

BIOACTIVITIES AND FITTING MODELS OF *QUERCUS INFECTORIA* GALLS  
EXTRACTS USING SUPERCRITICAL CARBON DIOXIDE

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To my beloved parents

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## ABSTRACT

The extraction of natural plants has gained interest from the researchers due to their therapeutic values. In this study, the bioactive compounds of *Quercus infectoria* galls were extracted using supercritical carbon dioxide. The optimization of extraction conditions was performed using response surface methodology. The effect of extraction conditions (pressure, temperature, particle size) on extraction yield and hydrolysable tannins content of *Q. infectoria* were investigated. The biological properties of the extracts were evaluated by *in vitro* wound healing assay including total phenolic content, free radical scavenging, cell proliferation and scratch assay. The density-based models for simulation of extract solubility were also correlated. The mass transfer phenomena for extraction process of *Q. infectoria* galls was also investigated using both single sphere model and the broken and intact cells model. The extraction was conducted at 2 mL/min of carbon dioxide flow rate with the addition of methanol (purity: 99.8%) at ratio of 1:3 (weight of sample/volume of methanol) and was kept constant throughout this study. The study revealed that pressure, temperature and particle size were critical parameters that significantly affect the extraction yield, but did not contribute to the hydrolysable tannins content. The overall yield increased with increased pressure, temperature and particle size. The best conditions obtained from the optimization process were pressure (28.11 MPa), temperature (50.43°C) and particle size (1.25 mm) with predicted yields of 6.02%, tannic acid composition (6149.71 mg/g) and gallic acid concentration (96.85 mg/g). The galls extract showed high biological properties in terms of total phenolic content, antioxidant activity, cell proliferation and migration properties. Bartle model successfully fitted to the experimental solubility data with low absolute average relative deviation which was 1.52%. Single sphere model provides better correlation for mass transfer coefficient estimation than the broken and intact cell model. The findings from both models suggested the importance of internal diffusion and mass transfer in the extraction process of the galls.

## ABSTRAK

Pengekstrakan tumbuhan semulajadi telah menarik minat para penyelidik disebabkan oleh nilai-nilai terapeutiknya. Dalam kajian ini, komponen aktif daripada hempedu *Quercus infectoria* telah diekstrak menggunakan pengekstrakan karbon dioksida lampau genting. Pengoptimuman keadaan pengekstrakan dilakukan dengan menggunakan kaedah tindak balas permukaan. Kesan keadaan pengekstrakan (tekanan, suhu, saiz zarah) pada kadar pengeluaran dan kandungan tannin terhidrolisis daripada *Q. infectoria* telah dikaji. Sifat-sifat biologi ekstrak telah dinilai oleh cerakin penyembuhan luka *in vitro* termasuk jumlah kandungan fenolik, penangkapan radikal bebas, percambahan sel dan cerakin goresan. Model berasaskan ketumpatan untuk simulasi kelarutan ekstrak juga telah dihubungkan. Fenomena pemindahan jisim untuk proses pengekstrakan hempedu *Q. infectoria* juga dikaji dengan menggunakan model sfera tunggal dan model sel pecah dan tak terusik. Pengekstrakan ini dijalankan pada kadar aliran karbon dioksida 2 mL/min dengan tambahan metanol (ketulenan: 99.8%) pada nisbah 1:3 (jisim sampel/isipadu metanol) dan dimalarkan sepanjang kajian ini. Kajian ini menunjukkan bahawa tekanan, suhu dan saiz zarah adalah parameter penting yang member kesan ketara terhadap hasil pengekstrakan, tetapi tidak menyumbang kepada kandungan tannin terhidrolisis. Hasil keseluruhan meningkat dengan peningkatan tekanan, suhu dan saiz zarah. Keadaan terbaik diperolehi daripada proses pengoptimuman adalah tekanan (28.11 MPa), suhu (50.43°C) dan saiz zarah (1.25 mm) dengan ramalan hasil 6.02%, komposisi asid tanik (6149.71 mg/g) dan kepekatan asid galik (96.85 mg/g). Ekstrak hempedu menunjukkan sifat-sifat biologi yang tinggi daripada segi jumlah kandungan fenolik, aktiviti antioksidan, sifat-sifat percambahan dan migrasi sel. Model Bartle berjaya disesuaikan kepada data kelarutan ujikaji dengan purata mutlak sisihan relatif yang rendah iaitu 1.52%. Model sfera tunggal menunjukkan hubungan yang lebih baik bagi anggaran pekali pemindahan jisim daripada model sel pecah dan tak terusik. Penemuan daripada kedua-dua model mencadangkan kepentingan penyebaran dalaman dan pemindahan jisim dalam proses pengekstrakan daripada hempedu.

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**LIST OF ABBREVIATIONS**

AARD	-	Absolute average relative deviation
ANOVA	-	Analysis of variance
Ar	-	Argon
BHA	-	Butylated hydroxyanisole
CCD	-	Central composite design
CH <sub>3</sub> CN	-	Acetonitrile
CO <sub>2</sub>	-	Carbon dioxide
CP	-	Critical point
DMEM	-	Dulbecco's modified Eagle's medium
DMSO	-	Dimethyl sulfoxide
DPPH	-	2,2-diphenyl-1-picrylhydrazine
IC <sub>50</sub>	-	Concentration of sample required to scavenge 50% of DPPH radicals
E	-	Error
FBS	-	Fetal Bovine Serum
FC	-	Folin-Ciocalteu
GA	-	Gallic acid
H <sub>2</sub> O	-	Water
H <sub>3</sub> PO <sub>4</sub>	-	Orthophosphoric acid
HC	-	Hydrocarbon
HPLC	-	High Performance Liquid Chromatography
MeOH	-	Methanol
MS	-	Mean squared
MTT	-	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
n.d.	-	Not defined
Na <sub>2</sub> CO <sub>3</sub>	-	Sodium carbonate
NaCl	-	Sodium chloride

PBS	-	Phosphate bovine saline
PDGF	-	Platelet derived growth factor
OEC	-	Overall extraction curve
FER	-	Falling extraction rate
CER	-	Constant extraction rate
R	-	Regression
ROS	-	Reactive oxygen species
RSM	-	Response surface methodology
ScCO <sub>2</sub>	-	Supercritical carbon dioxide
SCF	-	Supercritical fluid
SFE	-	Supercritical fluid extraction
SL	-	Saturated liquid
SS	-	Sum of squared
SV	-	Saturated vapour
TPC	-	Total phenolic content

## LIST OF SYMBOLS

$\Delta H_{solv}$	-	Heat of salvation
$\Delta H_{vap}$	-	Heat of vaporization
$\alpha_0$	-	Bed void fraction
$a_{ij}$	-	Coefficients of the function i, j
$\varepsilon_p$	-	Particle porosity
$\theta_e$	-	External mass transfer resistance
$\theta_i$	-	Internal mass transfer resistance
$\tilde{\rho}$	-	Molar density
$\rho_{CO_2}$	-	Density of carbon dioxide
$\rho_{MeOH}$	-	Density of methanol
$\rho_b$	-	Apparent density
$\rho_f$	-	Solvent density
$\rho_{ref}$	-	Reference density
$\rho_s$	-	Particle density
$\mu$	-	Viscosity of solvent
$\rho$	-	Solvent density
$\beta$	-	Simplified mathematical expression in BIC model
$\gamma$	-	Solvent to matrix ratio in the bed
$a, b, c, d, e$	-	Constant in solubility equations
$A_{control}$	-	Absorbance of control
$A_{sample}$	-	Absorbance of sample
$B_i$	-	Biot number
$B, X$	-	Equation's parameter
$C$	-	Cells concentration
$C_1, C_2, C_3, C_4$	-	Constants for methanol density calculation
$C_1, C_2$	-	Adjustable parameters in simplified BIC model

$c_u$	-	Solute content in the untreated solid
$DF$	-	Dilution factor
$D$	-	Diffusion coefficient of the solute
$d$	-	Mean particle size
$D_e$	-	Intraparticle diffusion coefficient (effective diffusivity)
$E$	-	Amount of oil extracted
$e$	-	Model extraction yield
$e_{exp}$	-	Experimental extraction yield
$f$	-	Flow rate
$j_f$	-	Flux from broken cells to the fluid
$j_s$	-	Flux in solid phase
$K$	-	Equilibrium constant
$k$	-	Association constant
$k_f$	-	External mass transfer coefficient
$K_f$	-	Film mass transfer coefficient
$k_f a_0$	-	Product between external mass transfer coefficient and specific surface area between broken and intact cells
$k_p$	-	Overall mass transfer coefficient
$k_s$	-	Internal mass transfer coefficient
$k_s a_s$	-	Product between internal mass transfer coefficient and specific surface area between broken and intact cells
$M$	-	Moisture content
$M$	-	Mass of passed solvent
$m_0$	-	Mass of sample
$m_0$	-	Weight of petri dish
$m_1$	-	Mass of the extract
$m_1$	-	Weight of petri dish and sample before drying
$m_2$	-	Weight of petri dish and sample after drying
$M_\infty$	-	Total amount of solute
$M_t$	-	Total amount of solute diffused from sphere at time
$MW_A$	-	Molecular weight of solute
$MW_B$	-	Molecular weight of solvent
$N$	-	Mass of solid loaded in the extractor
$N$	-	Number of experiment run

$n$	-	Number of iterations
$n$	-	Number of mixers in series
$N_m$	-	Insoluble mass of matrix loaded in the extractor
$n_p$	-	Number of particles in the bed
$P$	-	Pressure
$P$	-	Number of term in model used for analysis
$P_c$	-	Critical pressure
$P_{ref}$	-	Reference pressure
$\dot{Q}$	-	Solvent mass flow rate
$q$	-	Relative amount of passed solvent
$q$	-	The concentration of solute within the particle at radius $r$
$q_\infty$	-	Concentration of solute at the surface after infinite time
$q_c$	-	Relative amount of the passed solvent at the end of fast extraction period
$r$	-	Grinding efficiency
$R$	-	Universal gas constant
$r, R$	-	Radius of particle
$Re$	-	Reynolds number
$S$	-	Solubility of solute
$Sc$	-	Schmidt number
$Sh$	-	Sherwood number
$T$	-	Temperature
$t$	-	Time
$T_c$	-	Critical temperature
$U$	-	Interstitial velocity
$V$	-	Volume of passed solvent
$v_2$	-	Molar volume of the solute
$V_{solv}$	-	Solvent volume for dissolving extract
$W_{t=0 \text{ hr}}$	-	Width of wound at 0 hour (pixel)
$W_{t=24 \text{ hr}}$	-	Width of wound at 24 hour (pixel)
$x_1$	-	Solute concentration in broken cells
$X_1$	-	Pressure
$X_2$	-	Temperature

$X_3$	-	Mean particle size
$x_u$	-	Weight fraction of solute content in the untreated solid
$Y$	-	Total oil yields in supercritical as g oil/g sample
$y_{exp}, y_{calc}$	-	Data obtained from experiment and model equations
$y_s$	-	Solubility of solute in BIC model



**LIST OF APPENDICES**

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## CHAPTER 1

### INTRODUCTION

#### 1.1 Background of Study

In the recent years, there has been increasing demand for functional ingredients obtained from natural resources as consumers are getting more interested in functional foods. New leads in food, nutraceutical and pharmaceutical advance have always been served by natural product substances. In the early 20th century, medicines were mostly made from roots, barks and leaves of plants as fluid extracts were in trend (McChesney *et al.*, 2007). Besides, Esnon (2000) tells that in the history of Egyptians, Chinese and Romans, the reliance of early human evolution on medicinal plants and herbs for the use of curing the sick were well documented. In advance, Soon and Hasni (2005) reported that the researchers would keep on using the medicinal herb and should be incorporated into modern medicine.

*Quercus infectoria*, also known as manjakani, is a type of medicinal plant that can be used in treating diseases and it is already well-known since ancient time. Oak (Quercus) is a part of Fagaceae family. Early studies shows *Q. infectoria* has been traditionally used for post-childbirth care to strengthen the mother's womb. The galls was also claimed to be extremely valuable for the postpartum women and there are no risky effects reported until now (Soon and Hasni, 2005). These benefits are due to the content of bioactive compounds inside the plant solid.

Bioactive compounds are additional nutritional constituents that naturally occur in small quantities in food and plant products (Kris-Etherton *et al.*, 2002). Most frequent bioactive compounds consist of alkaloids, food grade pigments, antibiotics, mycotoxins, plant growth factors and phenolic compounds (Kris-Etherton *et al.*, 2002; Hölker *et al.*, 2004; Nigam, 2009). Basically, *Q. infectoria* galls contained phenolic compounds that are responsible for their biological activities such as antioxidant (Dicko *et al.*, 2006), anti-allergenic, anti-atherogenic (Puupponen-Pimiä *et al.*, 2001), anticancer (Cai *et al.*, 2004) and antimicrobial activities (Owen *et al.*, 2000). These constituents are a group of aromatic secondary plant metabolites which usually spreads throughout the plant, present either in the free form or in the bound form. There is a huge attention of phenolic compounds in food industry due to the food's quality enhancement and nutritional value (Parr and Bolwell, 2000).

Solvent extraction offers good recovery of phytochemicals from various samples, such as fruits and vegetables. Supercritical fluids have been widely used as a solvent for various applications. The state of supercritical fluid can only be achieved if the fluid operates at the pressure and temperature that is near its critical conditions (Pereda *et al.*, 2008). This type of extraction process is known as supercritical fluid extraction (SFE). Generally, supercritical fluid extraction is based on the utilization of a fluid under supercritical conditions. It is suitable for extraction and purification of various compounds, especially for those with low volatility or susceptible to thermal degradation, if cost is not the limiting factor. According to Díaz-Reinoso *et al.* (2008), supercritical fluids have higher diffusivity and lower density, surface tension and viscosity compared to conventional solvent used for extraction. These properties can be altered by manipulating the operating conditions (pressure and temperature), which provide more effective extraction process.

There are many advantages of SFE reviewed by Abbas *et al.* (2008). SFE allows the removal of active ingredients from herbs and plants with better flavour or fragrance reproduction than the conventional extraction. The operation at reduced temperature avoids thermal degradation and decomposition of labile compounds, whereas the absence of light and oxygen prevents oxidation reactions. Besides, the separation and recovery of active ingredients is in higher quality by using selective

fractionation. In practice, more than 90% of all analytical SFE was performed with carbon dioxide (CO<sub>2</sub>) as a solvent, because of its practical reasons such as relatively low critical temperature (31.1°C) and pressure (73.9 bar), nontoxic, non-flammable, available in high purity at considerably low cost and easily separated because of its volatility. CO<sub>2</sub> is suitable to extract heat labile, natural compounds with low polarity and volatility (Díaz-Reinoso *et al.*, 2006) and best suited for lipophilic compounds (Pourmortazavi and Hajimirsadeghi, 2007). In addition, the gas-like characteristic of CO<sub>2</sub> helps the fluid diffuse into the matrix and access the phytochemicals while the liquid-like characteristics provide good salvation power. Many reviews have been reported that supercritical extraction utilizing CO<sub>2</sub> as solvent gave high recovery of interest compound than typical organic solvents (Tena *et al.*, 1997; Kaplan *et al.*, 2002; Rajaei *et al.*, 2005; Prandhan *et al.*, 2010).

The main negative aspect of CO<sub>2</sub> is its lack of polarity for extraction of polar analytes (Wang *et al.*, 2003). Thus, CO<sub>2</sub> does not dissolve any mineral species such as salts and metals, and hydrophilic compounds, such as proteins and sugars (Perrut, 2004). In addition, the storage tank for CO<sub>2</sub> and extractors must be suitably isolated and equipped with relief system (Lucas *et al.*, 2003). In order to enhance solubility of target compounds and extraction efficiency, the small amount addition of co-solvents (methanol or ethanol) will be useful and it will allow the process to operate at both low pressure and temperature. Supercritical carbon dioxide (ScCO<sub>2</sub>) is suitable for various applications with the following conditions; processing cost is not a limiting factor, restriction of conventional solvent extraction by environmental regulations, consumer demands or health considerations, products have improved in quality and/or marketability; and traditional processing is not applicable because the product is thermally labile or morphologically unique.

The ScCO<sub>2</sub> extraction of the phenolic compounds which in this study is hydrolysable tannins from *Q. infectoria* galls can be explained using mathematical expressions in terms of solubility and mass transfer phenomena. The feasibility and scaling-up of the extraction process can be evaluated using the kinetic parameters obtained from the solubility and mass transfer models.

## 1.2 Problem Statement

The benefits of supercritical carbon dioxide (ScCO<sub>2</sub>) extraction as a green extraction method such as suitable for heat labile compounds, low toxicity, reduce extraction time, minimize solvent used and produce high quality of product is well known (Chen and Ling, 2000; Mohamed and Mansoori, 2002). However, the extraction of polar compounds is not favourable in this method due to polarity properties of carbon dioxide. Hydrolysable tannin, tannic acid and gallic acid, which is the interest compounds in this study is water soluble, hence the addition of polar solvent, i.e. methanol is needed in this study to increase the solubility of these compounds (Jin *et al.* 2012). The extraction of polar bioactive compounds implementing CO<sub>2</sub>-modifier system has been widely applied by previous researchers (Chafer *et al.*, 2007; Fan *et al.*, 2010; Ghafoor *et al.*, 2012; Kukula-Koch *et al.*, 2013). Furthermore, although numerous reports on supercritical fluid extraction of medicinal plants or seeds have been published, however, the extraction of substances from *Quercus infectoria* galls remains scarce in the literature, for instance their solubility data and mass transfer behaviour during the extraction process are rather limited.

Most of *Q. infectoria* extraction researches were performed using conventional solvent extraction. The extraction of oak gall has conducted by Calam in 1966 using Soxhlet extraction. Initially, the aims of the study are to isolate the active compounds from a fresh supply of galls and to prove that the plant extract can produce histamine protection. Even though the findings on the oak gall extracts were appeared to have significant antihistamine activity, but it is only for a short duration and shows non-specific effect. The extracts also have been signified to contain toxic ingredients. Pithayanukul *et al.* (2009) used maceration process with 50% aqueous to investigate the hepatoprotective potential of the plant extract. In another research, Ghafour *et al.* (2010) used soaking method in distilled water to extract tannin, saponins, alkaloid, glycoside and other phenolic compounds present in the galls. Basri *et al.* (2012) also applied soaking method with different solvent which was methanol and determine the effectiveness of the galls extracts against oral pathogens. The only research which applied modern technology such as SFE in galls extraction

was done by Stashia (2013), where the bioactivities and transport processes involved have not been explored yet. During the study, the author found that only a trace amount of gallic acid in the sample could be due to unpolar properties of CO<sub>2</sub>. This study does not utilize the application of modifier in the extraction process.

Considering the importance of medicinal plants in pharmaceutical industries nowadays and the increasing demands for green technologies, it is remarkable to find alternative methods to prepare bioactive compounds from *Q. infectoria* galls. In addition, solubility data and mass transfer relationship for the extraction of *Q. infectoria* using ScCO<sub>2</sub> extraction with the help of modifier are not yet established. Hence, a reliable model is needed as it is an effective method to support the application of supercritical fluid in natural products extraction in terms of scaling up and design the process.

### 1.3 Objectives of Study

The aims of this study are:

- a) To investigate the effect of supercritical carbon dioxide extraction conditions such as pressure, temperature and particle size on the extraction yield and hydrolysable tannins content from *Q. infectoria* galls and followed by the optimization using response surface methodology (RSM).
- b) To determine the bioactivities of extracted *Q. infectoria* galls including antioxidant activity, cytotoxicity and cell migration ability using *in vitro* wound healing related assays.
- c) To model the solubility data using density-based equations and kinetic coefficients for the extraction of *Q. infectoria* galls using supercritical carbon dioxide.

## 1.4 Scope of Study

The tasks that need to be accomplished in order to achieve the aim of this study are:

- a) Pre-treatment and preliminary experiments were studied to determine moisture content, total solute content and constant solvent flow rate.
- b) Extraction of *Q. infectoria* galls was performed using supercritical carbon dioxide extraction at pressures (20 to 30 MPa), temperatures (50 to 70°C) and mean particle sizes (0.50 to 1.50 mm). Extraction pressure was kept above 20 MPa because the application of pressure below than that showed no obvious extractable yield detected. 30 MPa was used as the maximum pressure used because of the equipment limitation. For extraction temperature, 50°C was applied to ensure supercritical condition during the extraction and the extraction above 70°C is not suitable for extracting bioactive compound. . The selection of particle size range was done by trial and error runs. It was found that sizes < 0.50 mm lowering the extracted yield and clogging also occur inside the vessel. The unavailability of mesh size larger than 1.50 mm limits the selection of the mean particle size used in this study.
- c) Identification of hydrolysable tannins content in extracted *Q. infectoria* galls using High Performance Liquid Chromatography (HPLC).
- d) Optimization of extraction conditions for the extraction yield and hydrolysable tannins content of *Q. infectoria* galls using software of Design Expert 7.0.
- e) Determination of total phenolic content, antioxidant activity and cell migration properties of extracted *Q. infectoria* galls by experimenting total phenolic content, free-radical scavenging, cytotoxicity assay and scratch assay analysis on the human skin fibroblast (HSF1184) cell.
- f) Correlation of solubility constants at different temperatures and pressures range by fitting the experimental data with six density-based solubility equations; Chrastil, Adachi-Lu, del Valle-Aguilera, Sparks, Kumar and Johnston, and Bartle equations; and comparison among them.

- g) Determination of diffusion coefficient and mass transfer coefficient for extraction of *Q. infectoria* galls using single sphere model and broken and intact cell model and their comparison.

## 1.5 Significance of Study

The key contributions that have emerged from this work can be divided into two aspects; which are academic and application. Academically, the manipulation of extraction conditions to extract more polar compound from *Quercus infectoria* galls using supercritical fluid for medicinal purposes is considered new since there are no available *Q. infectoria* galls research reported, specifically in Malaysia. Besides, the medicinal properties of *Q. infectoria* have been proved by scientific study using living cell like fibroblasts or HaCaT. The establishment of database for solubility behaviour, diffusion coefficient and mass transfer provides a significance reference for further studies of supercritical fluid extraction of the galls.

In application point of view, one of the main contributions is the application of suitable supercritical fluid extraction conditions to access high quality of valuable compounds in *Q. infectoria* galls. By knowing the data for wound healing analysis, appropriate extracts dosage to be applied as medicine without being harmful to human being can be noted. In addition, the available modelling data is useful in scaling up and economic evaluation of industrial SFE processes. Apart from that, by doing this research, it is hope that it can enrich the field of global studies with the production of products by applying supercritical fluid extraction method, especially carbon dioxide fluid in publication, patent and networking.



## 1.6 Thesis Outline

This thesis is organised in 5 chapters. Chapter 1 begins with the introduction of this research project i.e. the brief introduction of supercritical fluid extraction, medicinal properties of *Quercus infectoria* galls and models to be used in this study. This chapter also includes problem statements that had motivated this research, the research objectives, scopes and significance of this research conducted.

Chapter 2 presents the overview of the pharmacology properties of the galls. This chapter also describes the fundamental theory of supercritical fluid extraction, comprises of chemical and physical properties, selection of extraction conditions and solvent, and review of previous research on the topic of interest. Optimization and modelling of supercritical fluid extraction also reviewed in this chapter. This chapter ends with a brief about factors influencing wound healing properties.

Chapter 3 describes the detailed methodology in order to achieve the research objectives. The experimental work for extraction process, compound analysis and biological analysis are mentioned as a guideline for this research. The design of experiments is also presented in this chapter.

Chapter 4 are discussed in two different parts. The first part discussed the findings through experimental work including the effects of operating conditions on extracted yield and bioactive compounds of the galls; and the effect of the extracts on antioxidant activity, fibroblast proliferation assay and scratch wound assay. The mathematical models on solubility behaviour and mass transfer are discussed in the latter part.

Finally, Chapter 5 highlights the conclusions and recommendations of the work. The conclusions are summarised depends on the results and discussion in Chapter 4. The recommendations also suggested for guidance and improvement of future work related to supercritical carbon dioxide extraction and *Quercus infectoria*.

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