UNIVERSITI PUTRA MALAYSIA

PHYTOCHEMICAL AND GLUCOSE LOWERING POTENTIAL OF SEAWEED Eucheuma denticulatum (N.L. Burman) F.S. Collins & A.B. Hervey IN VITRO

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

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September 2017

Chair : Professor Amin Ismail, PhD
Faculty: Medicine and Health Sciences

Type 2 Diabetes Mellitus (T2DM) represents a serious global epidemic of the 21st century as reported by World Health Organisation (WHO). T2DM causes its own direct adverse effects as well as predisposes patients to the development of other chronic metabolic diseases such cardiovascular complications which lead to premature mortality. Thus, continuous search for remedies with minimum side effects were paramount. Scores of studies have demonstrated the health benefits derived from eating seaweed which promotes seaweed as a nutritional foodstuff. Moreover, research is advancing into using marine macroalgae also known as seaweed for production of novel foods and nutraceuticals. Modulating digestion with natural compounds has been shown to be a fruitful approach to the treatment of diabetes. The objectives of this study were to assess Malaysian seaweed species for their potential to regulate postprandial hyperglycaemia which is a pivotal feature of T2DM. Three species of Malaysian edible seaweed (*Eucheuma denticulatum, Sargassum polycystum and Caulerpa lentillifera*) found in coastal area of Sabah were selected and subjected to evaluation of their anti-diabetic potential *in vitro* in terms of their inhibition towards digestive enzymes that involve in hydrolysis of dietary carbohydrates (α-amylase and α-glucosidase). The seaweed were further subjected to other analyses related to glucose lowering properties such as antioxidant capacity, anti-inflammatory, adipogenesis, lipase enzyme inhibition and glucose uptake activities. Initially, the seaweed were screened and characterized for the presence of natural functional bioactive compounds which can be related to its health benefits. Following that, dinitrosalicylic acid assay was adapted in microplate to assess the inhibition of α-amylase activity while colorimetry method for α-glucosidase inhibition assay. Antioxidant capacity was evaluated for their free radical-scavenging capacity using 1, 1-diphenyl-2-pricrylhydrazyl (DPPH) assay and oxygen radical absorbance capacity (ORAC). The anti-inflammatory potential and cytotoxic effects of the seaweed samples were evaluated by the inhibitory activity of nitric oxide (NO), interleukin-6 (IL-6), interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), and monocyte chemoattractant protein-1 (MCP-1) on interferon-gamma/ lipopolysaccharide (IFN-γ/LPS) stimulated murine macrophage cell line (RAW 264.7) and adipocytes (3T3-L1) using Griess reaction, immunoassays and MTS assay. Adipogenesis and glucose uptake

in 3T3-L1 were measured using commercial kits while lipase assay was measured by turbidimetric method. HPTLC, UHPLC and LC-MS/MS methods were established and validated for the quantitative determination of the identified compounds. The ethanolic extracts of the three species of seaweed showed the presence of carotenoids and the most notable being fucoxanthin, lutein, zeaxanthin, astaxanthin, canthaxanthin, β-cryptoxanthin, β-carotene and fatty acids such as palmitoleic acid (PA), docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Fucoxanthin was the major carotenoid detected in the brown seaweed (*S. polycystum*) (2,740 mg/ 100 g DW). In the case of red seaweed (*E. denticulatum*), lutein (88 mg/ 100 g DW) and zeaxanthin (21 mg/ 100 g DW) were the major carotenoids, apart from small amount of fucoxanthin, while for the green seaweed (*C. lentillifera*), β-carotene (20 mg/ 100 g DW) and canthaxanthin (15 mg/ 100 g DW) were detected as major carotenoids. The method exhibited (a) linear calibration curves (R^2>0.97), (b) satisfactory recoveries for most of the pigments (between 74 and 104%), and (d) low detection (from 0.001 to 0.01 ng/µl) and quantification limits (from 0.004 to 0.02 ng/µl) (LOD and LOQ, respectively). Ethanolic and methanolic extracts from the studied seaweed were found to display inhibitory effects against α-amylase (11-67%; n=3), but have no effect on α-glucosidase activity *in vitro*. Amongst the 3 genera, *E. denticulatum* ethanolic extract was found to be most effective *in vitro* inhibitors of α-amylase with IC_{50} of 0.14 mg/ml. Thus, this seaweed was selected for further solvent fractionation and bioactivity assays. Among the five investigated fractions (hexane, ethyl acetate, acetone, butanol and water), the hexane, ethyl acetate and acetone fractions exhibited good inhibition with a mean of 42%. The brown seaweed, *S. polycystum* displayed the highest DPPH radical scavenging and TPC (20%; 400 mg GAE/ 100 g respectively) whilst for ORAC analysis, *E. denticulatum* exhibited the highest activity at 112,762 µmol TE/ 100 g. *E. denticulatum* ethanol extract and fractions (1–100 µg/ml), also exhibited anti-inflammatory activity without showing any cytotoxic effect to RAW 264.7 cells. The crude and fractions seem to inhibit adipogenesis and enhances glucose uptake in the 3T3-L1 cell model while ethanolic extract showed the highest lipase enzyme inhibitory (83%) compared to other sample preparation. The presence of fatty acids such as PA and EPA, antioxidant compounds such as polyphenols and carotenoids may probably contributed to the glucose lowering efficacy of these seaweed. In conclusion, this study demonstrated that *E. denticulatum* was able to exert bioactive actions such as anti-diabetic, antioxidant, immune modulating and anti-obesity properties *in vitro* which suggesting its potential source as functional ingredient that can be further exploited to generate new valuable products for various commercial applications.

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

PENCIRIAN FITOKIMIA DAN POTENSI PENURUNAN GLUKOS OLEH RUMPAI LAUT *Eucheuma denticulatum* (N.L. Burman) F.S. Collins & A.B. Hervey SECARA *IN VITRO*

Oleh

B.VIMALA A/P R.M.T. BALASUBRAMANIAM

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Diabetes Melitus- Jenis 2 (T2DM) merupakan satu wabak global yang serius pada abad ke-21 menurut Pertubuhan Kesihatan Sedunia (WHO). T2DM bukan sahaja menyebabkan kesan-kesan buruk secara langsung tetapi juga mempengaruhi pesakit untuk mendapat penyakit kronik yang lain seperti penyakit jantung dan penyakit buah pinggang. Oleh itu, usaha berterusan untuk mencari penawar dengan kesan sampingan yang minimum adalah paling utama. Kajian telah menunjukkan manfaat kesihatan daripada pemakanan rumpai laut. Selain itu, penyelidikan rumpai laut telah maju dan semakin berkembang dalam bidang pengeluaran makanan baharu atau unik dan nutraseutikal. Modulasi pencernaan makanan dengan sebatian semula jadi telah terbukti sebagai salah satu pendekatan yang bermanfaat untuk rawatan kencing manis. Objektif kajian ini adalah untuk mengumpul, menyaring dan menilai spesies rumpai laut Malaysia sebagai potensi untuk mengawal hiperglisemia atau peningkatan gula dimana ia merupakan ciri penting untuk mengawal T2DM. Tiga spesies rumpai laut (*Eucheuma denticulatum*, *Sargassum polycystum* dan *Caulerpa lentillifera*) yang terdapat di kawasan pesisiran pantai Sabah telah dipilih bagi penilaian potensi anti-diabetes mereka dalam kajian *in vitro* iaitu dari segi perencatan terhadap enzim pencernaan yang terlibat dalam hidrolisis karbohidrat (α-amylase dan α-glucosidase) dan seterusnya menilai kapasiti antioksidan, aktiviti anti-inflamatori, perencatan lemak di dalam sel, pengambilan glukosa oleh tisu dan perencatan enzim lemak lipase. Rumpai laut juga telah dianalisis untuk mengetahui kehadiran sebatian bioaktif berfungsi semula jadi yang boleh dikaitkan dengan manfaat kesihatan. Analisis asid dinitrosalicylic telah dijalankan untuk menilai aktiviti α-amylase manakala kaedah kolorimetri untuk α-glucosidase. Kapasiti antioksidan dinilai dengan menggunakan 1, 1-Diphenyl-2-pricrylhydrazyl (DPPH) assay dan analisis ORAC. Kesan-kesan anti-radang dan sifat keracunan oleh sampel rumpai laut telah dinilai dari segi penurunan biomarker seperti nitrik oksida (NO), interleukin-6 (IL-6), interleukin-1 (IL-1), tumor nekrosis faktor-alpha (TNF-α), dan monocyte chemoattractant protein-1 (MCP-1) di dalam sel makrofaj (RAW 264,7) dan lemak (3T3-L1) yang telah di aktifkan oleh interferon gamma / lipopolysaccharide (IFN-γ/ LPS) menggunakan analisis Griess,

immunoassays dan kit MTS. Adipogenesis dan penyerapan glukosa dalam sel lemak, 3T3-L1 diukur menggunakan kit komersial manakala analisis perencatan enzim lemak lipase menggunakan kaedah turbidimetric. Kaedah HPTLC, UHPLC dan LC-MS/MS telah digunakan untuk penentuan kandungan sebatian atau komponen yang dikenal pasti di dalam ekstrak rumpai laut. Ekstrak ethanol ketiga-tiga rumpai laut yang di kaji mengandungi karotenoid seperti fucoxanthin, lutein, zeaxanthin, astaxanthin, canthaxanthin, β-cryptoxanthin, β-carotene dan asid lemak seperti asid palmitoleic (PA), asid docosahexaenoic (DHA) dan asid eicosapentaenoic (EPA). Fucoxanthin adalah karotenoid utama dikesan dalam rumpai laut *S. polycystum* (2,740 mg/ 100 g DW). Dalam kes rumpai laut merah (*E. denticulatum*), lutein (88 mg/ 100 g DW) dan zeaxanthin (21 mg/ 100 g DW) merupakan karotenoid utama, selain fucoxanthin, manakala bagi rumpai laut hijau, β -carotene (20 mg/ 100 g DW) dan canthaxanthin (15 mg/ 100 g DW) dikesan sebagai karotenoid utama. Kaedah yang digunakan mempamerkan (a) keluk penentukuran linear (R^2>0.97), (b) *recovery* yang memuaskan bagi kebanyakan pigmen (antara 74 dan 104%), dan (d) pengesanan rendah (0.001-0.01 ng/µl) dan had kuantifikasi (0.004-0.02 ng/µl) (LOD dan LOQ, masing-masing). Ekstrak ethanol dan metanol dari rumpai laut yang dikaji didapati memaparkan kesan pengurangan terhadap α-amylase (11-67%; n=3), tetapi tidak menunjukkan kesan ke atas aktiviti α-glucosidase secara *in vitro*. Di antara 3 jenis rumpai laut, ekstrak ethanol *E. denticulatum* didapati paling berkesan merencat α-amylase dengan IC_{50} 0.14 mg/ml. Oleh itu, rumpai laut ini telah dipilih untuk kajian selanjutnya. Antara lima *fraction* rumpai laut *E. denticulatum* (hexane, ethyl acetate, acetone, butanol dan air), hexane, ethyl acetate dan aceton menunjukkan kadar perencatan enzim yang baik dengan purata penurunan sebanyak 42%. *S. polycystum* menunjukkan aktiviti DPPH dan TPC yang tinggi (20%; 400 mg/ GAE 100 g masing-masing) manakala bagi analisis ORAC, *E. denticulatum* mencatatkan aktiviti tertinggi iaitu 112.762 µmol TE / 100 g. Ekstrak etanol *E. denticulatum* dan *fractions* (1-100 µg/ml), juga menunjukkan aktiviti anti-radang tanpa menunjukkan apa-apa kesan sitotoksik kepada sel-sel RAW 264.7. Ekstrak rumpai laut yang sama juga menurunkan aktiviti adipogenesis dan meningkatkan penyerapan glukosa dalam model sel 3T3-L1 manakala penurunan enzim lipase sebanyak 83%. Kehadiran asid lemak EPA dan PA, sebatian antioksidan seperti *polyphenol* dan karotenoid mungkin menyumbang kepada bioaktiviti keberkesanan penurunan glukosa oleh rumpai laut ini. Kesimpulannya, kajian ini menunjukkan bahawa rumpai laut yang dikaji menunjukkan ciri-ciri kesihatan seperti anti-diabetes, anti-obesiti, anti-oksida dan modulasi imun dalam kajian *in vitro*. Kesimpulan yang dapat dibuat daripada keputusan kajian ialah rumpai laut ini berpotensi untuk menjadi sumber makanan berfungsi yang boleh terus dibangunkan untuk aplikasi komersial.

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I certify that a Thesis Examination Committee has met on 11 September 2017 to conduct the final examination of B.Vimala a/p R.M.T Balasubramaniam on her thesis entitled "Phytochemical and Glucose Lowering Potential of Seaweed *Eucheuma denticulatum* (N.L.Burman) F.S.Collins and A.B.Harvey *In Vitro*" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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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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LIST OF ABBREVIATIONS

APCI	Atmospheric pressure chemical ionization
DMEM	Dulbecco's modified Eagle's medium
FBS	Fetal bovine serum
DMSO	Dimethyl sulfoxide
DPPH	2,2-diphenyl-1-picrylhydrazyl
ESI	Electrospray ionization
GAE	Gallic acid equivalents
GC-MS	Gas chromatography-mass spectrometry
HPTLC	High performance thin layer chromatography
LC	Liquid chromatography
LOD	Limit of detection
LOQ	Limit of quantitation
MS	Mass spectrometry
MS/MS	Tandem mass spectrometry
2-NBDG	2-deoxy-2-[(7-nitro-2, 1, 3-benzoxadiazol-4-yl) amino]-D-glucose
SD	Standard deviation
TIC	Total ion chromatogram
MCP-1	Monocyte chemoattractant-1
IL-6	Interleukin-6
IL-1β	Interleukin -1β
TAG	Triacylglycerol
T1DM	Type I Diabetes Mellitus
T2DM	Type II Diabetes Mellitus
TNF-α	Tumour necrosis factor-α

CHAPTER 1

INTRODUCTION

1.1 Background

Diabetes Mellitus (DM) is a metabolic disorder which occurs due to insulin resistance and impaired insulin secretion in the body. DM mainly falls into two broad etiopathogenetic categories; insulin dependent DM (type 1 diabetes) and non-insulin dependent DM (type 2 diabetes). Type 1 diabetes (T1DM) is generally treated through insulin replacement therapy while type 2 diabetes (T2DM) is treated with oral hypoglycemic agents (Rengasamy, Aderogba, Amoo, Stirk, & Van Staden, 2013).

T1DM is an auto-immune mediated impairement of pancreatic β-cells which lead to lack of insulin production while T2DM, is a metabolic disorder that is distinguished by a high level of glucose in the blood due to a defect in insulin production and/or action, or both (American Diabetes Association, 2014; Low, 2010). Improper glucose metabolism occurs during onset and development of T2DM which subsequently affects the lipid metabolism (Chang et al. 2002; Cheplick, Kwon, Bhowmik, & Shetty, 2010). Pathological changes like nephropathy, retinopathy and cardiovascular complications start occurring with the progression of disease in the body which led to increased morbidity and mortality (Rother, 2007).

Postprandial phase in diabetes is potrayed by a sudden increase in blood glucose levels, and evidence suggest that the postprandial "hyperglycemic spikes" may be linked to the pathophysiological conditions of late diabetes (Bonora & Muggeo, 2001; Ceriello, 2005). Therefore, the control of postprandial hyperglycemia is suggested to be paramount in the treatment of diabetes and its complications.

Diabetes mellitus (DM) is termed as the emerging pandemics in the 21st century and declared as a major health problem rising rapidly throughout the world (Maeda, Tsukui, Sashima, Hosokawa, & Miyashita, 2008) which is projected to reach 552 million people by 2030 (Whiting, Guariguata, Weil, & Shaw, 2011). T2DM previously referred as "non–insulin-dependent diabetes" or "adult-onset diabetes," accounts for 90–95% of all diabetes (American Association Diabetes, 2016) and is responsible for 85–95% of the cases globally (Zimmet, 1999) with Asian countries contribute to more than 60% of the world's diabetic population (Ramachandran, 2012). As a matter of fact, for Malaysia alone an estimated 3.5 million adults (18 years and above) or 17.5% are living with diabetes (NHMS, 2015). Socio-economic growth and industrialisation are rapidly occurring in many of these countries. Increased rates of urbanization, modernization, readily available fast foods and sedentary habits have altered the lifestyle of the population, mainly among the youth were the main causes of prevalence of T2DM (Ramachandran, 2012).

In diabetes, oral hypoglycemic and anti-hyperglycemic drugs are administered to maintain blood glucose level near the normal range. However, the DM drugs have limitation such as undesirable side effects like weight again, stomach discomfort and vomiting (Egan, Bulotta, Hui, & Perfetti, 2003), thus more researches are diverting to the use of natural products as an alternative measure for management of T2DM. Medicinal herbs as a substitute and complementary medicine have been long practised due to its rich source of functional metabolites which ascribed as DM remedies. Rios, Francini, & Schinella (2015) reviewed the use of natural products as a source of therapeutic agent for the treatment of Type 2 Diabetes Mellitus. More than 1200 species of organisms have been reported for the use to treat symptoms of DM. They represent more than 725 genera in 183 families, ranging from seaweed and fungi to advanced plants. *Galega officinalis* L. (Fabaceae) is the first medicinal plant reported with a definite anti-diabetic effect (Marles & Farnsworth, 1995).

Edible seaweed products have been used in many Asian countries as a food item since ancient times and currently considered with high economic potential in food and pharmaceutical industry as well as human health (Dhargalkar & Pereira, 2005)**.** In general, seaweed-derived compounds have shown to contribute to vast biological activities including anti-diabetes (Chin et al., 2014; Sharifuddin, Chin, Lim, & Phang, 2015). Furthermore, an increasing number of scientific papers published correlating seaweed and health benefits from diet replacements or extracts (Holdt & Kraan, 2011) and these activities may be attributed to antioxidants, polyunsaturated fatty acids (PUFA), pigments or the unique mineral contents present in the seaweed (Bocanegra et al. 2009; Ortega-Calvo et al. 1993; Rupérez 2001). Since, seaweed exhibited promising source of natural agent with potential biological effects, thus more efforts were taken to isolate the bioactive compounds and explore its action mechanisms (Holdt & Kraan, 2011; Heo et al., 2009). Seaweed are the largest and most complex marine source with unique bioactive ingredients. The seaweed are characterized as photosynthetic like plants that occupy a wide range of ecological niches. They are important living resources of the world oceans which form a basic biomass in the intertidal zone and contribute ecologically and economically. The seaweed are catogerised as two major types; microalgae which are found in both benthic and littoral habitats and also throughout the ocean waters as phytoplankton and the macroalgae or seaweed which occupy the littoral zone area up to a certain depth where very little photosynthetic light is available (Braune and Guiry, 2011).

Seaweed belong to three different groups, distinguished on the basis of thallus colour: brown seaweed (phylum Ochrophyta; Class Phaeophyceae), red seaweed (phylum Rhodophyta) and green seaweed (phylum Chlorophyta; Classes Bryopsidophyceae, Chlorophyceae, Dasycladophyceae, Prasinophyceae and Ulvophyceae) (Braune and Guiry, 2011).

Seaweed consist of key ingredients such as fibres, proteins, minerals, vitamins, antioxidants, phytochemicals, and polyunsaturated fatty acids with low caloric values. However, their nutrient composition are affected by external factors such as the salinity, geographic location, environmental, harvesting season, sampling methods (Rohani-Ghadikolaei, Abdulalian, & Ng, 2012; Dawes, Kovach, & Friedlander, 1993). High essential nutrients and phytochemical composition complimented with high rate

growths of seaweed make it as a sustainable functional ingredient for complementary and alternative therapy.

1.2 Problem statements

Seaweed industry has been identified by the government as a high potential sector which could contribute to the country's economy and therefore could increase the income of Malaysians, especially at the coastal areas (Lunkapis & Danny, 2016; Galid, 2003). This industry has commercial values based on its use as raw material for pharmaceutical, cosmeceutical and nutraceuticals product development. Currently, the seaweed researches in Malaysia mostly focus on food and non-food based product development (Phang, 2010). However, this potential marine source has remained not investigated or dearth in research especially for its possible glucose lowering properties. On the other hand, T2DM prevalence in Malaysia is at an alarming rate (17.5%) and expected to increase further (NHMS, 2015). Due to limited number of anti-diabetic drugs as well as high cost of medication with potentially hazardous side effects, there is a need and high demand for a therapeutically potent, yet safe, anti-hyperglycemia agent derived from natural products, such as marine macroalgae (seaweed).Thus, finding effective ways to treat or prevent these problems is paramount.

1. 3 Significance of the study

The increasing number of scientific evidences in the last two decades relating diet and health has substantiate the remarkable potential of foods to promote and enhance health. The findings correlate the intake of certain food and their modulation of chronic diseases (Willett, Koplan, Nugent, Puska, & Gaziano, 2006; Simopoulos, 2008). As a result, there is now a huge interest on products that can promote health and well-being among consumers and the food industry. Interestingly, the marine world represents a largely untapped reserve of bioactive ingredients and as reported in numerous studies of late, Eucheuma species have been commercially introduced throughout mostly tropical parts of the world for cultivation, serving as a means of livelihood for the locals, and as an additional source of revenue for the economy of the country. Many recent studies have associated seaweed with anti-diabetic properties (Sharifuddin et al., 2015; Chin et al., 2014; Motshakeri, Ebrahimi, Goh, Matanjun & Mohamed, 2013). Hence, this study will further enhance the scientific information and knowledge on the health-promoting properties of our local seaweed especially as anti-hyperglycemia agent which will further strengthen the claims of seaweed as a healthy food product as well as uplifting our local seaweed industry.

1.4 Objectives

1.4.1 General objective

To evaluate phytochemical content and glucose lowering potential of selected Malaysian seaweed.

1.4.2 Specific objectives

- To identify and characterize the bioactive components present in the studied seaweed
- To evaluate the regulatory effects of seaweed extracts on the starch digestive enzymes (α-amylase and α-glucosidase) and antioxidant capacity of the seaweed
- To determine the effect of the seaweed on the inflammatory biomarkers associated with hyperglycemia using RAW 264.7 and 3T3-L1 cell line models
- To determine the effect of the seaweed extract(s) / fraction(s) on the lipase enzymes, adipogenesis activity and glucose uptake in 3T3-L1 cell line

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