



UNIVERSITI PUTRA MALAYSIA

***TOCOTRIENOLS RICH FRACTION FROM PALM OIL
(*Elaeis guineensis* Jacq.) AS POTENTIAL WOUND
HEALING DIETARY AGENT FOR DIABETES***

TING THING MIN

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POTENTIAL WOUND HEALING DIETARY AGENT FOR DIABETES**

By

TING THING MIN

**Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia,
In Fulfilment of the Requirement for the Degree of Master of Science**

January 2022

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

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TING THING MIN

January 2022

Chairman : Patricia King Jie Hung, PhD
Faculty : Agricultural and Forestry Sciences, Bintulu Campus

Diabetic patients are exposing to high probability of chronic wound and increase risk of wound infection. Metformin is recognised as the standard drug for diabetes treatment to lower both basal and postprandial plasma glucose. Past research has reported that the treatment with metformin could accelerate wound healing besides regulating glucose level. However, overdose intake of metformin among patient with renal impairment may cause gastrointestinal discomforts, rare but high mortality rate in the case of lactic acidosis. This study aims to investigate a safe alternative to metformin to reduce its negative effects especially on diabetic subject. Tocotrienols Rich Fraction (TRF), a natural phytonutrient extracted from *Elaeis guineensis* (palm) oil has been researched and found to have many health benefits and potential medicinal effects. The potency of TRF extracted from palm oil in wound healing and diabetes management was investigated using Streptozotocin (STZ)-induced diabetes Sprague Dawley rat model. Two 6 mm full thickness excisions were created utilizing the sterile 6 mm punch biopsies on diabetic rats. A 400 mg/kg dosage of TRF per day was supplemented through oral gavage for 10 days. The wound closure rate, platelet derived growth factor-BB (PDGF-BB) content, malondialdehyde (MDA) content, blood glucose level and body weight of the rats were monitored for a period of 10 days after wound creation. The results showed that TRF was comparable to metformin in stabilizing blood glucose, and stabilized the body weights of the diabetic rats suitable for diabetes use. TRF treatment as well as metformin treatment up-regulated the PDGF-BB in the blood on Day 2 of wound creation and 100% dry wound contraction at Day 10; indicated the non-delayed of growth factor at initial stage and total clean wound closure. TRF treated group detected significantly lower MDA content compared to metformin treated group. This shows TRF may have greater potency than metformin in reducing lipid peroxidation and promote better wound healing. Further analysis on the impact of TRF in modulating immune response in wound healing is recommended.

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

**POTENSI TOCOTRIENOLS RICH FRACTION DARIPADA MINYAK
KELAPA SAWIT (*Elaeis guineensis* Jacq.) SEBAGAI EJEN PEMAKANAN
PENYEMBUH LUKA UNTUK DIABETES**

Oleh

TING THING MIN

Januari 2022

Pengerusi : Patricia King Jie Hung, PhD
Fakulti : Sains Pertanian dan Perhutanan, Kampus Bintulu

Pesakit diabetes terdedah kepada kebarangkalian tinggi untuk mengalami luka kronik dan meningkatkan risiko jangkitan luka. Metformin diiktiraf sebagai ubat standard untuk rawatan diabetes demi menurunkan glukosa plasma basal dan postprandial. Penyelidikan lepas telah melaporkan bahawa rawatan dengan metformin boleh mempercepatkan penyembuhan luka selain daripada mengawal tahap glukosa. Walau bagaimanapun, pengambilan metformin yang berlebihan dalam kalangan pesakit yang mengalami masalah buah pinggang boleh menyebabkan ketidakselesaan gastrousus, jarang tetapi kadar kematian yang tinggi dalam kes asidosis laktik. Kajian ini bertujuan untuk menyiasat alternatif yang selamat untuk mengurangkan kesan negatif metformin terhadap subjek diabetes. Tocotrienols Rich Fraction (TRF), fitonutrien semulajadi yang diekstrak daripada minyak sawit (*Elaeis guineensis*) telah dikaji dan didapati mempunyai banyak manfaat kesihatan dan potensi kesan perubatan. Potensi TRF yang diekstrak daripada minyak sawit dalam penyembuhan luka dan pengurusan diabetes telah disiasat menggunakan model tikus Sprague Dawley diabetes yang disebabkan oleh Streptozotocin (STZ). Dua pemotongan ketebalan penuh 6 mm telah dibuat menggunakan biopsi tebuk 6 mm steril pada tikus diabetes. Dos 400 mg/kg TRF sehari diberi melalui gavage oral selama 10 hari. Kadar penutupan luka, kandungan platelet derived growth factor-BB (PDGF-BB), kandungan malondialdehid (MDA), paras glukosa darah dan berat badan tikus dipantau untuk tempoh 10 hari selepas penciptaan luka. Keputusan menunjukkan bahawa TRF adalah setanding dengan metformin dalam menstabilkan glukosa darah, dan menstabilkan berat badan tikus diabetes untuk kegunaan diabetes. Rawatan TRF serta rawatan metformin mengawal selia PDGF-BB dalam darah pada hari ke-2 penciptaan luka dan 100% pengecutan luka kering pada hari ke-10; menunjukkan faktor pertumbuhan tidak tertangguh pada peringkat awal dan penutupan luka bersih menyeluruh. Kumpulan yang dirawat TRF mengesan kandungan MDA yang lebih rendah berbanding kumpulan yang dirawat dengan metformin. Ini menunjukkan TRF mungkin mempunyai potensi yang lebih besar daripada metformin dalam mengurangkan peroksidasi lipid dan menggalakkan penyembuhan luka yang lebih

baik. Analisis lanjut mengenai kesan TRF dalam memodulasi tindak balas imun dalam penyembuhan luka adalah disyorkan.



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I certify that a Thesis Examination Committee has met on 14 January 2022 to conduct the final examination of Ting Thing Min on her thesis entitled "Tocotrienols Rich Fraction from Palm Oil (*Elaeis guineensis* Jacq.) as Potential Wound Healing Dietary Agent for Diabetes" 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 Master of Science.

Members of the Thesis Examination Committee were as follows:

Marina binti Mohd. Top @ Mohd. Tah, PhD

Associate Professor

Choose an item.

Universiti Putra Malaysia

(Chairman)

Shahrulrazid Sarbini, PhD

Professor

Faculty of Agricultural Science and Forestry (Bintulu Sarawak Campus)

Universiti Putra Malaysia

(Internal Examiner)

Irine Runnie anak Henry Ginjom, PhD

Senior Lecturer Ts.

Faculty of Engineering, Computing and Science

Swinburne University of Technology Sarawak Campus

Malaysia

(External Examiner)

SITI SALWA ABD GANI, PhD

Associate Professor ChM. and Deputy Dean

School of Graduate Studies

Universiti Putra Malaysia

Date: 28 June 2022

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:

Patricia King Jie Hung, PhD

Associate Professor
Faculty of Agriculture and Food Sciences
Universiti Putra Malaysia Bintulu Sarawak Campus
(Chairman)

Ho Kok Lian, PhD

Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

Harrison Lau Lik Nang, PhD

Principal Investigator
Engineering and Processing Division
Malaysia Palm Oil Board
(Member)

ZALILAH MOHD SHARIFF, PhD

Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

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Signature: _____
Name of
Chairman of
Supervisory
Committee: Assoc. Prof. Dr. Patricia King Jie Hung

Signature: _____
Name of
Member of
Supervisory
Committee: Assoc. Prof. Dr. Ho Kok Lian

Signature: _____
Name of
Member of
Supervisory
Committee: Dr. Harrison Lau Lik Nang

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LIST OF ABBREVIATIONS

TRF	Tocotrienols rich fraction
CPO	Crude palm oil
SD rats	Sprague-Dawley rats
STZ	Streptozotocin
PDGF-BB	Platelet derived growth factor-BB
MDA	Malondialdehyde
SAS	Analysis software & solutions
ANOVA	Analysis of variance
T01	Treatment 01
T02	Treatment 02
rPDGF	Recombinant platelet derived growth factor
α	<i>alpha</i>
β	<i>beta</i>
δ	<i>delta</i>
γ	<i>gamma</i>
ROS	Reactive oxygen species
PPG	Postprandial plasma glucose
<i>i.p.</i>	Intraperitoneal

CHAPTER 1

INTRODUCTION

Skin is the largest protective organ of human body. It provides protection against pathogen, sensation hence part of coordination for action and mobility, the site for vitamin bioprocess, waste secretion and thermal as well as hemostatic regulation for vital living (Lopez-Ojeda *et al.*, 2021). The functions made the wound healing crucial and severe chronic non-healing wound can be life-threatening. Acute wound healing a series of restoration process involving complex biological signal interactive events of four phases, non-distinctive overlapping phases including coagulation of white blood cells, inflammation, migration-proliferation of cells and tissue remodeling to the total healing process (Tottoli *et al.*, 2020). The ideal wound healing process should happen rapidly without infection and sepsis.

Diabetic patients are exposed to higher risk of incomplete or uncoordinated wound healing (Patel *et al.*, 2019). They were recorded to be more likely to experience disruption in hemostasis (Liu *et al.*, 2017; Nurden *et al.*, 2008) which cause prolong inflammation response (Schürmann *et al.*, 2014), lose ability of coordination of hormones, growth factors and chemokine (Ochoa *et al.*, 2007), alterations in the employment of macrophages, neutrophils and vasoconstriction (Goren *et al.*, 2009; Lin *et al.*, 2018; Lioupis, 2005; Mirza *et al.*, 2009), changes in proliferation, granulation, angiogenesis (Altavilla *et al.*, 2001; Guo *et al.*, 2020; Okonkwo *et al.*, 2020), microcirculation (Lioupis, 2005), and prolonged loss of balancing of oxidative stress (Xu *et al.*, 2020; Johansen *et al.*, 2005). These factors that delayed and impaired the wound healing progress in the diabetic patients increase the potential of chronic wound and pathogenic infection and toxic accumulation (Dong *et al.*, 2020; Xu *et al.*, 2020) and becoming life threatening

Metformin have been used as standard drug for diabetes treatment. It is an orally administered drug utilized to regulate the blood glucose through improving insulin sensitivity and decrease insulin resistance (Bailey & Turner, 1996). The efficacy and uses of metformin on tackling among other complications of the diabetes patients also been highlighted on the non-delayed wound healing (Han *et al.*, 2017; Inouye *et al.*, 2014; Qing *et al.*, 2019; Yu *et al.*, 2016). The adverse effect of metformin intake might cause short term gastrointestinal discomfort include diarrhea, nausea, and abdominal discomfort, anorexia (Bailey & Turner, 1996). The most worrisome adverse effect is lactic acidosis or metformin associated lactic acidosis (MALA). It is observed in case of overdose of metformin is taken or when with renal impairment (Blumenberg *et al.*, 2020; DeFronzo *et al.*, 2016; Graham *et al.*, 2011) with high fatality rate. Metformin is also to be avoided among pregnant women due to potential genotoxin and embryotoxin (Amador *et al.*, 2012; Li L. *et al.*, 2015). Therefore, the use of tocotrienols rich fraction (TRF) as safe alternative to metformin was investigated.

Tocotrienols is the natural phytonutrients present in many plants and fruits. The palm fruit (*Elaeis guineensis*) is the source with the highest content of tocotrienols.

Tocotrienols have gained recognition from research academy with findings since 1980s and tested with the properties on maintain cardiovascular health, good immunology modulation properties, neuro-protective properties and cognitive function maintenance, anti-cancer properties, skin protection properties, anti-aging and other biological effects of anti-oxidative properties and anti-inflammatory properties (Meganathan and Fu, 2016).

TRF contains 50% concentration of tocopherol and tocotrienols is proposed to potentially in promoting wound healing among diabetic patients. Earlier researches showed TRF improve insulin sensitivity by reducing the blood glucose level (Fang *et al.*, 2010), down regulate the blood glucose level and glycated hemoglobin (Wan Nazaimoon & Khalid, 2002), improve dyslipidemia, lower oxidative stress and maintain functionality of vascular wall (Budin *et al.*, 2009), reduce neuropathic pain (Kuhad & Chopra, 2009), prevent cognitive deficits (Kuhad *et al.*, 2009), improve the glycemic status and renal functionality (Siddiqui *et al.*, 2010) and prevent hyperglycemia induced skeletal muscle damage (Lee & Lim, 2018); all with diabetes subjects.

In the diabetic wound healing, TRF increases the activities of glutathione peroxidase (GPx) and superoxide dismutase (SOD) and lower the malondialdehyde (MDA) (Musalmah *et al.*, 2005), thus decreased the lipid peroxidation. The antioxidant properties of TRF normalized the level of DNA damage (Matough *et al.*, 2014), promote epidermal and dermal component regeneration (Elsy *et al.*, 2017) and up-regulation of the genes for cell growth, motility and angiogenesis and mitochondria function (Xu *et al.*, 2017).

For the past 40 years, TRF has been studied as cholesterol lowering agents, anti-cancer and neuron-protection supplements (Aggarawal *et. al.*, 2010; Meganathan & Fu, 2016). Studies on wound healing are limited and mainly concentrated on histological and oxidative aspects.

The past research has shown that TRF has the potential to improve wound healing, however the underlying mechanism are yet to be understood. Hence, this project aims to investigate the roles of TRF in promoting wound healing, especially in the first three phases of wound healing; Phase 1 and Phase 2: hemostasis and acute inflammation which involve the present of platelet derived growth factor-BB (PDGF-BB) and activation of macrophages by PDGF; monitoring the lipid peroxidation that might interfere the wound healing in Phase 3 (proliferation and new tissue formation) and Phase 4 (remodeling), where free radicals may impaired the keratinocytes, endothelial cells, capillary permeability and collagen metabolism.

The objectives of this project are:

1. to evaluate the anti-microbial properties of TRF against selected pathogen using disc diffusion method.
2. to evaluate the effect of TRF in wound contraction.
3. to evaluate the effect of TRF in promoting PDGF-BB secretion.

4. to evaluate the effect of TRF in inhibiting lipid peroxidation in wound healing based on MDA concentration.
5. to evaluate the effect of TRF in glucose level and body weight modulation among diabetic subjects.

The potency of TRF in diabetic wound healing was compared to standard drug - metformin. The antibacterial property of TRF was tested as preliminary evaluation through *in vitro* model to investigate the ability of TRF to prevent infection of wound on its anti-microbial properties. Infection could increase the healing time, reduce the quality of wound recovery and risk may occur to turn into chronic wound. The comparison of the wound contraction rate of full thickness excision, the content of PDGF-BB, the ability of counteracting of oxidative stress at wound site by testing on the of its lipid peroxidation by product (MDA), the fluctuations of blood glucose level and body weight were also evaluated using diabetic rat model to investigate the potency of TRF in diabetic wound healing.

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BIODATA OF STUDENT

Ting Thing Min was born on 9th March 1980 in Bintulu, Sarawak, Malaysia. She received her primary education at Sekolah Rendah Bantuan Chung Hua, Bintulu year 1987-1992. She resumed her lower secondary education at Sekolah Jenis Kebangsaan Baru, Bintulu year 1993-1996 and higher secondary education at Sekolah Jenis Kebangsaan Bandar, Bintulu year 1997-1998. The following year, she persuaded tertiary education at Tunku Abdul Rahman College, Kuala Lumpur and graduated Bachelor in Science (Chemistry and Biology) at year 2003. In year 2018, she decided to pursue in Master of Science in Food Science at University Putra Malaysia, Campus Bintulu.

