It is widely used for the traditional treatment of many illnesses in South East Asian countries, including migraines, constipation, liver problems, and inflammatory conditions. It has been reported that *C. xanthorrhiza* has utility for hepatitis, rheumatism, cancer, hypertension liver problems, diabetes, and heart disorders (Erpina *et al*., 2017). *C. xanthorrhiza* commercially has an interest in the development of new medicines for the treatment of different diseases by both research centres and medicinal companies (Anjusha & Gangaprasad, 2014).

C. xanthorrhiza consists of non-volatile curcuminoids and volatile essential oil (Darmawan & Pramono, 2016). Xanthorrhizol **(1)** is known as the major component of *C. xanthorrhiza* that can be extracted from either essential oil or dried powder of *C. xanthorrhiza* rhizome. It is a sesquiterpenoid-type bisabolane. This compound accounts for almost 46.3% of the whole essential oil component via hydrodistillation techniques (Devaraj *et al*., 2013; Tusek *et al*., 2018). Besides, other extraction techniques can be utilized to extract xanthorrhizol **(1)** from dried rhizome of *C. xanthorrhiza* such as ultrasound-assisted extraction (UAE), maceration, microwave-assisted extraction, Soxhlet, supercritical extraction of carbon dioxide, and solid-phase extraction methods (Başpınar *et al*., 2017). Moreover, xanthorrhizol **(1)** is a highly potent bioactive compound capable of achieving the current need for new drug discovery (Oon *et a*l., 2015). Also, other major compounds that have been discovered from *C. xanthorrhiza* are curcuminoids mainly curcumin **(2)** (Aziz *et al*., 2018). Curcumin **(2)** is a diarylheptanoids phenolic compound which extracted from dried rhizome of *C. xanthorrhiza* using different extraction methods (Xu *et al*., 2017).



(1)



(2)

The optimization of bioactive compounds and extraction methods are of great interest in the food and medicinal industries for further research and development. Over the years, medicinal plants in their native and processed from have been commonly used in traditional medicine, due to the various biologically active molecules found within them (Taher & Sarmidi, 2015). Extraction is the most critical step in making full use of the bioactive molecules found in medicinal plants (Başpınar *et al.*, 2017).

One of the effective techniques for extracting desirable components from plant materials is ultrasonic-assisted extraction that is completely adaptable on small or large scales (i.e. on an industrial scale or laboratory scale). Conventionally, an ultrasonic tool is much simpler and easier to operate (Tatke & Rajan, 2014). Additionally, Ultrasound-assisted extraction (UAE) has been commonly utilized for the laboratories with outstanding benefits including lower energy consumption, less use of solvents, more efficient mixing, and shorter extraction time (Zhang *et al.*, 2020). Alternatively, Ultrasonic-assisted extraction can be conducted at a lower temperature to prevent thermal damage during extraction and volatile components degradation during boiling (Xia *et al.*, 2006).

Response surface methodology (RSM) is an effective mathematical tool commonly utilized for optimizing the experimental conditions for technical operations in many industries. RSM also has benefits for maximizing or minimizing different independent variables as it simultaneously measures the impact of various factors and their respective interplay on one or more variables (Azahar *et al.*, 2017). Meanwhile, RSM is an empirical statistical experiment method design that aims at finding the optimum parameters and achieving the best response. Also, RSM helps to reduce the number of experimental trials required and reveals the relationship between independent variables to multiple regression responses (Subuki *et al.*, 2018).

Quantification of phytochemicals is important to quantify and find concentration of targeted compounds from analyt. HPLC was commonly used to measure concentration of phytochemicals. The retention time of HPLC analysis was affected by several factors such as mobile phase, stationary phase, detectors and the type of columns to be used (Anggarani & Maulana, 2018). Generally, methanol and acetonitrile are commonly used in the mobile system. In addition, reversed-phase C_{18} HPLC and polar organic solvents are also widely used for phytochemical compound quantification. HPLC is a system widely used in terms of simplicity, speed and high efficiency. Photodiode array detector (PDA) has many benefits, such as high selectivity, high sensitivity and fast analyses (Zhu *et al*., 2018).

1.2 Problem Statements

For decades, *C. xanthorrhiza* has been widely utilized in medicinal industries to treat harmful diseases, as it consists of therapeutic benefit components. Nevertheless, comparatively important among big industrial groups is the low yield of cold maceration technique (Mary *et al*., 2012). Extraction yields can be increased significantly and the extraction time can be significantly reduced by several methods to damage cell walls and membranes. To overcome to this problem, UAE can be applied and efficiency of extraction verified via results obtained from extraction process. Therefore, UAE is known as a fast technique to screen the presence of phytochemicals. The problem posed by what the best extraction operating parameters are in terms of extraction time, temperature and liquid-solid ratio. Besides, observation of the extraction on the key parameters is important to be investigated in order to maintain the maximum extraction yield at the optimum condition.

Pharmacologically, active compounds are typically in the small amount included in herbal plants and various effective and selective extraction methods have been introduced to extract those compounds from the raw material (Salea *et al*., 2014). Recently, UAE was commonly used among all of these techniques for the extraction of bioactive components from plants cause at relatively low temperatures, the high extraction efficiencies can be obtained. As a result, the traditional extraction methods were certified to have specific limitations regarding solvent consumption, reaction time and cost. Ultrasound-assisted extraction was a simple solution, an environment friendly, and an alternative efficient method to traditional extraction techniques. This process improved the efficiency of the extraction, faster kinetics, and can be used with several different solvents with less quantity (Le *et al*., 2018). Based on these considerations, it is of great interest to conduct this study to use UAE as an eco-friendly extraction method and explore the relationship between extraction parameters and responses via RSM to obtain efficiency of extraction yield and bioactive compounds from *C. xanthorrhiza* (Mary *et al*., 2012). RSM is a statistical technique that finds optimum condition of extraction parameters to obtain high percentage yield and concentration of phytochemicals. It also has benefit for interaction between extraction parameters and reduces experimental trails to avoid wasting time and materials.

1.3 Objectives of the Study

The objectives of the study are:

1. To extract the essential oil of *Curcuma xanthorrhiza* and identify the chemical components using GC and GC-MS.
2. To optimize the extraction parameters on ultrasound-assisted extraction (UAE) of the extract from *Curcuma xanthorrhiza* via response surface methodology (RSM).
3. To quantify the presence of yield, xanthorrhizol **(1),** and curcumin **(2)** of the extract from *Curcuma xanthorrhiza* using RP HPLC-PAD.

1.4 Scope of the Study

This study was directed to extract the essential oil from fresh rhizome of *C. xanthorrhiza*. Extraction of essential oil was carried out using the hydrodistillation method. In this method a Clevenger-type apparatus was used. 5 mL diethyl ether was utilised to separate oily layer from water layer. Further dryness was done with anhydrous magnesium sulphate. Moreover, identification of chemical compounds from obtained essential oils was applied via GC and GC-MS equipped with flame ionization detector. This research was also aimed at finding the optimum condition of phytochemicals extraction from *C. xanthorrhiza* using Box-Behnken (BBD) design from response surface methodology (RSM) and verified using ANOVA analysis. The monitored parameters were temperature, extraction time, and liquid-solid ratio. Box-Behnken (BBD) design provided 17 runs as an experimental design to operate in the laboratory using UAE. The optimization of Ultrasound-assisted extraction (UAE) from *C. xanthorrhiza* were responses on the percentage of yield, quantification of phytochemicals. The quantification of xanthorrhizol **(1)** and curcumin **(2)** on the extracts were carried out using Reversed-Phase High-Performance Liquid Chromatography (RP-HPLC) equipped with a Photodiode Array detector (PDA).

1.5 Significance of the Study

This study provides a simple method regarding ultrasound-assisted extraction (UAE) optimization for the extraction of phytochemicals from the rhizome of *C. xanthorrhiza* and extraction of essential oil from fresh rhizomes of *C. xanthorrhiza*. When using this optimization, it is very beneficial to satisfy the need for the better quality of final product. Recently, using an environmentally friendly approach is becoming ever more desirable. Extraction of bioactive compounds under ultrasonic-assisted is considered as one of the important extraction techniques that can highly provide reproducibility in a shorter period, easier handling, decreased solvent consumption and temperature, and lower energy intakes. Moreover, UAE optimizes the production of phytochemicals from *C. xanthorrhiza* extract using RSM is greatly preferred. This analysis would also be able to obtain optimum results on the percentage of yields and phytochemicals from *C. xanthorrhiza* rhizome.

Nevertheless, the economic viability of an industrial procedure often demands work to obtain high extraction quality which is achieved to affect the output of extraction. Response surface methodology (RSM) which has been used in this study allows the evaluation of the effects of variables on response variables and their interactions. Even though, bioactive compounds extraction from medicinal plants allows proof of physiological activity. It also facilitates the study of pharmacology which leads to the synthesis of more potent drugs to meet the demand for effective and safe use in human health. Besides, this study will be able to get the optimum condition on the percentage of yields and phytochemicals from *C. xanthorrhiza*. Moreover, in terms of the percentage of yield, this study can provide the desired outcome for the quality of the final product and preserves the amount of nutrient content in the plants via optimization of the extraction method. Therefore, belonging to the standardization of extraction able to apply, this leads to raising the food supplement production from natural resources. Economically, increasing demand from industrial processes such as pharmaceutical, food, and cosmetics industries can accelerate the production using the standard operating procedure of extraction.

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