UNIVERSITI PUTRA MALAYSIA

EVALUATION OF ANTI-DIABETIC AND IMMUNOMODULATORY ACTIVITY OF POLYPHENOLS DERIVED FROM CASSIA AURICULATA L. ON INDUCED DIABETIC RATS

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By

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EVALUATION OF ANTI-DIABETIC AND IMMUNOMODULATORY ACTIVITY OF POLYPHENOLS DERIVED FROM *CASSIA AURICULATA* L. ON INDUCED DIABETIC RATS

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August 2012

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Faculty : Faculty of Medicine and Health Sciences

Diabetes mellitus (DM) is considered as an immuno-metabolic disease as the immune system impairment is leads to the progression of the disease. In this study we have examined the potential effect of *Cassia auriculata* flowers derived polyphenols (CAP) in modulating immune integrity and antidiabetic activity on experimentally induced (Streptazocin induced & Streptazocin+ Nicotinamide induced) diabetic rats. Normal and diabetic induced Sprague Dawley male rats at age of ~12 weeks were orally administrated with various CAP doses (10, 25, 50 &100 mg/kg) and observed for 28 days. Upon sacrifice measurement of glucose, insulin and HbA1c levels were done to assess the responses to therapy that facilitate reaching antidiabetic effect. Splenocytes were consumed to measure the expression of total T, B and NK and regulatory

Tcells through flow cytometer analysis. The functional assay for Tcells and neutrophils were conducted using tritiated thymidine assay and oxidative burst assay respectively. In addition, biochemical parameters (cholesterol, triglyceride & albumin) and haematological parameters (Leukocyte count, haemoglobin level, neutrophils& lymphocytes counts) were also analysed. Supplementation of CAP in all dosages had reduced the blood glucose and increased the insulin level towards the normal in both rat models. Despite gaining of body weight, CAP supplementation also significantly normalised the biochemical and haematological parameters of diabetic rats in comparison to normal control. Flow cytometer analysis revealed that the CAP supplementation reduced the percentages of pan splenic T and B cells; however a gradual increase in T helper cell sub-population along with reduction in T cytotoxic cells were noted. Although, the percentage of T cells was reduced yet, their ability of respond to mitogen (Lipopolysaccharide) and cellular expansion was enhanced when treated with CAP. Such expansion was not confined to T cells only, but also extends towards regulatory T cells, whose expression was escalated in the presence of CAP supplementation. In term of innate immune cell activity, CAP treatment reduced the oxidative burst activity of neutrophils indicating abridged oxidative stress in diabetes. The results collectively showed that CAP supplementation has normalised the diabetic indicators by reducing glycaemic level and inducing insulin secretion. This anti-diabetic activity of CAP also imposed an immunomodulatory function on adaptive and innate immune cells. The enhanced proliferation of T cells; specific expansion of T helper sub-

population and reduced oxidative burst activity of neutrophils are important to prevent the macromolecular damages that related to diabetes. Thus CAP could serves as holistic treatment that exerts anti-diabetic and immunomodulatory activity and maintains a protective mechanism by minimising complications in long term treatment for diabetes.

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

PENILAIAN AKTIVITI ANTI-DIABETIK DAN IMMUNOMODULASI POLIFENOL DARI BUNGA *CASSIA AURICULATA* L. PADA TIKUS DIARUH DIABETIK

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Kencing manis dianggap sebagai penyakit immuno-metabolik yang membawa implikasi terhadap kemerosotan sistem imun serta menyumbang kepada perkembangan penyakit. Dalam kajian ini, kesan dan potensi polifenol bunga Cassia awara (CAP) terhadap integriti sistem imun dalam memodulasi dan mengawal aktiviti antidiabetic pada tikus (tikus teraruh Streptazocin & Streptazocin + nicotinamide) telah dikaji. Tikus jantan Sprague Dawley yang berumur ~ 12 minggu (normal atau diabetic) telah diberikan dos CAP (10, 25, 50 & 100 mg / kg) secara oral dan pemerhatian dilakulan selama 28 hari. Paras glukosa, insulin dan HbA1c telah diukur ke atas tikus yang telah dikorbankan demi mendapatkan unjuran keberkesanan terapi antidiabetik. Splenocyt telah diekstrak untuk mengungkapkan kandungan sel-sel T, B dan NK melalui kaedah 'flow cytometer'. Kaedah Thymidine bertritium dan 'reactive oxidative species' juga telah di implikasikan untuk menganalisi perkembangan sel-sel T dan

neutrophil secara beasingan. Di samping itu parameter biokimia (kolesterol, trigliserida & albumin) dan parameter hematologi (kiraan Leukocyte, tahap hemoglobin, neutrofil & limfosit tuduhan) turut dianalisis. Kesemua dos CAP dalam kajian ini telah menunjukkan pengurangkan kadar glukosa darah dan meningkatkan aras insulin ke tahap normal dalam kedua-dua model tikus. Berbanding dengan tikus kawalan (normal), terdapat tambahan berat badan yang ketara disamping peningkatan ketara dalam parameter biokimia dan hematologi tikus kencing manis apabila diberikan suplemen CAP. Walaupun analisis Flow Cytometer menunjukkan bahawa suplemen CAP mengurangkan peratusan sel T dan sel B secara umumnya; namun peningkatan secara beransur dalam sel T- helper diperhatikan di samping pengurangan sel T sitotoksik. Namun demikian, keupayaan tindak balas sel T terhadap mitogen (lipopolysaccharide) dan perkembangan selularnya telah meningkat apabila dirawat dengan CAP. Pengembangan ini tidak terhad kepada sel-sel T sahaja, tetapi juga telah menjangkau ke arah perkembanagan 'regulatory T' sel, di mana keberkesanan sel T telah meningkat dengan kehadiran suplemen CAP. Dalam masa yang sama, rawatan CAP menunjukkan pengurangkan dalam aktiviti oxidative reactive species' neutrofil yang mengalakkan tekanan oksidatif ringkas terhadap diabetes. Secara kesimpulanya suplemen CAP telah membantu dalam mengurangkan tahap glisemik serta mendorong perkembangan insulin dalam pesakit diabetes. Aktiviti anti-diabetik CAP secara amnya juga berfungsi dalam memodolasikan sel-sel imun 'adaptive' dan 'innate'. Perkembangan serta peningkatkan sel-sel T; khusus sel 'T helper' dan

pengurangkan aktiviti ‘oxidative reactive species’ neutrofil adalah penting untuk mencegah kerosakan makromolekul yang berkaitan dengan diabetes. Oleh yang demikian CAP boleh berpotensi sebagai rawatan holistik yang dapat mengawal aktiviti anti-diabetes serta mengkordinasikan sistem imun disamping mengekalkan mekanisme perlindungan terhadap imunasi kompleks dalam rawatan kencing manis untuk jangka masa panjang.

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I certify that a Thesis Examination Committee has met on 28 August 2012to conduct the final examination of **Cini Mathew John** on her thesis entitled "Evaluation of anti-diabetic and immunomodulatory activity of polyphenols derived from *Cassia auriculata* on induced diabetic rats" 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 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 Supervisory Committee were as follows:

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DECLARATION

I declare that the thesis is my original work except for the quotations and citations which have been duly acknowledged. I also declare that it has not been previously, and is not concurrently, submitted for any other degree at Universiti Putra Malaysia or at any other institution.

CINI MATHEW JOHN

Date: 28 August 2012

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LIST OF ABBREVIATIONS

±	Plus minus
α	Alpha
β	Beta
AGE	Advanced Glycation end products
ALA	Alpha-Linolenic acid
ALB	Albumin
AR	Aldose reductase
ATP	Adenosine Triphosphate
CAD	Coronary Artery disease
Chol	Cholestrol
COX-1	Cyclooxygenase -1
COX-2	Cyclooxygenase -2
CRP	C-Reactive protein
cpm	counts per minute
CVD	Cardio Vascular Disease
d	Day
ºC	Degree Celcius
DHA	Decosahexaenoic
DM	Diabetic Mellitus
DNA	Deoxyribonucleic Acid
EA	Elligic acid

EGCG	Epigallocatechin-3-gallate
ELISA	Enzyme Linked Immuno-Sorbent Assay
ER	Endoplasmic Reticulum
g	Gram
GFAT	Glutamine fructose-6-phosphate amidotransferase
GK	Goto-Kakisaki
GLUT2	Glucose Transporter 2
GSH	Glutathione
GSSG	Oxidized glutathione
h	Hour
HBP	Hexosamine biosynthesis pathway
HK	Hexokinase
HDL	High density lipoprotein
HMG-COA	3-hydroxy-3-methylglutaryl-coenzyme A
HSP	Heat shock protein
HUVECS	Human Umbilical Vein Endothelial Cells
ICAM-1	Inter-Cellular Adhesion Molecule 1
IκB	Inhibitor of κB
IL-1	Interleukin-1
IL-6	Interleukin-6
IR	Insulin Resistance
IU	International Unit
Kg	Kilogram

L	Litre
LDL	Low Density Lipoprotein
Lox	5-Lipoxygenase
LPS	Lipopolysaccharide
LTB4	Leukotriene B 4
μg	Microgram
Mg	Milligram
μm	Micromole
μl	Microlitre
Ml	Millilitre
Mmol	Millimole
NAD	Nicotinamide Adenine Dinucleotide
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
NFκB	Nuclear Factor kappa-B
NHANES III	Third National Health and Nutrition Examination Survey
NPPEs	Naturally processed and presented epitope
%	Percent
PARP	Poly (ADP-ribose) polymerase
PBS	Phosphate buffer saline
PHA	Phytohemagglutinin
PKC	Protein Kinase C
PMA	Phorbal 12-myristate 13-acetate
P-NH_2	Free amino-residue of protein

PGE2	Prostaglandin E-2
PPAR	Peroxisome Proliferator- Activated Receptors
PPM	Parts per million
PP2A	Phosphatase type A Activity
PTPs	Phosphatases
RNS	Reactive nitrogen species
ROS	Reactive Oxygen Species
SDH	Sorbitol dehydrogenase
SD	Standard deviation
SNP	Single Nucleotide Polymorphism
STZ	Streptozotocin
TCR	T cell Receptors
TNF-α	Tumor Necrosis Factor-α
UDP-GlcNAc	UDP-N-Acetyl glucosamine
VEGF	Vascular endothelial growth factor
VLDL	Very Low Density Lipoprotein
W.H.O	World Health Organization

CHAPTER 1

INTRODUCTION

Diabetes Mellitus (DM) is a chronic disease of carbohydrate, fat and protein metabolism which results from the marked inability of the pancreas to secrete insulin because of the damage of pancreas which affects the production of insulin or autoimmune destruction of the β cells (Wysocki *et al.*, 2005). DM is considered as an immuno-metabolic disease as the immune system impairment is commonly reported in metabolic disorders or vice versa and progression of the disease (Falorni, 2003).

The pathogenesis of diabetes mellitus arises from high blood glucose which leads to increase oxidative stress in cells and tissues (Lee *et al.*, 2005). Briefly a high level of glucose during diabetes mellitus causes over production of superoxide in the mitochondrial electron transport chain, which inhibits the activity of the glycolytic enzyme glyceraldehyde 3-phosphate dehydrogenase (GAPDH). The inhibition of GAPDH by superoxide escalates upstream metabolites products from glycolysis which contributes to the pathogenesis of diabetic complications (Sakai *et al.*, 2003; Lee *et al.*, 2005). Insulin ill-response or resistance is resulted from a combination of altered functions of insulin target cells and the accumulation of microphages which has also been shown to activate proinflammatory innate immune receptors and intracellular oxidative stress (Nilsson *et al.*, 2008). Generally diabetes affects the immune system and make the body more prone to the risk of other harmful diseases and infections such as micro-vascular (diabetic retinopathy, diabetic nephropathy, diabetic peripheral neuropathy) and

macro-vascular diseases (coronary heart disease, peripheral vascular disease, cerebrovascular disease) (Lopes-Virella & Virella, 2003).

Problem statement

There are accumulating evidence suggesting inefficient immunological responses in DM and the use of oral anti-diabetic drugs can aggravate this situation in long term (Kuliczkowska-Plaksej *et al.*, 2006). The clinical potential of allopathic drugs used in the management of diabetic complications is still controversial due to the lack of conclusive evidence in glycemic control and uncertainty of its safety. Therapeutic approaches to manage the progression of diabetic complications are currently being undertaken by targeting the molecular pathogenesis of diabetic complications (Misra *et al.*, 1996). These therapeutic targets inhibit the formation of advanced glycated end products and reduce the overproduction of superoxides which associated with oxidative tissue damage. It is clearly understood that regiment that reduces free radicals has significant beneficial effect in the management of hyperglycaemia induced complications.

Besides that tolerance of diabetic oral drugs and gradual failure of insulin injection in Type 1 diabetic patients urged an alternative way to treat and control diabetes and diabetes associated complication. In line with this, naturopathy that consuming herbal products are found to be beneficial in treating diabetes with minimised side effects. However, only few herbal plants that utilised for diabetic treatments were investigated through an

integrated scientific approach, received scientific scrutiny and the world health warrants attention.

Significance of study

Evaluating the causes and changes in development of diabetes enables to suggest some perspective therapeutic approaches in DM (Li *et al*., 2007). Along with normalising glycemic levels and insulin levels, therapy which targets inflammatory mechanisms, normalizing T cell subsets, cytokine imbalance and insulin sensitivity have become therapeutic options (Kim *et al*., 2010). Suppression of both oxidative stress and inflammation through the modulation immune system factors may exert a beneficial efficacy in DM, (Skrha*et al.*, 2011). An ideal drug or drug combination for DM should target key pathogenic mechanisms and modulates immune system. Herbal based diabetic medicines are being acceptable globally through an effective management, which minimises complications due to the long term treatment. This study thus tried to find the relationship of antidiabetic action of *Cassia auriculata* derived polyphenol on experimentally induced diabetic rats. *Cassia auriculata* (CA), commonly known as tanner's cassia belongs to the family Caesalpiniaceae. It is an annual or biennial shrub found in tropical climate. It has been widely used in Indian Ayurvedic and Sidha medicine (Pari *et al.*, 2001; Babu & Stanely Mainzen Prince, 2004). The ancient Ayurvedic and Sidha medicine often consume all components (leaf, stem, root & flower) of CA in their medicinal preparation. It has been used as remedy for rheumatism, conjunctivitis, diabetes, general wellbeing, fair

complexion, hair care and pre & postnatal treatment. (Arseculeratne*et al*., 1981, Latha&Pari, 2003a; Duraipandiyan *et al*., 2006; Gupta *et al*., 2009a). CA contains several active constituents such as flavonoids, polyphenols, β-sitosterol, β-D-glycoside, polysaccharides, anthracene, dimeric procyanidins and myristyl alcohol (Nageswara Rao *et al.*, 2000). Where by polyphenols are found abundant in CA (Puranik *et al*., 2011). Polyphenols are highly recognised recently due to its efficacy and are used as adjunct therapy in diabetes, obesity, cancer and cardiac disorders (Tomas-Barberan& Andres-Lacueva, 2011).

Understanding the potential of *Cassia auriculata* flower on diabetes in addition with the significance of polyphenols, our study designed to evaluate the effect of *Cassia auriculata* derived polyphenols (CAP) in the immune system of experimentally streptazocin (STZ) induced diabetic rats & Streptazocin+ nicotinamide (STZ+NA) induced diabetic rats.

The objective of this study

To evaluate the anti diabetic and immunomodulatory effect of *Cassia auriculata* flower derived polyphenols (CAP) in experimentally streptazocin induced diabetic rats & streptazocin+ nicotinamide induced diabetic rats.

Specific objectives:

i) To evaluate the effect of CAP on glucose, insulin and HbA1c levels in experimentally streptazocin induced diabetic rats & streptazocin + nicotinamide induced diabetic rats.

ii) To explore the effect of CAP on adaptive and innate immune cells of experimentally streptazocin induced diabetic rats & streptazocin + nicotinamide induced diabetic rats.

iii) To investigate the effect of CAP on haematological and biochemical parameters in experimentally streptazocin induced diabetic rats & streptazocin + nicotinamide induced diabetic rats.

iv) To determine the safest therapeutic dosage of CAP in experimentally streptazocin induced diabetic rats &streptazocin + nicotinamide induced diabetic rats.

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