UNIVERSITI PUTRA MALAYSIA

EFFECTS OF Momordica cochinchinensis SPRENG, FRUIT ON THE PROLIFERATION AND ANGIOGENESIS BIOMARKERS OF HUMAN RETINAL PIGMENT EPITHELIAL CELLS UNDER HIGH GLUCOSE CONDITIONS

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Tropical fruits have been reported to contain health-promoting compounds for human benefits. Fruit of *Momordica cochinchinensis* (*M. cochinchinensis*) is one of these fruits that believed to be rich source of bioactive constitutes. However, the studies on its phytochemical composition and biological activities against hyperglycaemia-related eye disease were found to be limited. Thus, this study attempted to investigate the phytochemical composition, antioxidant activities and the effects of *M. cochinchinensis* parts extracts grown in Malaysia on cell viability and angiogenic activity of human retinal pigment epithelial (ARPE-19) cells under high glucose (HG) conditions. UV-Vis was used for the estimation of phenolics, flavonoids, and carotenoids contents. Lycopene and β-carotene were quantified using a HPLC technique. LC-MS/MS was used for the identification of antioxidant compounds. DPPH and FRAP assays were employed to evaluate the antioxidant capacities. MTT assay, morphological observations and Trypan blue dye were employed for the cell viability evaluation. Enzyme linked immunosorbent-based assay was performed the evaluate the effect of the fruit extracts on the reactive oxygen species (ROS), vascular endothelial growth factor (VEGF) and pigment epithelium-derived factor (PEDF) secretions. The results showed carotenoids, phenolics and flavonoids were present in all fruit parts. Comparatively, the fruit aril showed the highest carotenoids and phenolics content (1106 ± 2.1 µg/g, 308 ± 2.7 µg/g) respectively, whereas the peel showed the highest flavonoid content (381 ± 2.2 µg/g). Lycopene and β-carotene were found to be significantly high ($p < 0.05$) in aril (579.3 ± 22.7 and 621 ± 35 µg/g DW) and relatively high in peel and pulp. Furthermore, rutin, quercetin, linolenic acid and cinnamic acid were identified in peel, seed, pulp and aril. The antioxidant capacity evaluations revealed that, aril possessed the highest scavenging activity IC_{50} = 865 µg/mL, while the peel appeared to possess the highest ferric reducing power of 140 µmol $FeSO_4$/µg. Cell culture experiments demonstrated HG condition at (30 mmol/L) condition increased the proliferation of ARPE-19 cell proliferation, ROS

and VEGF secretions compared to low glucose (LG) at (5.5 mmol/L). While the exposure of ARPE-19 cells in HG conditions to *M. cochinchinensis* led to inhibition of cell viability, induced morphological changes, decreased ROS and VEGF, and increased PEDF levels. *M. cochinchinensis* pulp, seed, and aril at 1 000 µg/mL showed significant inhibition activities [(7.5 ± 5.1)%, (2.7 ± 0.5)%, (3.2 ± 1.1)%, respectively] against HG-induced ARPE-19 cell viability. The findings also demonstrated that aril at 250 µg/mL significantly decreased ROS and VEGF levels [(40.6 ± 3.3) pg/mL, (107.4 ± 48.3) pg/mL, respectively] compared to ROS [(71.7 ± 2.9) pg/mL] and VEGF [(606.9 ± 81.1) pg/mL] in HG untreated cells. Moreover, 250 µg/mL of Gac peel dramatically increased PEDF level [(18.2 ± 0.3) ng/mL] compared to that in HG untreated cells [(0.48 ± 0.39) ng/mL]. The current results demonstrated that *M. cochinchinensis* fruit was found to be rich source of phytochemical compounds especially carotenoids and to possess antioxidant capacity. In addition, *M. cochinchinensis* fruit extracts reduced ARPE-19 cell viability, minimized ROS generations and showed angiogenic activities. Therefore, our findings open new insights towards the potentiality of utilizing *M. cochinchinensis* fruit as a source of antioxidant plant and against HG-related diabetic retinopathy disease.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

KESAN BUAH *Momordica cochinchinensis* SPRENG. KE ATAS PROLIFERASI DAN BIOPENANDA ANGIOGENESIS BAGI SEL EPITELIAL PIGMEN RETINA MANUSIA DI BAWAH KEADAAN GLUKOSA TINGGI

Oleh

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Januari 2019

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Buah-buahan tropika telah dilaporkan mengandungi sebatian mempromosikan kesihatan bagi manfaat manusia. Buah *Momordica cochinchinensis* (*M. cochinchinensis*) merupakan antara spesies buah yang dikatakan kaya dengan pelbagai sumber bahan aktif. Walau bagaimanapun, kajian ke atas komposisi fitokimianya dan aktiviti biologikalnya terhadap penyakit mata berkaitan hiperglisemia adalah terhad. Oleh sebab itu, kajian ini dijalankan untuk menilai komposisi fitokimia, aktiviti antioksida dan kesan ekstrak bahagian *M. cochinchinensis* yang ditanam di Malaysia ke atas viabiliti sel dan aktiviti angiogeni sel epitelial manusia (ARPE-19) di bawah keadaan glukosa tinggi (HG). UV-Vis telah digunakan bagi menganggarkan kandungan fenolik, flavonoid, dan karotenoid. Penentuan kandungan likopen dan β-karotena telah dijalankan menggunakan teknik HPLC. LC-MS/MS telah digunakan untuk mengenal pasti sebatian antioksida. Asai DPPH dan FRAP telah digunakan untuk menilai kapasiti antioksida. Asai MTT, pemerhatian morfologikal dan pencelup biru Trypan telah digunakan bagi menilai viabiliti sel. Asai imunoserap terangkai enzim telah dijalankan bagi menilai kesan ekstrak buah ke atas spesies oksigen reaktif (ROS), faktor pertumbuhan endolial vaskular (VEGF) dan rembesan faktor perolehan epitelium pigmen (PEDF). Keputusan menunjukkan karotenoid, fenolik dan flavonoid wujud dalam semua bahagian buah. Secara bandingan, bahagian aril buah memperlihatkan kandungan karotenoid dan fenolik paling tinggi, iaitu (1106 ± 2.1 µg/g dan 308 ± 2.7 µg/g), manakala bahagian kulit memperlihatkan kandungan flavonoid paling tinggi, iaitu (381 ± 2.2 µg/g). Likopen dan β-karotena didapati tinggi ($p< 0.05$) dalam bahagian aril (579.3 ± 22.7 dan 621 ± 35 µg/g DW) dan secara relatif adalah tinggi dalam bahagian kulit dan pulpa. Di samping itu, rutin, asid kuersetin, asid linolenik dan asid sinamik telah dikenal pasti dalam kulit, biji, pulpa dan aril. Penilaian kapasiti antioksida memperlihatkan bahawa, aril mengandungi aktiviti hapus-sisa paling tinggi, iaitu IC_{50} = 865 µg/mL, manakala kulit didapati mengandungi kuasa pengurangan ferik paling tinggi, iaitu 140 µmol $FeSO_4$/µg. Eksperimen kultur sel mempamerkan keadaan HG (30 mmol/L) dan meningkatkan

proliferasi sel ARPE-19, hapus-sisa ROS dan VEGF berbanding dengan glukosa rendah (LG) pada (5.5 mmol/L). Manakala pendedahan sel ARPE-19 dalam keadaan HG kepada *M. cochinchinensis* mengakibatkan perencatan viabiliti sel, mencetuskan perubahan morfologikal, mengurangkan ROS dan VEGF, dan meningkatkan tahap PEDF. Pulpa, biji dan aril *M. cochinchinensis* pada 1000 µg/mL menunjukkan aktiviti perencatan yang signifikan [(7.5 ± 5.1)%, (2.7 ± 0.5)%, (3.2 ± 1.1)%] terhadap viabiliti sel ARPE-19 tercetus HG. Keputusan juga mempamerkan bahawa aril pada 250 µg/mL, secara signifikan mengurangkan tahap ROS dan VEGF [(40.6 ± 3.3) pg/mL, (107.4 ± 48.3) pg/mL] berbanding dengan ROS [(71.7 ± 2.9) pg/mL] dan VEGF [(606.9 ± 81.1) pg/mL] dalam sel tidak terawat HG. Tambahan pula, 250 µg/mL kulit *M. cochinchinensis* secara dramatik meningkatkan tahap PEDF [(18.2 ± 0.3) ng/mL] berbanding dengan dangan sel tidak terawat HG [(0.48 ± 0.39) ng/mL]. Keputusan kajian ini mempamerkan bahawa buah *M. cochinchinensis* merupakan sumber sebatian fitokimia yang kaya terutama karotenoid dan mengandungi kapasiti antioksida. Di samping itu, ekstrak buah *M. cochinchinensis* mengurangkan viabiliti sel ARPE-19, meminimumkan penjanaan ROS dan menunjukkan aktiviti angiogenik. Oleh itu, keputusan kajian ini, membuka penemuan baharu terhadap potensi penggunaan buah *M. cochinchinensis* sebagai sumber antioksida dan terhadap penyakit retinopati diabetik berkaitan HG.

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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 Master of Science. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

DR	Diabetic retinopathy
HG	High glucose
LG	Low glucose
AGEs	Advance glycation end products
PKC	Protein kinase C
PDR	Proliferative diabetic retinopathy
VEGF	Vascular Endothelial Growth Factor
IGF	Insulin Growth Factor
PEDF	Pigmented Epithelium Derived Factor
PlGF	Placenta like Growth Factor
FGF	Fibroblast Growth Factor
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
ARPE-19	Human Retinal Pigment Epithelial Cells
Momordica cochinchinensis	*M. cochinchinensis*
NPDR	Non-Proliferative Diabetic Retinopathy
IDF	International Diabetes Federation
NHMS	National Health and Morbidity Survey
ELISA	Enzyme Linked Immunosorbent Assay
AMD	Age-related Macular Degradation
PDGF	Platelet Derived Growth Factor
NGF	Nerve Growth Factor

TNF-α	Tumor Necrosis Factor α
HIF-1α	Hypoxia-Inducible Factor 1
MMP	Matrix Metalloproteinase
HPLC	High Performance Liquid Chromatography
UV/Vis	Ultra Violet Visible
LC-MS	Liquid Chromatography-Mass Spectrum
FW	Fresh Weight
DW	Dry Weight
FRAP	Ferric Reducing Antioxidant Power
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
DPPH	2,2-Diphenyl-1-picrylhydrazyl
TPTZ	2,4,6-tripyridyl-s-triazine
BHT	Butylated Hydroxytoluene
W/V	Weigh/Volume
V/V	Volume/Volume
DMSO	Dimethyl Sulphate
PBS	Phosphate Buffer Saline
LG	Low Glucose
HG	High Glucose
ROS	Reactive Oxygen Species
ATCC	American Type Culture Collection
DMEM	Dulbecco's Modified Eagle's Medium
FBS	Fetal Bovine Serum

CHAPTER 1

INTRODUCTION

1.1 Background of the study

Diabetes Mellitus (DM) is an epidemic concern and one of the most growing disease. Diabetes characterized by chronic hyperglycaemia (World Health Organization, 2016). Overtime diabetes can lead to several complications in both macro and micro vascular which finally lead to organs failure. Vascular diseases are the leading cause of morbidity and mortality among both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) (Abdul-Ghani *et al*., 2017; Kibel *et al*., 2017; Kayama *et al*., 2015). In particular, diabetic retinopathy (DR) is one of the most serious complication of diabetes. DR is an ocular disease and one of the leading cause of blindness worldwide (Boscia, 2010). It has established that chronic exposure to hyperglycaemia by the retina gives rise to cause many pathophysiological changes. These changes are including accumulation of advance glycation end products (AGEs), activation of protein kinase C (PKC), increase levels of sorbitol, reactive oxygen species (ROS) and inflammation factors, homeostasis of angiogenic markers (Zong *et al*., 2011; Brownlee, 2005; Ahsan, 2015).

DR classified according to its severity into non-proliferative DR (NPDR) and proliferative DR (PDR) (Wilkinson *et al*., 2003; Al-Jarrah & Shatnawi, 2017). NPDR characterized by the presence of vascular abnormalities and PDR known by the excessive formation of abnormal blood vessels (Babapoor-Farrokhran *et al*., 2015). The formation of new blood vessels known as neovascularization and its tightly regulated by angiogenic markers (Bussolino *et al*., 1997). Angiogenesis is the process of formation new blood vessels from exciting vessels. Many growth factors are mainly involved in the regulation of the angiogenesis process including but not limited vascular endothelial growth factor (VEGF) and pigmented epithelium-derived factor (PEDF) (Paine *et al*., 2017; Al Kahtani *et al*., 2017; Behl & Kotwani, 2015).

Natural sources (plants, fruits and vegetables) are rich sources of phytochemicals and bioactive compounds such as; carotenoids and polyphenols (Singh *et al*., 2013). These constitutes have gained attention due their pharmaceutical properties such as; antidiabetic, antioxidant, cancer chemoprevention, anti-inflammatory and angiogenic activities (Kuppusamy *et al*., 2014; Kaur *et al*., 2017; Cicero *et al*., 2015). Studies have shown that, high levels of phytochemicals and carotenoids have positively correlated with reverse DR progression (Singh *et al*., 2013). However, the information regarding tropical-underutilized fruit and its roles in the prevention of DR were found to be very limited. Among all the tropical fruits, *Momordica cochinchinensis* Spreng fruit (*M. cochinchinensis*) was claimed to be an exceptional source of phytochemicals especialy carotenoids (Aoki *et al*., 2002; Ishida *et al*., 2004; Kubola & Siriamornpun, 2011). This fruit commonly known as Gac in Vietnam and found to be grown in tropical area such as; Thai, Malaysia and Laos. Traditionally, *M. cochinchinensis* fruit used in folk and

ancestral medicine. However, phytochemical composition and biological activities of *M. cochinchinensis* fruit have not well illustrated, also no studies have found on *M. cochinchinensis* fruit grown in Malaysia. Extraction process was found to play a key role in the recovering of bioactive compounds of plant extracts. Ethanol is commonly used in the extraction process due to its nontoxic, availability and ability to extract polar and non-polar bioactive compounds (Chuyen *et al*., 2017).

1.2 Problem statements

DR is one of the leading cause of loss vision. Reports showed that, one third of diabetes patients may develop signs of DR (Lee *et al*., 2015). Thus, continuously increasing level of diabetes will be accompanied with increasing rates of DR to become a series burden for the community that affected their life style and currency. Globally, 126.6 million were living under the risk of DR in 2010 (Zheng *et al*., 2012). Particularly, based on the report of Malaysian National Health and Morbidity Survey (NHMS) diabetes trend in Malaysia has been elevated through the last two decades 6.3 % in 1986 to 17.5 % in 2015 (Hussein *et al*., 2015; Yen *et al*., 2017; Tee & Yap, 2017).

Currently, DR treatment strategies are included VEGF inhibitors drugs (anti-VEGF), laser photocoagulation and vitreous surgery (Duh *et al*., 2017; El-Asrar *et al*., 2009; Joussen & Joeres, 2007; Parikh *et al*., 2017). In spite of the effective role of the mentioned patterns to cure DR, these patterns are extremely expensive and must be performed by specialist and experts (Dakin *et al*., 2014). In addition, these strategies might have several side effects. For example, laser photocoagulation considers as a destructive tool that do not work to recover the lose vision and cannot be fully safe (Selvaraj *et al*., 2017; Stitt *et al*., 2016). Moreover, these treatments may lead to some undesired results such as; retinal damage, retinal detachment, vitreous haemorrhage, endophthalmitis, retinal tears, and intraocular haemorrhage (Simó & Hernandez, 2008; Austeng *et al*., 2016; Ventrice *et al*., 2013). Furthermore, Dr is a complex and multi factorial disease which need for new and novel treatments that able to have multi-target activity. Thus, finding new strategies that might be available, cost-effective and safer to treat/prevent or slow the progression of DR are highly required.

1.3 Significance of the study

The role of plants and their bioactive compounds in the prevention of several diseases have been established as alternative potential strategy in folk medicine. Out of the plants, *M. cochinchinensis* fruits were found to be extremely high source of phytochemicals especially carotenoids. Carotenoids and other phytochemicals have known about their abilities to improve overall health vision, safety and to possess multi-target activity which might potentially be a good alternative treatment compare to DR treatments that mostly work on one target such as anti-VEGF injections that only work to reduce VEGF secretions in addition to its risk to cause retinal detachment. Retinal pigmented epithelial (RPE) cells were found to play a crucial role in the progression of DR due to its

anatomical position and its multi functions. According to the literature, there have been no studies investigated the role of *M. cochinchinensis* fruit extracts on hyperglycaemia-related DR disease using RPE cells or other retina cells as a model for DR. The current study is the first to investigate the effect of *M. cochinchinensis* extracts on human retinal pigment epithelial (ARPE-19) under high glucose conditions. Thus, this study might open new insights into the potentiality of using *M. cochinchinensis* fruit as alternative medicine in ethno-pharmacology and biomedicine applications. More specifically, the data of this research can be exploiting to formulate a new dietary supplement or nutraceuticals from natural sources as a remedy to prevent/treat or delay DR.

Furthermore, the majority of the previous studies have only given attention to the aril part of fruit with insignificant concern about other fruit parts which may contribute to waste issues. Therefore, the present study was aimed to study all *M. cochinchinensis* fruit parts which may encourage researches to consider all *M. cochinchinensis* parts as a significant sources of phytochemicals and thus lead to minimize disposal and waste problems. To the best of our knowledge, this study is the first to study *M. cochinchinensis* fruit grown in Malaysia. Thus, the findings of this study might appeal attention towards to study and utilize *M. cochinchinensis* fruit.

1.4 Objectives

The main objective of this research was to study the effect of *M. cochinchinensis* parts extracts on the antioxidant, proliferation and angiogenesis process using human ARPE-19 cell line as a model for DR in high glucose condition. This objective included few other specific objectives that were the following:

1. To estimate total carotenoid, phenolic and flavonoid contents, and to quantify β-carotene and lycopene concentrations in the fruit part.
2. To identify unknown chemical compounds and to evaluate the antioxidant activities of the fruit parts.
3. To assess the effect of the fruit parts extracts on ARPE-19 cell proliferation under high glucose conditions.
4. To evaluate the effect of the fruit parts on the secretion of reactive oxygen species of ARPE-19 cells under high glucose conditions.
5. To evaluate the effect of the fruit parts extracts on angiogenesis (VEGF and PEDF) markers of ARPE-19 cells under high glucose conditions.

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LIST OF PUBLICATIONS

Abdulqader, A., Ali, F., Ismail, A., & Esa, N. M. (2018). Gac fruit extracts ameliorate proliferation and modulate angiogenic markers of human retinal pigment epithelial cells under high glucose conditions. Asian Pacific Journal of Tropical Biomedicine, 8(12), 571.

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Abdulqader, A., Ali, F., Ismail, A., & Esa, N. M. (2019). Antioxidants compounds and capacities of Gac *(Momordica cochinchinensis* Spreng) fruits". Research paper-accepted for publication in the Asian Pacific Journal of Tropical Biomedicine.

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