UNIVERSITI PUTRA MALAYSIA

METABOLIC EFFECTS OF Cosmos caudatus Kunth (ULAM RAJA) SUPPLEMENTATION IN TYPE-2 DIABETES MELLITUS PATIENTS

CHENG SHI HUI

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By

CHENG SHI HUI

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Doctor of Philosophy

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January 2017

Chair : Barakatun Nisak Mohd Yusof, PhD

Faculty : Medicine and Health Sciences

Cosmos caudatus, or locally known as "*Ulam Raja*" is a medicinal plant in Southeast Asia countries with reported medicinal benefits. Previously, supplementation with *C. caudatus* extract was found able to reduce plasma blood glucose in rats, but its effect in patients with type 2 diabetes mellitus (T2DM) was not established. To address this research gap, the present study aimed to determine the metabolic effects of *C. caudatus* in T2DM patients. The study was started by identifying the best way of *C. caudatus* supplementations. The first aim was to determine the antioxidant capacity of *C. caudatus* leaf extracts and juice using different extraction solvents (100% methanol, 100% ethanol, 95% ethanol, 50% ethanol). The findings found that *C. caudatus* leaves extracts had higher antioxidant capacity than *C. caudatus* juice. Following the first study, a two-arm randomized controlled clinical trial was carried out to determine the effectiveness and safety of *C. caudatus* supplementation in T2DM patients.

A total of 101 T2DM patients (age: 49.7 ± 9.1 years; mean HbA1C: 8.8 ± 1.6 %; BMI: 29.8 ± 4.7 kg/m^2; 56% male) were enrolled into the study. Participants were randomly assigned to diabetic-ulam group or diabetic controls. Patients in diabetic-ulam group consumed 15g of raw *C. caudatus* daily for 8 weeks while diabetic controls were abstained from taking *C. caudatus*. Both groups received standard lifestyle interventions. Changes in glycemic control, cardiovascular risk factors (anthropometric, blood pressure, lipid profile, high sensitivity C-reactive protein), renal profile, and liver function were measured at baseline, week 4, week 8 and week 12 (post-intervention follow-up) of the study.

As compared to diabetic controls, *C. caudatus* consumption significantly reduced serum insulin (−1.16 versus +3.91 μU/ml in controls), lowered homeostasis model assessment of insulin resistance (HOMA-IR) (−1.09 versus +1.34 unit in controls), and increased quantitative insulin sensitivity check index (QUICKI) (+0.05 versus −0.03 unit in

controls) in diabetic-ulam group. Subjects in diabetic-ulam group showed greater improvement in HbA1C (−0.76 %) as compared to diabetic controls (−0.37 %). Furthermore, supplementation of *C. caudatus* also resulted in the reduction of inflammation marker (hs-CRP) and systolic blood pressure, indicated its beneficial effect on reducing cardiovascular risk factors. Furthermore, *C. caudatus* consumption was found to be safe throughout the duration of the study as evident by no significant difference in liver and renal profile at the end of the study. Other parameters did not change significantly between the two groups.

In addition, a proton nuclear magnetic resonance spectroscopy (^{1}H NMR) based metabolomics approach was performed to determine the metabolic perturbation following *C. caudatus* consumption in T2DM patients. A total of 39 healthy individuals (age: 38.7 ± 8.5 years; BMI: 22.0 ± 1.7 kg/m^2; 44% male) were recruited as healthy controls, and their urine and blood serum metabolic profiles were compared with those obtained from diabetic controls and diabetic-ulam groups. As compared to healthy individuals, the concentrations of urinary lactate, branched-chain amino acids (BCAA, including valine, leucine and isoleucine), alanine, lysine, glutamate, glutamine, and pyruvate were significantly increased in T2DM patients, whereas the concentration of urinary urea was significantly decreased in T2DM patients. In addition, concentrations of blood serum lactate, BCAA (valine, leucine and isoleucine), alanine, lysine, glutamate, and N-acetylglutamate were significantly elevated in T2DM patients as compared to healthy individuals. These findings are consistent with published literature.

Following supplementation with *C. caudatus*, serum concentration of alanine, lactate and N-acetylglutamate were significantly decreased in diabetic-ulam group. The findings indicated a partial reversal of diabetes-induced metabolic changes through altered glycolysis, gluconeogenesis and glutamate metabolism. In addition, supplementation with *C. caudatus* was found to increase the concentration of urinary hippurate in diabetic-ulam group as compared to diabetic controls, suggesting changes in gut microflora metabolism.

In conclusion, the current study provided evidence that supplementation with *C. caudatus* improved insulin sensitivity in T2DM patients, evidenced by improved HOMA-IR and QUICKI parameters. It also improved hs-CRP and systolic blood pressure in T2DM patients, suggesting its effect in reducing the cardiovascular risk factors. The current results also showed that *C. caudatus* did not negatively affect liver and renal functions, suggesting that it is safe for T2DM patients. Furthermore, metabolomic data showed that *C. caudatus* supplementation partially reversed some known diabetes-induced metabolic changes such as lactate and BCAA in blood and urine. In summary, the current study uncovered the beneficial potential of *C. caudatus* for T2DM patients, and a longer term randomized controlled clinical trial is warranted to fully explore its therapeutic potential.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

KESAN METABOLIK SUPPLEMEN *Cosmos caudatus* KUNTH (ULAM RAJA) DI KALANGAN PESAKIT DIABETES MELLITUS JENIS DUA

Oleh

CHENG SHI HUI

Januari 2017

Pengerusi : Barakatun Nisak Mohd Yusof, PhD

Fakulti : Perubatan dan Sains Kesihatan

Cosmos caudatus, atau dikenali sebagai "Ulam Raja" adalah sejenis herba yang digunakan untuk tujuan perubatan di negara Asia Tenggara. Sebelum ini, didapati ekstrak *C. caudatus* dapat mengurangkan plasma glukosa darah dalam model tikus, tetapi kesannya di kalangan pesakit diabetes melitus jenis dua (T2DM) masih tidak diketahui. Untuk menangani jurang ini, kajian ini bertujuan untuk menentukan kesan metabolik supplemen *C. caudatus* di kalangan pesakit T2DM. Kajian ini dimulakan dengan mengenal pasti cara terbaik untuk supplemen *C. caudatus*. Matlamat pertama adalah untuk menentukan kapasiti antioksidan daun ekstrak *C. caudatus* dan jus menggunakan pelarut pengekstrakan yang berbeza (100% methanol, 100% ethanol, 95% ethanol, 50% ethanol). Hasil kajian mendapati bahawa ekstrak *C. caudatus* mengandungi antioksidan yang lebih tinggi daripada jus *C. caudatus*. Lanjutan dari kajian pertama, kajian kedua iaitu klinikal terkawal secara rawak telah dijalankan untuk menentukan keberkesanan dan keselamatan supplemen *C. caudatus* di kalangan pesakit T2DM.

Seramai 101 pesakit T2DM (umur : 49.7 ± 9.1 tahun; min HbA1C: 8.8 ± 1.6 %; BMI: 29.8 ± 4.7 kg/m^2; 56% lelaki) telah menyertai kajian ini. Peserta dibahagikan secara rawak kepada kumpulan diabetes-ulam atau kumpulan kawalan diabetes. Subjek dalam kumpulan diabetes-ulam mengambil 15g *C. caudatus* setiap hari selama lapan minggu manakala kumpulan kawalan diabetes telah dikecualikan daripada pengambilan *C. caudatus*. Kedua-dua kumpulan menerima nasihat gaya hidup yang sama. Perubahan dalam kawalan glisemik, faktor risiko kardiovascular (antropometri, tekanan darah, profil lipid, kepekaan tinggi protein C-reaktif), profil buah pinggang dan fungsi hati diukur pada minggu 0, minggu 4, minggu 8 dan minggu 12 (kajian susulan).

Berbanding dengan kumpulan kawalan diabetes, pengambilan *C. caudatus* dapat mengurangkan serum insulin (−1.16 berbanding +3.91 μU/ml dalam kawalan), menurunkan penilaian model homeostasis rintangan insulin (HOMA-IR) (−1.09

berbanding +1.34 unit dalam kawalan), dan meningkatkan pengambilan kuantitatif indeks insulin sensitiviti (QUICKI) (+0.05 berbanding −0.03 unit dalam kawalan) dalam kumpulan diabetes-ulam. Pesakit dalam kumpulan diabetes-ulam menunjukkan penurunan yang lebih banyak dari segi tahap HbA1c (−0.76 %) berbanding dengan kumpulan kawalan diabetes (−0.37 %). Tambahan lagi, supplemen *C. caudatus* juga menyebabkan pengurangan penanda keradangan (hs-CRP) dan tekanan darah sistolik, menunjukkan *C. caudatus* mempunyai kesan yang baik dalam mengurangkan faktor risiko kardiovaskular. Pengambilam *C. caudatus* didapati selamat sepanjang tempoh kajian kerana tiada perbezaan yang signifikan dalam profil hati dan buah pinggang pada akhir kajian. Parameter lain tidak berubah secara signifikan antara kedua-dua kumpulan.

Di samping itu, pendekatan metabolomik menggunakan spektroskopi nuklear magnet resonans proton (^{1}H NMR) telah dijalankan untuk menentukan perubahan metabolit selepas supplemen *C. caudatus* di kalangan pesakit T2DM. Sejumlah 39 individu yang sihat (umur: 38.7 ± 8.5 tahun; BMI: 22.0 ± 1.7 kg/m^2; 44% lelaki) telah diambil sebagai kawalan, dan profil metabolik urin and darah mereka dibandingkan dengan kumpulan kawalan diabetes dan kumpulan diabetes-ulam. Berbanding dengan individu yang sihat, kepekatan laktat, asid amino rantai bercabang (BCAA, termasuk valine, leucine, dan isoleucin), alanin, lisin, glutamat, glutamin, dan piruvat dalam urin telah meningkat dengan ketara dalam pesakit T2DM, manakala kepekatan urea dalam urin telah menurun dengan ketara dalam pesakit T2DM. Di samping itu, kepekatan laktat, BCAA, alanin, lisin, glutamat dan N-acetylglutamate dalam serum darah meningkat dengan ketara dalam pesakit T2DM berbanding individu yang sihat. Penemuan ini adalah konsisten dengan kertas jurnal yang diterbitkan.

Selepas supplemen dengan *C. caudatus*, kepekatan serum darah alanin, laktat dan N-acetylglutamate telah menurun dengan ketara dalam pesakit kumpulan diabetes-ulam. Dapatan kajian ini menunjukkan terdapat perubahan secara separa dalam metabolik diabetes melalui metabolisme glikolisis, glukoneogenesis dan glutamat. Di samping itu, supplemen *C. caudatus* didapati meningkatkan kepekatan hippurate urin dalam kumpulan diabetes-ulam berbanding dengan kumpulan kawalan diabetes, menunjukan perubahan dalam metabolism usus mikroflora.

Kesimpulannya, kajian ini membuktikan bahawa supplemen *C. caudatus* dapat meningkatkan sensitiviti insulin dalam pesakit T2DM melalui HOMA-IR dan QUIKI parameter. Ia juga mengurangkan hs-CRP dan tekanan darah sistolik dalam pesakit T2DM, menunjukkan kesannya dalam mengurangkan faktor risiko kardiovaskular. Kajian ini juga menunjukkan bahawa supplemen *C. caudatus* tidak memberikan kesan negatif terhadap fungsi hati dan profil buah pinggang, menunjukkan bahawa ia adalah selamat untuk pesakit T2DM. Tambahan pula, data metabolomik menunjukkan bahawa supplemen *C. caudatus* dapat mengubah sebahagian metabolik seperti laktat dan BCAA dalam darah dan urin. Secara ringkasnya, kajian ini menunjukkan supplemen *C. caudatus* adalah berfaedah untuk pesakit T2DM, dan satu percubaan klinikal terkawal dan rawak bagi tempoh masa yang lebih lama adalah wajar dijalankan untuk menerokai potensi terapeutik *C. caudatus* dengan sepenuhnya.

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I certify that a Thesis Examination Committee has met on 6th January 2017 to conduct the final examination of Cheng Shi Hui on her thesis entitled "Metabolic effects of *Cosmos caudatus* Kunth (Ulam Raja) supplementation in Type-2 Diabetes Mellitus patients" 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 Doctor of Philosophy.

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

Manohar Garg, PhD
Professor
University of Newcastle
Australia
(External Examiner)

NOR AINI AB. SHUKOR, PhD
Professor and Deputy Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 22 March 2017

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

Barakatun Nisak Mohd Yusof, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairperson)

Amin Ismail, PhD
Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

Joseph Anthony, M.B.B.S
Senior Medical Lecturer
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

Alfi Khatib, PhD
Associate Professor
Faculty of Pharmacy
International Islamic University Malaysia
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Name of Member of Supervisory Committee: Amin Ismail, PhD

Signature: _____
Name of Member of Supervisory Committee: Joseph Anthony, M.B.B.S

Signature: _____
Name of Member of Supervisory Committee: Alfi Khatib, PhD

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LIST OF ABBREVIATIONS

AA	Antioxidant activity
AACE	American Association of Clinical Endocrinologists
ABTS	2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonate)
ACD	Advance Chemistry Department
ADA	American Diabetes Association
AEAC	Ascorbic acid equivalent antioxidant capacity
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AR	Analytical reagent
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
ANOVA	Analysis of variance
BMI	Body mass index
BCAA	Branched-chain amino acids
CHO	Carbohydrate
CI	Confidence interval
CONSORT	Consolidated standards of reporting trials
CPG	Clinical Practice Guidelines
CPMG	Carr-Putcell-Meiboom-Gill
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
D_2O	Deuterium oxide
DPP-4	Dipeptidyl peptidase-4
DPPH	2,2-Diphenyl-1-picrylhydrazyl
DR	Degradation rate
DW	Dry weight
EC_{50}	Effective concentration (50%)
EDTA	Ethylenediaminetetraacetic acid
EI:BMR	Energy intake to basal metabolic rate
EtOH	Ethanol
FBG	Fasting blood glucose
FID	Free induction decays
FRAP	Ferric-reducing antioxidant power
FW	Fresh weight
GAE	Gallic acid equivalent
GC-MS	Gas Chromatography-Mass spectrometry
GLP-1	Glucagon-like peptide 1
GLUT4	Glucose transporter type 4
GGT	Gamma-glutamyl transpeptidase
^1H	Proton
HbA1C	Glycated hemoglobin
HCl	Hydrochloric acid
HDL	High-density lipoprotein
HMDB	The Human Metabolome Database
HOMA-IR	Homeostasis model of assessment for insulin resistance
HPLC	High-performance liquid chromatography
Hs-CRP	High sensitivity C-reactive protein
Il	Interleukin

IPAQ	International physical activity questionnaire
ITT	Intention-to-treat
LC-MS	Liquid Chromatography-Mass spectrometry
LDL	Low-density lipoprotein
MDA	Malondialdehyde
MeOH	Methanol
MET	Metabolic equivalent of task
MS	Mass spectrometry
MTF	Metformin
NHMS	National Health and Morbidity Survey
NMR	Nuclear magnetic resonance
NOESY	Nuclear overhauser effect spectroscopy
OPLS-DA	Orthogonal partial least squares-discriminant analysis
PBG	Postprandial blood glucose
PCA	Principal component analysis
PLS-DA	Partial least squares-discriminant analysis
PPAR-γ	Peroxisome proliferator-activated receptor gamma
ppm	Parts per million
QE	Quercetin equivalent
QUICKI	Quantitative insulin sensitivity check index
RE	Retinol equivalent
ROS	Reactive oxygen species
SBP	Systolic blood pressure
SD	Standard deviation
SIMCA	Soft independent modeling of class analogy
SOD	Superoxide dismutase
SPSS	Statistical package for the social science
SU	Sulphonylureas
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TAS	Total antioxidant status
TC	Total cholesterol
TCA	Tricarboxylic acid
TG	Triglycerides
TEAC	Trolox equivalent antioxidant capacity
TFC	Total flavonoid content
TPC	Total phenolic content
TPTZ	2,4,6-tris(2-pyridyl)-s-triazine
TSP	Sodium 3-trimethylsilyl-(2,2,3,3-d_4)-1-propionate
WC	Waist circumference

CHAPTER 1

INTRODUCTION

1.1 Research Background

Type 2 diabetes mellitus (T2DM) is a metabolic condition characterized by hyperglycemia resulting from insulin resistance and impaired insulin secretion (American Diabetes Association, 2015). T2DM is the most common form of diabetes which accounts for about 90-95% of all diabetes cases (American Diabetes Association, 2015). The prevalence of T2DM has been rising rapidly worldwide. In 2014, about 387 millions of people suffered from T2DM worldwide, and this number is projected to rise to 592 million people by 2035 (International Diabetes Federation, 2014).

Currently, management of T2DM involves multi-dimensional approach including the prescription of oral anti-diabetic drugs (such as metformin and sulphonylureas) and lifestyle interventions (Nauck et al., 2009). While the efficacy of sulphonylureas and metformin has been established, their use is associated with side effects such as increased weight gain and elevated risk of hypoglycemia and gastrointestinal disturbance (Inzucchi et al., 2012). In addition, researchers have shown that long-term treatment with oral anti-diabetic drugs is ineffective in protecting the declining function of the pancreatic beta cell (Ball et al., 2000; Van Raalte & Diamant, 2011). The deterioration of pancreatic beta-cell function has also been associated with the elevated oxidative stress in T2DM patients (Figueroa-Romero et al., 2008; Giacco & Brownlee, 2010). Despite the multi-approaches treatments in managing T2DM, poor glycemic control is still prevalent in T2DM patients (Ramachandran et al., 2010).

Medicinal plants have been used as an alternative treatment for treating T2DM (Surya et al., 2014). *Cosmos caudatus*, or known locally as Ulam Raja, is a medicinal herb that popularly consumed in South East Asia. It has been identified as one of the ten commonly used medicinal plants in Malaysia for the treatment of T2DM (Sekar et al., 2014). In addition, *C. caudatus* has been reported to contain a variety of bioactive compounds, including ascorbic acid, quercetin, proanthocyanidins, chlorogenic acid and catechin (Abas et al., 2003; Mustafa et al., 2010; Shui et al., 2005; Sukrasno et al., 2011). Notably, treatment with *C. caudatus* was found to confer beneficial effect in the animal model, but its effect in T2DM patients has not been established.

Previous studies showed that metabolomics applications in dietary interventions enable researchers to study the therapeutic mechanism effects of the dietary interventions (Martin et al., 2009; Moazzami et al., 2012; Van Dorsten et al., 2006). Metabolomics measures metabolites within a biological system at a given time (Zhang et al., 2014), and the profiling of these metabolites can provide detailed information on how the dietary intervention affects the metabolites in the biological system (Friedrich, 2012). In view of this, metabolomics approach can provide a clearer understanding on the effects of *C. caudatus* consumption in T2DM patients.

1.2 Statement of Problem

Today T2DM is a common chronic metabolic disease worldwide. One in twelve people worldwide has T2DM (International Diabetes Federation, 2014). The prevalence of T2DM in Malaysia showed the same worrying trend. The most recent NHMS IV has revealed that one in every five Malaysians age over 30 is having diabetes (Feisul, 2012). Despite the drug treatment, a majority (78%) of T2DM patients in Malaysia still have poor glycemic control with mean HbA1C of 8.7% (Mafauzy et al., 2011).

Medicinal plants played a crucial role in T2DM research (Surya et al., 2014). Indeed, the important role of plants as T2DM treatment was evidenced by the discovery of the metformin from *Galega officinalis* (Bailey et al., 2007). *C. caudatus* (*Ulam raja*) is widely consumed among the local Malays in Malaysia. It has been used since ancient times for its curative properties such as boosting blood circulation, strengthening the bone, and treating infectious disease (Bodeker, 2009). In addition, *C. caudatus* has been reported to have the highest antioxidant capacity as compared to other 25 plants using 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical *scavenging* activity and ferric ion antioxidant potential (FRAP) assays (Wong et al., 2006). This result was in agreement with a recent study which reported that *C. caudatus* have the highest antioxidant activity when compared to four common *ulams* in Malaysia (including *pegaga*, *selom*, curry leaf and *petai*) (Reihani & Azhar, 2012). This high antioxidant content may suggest its potential in reducing oxidative stress in humans (Shui et al., 2005).

In addition to its beneficial effect on antioxidant, *C. caudatus* has been shown to exhibit anti-diabetic (Perumal et al., 2014), anti-hypertensive (Amalia et al., 2012) and anti-inflammatory effect (Ajaykumar at al., 2012) in animal studies. Recent study in rats demonstrated a significant improvement in fasting blood glucose and lipid profile after 4 weeks of *C. caudatus* supplementation (Perumal et al., 2014). However, its effect in T2DM patients remains unclear. To address this gap, therefore, the objective of this study is to investigate the effect of an eight weeks *C. caudatus* supplementation on glycemic status, cardiovascular risk factors and metabolic profile in T2DM patients.

Furthermore, there is a lack of knowledge on the potential mechanism of action of *C. caudatus* supplementation in T2DM patients. To date, no studies have been reported on the metabolite changes following the *C. caudatus* supplementation. Metabolomics is a powerful tool to study the altered metabolism, identify short-term changes in biological fluids and serve as biomarker detection (Friedrich, 2012). We hypothesized that the therapeutic effect of *C. caudatus* in T2DM patients would reflect as a change of metabolite profile in urine and blood serum. Therefore, we perform metabolomic analysis in an attempt to elucidate the altered metabolite concentration following *C. caudatus* supplementation in T2DM patients.

1.3 Significance of the Study

Herbs have received increasing interest among researchers because of its health benefits. To the best of knowledge, there is no study reported on the effect of *C. caudatus* in T2DM patients. Considering *C. caudatus* is widely consumed among the locals in South East Asian countries, the findings of this study will provide useful insight into effectiveness and safety of *C. caudatus* supplementation in T2DM patients. Results from this study will contribute to the knowledge on the potential use of *C. caudatus* as an adjuvant therapy in the management of T2DM.

Besides, metabolomics approach used in this study will fill in the gap and provide a better understanding of metabolite perturbation following the supplementation of *C. caudatus* in T2DM patients. Likewise, it can undoubtedly enhance the knowledge on the potential anti-diabetic mechanism of *C. caudatus* supplementation.

1.4 General Objective

To investigate the metabolic effect of *C. caudatus* supplementation in T2DM patients.

1.5 Specific Objectives

1. To determine the antioxidant capacity of *C. caudatus* extracted by different solvents.
2. To determine the effect of *C. caudatus* supplementation on glycemic status (fasting glucose, insulin, HbA1C, fructosamine) in T2DM patients
3. To determine the effect of *C. caudatus* supplementation on cardiovascular risk factors (including blood pressure, lipid profile and high sensitivity C-reactive protein) in T2DM patients.
4. To determine the safety of *C. caudatus* supplementation on liver and renal profile in T2DM patients.
5. To determine and compare the metabolomic profiles of urine and blood serum between diabetic-ulam group, diabetic controls and healthy individuals.

1.6 Research conceptual framework

The conceptual framework of this study is presented in Figure 1.1. T2DM patients are usually advised to make lifestyle modifications which include dietary intervention and physical activity recommendations. In addition, medications including insulin therapy, anti-diabetic, anti-hypertensive and lipid-lowering drugs are used to achieve the targeted blood glucose and reduced cardiovascular risk factors in T2DM patients. Hence, the confounding factors in this study namely dietary intake, physical activity and medications were controlled throughout the study.

Oxidative stress plays a significant role in the development of insulin resistant (Styskal et al., 2012). Hyperglycemia and hyperlipidemia increase mitochondrial reactive oxygen species production and lead to oxidative stress (Evans et al., 2002). Oxidative stress affects insulin secretion and action, subsequently leads to beta cell dysfunction and insulin resistance (Bonnard et al., 2008; Lowell & Shulman, 2005).

It was hypothesized that *C. caudatus* used as a dietary antioxidant in this trial may reduce the oxidative stress, subsequently reduce the insulin resistance and improve the outcomes measurements (including glycemic status, cardiovascular risk factors, inflammation) in T2DM patients. In order to measure the altered metabolite in the urine and blood serum following *C. caudatus* supplementation in T2DM patients, a metabolomic approach is used in this study.

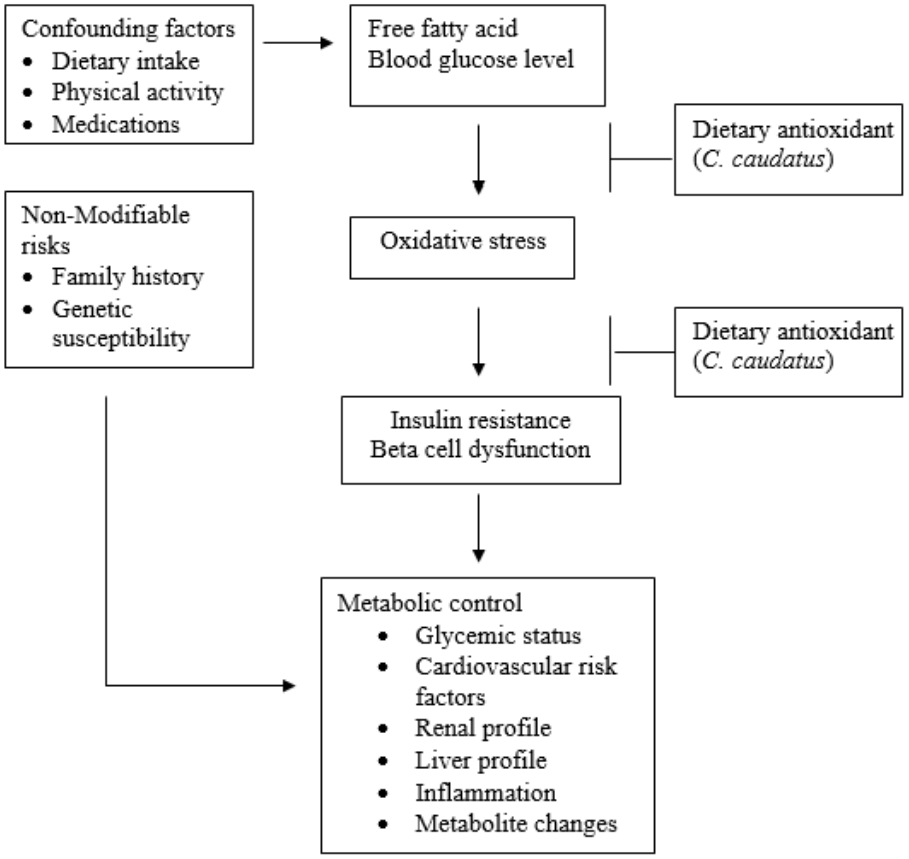

Figure 1.1: Conceptual framework of the study

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