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SUB-CRITICAL WATER EXTRACTION OF FUCOIDAN FROM BROWN ALGAE PADINA SP.

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By

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

SUB-CRITICAL WATER EXTRACTION OF FUCOIDAN FROM BROWN ALGAE *PADINA SP.*

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Chairman : Assoc. Prof. Mohd Razif bin Harun, PhD
Faculty : Engineering

Chemical, mechanical, and biological approaches are the common extraction techniques used to extract bioactive compounds. These techniques use chemical solvents, have long processing steps, and produce low yields. An important aspect being considered in extracting bioactive compounds is fast extraction techniques and environmentally friendly extraction processes. One of the emerging green extraction processes is called Subcritical Water (Sub-CW) Extraction. The advantages of this technique include significant reduction of solvents, non-toxic green solvent (water), higher extraction yields, less extraction time, and low costs of extracting agents.

This study investigates the extraction of fucoidan compounds in brown algae using Sub-CW technology. The study covers screening and optimizing Sub-CW parameters, evaluating the process kinetics and thermodynamics, and comparing the yield of fucoidan with the conventional methods. The presence of fucoidan was confirmed by running the standard fucoidan using high performance liquid chromatography (HPLC), and the biomass was further analyzed using standard analytical instruments. Several analyses have been done to support the HPLC results. The samples were characterized with Fourier-transform infrared (FTIR) spectroscopy, scanning electron microscopy (SEM), and elemental analyzer CHNS to identify the $-SO_3H$ functional group and other organic compounds, surface morphology, and elemental analysis accordingly.

The effect of three different variables, which were temperature, reaction time, and biomass concentration, were investigated according to a single factor to achieve maximum fucoidan yield. The result showed that the highest extraction yield was achieved at 180°C, 10 min extraction, and 2 % biomass concentration. In the optimization study, the Sub-CW was carried out based on the data generated from central composite design (CCD) by varying different process parameters, including reaction temperature, reaction time, and biomass concentration. The experimental range and levels of the independent process variable were set based on the parameters from the screening experiment. The optimum fucoidan of 50.65 wt% was achieved at 176 °C,12 min, and a concentration of 2%. A single, consecutive reaction model used for data validation showed a good agreement between the experimental and theoretical data generated.

In terms of the kinetic and thermodynamic behavior of fucoidan extraction from brown algae by Sub-CW, it was observed that the fucoidan yield could be rapidly produced and decomposed from the subcritical water extraction process. Thermodynamic analysis by transition-state theory showed the subcritical water reaction process as endothermic, while the Gibbs free energy of activation showed the reaction as non-spontaneous, requiring constant external energy to support it.

Overall, this study shows the capability of Sub-CW in extracting fucoidan from brown algae. Thus, the findings will benefit the food and pharmaceutical industries to utilize a green method for extracting biomolecules from macroalgae for new products with high added value.

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

AIR SUB-KRITIKAL DIGUNAKAN UNTUK MENGEKSTRAK FUCOIDAN DARIPADA RUMPAI LAUT COKLAT *PADINA* SP.

Oleh

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Antara teknik pengekstrakan yang biasa digunakan untuk mengekstrak sebatian bioaktif ialah teknik pengesktrakan secara kimia, mekanikal dan biologi. Walaubagaimanapun, kaedah pengekstrakan secara konvensional mempunyai beberapa kekurangan iaitu, penggunaan pelarut organik dalam pengekstrakan, masa pengekstrakan yang panjang dan penghasilan produk yang sedikit. Kajian giat dijalankan untuk menambahbaik kaedah pengekstrakan sedia ada dengan kaedah pengekstrakan yang lebih mesra alam sekitar dan melibatkan proses pengekstrakan yang singkat. Salah satu proses pengekstrakan yang mesra alam dikenali sebagai pengekstrakan menggunakan air subkritikal. Antara kelebihan teknik ini termasuklah menggantikan penggunaan bahan pelarut organik dengan air sebagai pelarut, menghasilkan produk yang lebih banyak, mengurangkan masa pengekstrakan serta mengurangkan kos pengendalian sepanjang proses pengekstrakan dijalankan.

Kajian ini dijalankan untuk mengekstrak sebatian *fucoidan* daripada rumpai laut melalui kaedah pengekstrakan menggunakan air subkritikal. Ia melibatkan penyediaan sampel, pemilihan parameter dan penghasilan produk yang optimum. Di samping itu, kajian tentang tenaga kinetik, tenaga pengaktifan dari segi termodinamik turut dilakukan. Sebatian *fucoidan* telah berjaya diekstrak dan pengekstrakan dianalisa menggunakan kromatografi cecair prestasi tinggi (HPLC). Kehadiran *fucoidan* disahkan dengan membandingkan keputusan yang diperoleh menggunakan piawai *fucoidan*. Beberapa analisa juga telah dilakukan untuk menyokong hasil HPLC. Sampel dianalisa menggunakan spektroskopi inframerah transformasi Fourier (FTIR), microskop electron imbasan (SEM) dan mesin untuk menganalisis unsur karbon, hydrogen, nitrogen dan sulfur iaitu CHNS yang berfungsi untuk mengesan kehadiran kumpulan berfungsi SO_3H dan sebatian organik lain, morfologi permukaan serta analisis unsur-unsur yang bersesuaian.

Eksperimen dijalan untuk mengetahui kesan daripada tiga pemboleh ubah yang berbeza iaitu suhu, masa tindak balas dan kepekatan biomas. Tindakbalas pemboleh ubah ini disiasat mengikut faktor tunggal bertujuan mencapai hasil *fucoidan* yang maksimum. Hasilnya menunjukkan bahawa suhu, masa tindak balas and kepekatan biomas yang terbaik masing-masing di catat pada 180 °C, 10 min dan 2%. Kemudian, kajian pengoptimumam dijalan berdasarkan keputusan eksperimen faktor tunggal. Julat eksperimen daripada kajian faktor tunggal seperti suhu, masa tindak balas dan kepekatan biomas di masukkan ke dalam sistem *central composite design* (CCD) dengan menghasilkan 20 variasi proses parameter yang berbeza. Eksperimen dijalankan berdasarkan 20 variasi proses parameter tersebut. Hasil *fucoidan* yang optimum iaitu sebanyak 50.65% dicapai masing-masing pada suhu, masa dan kepekatan biomass iaitu pada 176 °C, 12 min, dan 2%. Model yang dihasilkan menunjukkan bahawa kedua-dua data samada secara teori dan eksperimen adalah selari.

Kajian kinetik dan termodinamik yang dijalankan menunjukkan bahawa *fucoidan* dihasilkan dan diuraikan dengan cepat semasa tindak balas berlaku. Analisis ini juga mengenalpasti proses yang terlibat semasa tindak balas ialah endotermik, sementara tenaga bebas *Gibb* menunjukkan tindak balas yang berlaku adalah secara tidak spontan dan memerlukan tenaga luar untuk menyokongnya.

Kajian ini menunjukkan bahawa pengekstrakan *fucoidan* daripada rumpai laut mengggunakan air subkritikal adalah berjaya. Dalam masa yang sama produk yang dihasilkan juga lebih tinggi jika dibandingkan dengan kaedah pengekstrakan secara konvensional. Oleh itu, hasil penyelidikan ini diharapkan dapat memberi manfaat kepada industri makanan dan farmasi dengan mengetengahkan kaedah pengekstrakan yang menggunakan air subkritikal sebagai pelarut. Kaedah ini lebih mesra alam sekitar dengan mempunyai beberapa ciri kelebihan yang lain.

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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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Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision.
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

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LIST OF ABBREVIATIONS

Sub-CW	Subcritical Water
sp.	Species
USD	United State Dolar
M	Molar
HCl	Hydrochloric Acid
MAE	Microwave-assisted extraction
UAE	Ultrasound-assisted extraction
PHWE	Pressurized Hot Water Extraction
EAE	Enzyme-assisted extraction
SHWE	Superheated Water Extraction
PLE	Pressurized liquid extraction
min	Minutes
BA	Betulinic acid
USWE	Ultrasonic enhance subcritical water extraction
T	Temperature
t	Time
P	Pressure
hr	Hour
CCD	Central Composite Design
RSM	Respond Surface Methodology
BBD	Box-Behnken design
ANOVA	Analysis of Variance
k	Rate constant
A	Preexponential factor

R	Gas constant
T	Absolute temperature
ΔH	Change in enthalpy
ΔS	Change in entropy
ΔG	Gibb's free energy
IOES	Institute of Ocean and Earth Sciences
DPPH	2,2-diphenyl-1-picrylhydrazyl hydrate
TGA	Thermo-Gravimetric Analyser
CHNS	Carbon Hydrogen Nitrogen Sulfur
C	Carbon
H	Hydrogen
N	Nitrogen
S	Sulfur
rpm	Revolutions per minute
kb	Boltzmann constant
H	Planck's constant
HPLC	High-Performance Liquid Chromatography
FTIR	Fourier transform infrared
SEM	Scanning Electron Microscope
EDS	Energy dispersive
UV-Vis	Ultraviolet-visible
O	Oxygen
FCPs	Fucose-containing sulfated polysaccharides

CHAPTER 1

INTRODUCTION

1.1 Background of study

The demand for natural products has increased and is expected to double by 2030 compared to 2010, as consumer wellness and health consciousness are currently the main drivers for the agri-food market (Garcia-Vaquero et al., 2020; Islam & Karim, 2016). For this reason, the functional foods and nutraceuticals market has experienced rapid growth over the past decade and is estimated to reach USD 94.21 billion USD by 2023 (Garcia-Vaquero et al., 2020).

One of the natural sources is marine algae. This situation urges the research on product development from marine algae because of its benefits to humans. Marine algae can be categorized into different pigmentation groups, namely Rhodophyceae (red algae), Chlorophyceae (green algae), and Phaeophyceae (brown algae). The color of marine algae is contributed by the pigments such as phycobilins for red, chlorophyll for green, and fucoxanthin for brown algae (Kadam et al., 2013).

The bioactive compounds in marine algae that have most interestingly been explored are fucoidan (Alboofetileh, Rezaei, Tabarsa, You, et al., 2019; Wang & Chen, 2016; January et al., 2019; Sinurat et al., 2015), laminarin (Abraham et al., 2019; Kadam, Donnell, et al., 2015; Kadam, Tiwari, et al., 2015), and alginate (Abraham et al., 2019). These bioactive compounds need to be extracted from their original plant before being applied in pharmaceutical products (Liang & Fan, 2013), food industries, and cosmeceutical areas. The current trend shows that the marine plant catches more attention due to the overpopulation, simple growing method, and easy harvesting (Anastasakis et al., 2011; Rodríguez-Jasso et al., 2013).

Among the other types of bioactive compounds, fucoidan has been the focus of this work due to its wide application in the pharmaceutical field. It has antioxidant, antimicrobial, anticoagulant, antithrombotic, immunomodulatory, and anticancer properties (Dore et al., 2013; Meillisa et al., 2013; Pádua et al., 2015). Brown algae are the most common source of fucoidan (C. Yang et al., 2008). Therefore, in this project, it was decided to obtain the fucoidan from the brown alga *Padina sp*.

Fucoidans are water-soluble. It has a very complex structure (Bilan et al., 2013; Kopplin et al., 2018; Senthilkumar et al., 2013). The linkage, branching, sulfate positions, and composition of monosaccharides differ significantly (Dore et al., 2013). The structure also depends on the time of harvesting, season, species, and the place of growth (K. T. Kim et al., 2014). The biological activity and medicinal impact of fucoidan depend on its structural properties (Dobrinčić et al., 2020; Oliveira et al., 2020). The simplest fucoidan structure contains L-fucose, sulfate, and glycosidic bond (Ale & Meyer, 2013; Bilan et al., 2014; Hahn et al., 2012; Synytsya et al., 2010). A more complex fucoidan structure may additionally contain several other monosaccharides, such as galactose, mannose, and xylose (Bilan et al., 2014).

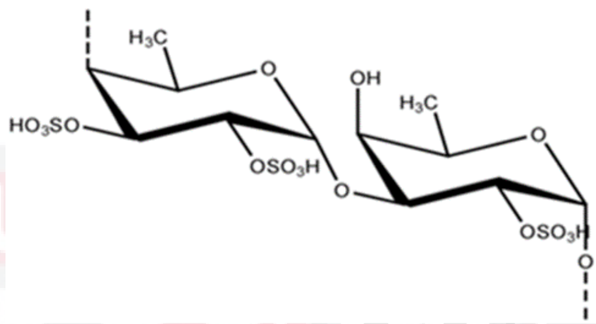

Figure 1.1: Basic structure of fucoidan (Thomas & Kim, 2013).

Most industries and researchers use conventional extraction methods to extract the target compounds from the sample matrix. The conventional solid-liquid extraction methods that are commonly used are Soxhlet, maceration, and reflux extraction. However, conventional extraction techniques often involve a longer extraction time and require large amounts of toxic organic solvents. Safety concerns have been raised for workers exposed to these chemicals and for consumers of the final products (Garcia-Vaquero et al., 2020). However, conventional extraction technologies are still used, and a method has been developed to adapt the traditional method to current market needs. These modifications to the conventional apparatuses are aimed at developing a more environmentally-friendly extraction method by reducing time, energy, and solvent to ensure the continued use of these technologies by adapting the equipment to the new technological trends and the current needs of the industry (Garcia-Vaquero et al., 2020). For example, Soxhlet extraction has been developed into the new generation of automated Soxhlet extraction. The work tries to improve the conventional Soxhlet extraction with some modifications. In the early 1970s, Randall developed the submersion technique, which was a milestone in this field. The modification offers the possibility of reducing the extraction time (Zygler et al., 2012).

Instead of the conventional extraction methods, several new and novel extraction techniques have attracted attention, aiming to overcome the main shortcomings of the conventional extraction methods. The poor steps of the conventional extraction method are replaced by more environmentally friendly steps that shorten the extraction process, use non-toxic solvents, and provide high extraction yields. Examples of novel extraction techniques include ultrasonic-assisted extraction (UAE), microwave-assisted extraction (MAE), supercritical fluid extraction (SFE), and subcritical water extraction (sub-CW) (Tatke & Rajan, 2014). Basically, organic solvents are still used in novel extraction techniques. But their amount is much lesser compared to the conventional extraction methods. However, in both SFE and sub-CW extraction, CO_2 and water are used as solvents, respectively. By using CO_2 and water, the extraction process can be carried out in an environmentally friendly medium (Danlami et al., 2014). However, due to the high operating temperature of the SFE, thermal degradation of the targeted bioactive compounds may occur, making this method unsuitable for this project. The only novel extraction technique that uses safe and environmentally friendly solvents is subcritical water extraction. In addition, subcritical water extraction is expected to have a higher yield compared to the conventional extraction technique, and the operating temperature is suitable for the extraction of bioactive compounds.

Although the discovery of the human health benefits of fucoidan is very exciting, there have been few studies on the green extraction of fucoidan, which limits its commercialization. Therefore, in this study, subcritical water extraction technology is used as a green extraction technique for the extraction of fucoidan from *Padina sp*. alga. This study aims to identify and understand the factors, mechanisms, and suitable operating conditions for fucoidan production using subcritical water technology. This is vitally important in establishing the bioactive compounds of *Padina sp.* in this study.

1.2 Problem statement

The conventional extraction methods for fucoidan from brown algae used organic solvents during the extraction process. These approaches have also required the use of different types of chemicals during the process (pre-treatment, extraction, purification), such as hydrogen peroxide, ozone, methanol, and ionic liquid.

The disadvantage of using varieties of chemicals is the removal of the chemicals after the extraction is completed. These chemicals may contaminate the bioactive compounds if the process does not properly handle since the product is edible (Molino et al., 2020). Furthermore, the extraction process obtained by organic solvent contributes to the long process time. For instance, the acid extraction by HCl and citric acid to extract brown algae species required up to 2 to 24 h to be completed (Hifney et al., 2016; Lutfia et al., 2020; Serrão et al., 2019). The extraction process by organic solvent also produces a low extraction yield. The three brown seaweed species, *Turbania sp*., *Sargassum sp*., and *Padina sp*. that were extracted using the acid extraction method produced a fucoidan yield of 4.8, 2.7, and 2.6 %, accordingly (Serrão et al., 2019). A different set of experiments on the same species of brown algae resulted in a fucoidan yield of 2.68, 4.02, and 2.01 %, respectively (Essien et al., 2020).

The main concern of this project is to look for a greener alternative extraction method. Therefore, the subcritical water (sub-CW) extraction method is proposed. This method utilizes water as the solvent instead of the organic solvents. The use of water as a solvent has made this method sustainable, economical, and environmentally friendly to be used for various product development. The subcritical water technology is considered economical and sustainable as water is readily available and has a positive life cycle assessment, ensuring a safe and superior technology (Gbashi, Madala, et al., 2017). Also, subcritical water adopts a relatively less sophisticated technology, thus requiring much lower engineering costs for process-scale apparatus/equipment (Gbashi, Madala, et al., 2017; Kubátová et al., 2001). The dielectric constant and ionic properties of water change at subcritical conditions (101-374°C, 0.1-22.1 MPa), making water act as an organic solvent and acid catalyst (Espinoza & Morawicki, 2012; Shitu et al., 2015; Thiruvenkadam et al., 2015). It is expected that the application of the sub-CW technique in the extraction of fucoidan from brown algae would reduce the environmental health issue and operating time, enhance production yield, and reduce the operating cost compared to the conventional extraction methods.

1.3 Research objectives

The overall aim of this study is to determine the feasibility of the subcritical water technique as a green technology approach for fucoidan production from brown algae.

The objectives of this study are;

1. To investigate the parameters (temperature, time, biomass concentration) that affect the extraction yield of fucoidan from brown algae via the Sub-CW extraction technique.

2. To evaluate the interactions of different Sub-CW extraction parameters on the yield of fucoidan extracted from brown algae.

3. To evaluate the kinetic and thermodynamic parameters of fucoidan production from brown algae using Sub-CW extraction.

1.4 Scope of study

1.4.1 Investigation of the parameters that affect the extraction yield of fucoidan from brown algae via the sub-CW extraction technique

The main scope of this study is to identify the yield of fucoidan composition obtained via subcritical water technology at different ranges of temperatures, biomass concentrations, and time. The effects of various parameters in the production of fucoidan from brown algae were evaluated, and the range of values that resulted in the highest production of fucoidan was obtained. The findings provide a basis or reason for the range of parameters in the kinetic and RSM study.

1.4.2 Evaluation of the interactions of different sub-CW extraction parameters on the yield of fucoidan extracted from brown algae

Response surface methodology (RSM) under central composite design (CCD) was employed to develop the empirical equations. The empirical equations can be used to predict the yield of fucoidan production from brown algae via subcritical water technology. The adequacy of the empirical model developed was then tested and verified. Significant factors or parameters that could affect the production of fucoidan were identified by the analysis of variance (ANOVA) method, and the interaction of each factor on fucoidan production was evaluated by 3D-graphical representation.

1.4.3 Evaluation of the kinetic and thermodynamic parameters of fucoidan production from brown algae using sub-CW extraction

A kinetic model is required to describe the production of fucoidan from brown algae. The range of experimental conditions selected in this study was based on the suggested operating conditions from RSM. The data obtained from the experimental study was used to determine the rate of fucoidan production and decomposition via subcritical water. Computer software MATLAB was used in the kinetic modeling to determine the rate constant of fucoidan production and decomposition. The activation energy as well as the pre-exponential factor (A), were calculated using this so-called Arrhenius plot. The thermodynamic analysis was evaluated using the transition-state theory and focused on determining the enthalpy, entropy, and Gibbs free energy of activation of the reaction.

1.5 The significance of the study

Fucoidan is the most bioactive compounds contain in brown algae. The application of fucoidan as biological activity creates the interest of many scientists in studying fucoidan extraction. Some examples of biological activities of fucoidan are antioxidant, antitumor, anticoagulant, antiviral, and anti-inflammatory.

Fucoidan has been extracted from brown algae using a conventional extraction method (Pielesz et al., 2011; Sinurat et al., 2015; Sugiono et al., 2014; Yuan & Macquarrie, 2015). However, the trend has changed. Currently, fucoidan has been extracted from various brown algae types using the green extraction method, especially Sub-CW extraction (Alboofetileh, Rezaei, Tabarsa, You, et al., 2019; Saravana, Cho, Patil, et al., 2018).

To the best of my knowledge, no extraction of fucoidan from brown algae species *Padina sp.* using sub-CW extraction had been studied before. Hence, the study is essential to investigate the potential of sub-CW to extract fucoidan from *Padina sp.* by producing the compound at the optimum yield. This study is important to establish the extraction method that utilizes less sophisticated technology, thus requiring much lower engineering costs for process-scale apparatus/equipment. Also, this study helps to investigate the reaction mechanism and energy needed during the extraction process. Overall, this study will give a better picture of how extraction occurs and affects fucoidan yield.

1.6 Thesis layout

The overall research work is organized into five chapters in this thesis.

Chapter 1 discusses the factors of choosing green extraction techniques for the extraction of fucoidan from brown algae. This chapter contains the significance of the study, the objectives of the research, and the scope of work.

Chapter 2 reports the findings of the extraction of bioactive compounds from brown algae and other plant materials using both the conventional method and the green extraction method. The advantages and disadvantages of both techniques are highlighted to find the best techniques for extraction purposes.

Chapter 3 listed the materials used in the experiment. The methods started with the preparation of raw samples, the characterization of raw samples, the extraction process, and the analysis of both raw and final products.

Chapter 4 provides the results and discussions of the research. The discussion included the three extraction parameters and their correlation. The optimum parameters to produce the optimum yield are presented. The result of the kinetic study is explained.

Chapter 5 summarises all the conclusions and recommendations of the research. The best results and recommendations are stated.

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