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SUBCRITICAL WATER EXTRACTION OF LIPID CONTAINING OMEGA-3 FROM MICROALGAE Nannochloropsis gaditana

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By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

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SUBCRITICAL WATER EXTRACTION OF LIPID CONTAINING OMEGA-3 FROM MICROALGAE *Nannochloropsis gaditana*

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Omega-3 fatty acids, mainly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are known to have many health benefits. Many researchers have found different algal species which have high omega-3 content. Conventional techniques such as to extract microalgal omega-3 have too many disadvantages. This hinders the application of the extracted products to be fully utilized for human consumption. Therefore, a need for green, fast, and robust approach to extract the lipids from microalgae is essential. This study investigates the effectiveness of subcritical water extraction (SWE) in extracting lipid and EPA from microalgae, *Nannochloropsis gaditana*.

The preliminary screening of SWE experiments were carried out to identify the suitable range of parameters. The highest yield of lipid for the preliminary screening was at a temperature of 210℃ and reaction time of 10 min yielding 20.79 wt% of lipid. After screening, an optimization is done with the parameters set on extraction temperature (156.1-273.9℃), time (6.6-23.4 minutes), and biomass loading (33-117 g algae/L) that are further optimized for lipid yield and EPA composition using central composite design (CCD). All three parameters were found to be significant factors for the changes in lipid yield, but extraction time was not a significant factor for EPA composition change. It was found that the predicted optimum lipid yield and EPA composition at 236.54 ℃, 13.95 minutes and 60.50 g algae/L was 18.278 wt% of total biomass and 14.036 wt% of total fatty acid methyl ester (FAME), respectively.

Furthermore, the separation of the lipid extracts was performed using a solid phase extraction (SPE) method, where the lipids were classified into polar lipid (POL), neutral lipid (NL) and free fatty acid (FFA) component. From the findings, the POL was more susceptible to hydrolysis than NL. The highest recoveries of NL and POL from the biomass were 81.16 wt% and 66.45 wt% of lipid as compared to B&D method, respectively.

A reaction pathway for SWE of *Nannochloropsis gaditana* was also developed and used to derive the kinetic equation. The highest rate constant and lowest activation energy was the pathway of algal EPA-POL to be converted into by-products showing further that EPA-POL have high rate of hydrolysis at higher temperature with activation energy of 37.56 kJ/mol. It was also found that the model successfully incorporated to both major and minor fatty acids present in the microalgae such as palmitoleic acid, linolenic acid, and arachidonic acid.

Overall, the outcome of this study contributes to a better utilization of microalgae as an available source of omega-3 fatty acids for food and pharmaceutical industry as well as achieving the green and fast extractions with high concentration of omega-3.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

PENGEKSTRAKAN LEMAK MENGANDUNGI OMEGA-3 DARIPADA MIKROALGA *Nannochloropsis gaditana* DENGAN MENGGUNAKAN KAEDAH AIR SUB-KRITIKAL

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Omega-3 asid lemak terutamanya asid eikosapentaenoik (EPA) dan asid dokosahexaenoik (DHA) mempunyai banyak faedah kesihatan seperti anti radang, mencegah penyakit kardiovaskular, meningkatkan kesihatan mental dan lain-lain. Banyak penyelidik telah menemui pelbagai spesis alga yang mempunyai kandungan omega-3 yang tinggi. Teknik lama untuk mengekstrak omega-3 daripada mikroalga mempunyai terlalu banyak kekurangan seperti pengunaan pelarut berbahaya, proses pengekstrakan yang panjang dan hasil produk yang rendah. Ini menghindarkan hasil pengekstrakan daripada dimanfaatkan untuk pengunaan oleh manusia. Oleh itu, proses hijau, cepat dan kukuh diperlukan untuk mengekstrak lemak daripada mikrolaga. Dengan itu, tujuan penyelidikan ini adalah untuk menganalisis keberkesanan kaedah air sub-kritikal (SWE) untuk mengekstrak EPA daripada *Nannochloropsis gaditana*.

Analisis awal bagi eksperimen SWE dilaksanakan untuk mengetahui jangkaan jarak. Hasil lemak tertinggi pada analisis awal boleh diperolehi dalam suhu 210 ℃ dan masa 10 minit yang berjumlah 20.79 wt% hasil lemak. Selepas analisis awal, suhu (156.1-273.9 °C), masa (6.6-23.4 minit), dan komposisi biomas (33-117 g alga/L) digunakan dalam analisis pengoptimuman untuk hasil lemak dan komposisi EPA dengan menggunakan central composite design (CCD). Jangkaan optimum hasil lemak dan komposisi EPA pada 236.54 ℃, 13.95 minit dan 60.50 g alga/L adalah 18.278 wt% daripada jumlah biomas dan 14.036 wt% daripada jumlah ester metil asid lemak (FAME). Pengimbas mikroskop

elektron menunjukkan bahawa dinding sel telah dihancurkan dan komponen bioaktif dalam mikroalga telah berjaya diekstrak oleh kaedah SWE.

Penyifatan ekstrak lemak telah dilakukan dengan menggunakan kaedah pengekstrakan fasa pepejal (SPE) dengan mengklasifikasi lemak ke dalam komponen lemak berkutub (POL), lemak neutral (NL) dan asid lemak bebas (FFA). Daripada penemuan analisis, ekstrak lemak didapati mempunyai kandungan POL yang tinggi apabila dibandingkan dengan NL. Pendapatan NL dan POL daripada biomas adalah sebanyak 81.16 wt% dan 66.45 wt% daripada jumlah lemak.

Laluan tindak balas bagi SWE daripada *Nannochloropsis gaditana* juga telah dihasilkan dan digunakan untuk membentukkan penyamaan kinetik. Pemalar tindak balas yang tertinggi and tenaga pengaktifan yang paling rendah ialah laluan tindak balas bagi EPA-POL yang ditukarkan kepada produk yang tidak diingini dengan tenaga pengaktifan sebanyak 37.56 kJ/mol. Model tersebut berjaya digunakan untuk kedua-dua acid lemak utama dan acid lemak sebilangan kecil dalam mikroalga ini seperti asid palmitoleic, asid linolenic, dan asid arachidonic.

Kesimpulannya, penyelidikan ini akan memberi sumbangan kepada penggunaan mikroalga sebagai satu sumber omega-3 untuk makanan dan industry farmasi. Pada masa yang sama, ia akan menjayakan satu kaedah teknologi hijau dan pengekstrakan yang cepat dengan hasil kepekatan omega-3 yang tinggi.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy . The members of the Supervisory Committee were as follows:

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ALA	α-linolenic acid
ANOVA	Analysis of variance
B&D	Bligh and Dyer extraction
CCD	Central composite design
CO2	Carbon dioxide
CVD	Cardiovascular diseases
DGDG	Digalactosyl-diacylglycerol
DHA	Docosahexaenoic acid
E_a	Activation energy
EPA	Eicosapentaenoic acid
FAME	Fatty acid methyl ester
FFA	Free fatty acid
FID	Flame ionization detector
GC	Gas chromatography
GL	Glycolipid
GLA	γ-linolenic acid
HDL-C	High density lipoprotein cholesterol
IL	Ionic liquid
k_i	Rate constant
K_w	Ionic product of water
LDL-C	Low density lipoprotein cholesterol
MGDG	Monogalactosyl-diacylglycerol
M-SDE	Modified simultaneous distillation extraction

MUFA	Monounsaturated fatty acid
n-3	Omega-3
n-6	Omega-6
NL	Neutral lipid
PLRP2	Pancreatic lipase-related protein 2
POL	Polar lipid
PUFA	Polyunsaturated fatty acid
$SCCO_2$	Supercritical carbon dioxide extraction
SDA	Stearidonic acid
SEM	Scanning electron microscopy
SFA	Saturated fatty acid
SFE	Supercritical fluid extraction
SPE	Solid phase extraction
SWE	Subcritical water extraction
TFA	Total fatty acid
TG	Triglyceride
TLC	Thin layer chromatography
σ	Standard deviation

CHAPTER 1

INTRODUCTION

1.1 Background

Cardiovascular diseases (CVDs) are at top of the chart for causing death globally. A study conducted among United States adults from 2007 to 2014 estimated that 56.9 million people in United States (25.9%) have high levels of triglyceride (TG) in a range of 150 mg/dL to 400 mg/dL (Fan et al., 2020). TG-rich remnant lipoproteins are considered to have atherogenic effect that will increase the risk of CVDs (Jacobson et al., 2007). Meanwhile, hypercholesterolemia is one of the most common inherited disorders to Malaysians as the prevalence increased from 35.1% to 38.1% in year 2011 until 2019 (Institute for Public Health Malaysia, 2019; Mat Rifin et al., 2018).

It has been reported that an increase in non-high density lipoprotein cholesterol (non-HDL-C) level may cause an elevated level of low density lipoprotein cholesterol (LDL-C) and TG-rich lipoprotein which is the main cause of hypercholesterolemia and CVD (Liu et al., 2006). The intake of 2 g/d to 4 g/d of omega-3 free fatty acid (FFA) could significantly reduce the non-HDL-C and TG level of patients suffering from hypertriglyceridemia (Kastelein et al., 2014; Maki et al., 2013). According to the study by Russell & Bürgin-Maunder (2012), most national and international health and government organisations recommend a significant dosage intake of omega-3 fatty acid daily ranging from 250 mg/d for a healthy adult and up to 4000 mg/d for an adult suffering from different diseases. For example, the American Heart Association suggested 1000 mg/day of omega-3 for chronic heart disease sufferers (Turchini et al., 2012). Besides reducing the risk of CVD which is the most significant benefits from omega-3, there are also other health benefits that omega-3 might offer such as curbing mental health problem (Dyall, 2015; Gow & Hibbeln, 2014; Sublette et al., 2011) and has anti-inflammatory effects (Buckley et al., 2014). With that, omega-3 supplements might be able to help 2.3% of adults suffering from depression and 7.9% of children below 15 years of age having some sort mental health problem in Malaysia as reported in 2019 (Institute for Public Health Malaysia, 2019).

The most commercial sources of omega-3 are found in aquatic organisms and plants. Likewise, microalgae are also considered as the potential producer of long-chain omega-3 fatty acid mainly EPA and DHA. Many researchers found different algal species that have high omega-3 content (Griffiths et al., 2012). Usage of microalgae in the production of omega-3 supplements commercially may have many benefits such as reducing of the possibilities of getting methylmercury poisoning from fishes, creating another alternative source of long-chain omega-3 for vegan and non-fish eater, and becoming new source of antioxidants (Breivik, 2007; Freitas et al., 2012; Kris-Etherton et al., 2002).

Subcritical water extraction (SWE) has been used to extract various biomolecules, including omega-3. SWE is known to be a green extraction method as the process of extraction is performed without the usage of any harmful solvents. This method is able to extract high amount of nutraceuticals and lipids with just the changes in water properties at high temperature and high pressure conditions (Reddy et al., 2016).

Stakeholders such as Martek and Cellana who had lots of experience in omega-3 have already ventured into omega-3 production from microalgae hence proving its marketability and promising future (Adarme-Vega et al., 2012). In the meantime, Malaysia also currently has its own largest algae cultivation facility in Sarawak as the project is jointly organized by the Sarawak Biodiversity Centre and Mitsubishi Corporation (BERNAMA, 2019). Most of the research universities in Malaysia have developed interest in tapping into microalgae researches but their focus are more into the production of biodiesel instead of omega-3 extraction (Rajkumar & Sobri Takriff, 2016). However, some researchers believed in the potential of microalgae in global omega-3 market contributing nearly US$350 million of sales in 2012 (Matos, 2017).

1.2 Problem Statement

Most conventional extraction techniques such as mechanical extraction, Soxhlet, and Bligh & Dyer (B&D) methods involve long processing time and usually use hazardous chemicals as solvents. This hinders the application of the extracted products to be fully utilized for human consumption. Meanwhile, there is also an increase in demands for sustainable omega-3 sources in the market but farmed fishes had dropped in qualities in terms of omega-3 content over the years from about 3 g of omega-3 per 100 g fish oil to less than 2 g of omega-3 per 100 g of oil (Tocher et al., 2019). Microalgae, *Nannochloropsis gaditana* has great omega-3 production potentials that are not only suitable for human consumption but also beneficial to the environment.

Lipid extracts constructed by complex neutral lipid (NL) and polar lipid (POL) mixtures commonly pose extraction and purification challenge. Therefore, a need for green, fast and robust approach to extract the lipids from *Nannochloropsis gaditana* is essential. Green method such as supercritical carbon dioxide (CO_2) extraction still requires a need for co-solvent (hexane and ethanol) which is harmful for the environment for the extraction of both NL and POL (Patil et al., 2018). With the benefits offered by the SWE coupled with the correct choice of purification approach, the quality and the commercial viabilities of the omega-3 fatty acids produced can be ensured even without the usage of other harmful chemicals. The control in extraction temperature and time will be a key factor in optimizing the extraction of EPA existing in both NL and POL (Qu et al., 2018).

Also, scaling up the green extraction method of algal oil via subcritical water extraction (SWE) is still a major challenge. Currently, there are no extensive study on the optimization and kinetics on the extraction of omega-3 fatty acids from *Nannochloropsis* species from SWE method even though this compound exists abundantly in this microalgae species. Basic understanding of the extraction and conversion of microalgae biomass to lipid, aqueous product, and gas is not adequate to fully utilize the lipid into nutraceuticals (Hietala et al., 2016). Optimization of reaction parameters and understanding the kinetic reaction of the process in SWE in terms of EPA products will effectively help in scaling up the process (Mathimani et al., 2019).

Meanwhile, the growth of this industry in producing omega-3 from microalgae should not be overlooked as it is currently one of the growing industries in the world (Milledge, 2011; Tocher et al., 2019). Thus, the aims of this study are to investigate the potential of SWE technology in extracting lipid from *Nannochloropsis gaditana* and to optimize its parameters for high quality lipid with high EPA content yield. The outcome of this study will contribute to a better utilization of microalgae as an available source of omega-3 fatty acids for food and pharmaceutical industry as well as achieving a green and fast extraction with high concentration of omega-3.

1.3 Research Objectives

The main focus of the study is divided into the following specific objectives:

a) To investigate and optimize the factors that affect the extraction yield of lipid and eicosapentaenoic acid (EPA) composition from *Nannochloropsis gaditana* via subcritical water extraction (SWE) method.
b) To analyze the extracted lipid from SWE according to lipid composition and fatty acid profile of *Nannochloropsis gaditana*.
c) To develop the reaction network and kinetic model of SWE for EPA extracted from *Nannochloropsis gaditana*.

1.4 Research Scopes and Limitations

This study focuses on the extraction of lipid and EPA from *Nannochloropsis gaditana* using SWE method. The variables studied were the extraction temperature, time and biomass loading. The extraction volume of total biomass and water was limited to 32 mL due to the maximum size of the batch reactor. The extraction yield and quality of the lipids were analyzed using gas chromatography (GC) and optimized through central composite design (CCD).

Thin layer chromatography (TLC) and solid-phase extraction (SPE) method were incorporated into the study to separate the lipid into NL, POL and FFA. This separation of lipid classes clearly showed the content and quality of lipid extracted from *Nannochloropsis gaditana.* Further separations of NL and POL into sub-classes (acylglyceride, phospholipid, glycolipid (GL), etc.) were not done due to the small amount of lipid that can be extracted from the batch system of SWE per extraction cycle. Moreover, additional separation will cause more error in calculation and analysis. Hence, only the three major classes of lipid (NL, POL and FFA) were studied.

A reaction network of SWE of EPA from *Nannochloropsis gaditana* was also developed based on the literature. The reaction pathway will focus to the natural form EPA attached to NLs and POLs. With the reaction network developed, kinetic reaction equations can be formed. The Arrhenius parameters were solved and a mathematical model was established. The parity plot between experimental yield and model yield were also performed to validate the model.

1.5 Significance of Research

Various companies and research setups for algal cultivation and biofuels are coming up and established by major investors in Malaysia and abroad (BERNAMA, 2019). Algae have recently received a lot of attentions as a biomass source for the production of biofuels and bioproducts (Marrone et al., 2018). Some of the main characteristics which set microalgae apart from other biomass sources are that microalgae have high biomass yield per unit of light and area and high oil yield. Meanwhile, microalgae may not necessarily require agricultural land and fresh water for cultivation as the nutrients and CO_2 can be supplied by wastewater and flue gas, respectively (Hemaiswarya et al., 2011; Rosenberg et al., 2008). However, the commercialization of nutraceuticals from microalgae still has major hurdles to overcome. Therefore, this research is aiming to make the extraction of omega-3 from microalgae biomass more commercially viable and environmentally friendly by focusing on extracting microalgae compounds using SWE technique. To date, none of research has been reported in utilizing this technology for microalgae omega-3 extraction. With numerous advantages of this system, it is expected to be a good extraction method for producing omega-3 nutraceuticals from microalgal biomass.

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Bernard Ho Chon Han graduated with a degree from Universiti Putra Malaysia (UPM) in Bachelor of Engineering (Chemical) in 2015. Soon after graduation, he continued on his master's degree in UPM with the research in Subcritical water extraction (SWE) of lipid containing omega-3 from microalgae *Nannochloropsis gaditana*. In the midst of his master research, he managed to convert his study from master's degree to PhD degree as there are potential to expand the objectives of the study and to further improve the research. To date, he has published several papers in peer-reviewed journals and presented numerous papers in both national and international conferences.

LIST OF PUBLICATIONS

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