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IN VITRO ANTIOXIDANT AND ANTI-ATHEROSCLEROTIC ACTIVITIES OF PHENOLIC SAPONIN RICH FRACTION OF COSMOS CAUDATUS KUNTH

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By

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Chairman : Professor Muhammad Nazrul Hakim Bin Abdullah, PHD
Faculty : Medicine and Health Sciences

Cosmos caudatus or Ulam raja as it is known in Malaysia, is a tropical plant that has been known in South East Asia for many traditional uses, some were proved by pharmacological studies, while others yet to be validated. In this study, we are inspecting the atheroprotective effects for ulam raja extract/fractions through *in vitro*. The shoot samples were collected fresh from the plant stem, oven dried and grinded. A 100 gm sample was macerated in 50% (v/v) ethanol, twice for 48hours each time with intermittent shaking, after extract pooling, solvent was removed under reduced pressure and lyophilized to produce the crude extract. Subsequently, the crude extract was fractionated to produce the butanol and the aqueous fractions. In order to determine the phenolic, saponin and steroidal saponin contents, we employed folin-ciocalteu, vanillin-sulfuric acid and anisaldehyde-sulfuric acid methods respectively. Butanol fraction was the phenolic-saponin rich fraction (PSRF) due to the fact that it possesses the richest total phenolic, saponin and steroidal saponin contents (88.45 mg GAE/g DW, 64.23 and 23.3 mg DE/g DW) respectively ($P<0.05$), compared to the other *C. caudatus* derived fractions.

Similarly, butanol fraction showed the highest antioxidant activity in four assays namely, DPPH, ABTS, iron chelating and BCB activity assays. Antioxidant activities for butanol fraction were (72.65 mg TEAC/ g DW), (94.47 mg TEAC/ g DW), (16.03 mg EDTA/ g DW) and (19.43 mg TEAC/ g DW) respectively. Cytotoxic effects of crude, butanol and aqueous fractions were determined by MTT assay in rat aortic smooth muscle cell line (A-10) for 24 hours, and IC_{50} were as follows 460.78, 313.96 and 949.2 µg/mL respectively. IC_{50} for the three fractions was going in the same trend of the previous assays, as butanol was the most potent, followed by crude, and lastly the aqueous fraction. Three concentrations (IC_{10}, IC_{25} and IC_{50}) of the three fractions were used to treat A-10 cell line to assess their activities in inhibiting migration and invasion of cells using Boyden chamber assay. Butanol fraction Intermediate

concentration (IC_{25}) demonstrated the strongest activity to inhibit smooth muscle cells from migration and invasion in *in vitro* assays, as they were reduced by 53.93% and 59.94% respectively compared to untreated control cells. However, the invasion inhibition index referred to that butanol and crude mild concentrations (IC_{10}) showed the highest index value ~68%, which means the best cell invasion to cell migration inhibition *in vitro*.

Taken together, results strongly support that PSRF from *C. caudatus* can be used to reduce atherosclerotic plaque formation by reducing its key mechanism represented by SMCs migration and invasion, and its subsequent events such as myocardial infarction and strokes. This can be attributed to the high contents of phenolics, saponins and vitamins, and their ability to reduce the oxidative stress and free radicals, in addition to the other mechanism of action of other flavonoids.

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

AKTIVITI ANTIOKSIDAN *In Vitro* DAN ANTI-ATHEROSCLEROTIC DALAM *Cosmos caudatus* YANG KAYA DENGAN BAHAGIAN FENOLIK-SAPONIN

Oleh

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Cosmos caudatus (C.Caudatus) atau Ulam raja seperti yang dikenali di Malaysia adalah sejenis tumbuhan tropika yang terkenal di Asia Tenggara untuk pelbagai kegunaan tradisional. Walaubagaimanpun, beberapa penggunaannya telah disahihkan melalui kajian-kajian farmakologi namun yang selainnya yang masih belum disahkan. Kajian ini ekstrak/pecahan ulam raja untuk mengkaji kesan pencegahan *atherosclerosis* melalui kajian *in vitro*. Pucuk segar yang telah dipetik dari batang tumbuhan, dikeringkan di dalam ketuhar dan dikisar untuk dijadikan sampel. Sampel sebanyak 100g dihancurkan sambil direndam di dalam larutan (ip/ip) ethanol 50% selama 48 jam. Larutan sampel tersebut digoncang secara berkala. Proses penghancuran sampel di dalam larutan ethanol ini diulang sekali lagi. Supernatan dibuang dan ekstrak tersebut dikumpulkan serta di *lyophilize* untuk menghasilkan ekstrak mentah. Kemudian, ekstrak mentah tersebut dipisahkan untuk mendapatkan ekstrak butanol dan akueus. Kaedah *folin-ciocalteu,* asid *vanillin-sulfuric* and asid *anisaldehyde-sulfuric* masing-masing digunakan untuk mengenalpasti kandungan *phenolic, saponin* dan steroid *saponin*. Ekstrak butanol telah dikenalpasti sebagai *phenolic-saponin rich fraction (PSRF)* kerana ia menunjukkan jumlah kandungan jumlah *phenolic* paling tinggi, jumlah *saponin* dan jumlah steroid *saponin* masing masing adalah (88.45 ± 2.7 mg GAE/g DW, 64.23 ± 2.5 dan 23.3 ± 0.5 mg DE/g DW) pada ($P<0.05$) berbanding dengan ekstrak lain dari *C.caudatus*.

Bersamaan dengan itu, ekstrak butanol menunjukkan aktiviti anti-oksida paling tinggi di dalam empat *assay* iaitu DPPH, ABTS, *iron chelating* dan *assay* aktiviti BCB. Aktiviti antioksida bagi ekstrak butanol di dalam setiap *assay* masing-masing adalah (72.65 mg TEAC/ g DW), (94.47 mg TEAC/ g DW), (16.03 mg EDTA/ g DW) dan (19.43 mg TEAC/ g DW). Kesan sitotoksik untuk 24 jam bagi ekstrak mentah, ekstrak butanol dan ekstrak akueus terhadap sel otot licin vaskular Aorta tikus (A-10) ditentukan melalui *assay*

MTT dan nilai IC_{50} masing-masing adalah seperti berikut 460.78, 313.96 dan 949.2 µg/ml. Nilai IC_{50} bagi ketiga-tiga ekstrak menunjukkan corak yang sama dengan *assay* sebelum ini, dimana ekstrak butanol mempunyai kekuatan paling tinggi diikuti dengan ekstrak mentah dan ekstrak akueus. Tiga konsentrasi (IC_{10}, IC_{25} dan IC_{50}) untuk setiap ekstrak digunakan untuk merawat sel A-10 bagi menilai aktiviti-aktiviti setiap ekstrak dalam menghalang migrasi dan invasi cell A-10 menggunakan *Boyden chamber assay*. Dalam *assay in vitro*, konsentrasi pertengahan (IC_{25}) bagi ekstrak butanol menunjukkan aktiviti paling tinggi dalam menghalang migrasi dan invasi sel otot licin, di mana aktiviti migrasi dan invasi masing-masing mengalami pengurangan sebanyak 53.93% dan 59.94% berbanding dengan sel kawalan yang tidak dirawat. Bagaimanapun, indeks penghalang invasi yang merujuk kepada butanol dan konsentrasi sederhana mentah (IC_{10}) menunjukkan nilai indeks tertinggi ~68%, yang membawa maksud invasi sel terbaik kepada penghalangan migrasi sel secara *in vitro*.

Secara keseluruhan, hasil keputusan menyokong dengan kukuh bahawa PSRF dari *C. caudatus* boleh digunakan untuk mengurangkan pembentukkan plak *atherosclerosis* dengan mengurangkan mekanisma utamanya iaitu migrasi SMC dan invasi serta mampu mengurankan kejadian berkaitan seperti infarksi myokardia dan angin ahmar. Ini mungkin disebabkan oleh kandungan *phenolics*, *saponins* dan vitamin yang tinggi serta kebolehannya untuk mengurangkan keadaan tekanan oksidatif dan radikal bebas, termasuk mekanisma tindakan yang lain bagi flavonoid yang berbeza.

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I certify that a Thesis Examination Committee has met on 11 November 2016 to conduct the final examination of Said Faroq Saiyid Moshawih on his thesis entitled "*In Vitro* Antioxidant and Anti-Atherosclerotic Activities of Phenolic Saponin Rich Fraction of *Cosmos caudatus* Kunth" 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.

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This is to confirm that:

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Signature: _____
Name of Member of Supervisory Committee: Dr. Manraj Singh Cheema

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µl	Microliter
$^1O_2$	Singlet oxygen
ABC	ATP-binding cassette transporter
ABTS	2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid)
AI	Atherogenic index
AIDS	Acquired immunodeficiency syndrome
Akt	Protein kinase B
AP-1	Activation protein -1
AqF/Aq	Aqueous fraction
ATS	Atherosclerosis
BCB	B-carotene bleaching assay
BF	Butanol fraction
BHA	Butylated hydroxyanisole
BHT	Butylated hydroxytoluene
CD36	Cluster of differentiation 36
CEE/Cr	Crude ethanolic extract
COX	Cyclooxygenase enzyme
Cu-ZnSOD	Cupper-Zinc superoxide dismutase
DE	Diosgenin equivalent
DMEM	Dulbecco's Modified Eagle's medium
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DPPH	2,2-diphenyl-1-picrylhydrazyl
ECM	Extracellular matrix

EDTA	Ethylenediaminetetraacetic acid
eNOS	Endothelial nitric oxide synthase
ERK	Extracellular signal regulated kinases
FBS	Fetal bovine serum
FC	Folin–Ciocalteu
FH	Familial hyperlipidemia
FRAP	Ferric reducing ability of plasma
GAE	Gallic acid equivalent
GM-CSF	Granulocyte macrophages colony stimulating factor
GPx	Glutathione peroxidase
GSH	Glutathione
H_2O_2	Hydrogen peroxide
HDL	High density lipoprotein
HPLC	High performance liquid chromatography
IC	Inhibitory concentration
ICAM-1	Intracellular adhesion molecule -1
IFN-ɣ	Interferon gamma
IKB	Inhibitor of kappa B
IL	Interleukin
iNOS	Inducible nitric oxide synthase
JNK	c-Jun N-terminal kinases
LDL	Low density lipoprotein
LDLR	Low density lipoprotein receptor
LPL	Lipoprotien lipase
MAPK	Mitogen-activated protein kinase

mBar	Milli bar
MCP-1	Monocyte chemotactic protein-1
MHC	Major histocompatibility complex
MI	Myocardial infarction
mM	Millimolar
MMLDL	Minimally modified low density lipoprotein
MMP	Matrix metalloproteinase enzyme
MnSOD	Manganese superoxide dismutase
MTT	Microculture tetrazolium assay
NADP	Nicotinamide adenine dinucleotide phosphate
NF-kB	Nuclear factor kappa B
$NO^{\cdot}$	Nitric oxide
$O_2^{\cdot -}$	Superoxide
OD	Optical density
$OH^{\cdot}$	Hydroxyl radical
$ONOO^{-}$	Peroxynitrite
ORAC	Oxygen radical absorbance capacity
oxLDL	Oxidized low density lipoprotein
PAF	Platelet activating factor
PBS	Phosphate buffered saline
PCSK9	Proprotein convertase subtilisin/kexin type 9
PGC1	Peroxisome proliferator-activated receptor gamma coactivator 1
PI3K	Phosphoinositide 3-kinases
PPAR	Peroxisome proliferator-activated receptor
PSRF	Phenolic-saponin rich fraction

R	Pearson correlation
R.S.	Reactive species
RNS	Reactive nitrogen species
$RO^{\cdot}_2$	Peroxyl radical
ROS	Reactive oxygen species
RPM	Round per minute
SMC	Smooth muscle cells
SO_2	Sulfur dioxide
SOD	Superoxide dismutase
STAT-1	Signal transducers and activators of transcription -1
TC	Total cholesterol
TCM	Traditional Chinese medicine
TEAC	Trolox equivalent antioxidant capacity
TG	Triglyceride
T_h	T-helper lymphocytic cells
TIMP	Tissue inhibitor of metalloproteinases
TLC	Thin layer chromatography
TNF	Tumor necrosis factor
TPC	Total phenolic content
TSC	Total saponin content
TSSC	Total steroidal saponin content
USDA	United state department of agriculture
VCAM-1	Vascular cell adhesion molecule -1
VSMC	Vascular smooth muscle cells

CHAPTER 1

INTRODUCTION

Patients had become more dependent on herbal medicines in the second half of the 20th century than before, this was proceeded by fascination with patent medicines in the 19th century, when the scientific methods were advanced and preferred (Winslow et al., 1998). Nowadays, and due to the increasing use of natural resources by pharmaceutical industry and medicine synthesis, people realize that returning back to the nature is the best way to decrease side effects and high costs of synthetic medicines (Alsarhan et al., 2014). This is more appreciated in tropical and subtropical regions which contain 60% of the total world plant species (Goh et al., 1993). Due to the wide variety of flora and fauna in Malaysia, people are aware of its benefits as a rich source of antioxidants and vitamins (Bunawan et al., 2014). Eighty percent of plant species recorded in the Malaysian state of Sabah are being used by locals for traditional treatments and as a flavoring agents in food (Kulip et al., 2010).

Among this enormous legacy of plant species, *Cosmos caudatus* is within the most prominent and beneficial ones. *C. caudatus* in Malaysia is locally called "Ulam Raja" which means King's salad. (Figure 1.1). It is being used in food for its pungent flavor and distinct aroma, cooked or raw in salads (Rasdi et al., 2010). *Cosmos caudatus* is a short-lived annual plant, with aromatic leaves. It belongs to Asteraceae – formerly known as Compositae – family, only two species are available in Malaysia and around 26 worldwide (Abas, 2005). It grows up to 1.7 meters tall, and flowers at the 10th week of seeding, with a purple to pink and rarely white florets. The leaves are finely dissected, between 10 to 20 cm in length (Mediani, 2012). (Figure. 1.1). Spaniards brought *C. caudatus* along from tropical America to South East Asia during their travelling for its benefits as it was toning up their bodies for the long journey and poor nutrition conditions (Bodeker et al., 2009).

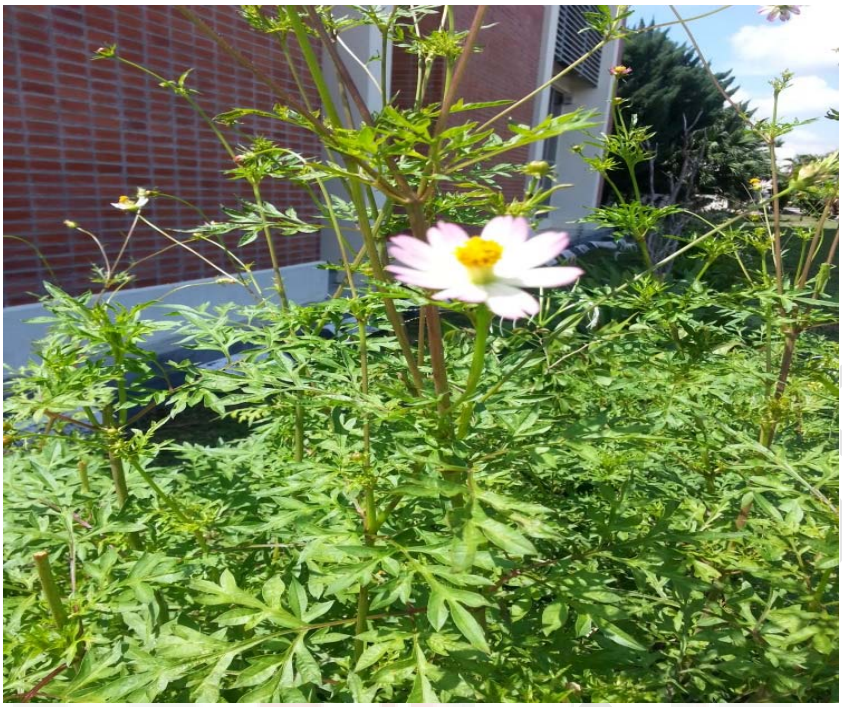

Figure 1.1 : *Cosmos caudatus* Kunth leaves and flowers.

Traditionally, *C. caudatus* is known for many medicinal uses, some of them were studied and others are being investigated and documented. Local people have used it for claims such as cleansing blood and bone reduced mineral density (Abas et al., 2006; Mediani et al., 2012). *Cosmos caudatus* Pharmacological reports proved its benefits as a bone healing herb in post-fracture (Rufus et al., 2015), and as a natural supplement to stop osteoporosis in ovariectomized rats (Mohamed et al., 2012; Mohamed et al., 2013). *Cosmos caudatus* was also found to possess a comparable efficacy with a currently used anti-hypertensive and diuretic medicines such as captopril and hydrochlorothiazide respectively (Amalia et al., 2012). Antibacterial, antifungal in addition to antidiabetic properties were documented in *in vitro* studies for *C. caudatus* (Fuzzati et al., 1995; Javadi et al., 2014; Loh et al., 2011; Ragasa et al., 1997; Rasdi et al., 2010).

Cosmos caudatus has also antihyperlipidemic properties, as described in animal model-induced hyperlipidemia (Perumal et al., 2014). Antimutagenic benefits, were tested by Ragasa et al. (1997) and Lee et al. (2011). Antioxidant activity has been described extensively by most of studies done on *C. caudatus* (Abas et al., 2003; Huda-Faujan et al., 2009; Mustafa et al., 2010; Shui et al., 2005). Furthermore, *in vivo* antioxidant and chemoprotective attributes have been recently documented by Abdullah et al. (2015).

Many flavonoids, phenols, phenylpropanoids, ascorbic acid, carotenoids, and terpenes were found in *C. caudatus* (Andarwulan et al., 2012). In addition to that, vitamins, carbohydrates, amino acids, minerals, organic acids and

essential oils were also detected (Javadi et al., 2014; Lee et al., 2011). The presence of other phytochemicals such as saponins and alkaloids were characterized by a preliminary tests in *C. caudatus* extracts by using bubble testing and TLC respectively (Musa et al., 2011; Rasdi et al., 2010).

Atherosclerosis is a chronic inflammatory disease for blood arterial walls, which allows for lipid accumulation and the formation atherosclerotic plaque. Beside genetic and environmental factors, inflammatory causes have been studied as an interpretation for the pathogenesis of atherosclerosis (Marín-García, 2014). Accumulation of lipids underneath blood vessels epithelium is the main feature of atherosclerosis (Djekic et al., 2015). This happens due to a sequence of events, starts from endothelial injury, and is followed by lipoproteins accumulation and blood monocytes mobilization to the site of action. Elevated levels of oxidized low-density lipoprotein (oxLDL) increase its engulfment by macrophages, which had differentiated from monocytes, and consequently, the formation of foam cells grows. Thereafter, these activated macrophages release factors to indicate the inflammatory status, and finally, the smooth muscle cells migrate to the intima layer and the atherosclerotic plaque developed (Palozza et al., 2010).

1.1 Study Justification

Currently, atherosclerosis is treated by three categories of medicines; antiplatelet aggregation, vasodilators and antihyperlipidemics (Bays, 2012). Up to date, there are no specific anti-atherosclerotic drugs. Even though atherosclerosis is defined as a chronic inflammatory disease, but anti-inflammatory drugs are not used for this purpose, except for acetylsalicylic acid, which is used for its antiplatelet aggregation properties (Kraus et al., 2014). On the other hand, since that the inflammatory cytokines play a significant role during the formation of atherosclerosis, therefore, anti-cytokine therapies have been studied on early stages of the subclinical atherosclerosis. They may form a promising trend for preventing atherosclerosis, but up to date, they still under investigation (Kirichenko et al., 2016).

The widely used medicines for both atherosclerosis and hyperlipidemia are statins. They have many beneficial activities in reducing LDL, TG, total cholesterol as well as their antiatherogenic properties. On the other flip, statins induce many side effects such as myopathies, hepatotoxicity and rhabdomyolysis. On top of this, upon long-term use, resistance may appear for statins due to genetic polymorphism (Reiner, 2014). Collectively, we found that it is imperative to seek a treatment for atherosclerosis from natural resources. *Cosmos caudatus* extract has been reported to contain a wide range of flavonoids and phenolics, in addition to saponins, alkaloids, and vitamins. Thus, this richness in bioactive constituents is promising to inhibiting atherosclerosis development.

1.2 Research objectives

1.2.1 General Objective

The general objective of this study is to evaluate the atheroprotective and antioxidant activities of *C. caudatus* extract and derived fractions *in vitro*.

1.2.2 Specific objectives

The specific objectives of this study are as follows:

1. To extract *C. caudatus* shoots to produce the crude ethanolic extract (CEE). Then, to fractionate the CEE into two more fractions; butanol fraction (BF) and aqueous fraction (AqF), and to determine the total phenolic contents (TPC), total saponin contents (TSC) and total steroidal saponin content (TSSC) for the produced extract/fractions.
2. To determine the antioxidant and free radical scavenging activities for *C. caudatus* extract/fractions using DPPH, ABTS, iron chelating and β-carotene bleaching assays.
3. To evaluate the cytotoxic and anti-atherosclerotic actions of CEE, BF and AqF on rat aortic vascular smooth muscle cell line, by employing microculture tetrazolium (MTT), and migration and invasion assays respectively.

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BIODATA OF STUDENT

Said Faroq Saiyid Moshawih was born in Syria, grew up in Amman, the capital city of Jordan. He has earned all of his school degrees in addition to the secondary education in the scientific stream from Jordan. His Bachelor degree was received from Al-Zaytoonah university of Jordan in 2005, in pharmacy, and his ranking was excellent. After graduation, he has tried to get scholarship to pursue his postgraduate studies, but all efforts were gone in vain. Therefore, he found himself obliged to work in the business sector as a pharmacist in a community pharmacy for five years, very far from his academic dreams, this was followed by another five years in a hospital pharmacy in Dubai – United Arab Emirates. However, because hope was still vivid in his mind, he left his family, work, salary and gossips and joined UPM to study Master of Science in pharmacology and toxicology.

His managerial experience in the hospital pharmacy was helpful for him to digest as much as possible from research tools and experimental studies within a short time, this experience was provided generously from UPM. His experience is especially in cell culture, antioxidation assays, animal studies and fluorescent microscopy. His research interests now and future intensions are mostly in stem cells, neurosciences and cancer research. Those are newly evolving topics can provide many medicinal benefits for patients afflicted with many diseases.

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