UNIVERSITI PUTRA MALAYSIA

ANTIOXIDANT AND ANTI-INFLAMMATORY ACTIVITIES OF FRACTIONS FROM Jatropha curcas Linn. ROOT EXTRACT AND ATTENUATION OF PRO-INFLAMMATORY MEDIATORS IN RAW 264.7 CELLS

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IB 2018 3

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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 Master of Science

Febuary 2017

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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Jatropha curcas Linn. plant belongs to the Euphorbiaceae family. This plant has been widely used in traditional medicine to treat injuries, fever, mouth infections, jaundice, guinea worm sores, and joint rheumatism. Among the different parts of the plant, the root has been widely used in ethno-medicine. However, extracts prepared from the roots could be variable in terms of efficacy and safety. The method of extraction and solvents used play a crucial role in determining the biological activities. It was hypothesized that liquid-liquid fractionation process could extract metabolites from *J. curcas* root which possessed antioxidant and anti-inflammatory activities without cytotoxic effect in the cell lines used. Therefore, the main objective of the present study was to investigate the biological activity and cytotoxicity of different solvents extract from *J. curcas* root. The metabolites were partitioned by using different solvents with different polarities. The phenolic and flavonoid contents of each solvent fraction were analyzed colorimetrically, and each fraction was evaluated for antioxidant and anti-inflammatory activities in macrophage RAW 264.7 cell lines. The nature of compounds present in each fraction was analysed by Liquid Chromatography Mass Spectrometry (LCMS). The active fraction with anti-inflammatory activity and low cytotoxicity was used to study the expression of pro-inflammatory genes by qPCR. The peripheral roots were collected from three *J. curcas* plants approximately 4 to 5 years old and subjected to 80% methanolic extraction for the preparation of dried root extracts. Then, the methanolic extract was used in the liquid-liquid fractionation technique with five different solvents (hexane, chloroform, ethyl acetate, n-butanol, and

aqueous). This was followed by determining the antioxidant activity of different fractions in vitro using 1,1-Diphenyl-2-Picrylhydrazyl (DPPH) free radical scavenging, ferric-reducing antioxidant power (FRAP) assay and scavenging of ABTS (2,2′-azinobis[3-ethylbenzothiazoline-6-sulphonate])-nitrogen-centred radical cation ($ABTS^{\bullet+}$) assay. The results showed that ethyl acetate and n-butanol fractions of the three root samples possessed high antioxidant activity with the highest total phenolic (36.74 ± 0.046 GAE µg /g DW and 33.12 ± 0.006 GAE µg /g DW) and total flavonoid content (11.76 ± 0.015 GAE µg /g DW and 10.11 ± 0.009 GAE µg /g DW). The anti-inflammatory activity of all five fractions was evaluated using murine macrophage RAW 264.7 cell line by determining the percentage of nitric oxide (NO) production by Griess reaction. The cytotoxicity activity of each fraction was determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) reduction method using murine macrophage RAW 264.7 cell line. The results showed that NO inhibition by n-butanol fraction at the concentration of 100 µg/mL in macrophage RAW 264.7 cells was 86% and cell viability was 105%, comparable to curcumin treated cells. The LCMS analysis showed that ethyl acetate contained epigenin and kaempferol glucoside isomer, which were categorised under flavone and phenolics that possessed antioxidant and anti-inflammatory properties. While n-butanol fraction contained high amount of coumaric acid and p-coumaroylquinic acid that could be involved in anti-inflammatory activity. The n-butanol fraction was evaluated using qPCR technique to study the expression of genes (iNOS, TNF-α, IL-6, and IL-1β genes) involved in inflammatory activity of induced lipopolysaccharide (LPS) and interferon-gamma (IFN-γ) RAW 264.7 cells, where cells treated with curcumin was used as positive control and normalized by expression of housekeeping gene transcript (G3DPH). The results showed that n-butanol fraction at 100 µg/mL, significantly ($P<0.05$) reduced the expression of iNOS, TNF-α, IL-6, and IL-1β genes. Hence, the anti-inflammatory effect was due to the down-regulation of the pro-inflammatory mediators. The present study showed that liquid-liquid fractionation was successful in partitioning the metabolites present in the *J. curcas* root methanolic extract, where n-butanol fraction was observed to be the most active fraction among other fractions. This fraction contained metabolites which possessed strong antioxidant and anti-inflammatory properties with low cytotoxicity activity and the ability to down-regulated the expression of all four pro-inflammatory genes evaluation.

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

AKTIVITI ANTIOKSIDAN DAN ANTI-KERADANGAN FRAKSI DARI EKSTRAK *Jatropha curcas* Linn. DAN PENGECILAN MEDIATOR PRO-RADANG DALAM SEL RAW 264.7

Oleh

SHAHIRAH ATIQAH BINTI OSMAN

Febuari 2017

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Jatropha curcas Linn. berasal daripada famili Euphorbiaceae. Pokok ini telah digunakan secara meluas di dalam perubatan tradisional untuk merawat kecederaan, demam, jangkitan mulut, jaundis, ubat cacing, dan juga sakit sendi. Di antara kesemua bahagian pokok ini, akarnya sering digunakan di dalam perubatan etho-perubatan. Namun, ekstrak yang diperolehi daripada akar pokok ini berpotensi untuk berubah-ubah dari segi kecekapan dan keselamatan. Cara pengekstrakan serta pelarut yang digunakan adalah sangat penting dalam menentukan aktiviti biologinya. Hipotesis telah menjangkakan bahawa proses fraksi cecair-cecair boleh mengekstrak metabolit daripada akar *J. curcas* di mana mempunyai aktiviti antioksidan dan anti-keradangan tanpa memberi kesan kepada sitotosik barisan sel yang digunakan. Oleh yang demikian, objektif utama bagi kajian ini adalah untuk mengenalpasti aktiviti biologi dan sitotosik bagi frakti ekstrak yang berbeza daripada akar pokok *J. curcas*. Metabolit kemudian diasingkan dengan menggunakan pelarut yang berbeza polariti. Kandungan fenolik dan flavonoid bagi setiap fraksi di analisa menggunakan analisa yang melibatkan bantuan reagen warna, dan setiap aktiviti antiosida dan anti-radang di uji bagi setiap fraksi dengan menggunakan makrofaj sel 264.7. Sifat bagi setiap kompaun yang ada di dalam setiap fraksi di analisa dengan menggunakan teknik Analisis Cecair Kromatografi Spektrometri Jisim (LCMS). Fraksi yang aktif dengan aktiviti anti-radang dan rendah sitotoksik di pilih dan digunakan untuk kajian ekspresi gen pro-radang dengan menggunakan teknik rantai polymerase masa-nyata (qPCR). Akar periferal dikumpulkan daripada tiga pokok *J. curcas* yang berlainan di mana usia pokok adalah di dalam lingkungan 4 ke 5 tahun dan ekstrak akar 80% metanol disediakan untuk menghasilkan ekstrak kering akar. Selepas itu, ekstrak metanol akar digunakan di di dalam proses teknik cecair-cecair pemeringkatan dengan menggunakan lima jenis pelarut yang berbeza (hexana, klorofom, etil acetat, n-butanol, dan aqua). Kemudian, kesemua fraksi berbeza yang terhasil di uji

keberkesanannya melalui aktiviti antioksida secara in vitro iaitu 1,1-Diphenyl-2-Picrylhydrazyl (DPPH) memerangkap bebas radikal, aktiviti penurunan kuasa ferik, dan aktiviti penurunan perapan radikal 2'-Azinobis (3-ethylene benzothiazoline) 6-Sulphonicacid (ABTS). Keputusan menunjukkan fraksi etil asetat dan n-butanol untuk ketiga sampel akar mempunyai sifat antioksida yang tinggi dengan kandungan fenol tertinggi pada (36.7 ± 0.046 GAE µg /g DW and 33.1 ± 0.006 GAE µg /g DW) dan flavonoid (11.76 ± 0.015 GAE µg /g DW and 10.11 ± 0.009 GAE µg /g DW). Keputusan analisa LCMS mendapati fraksi etil asetat mengandungi epigenin dan kaempferol glucosid isomer, di mana ianya dikategorikan di bawah kumpulan flavon dan fenolik yang mempunyai ciri-ciri antioksida dan anti-radang. Kemudian, n-butanol menggandungi asid komerik dan asid p-komerilquinik yang tinggi di mana ianya menyumbang kepada aktiviti anti-radang yang bagus. Aktiviti anti-radang bagi kesemua lima fraksi dikaji dengan menggunakan murin makrofaj barisan sel RAW 264.7 dengan mengenalpasti peratusan nitrik oksida (NO) yang terhasil melalui tindakbalas Griess. Aktiviti sitotoksik bagi setiap fraksi ditentukan dengan cara penurunan 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) yang digunakan pada murin makrofaj barisan sel RAW 264.7. Keputusan ujikaji menunjukkan 86% perencatan nitrik oksida (NO) oleh fraksi n-butanol pada kepekatan 100 µg/mL pada sel makrofaj RAW 264.7 dan daya maju sel sebanyak 105% berbanding curcumin. Analisa LCMS menunjukkan kehadiran epigenin dan isomer kamferol glucosida, di mana ianya diklasifikasikan di bawah kumpulan flavon dan fenolik yang mempunyai ciri-ciri antioksida dan anti-keradangan. N-Butanol pula mengandungi asid komarik dan asid p-komarolkuinik yang berpotensi untuk terlibat dalam aktiviti anti-keradangan. Fraksi n-butanol kemudiannya di nilai menggunakan teknik rantai polymerase masa-nyata (qPCR) untuk mengkaji ekspresi gen-gen (iNOS, TNF-α, IL-6, dan IL-1β) yang berkaitan dengan aktiviti radang oleh RAW 264.7 yang di rawat dengan lipopolisakarida (LPS) dan interferon-gamma (IFN-γ) di mana sel RAW 264.7 yang di rawat dengan curcumin telah digunakan sebagai pengawal positif dan diselaraskan oleh ekspresi gene pengawal (G3DPH). . Keputusan kajian menunjukkan bahawa fraksi n-butanol pada kepekatan 100 µg/mL dengan ketara ($P<0.05$) menurunkan ekspresi gen iNOS, TNF-α, IL-6, dan IL-1β. Oleh itu, kesan anti-keradangan adalah disebabkan menurunan regulasi pengantara pro-keradangan. Kajian ini menunjukkan proses fraksi cecair-cecair telah Berjaya membahagikan metabolit yang hadir di dalam ekstrak metanol bagi akar pokok *J. curcas*, di mana fraksi n-butanol dilihat mempunyai metabolit-metabolit yang memiliki ciri-ciri aktiviti antioksida dan anti-radang yang tinggi dan sitotoksik yang rendah serta kebolehan menggurangkan kesemua empat ekspresi gen pro-radang yang di uji.

ACKNOWLEDGEMENTS

I am very thankful to The Mighty Allah S.W.T. for giving me the opportunity to learn so many new things and help me in His own way to pass through all the obstacles and hardship during my research project. My deepest appreciations to my supervisor, Professor Dr. Norhani Abdullah who always believe in me, being supportive and guide me through my entire journey to finish this project. To my co-supervisor Associate Professor Dr. Syahida Ahmad and Dr. Faridah Abas who provide me with facilities required for my experiment, giving me a useful advices when ever I need one especially in her area of expertise.

To all staff that involved in finishing this project, especially from Natural Product Laboratory and Laboratory of Vaccine and Immunotherapeutic of the Institute of Biosciences particularly Dr. Tan Sheau Wei, Mrs. Mazina Mohd, Mrs. Nurul Huda, Mrs. Hafizah, Miss Nancy, who's contributed in so many way to this project.

Special gratitude to my laboratory mate, Mr. Mohd Nazri, Mrs. Nur Shafika, Miss Ashikin, and Mr. Leong for wonderful friendship and share tears and laugh together trough the entire years.

I am also appreciatively acknowledge Ministry of Science, Technology and Innovation (MOSTI) of Malaysia for funds provided under the Fundenmental Research Grant Scheme (Project Code: 5524176), and financial support from Mybrain15 from Minister of Higher Education, and Graduate Research Fund (GRF) from Universiti Putra Malaysia.

Thank you very much to my dearest parents, Osman Ismail and Salma Saim for their encouragement, love, and moral support that I could not imagine how can I survive without them. Last but not least, special appreciation to my little princess, Safeeya Eryna and beloved husband, Mohammad Saufi Ahmad for his love, patience, and endless support that give me strengths to finish my studies.

I certify that a Thesis Examination Committee has met on 6 February 2017 to conduct the final examination of Shahirah Atiqah binti Osman on her thesis entitled "Antioxidant and Anti-Inflammatory Activities of Fractions from *Jatropha curcas* Linn. Root Extract and Attenuation of Pro-Inflammatory Mediators in Raw 264.7 Cells" 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:

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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

DMEM	Dulbecco's modified eagle medium
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DPPH	1,1-diphenyl-2-picrl-hydrazyl
EA	Ethyl acetate
FBS	Fetal bovine serum
FRAP	Ferric reducing antioxidant power
GAE	Gallic acid equivalents
IC_{50}	Inhibitory concentration
IFN-γ	Interferon-γ
IL-1β	Interleukin-1 beta
iNOS	Inducible nitric oxide synthase
LCMS	Liquid Chromatography Mass Spectrometer
L-NAME	N_{ω}-nitro-L-arginine methyl ester
LPS	Lipopolysaccharide
MTT	3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide
NO	Nitric oxide
NOS	Nitric oxide synthase
PBS	Phosphate buffer saline
PCR	Polymerase chain reaction
RNA	Ribonucleic acid
ROS	Reactive oxygen species
rRNA	Ribosomal ribonucleic acid
RT-PCR	Reverse transcriptase Polymerase chain reaction
Real-time PCR	Real-time Polymerase chain reaction
ABTS	Scavenging of ABTS(2,2′-azinobis[3-ethylbenzothiazoline-6-sulphonate])-nitrogen-centred radical cation.
TPC	Total phenolic content
TFC	Total flavonoid content
SD	Standard deviation

LIST OF ANNOTATIONS

α	Alpha
β	Beta
γ	Gamma
%	Percentage
(v/v)	Volume per volume
(w/v)	Weight per volume
λ	Lambda
±	Plus and/or minus
≤	Less or equal
ω	
°C	Degree celcius
µ	Micro
µL	Microliter
µM	Micromolar
g	Gram
h	Hour
kDA	Kilo Dalton
Kg	Kilogram
L	Liter
mg/mL	Miligram per millilitre
µg/mL	Microgram per millilitre
Min	Minute
Mmol	Millimole
U	Units
V	Volt
S	Second

CHAPTER 1

INTRODUCTION

Jatropha curcas Linn. (*J. curcas)* is a multipurpose plant which belongs to the Euphorbiaceae family. This plant species is resistant to drought and disease and mostly grows in low to high rainfall area such as Africa and South-east Asia including Malaysia. Usually, this plant could be found in the farm as a commercial crop or on the boundaries as a hedge for protection from grazing animals and to avoid erosion (Henning, 1996; Gubitz, 1997; Uche, 2008).

It has been reported that all parts of *J. curcas* such as seeds, bark, leaves, and also roots have been used in traditional medicine for humans as well as for animals (Dalziel, 1995; Duke, 1988; Reddy Prasad, 2012). This plant is used for treating scabies, ringworm and gonorrhoea caused by either fungal or bacterial infections (Aiyelaagbe et al., 2007).

There are several parts of *J. curcas* that are traditionally used to treat inflammation, including latex, seeds, leaves and roots. Since 1989, De Feo had discovered *J. curcas* latex to possess anti-inflammatory activity when the latex was rubbed to the traumatic area. The seeds have been used to treat inflammation as well as other ailments like convulsions, burns, and fever (Osoniyi and Onajobi, 2003). Leave extracts from *J. curcas* showed anti-inflammatory activity when tested using *in vivo* technique involving mice and Wister albino rats (Uche at al., 2008).

There are several reports regarding the presence of metabolites such as alkaloid compounds, phenolic, flavonoid, and saponin in different parts of *J. curcas* plant (Thomas et al., 2008). According to Seyum et al. (2006) and Miliauskas et al. (2004), phenolic and flavonoids compound present in plants are well correlated to the free radical scavenging, nitric oxide (NO) scavenging, and also total antioxidant activities. This indicates that antioxidant is correlated with several compounds involved in anti-inflammatory activity.

Inflammation mediators, cytokines are glycoproteins that were synthesized in various types of cells under stress conditions. Generally, cytokines can be classified as pro-inflammatory or anti-inflammatory depend on how they influence inflammation. Pro-inflammatory cytokines such as iNOS, TNF-α, IL-1β and IL-6 are known as initiators and amplified the inflammatory process, while the anti-inflammatory cytokines like IL-10 inhibit the inflammatory mediator (Abebayehu et al. 2012). These genes were used in gene expression study by using real-time PCR (qPCR) to study the mechanism of action involve.

It is widely accepted that non-steroidal anti-inflammatory drugs (NSAIDs) can effectively prevent inflammation (Shen et al., 2011, Raz, 2002). However, several studies have showed side effects resulting from prolonged use of NSAIDs, which include several chronic diseases such as gastrointestinal (GI) ulcers, adverse cardiovascular side effects, and Alzheimer's disease (Sostres et al., 2010, McGeer and McGeer, 2007). Therefore, an alternative way of using natural resources from medicinal plant should be used in pharmaceutical industries to treat inflammation as it is more safe, gentle, and with no or less side effects.

Many studies have been carried out to determine potential plant-derived compounds with significant anti-inflammatory effects. Discovery of plant metabolites for treatment and/or controlling inflammatory diseases is important for developing new drugs. Oskoueian et al. (2011) had reported that the methanolic extract of root from *J. curcas* possessed anti-inflammatory activity, but the extract was toxic to the cells. This observation indicated the presence of bioactive compounds that are anti-inflammatory and cytotoxic to the cells. Therefore, it was necessary to obtain a root extract that contain bioactive compounds that are anti-inflammatory but non-toxic to the cells. Different solvents with different polarities (non-polar to polar) would be used to partition the *J. curcas* root and depending on the biological activity of the compounds, the correct solvent would be determined. It was hypothesized that liquid-liquid fractionation process could extract metabolites from *J. curcas* root which possessed antioxidant and anti-inflammatory activities without cytotoxic effect in the cell lines used.

Hence the main objective of this study was to obtain an active fraction from a methanolic extract of *J. curcas* root with anti-inflammatory activity without cytotoxicity activity and to evaluate its effects on the expression of the pro-inflammatory mediators. The specific objectives were:

1. To partition methanolic extract of *J. curcas* root into different solvents fractions with different polarities and to determine the compounds present in the different fractions.

2. To determine the antioxidant and anti-inflammatory activities of *J. curcas* roots fractions.

3. To evaluate pro-inflammatory mediators including iNOS through gene expression study in RAW 264.7 cell lines treated with an active fraction from *J. curcas* roots.

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