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EFFECTS OF WATERMELON [Citrullus lanatus (Thunb.) Matsum. & Nakai var lanatus] LEAF EXTRACTS ON BIOLOGICAL AND HISTOLOGICAL PARAMAETERS IN TYPE 2 DIABETES RAT MODEL

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By

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EFFECTS OF WATERMELON [C*itrullus lanatus* (Thunb.) Matsum. & Nakai var *lanatus*] LEAF EXTRACTS ON BIOLOGICAL AND HISTOLOGICAL PARAMAETERS IN TYPE 2 DIABETES RAT MODEL

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Chairman : Nurul Shazini binti Ramli, PhD
Faculty : Food Science and Technology

Type 2 diabetes mellitus is a chronic metabolic disorder with multiple etiologies, causing complications leading to heart attack and even death in individuals when not well managed or untreated. Unfortunately, the available oral drug treatments have failed due to unwanted side effects, prompting the search for and use of natural remedies. This study aimed to investigate the antidiabetic effects of watermelon [*Citrullus lanatus* (Thunb.)] extracts in a high-fat diet-fed, streptozotocin (HFD/STZ)-induced diabetes rat model using proton nuclear magnetic resonance (^{1}H NMR)-based metabolomics. Watermelon extracts were prepared from the flesh, rind and leaf, and extracted with 100%, 90%, 70%, 60%, 50% ethanol, and water. The extracts bioactivities were evaluated by α-amylase and α-glucosidase inhibition, and antioxidants assays, while their metabolites were profiled by ^{1}H NMR spectroscopy. The extract with the highest bioactivity (60% leaf extract) was investigated in vivo for 6 weeks, using HFD-STZ diabetic rats combined with multiple low doses of streptozotocin. Serum and urine samples from the rats were profiled by ^{1}H NMR spectroscopy and were analyzed for biochemical parameters. Moreover, the histopathological studies were done on their kidneys and liver by hematoxylin-eosin staining. Results showed that the IC_{50} for α-amylase inhibition of the 70% and 60% ethanol watermelon leaf extracts, were 42.0 ± 4.6 and 45.3 ± 2.2 µg/mL respectively, more potent than those of 60% ethanol rind, 59.5 ± 8.0 µg/mL and 60% ethanol flesh, 60.0 ± 3.3 µg/mL extracts. The IC50 for α-glucosidase inhibition of 60% ethanol leaf extract, 12.0 ± 0.2 µg/mL was more potent than those of 60% ethanol rind 24.7 ± 2.5 µg/mL, and flesh 23.0 ± 3.1 µg/mL extracts. The IC_{50} of 60% ethanol leaf extract, 51.9 ± 5.3 µg/mL for 2,2′-azino-bis (3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) radical inhibition was stronger than those of 60% the rind and flesh, 363.4 ± 16.3 and 487.4 ± 23.0 µg/mL respectively. The principal component analysis, partial least square discriminant analysis and biplots of the extracts

showed that phenolic acids, epicatechin, isoeugenol, and citrulline could be responsible for the most potent

α-amylase and α-glucosidase inhibition, and antioxidant effects of the leaf extracts. Six-week treatment with high dose (400 mg/kg body weight) of 60% ethanol watermelon leaf extract reduced the fasting blood sugar, serum insulin, and total cholesterol of diabetic rats. Also, serum antioxidant enzymes activities were increased and normalized, with high dose watermelon leaf extract better than the standard drug (Metformin). Histopathological examination of kidneys and liver revealed tubular necrosis and hyaline cast formation in the diabetic rats' kidneys, necrosis and hepatocytes leucocyte infiltration, which were also restored back to normal after the treatment period. Metabolomics studies on the serum and urine revealed increased metabolic markers of the perturbed carbohydrate, amino acids and lipid pathways in the diabetic rats. Dysregulated pathways were gradually brought back to normal in a slow pace. The high dose watermelon leaf extract also had better results in restoring the perturbed pathways than the standard, indicating that 60% ethanol watermelon leaf extract could be as potent as metformin. This study predicted that watermelon leaf may have more potent antidiabetic lead molecules than metformin when explored. Therefore, watermelon leaf could serve as a potential raw material for functional foods and nutraceuticals ingredients for the management of type 2 diabetes mellitus.

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

KESAN EKSTRAK TEMBIKAI [*Citrullus lanatus* (Thunb.) Matsum. & Nakai var *lanatus*] KE ATAS PARAMETER BIOLOGI DAN HISTOLOGI DALAM MODEL TIKUS DIABETES JENIS 2

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Diabetes mellitus jenis 2 adalah gangguan metabolik kronik dengan pelbagai etiologi, mengakibatkan komplikasi yang menyebabkan serangan jantung dan bahkan kematian pada individu apabila tidak diurus dengan baik atau tidak dirawat. Walaubagaimanapun, rawatan ubatan secara oral yang sedia ada tidak berkesan kerana kesan sampingan yang tidak diingini. Ini mendorong pencarian dan penggunaan ubatan semula jadi. Kajian ini bertujuan untuk mengkaji kesan antidiabetik ekstrak tembikai [*Citrullus lanatus* (Thunb.)] ke atas model tikus diaruh diet tinggi lemak, streptozotocin (HFD / STZ) menggunakan metabolomik berasaskan resonans magnetik nuklear proton (1HNMR). Ekstrak tembikai dihasilkan dari isi, kulit dan daun, dan diekstrak dengan etanol 100%, 90%, 70%, 60%, 50%, dan air. Bioaktiviti ekstrak dinilai oleh aktiviti perencatan α-amilase dan α-glukosidase, dan asai antioksida, manakala kandungan metabolitnya diprofilkan menggunakan 1HNMR. Ekstrak dengan bioaktiviti tertinggi (60% ekstrak daun tembikai) diuji secara in vivo, menggunakan tikus diaruh diabetes HFD-STZ yang digabungkan dengan beberapa dos streptozotocin yang rendah. Sampel serum dan urin dari tikus diprofilkan dengan spektroskopi 1H-NMR dan dianalisa untuk parameter biokimia. Selain itu, kajian histopatologi dilakukan pada buah pinggang dan hati dengan pewarnaan hematoxylin-eosin. Hasil kajian menunjukkan bahawa ekstrak daun tembikai dengan nilai perencatan IC50 α-amilase pada 42.0 ± 4.6 dan 45.3 ± 2.2 µg / mL untuk etanol 70% dan 60%, lebih kuat daripada ekstrak etanol 60% dari kulit, 59.5 ± 8,0 µg / mL dan etanol 60% dari isi, 60.0 ± 3.3 µg / mL ekstrak. Nilai perencatan IC50 α-glukosidase untuk ekstrak daun etanol 60% ialah 12.0 ± 0.2 µg / mL iaitu lebih kuat daripada etanol 60% dari kulit 24.7 ± 2.5 µg / mL, dan ekstrak isi 23.0 ± 3.1 µg / mL. Nilai IC50 bagi perencatan radikal ABTS dari ekstrak daun etanol 60%, 51.9 ± 5.3 µg / mL, lebih kuat daripada ekstrak kulit dan isi, masing-masing 363.4 ± 16.3 dan 487.4 ± 23.0 µg / mL. Analisis komponen utama dan biplot analisis kuasa dua terkecil separa ekstrak menunjukkan bahawa asid fenolik,

epicatechin, isoeugenol, dan citrulline berkemungkinan bertanggungjawab terhadap perencatan aktiviti α-amilase dan α-glukosidase yang paling kuat, dan kesan antioksida dari ekstrak daun. Rawatan selama enam minggu dengan dos tinggi (400 mg / kg berat badan) 60% ekstrak etanol daun tembikai mengurangkan glukosa darah berpuasa, insulin serum, dan mengembalikan profil lipid tikus diabetes ke paras normal. Selain itu, aktiviti enzim antioksida meningkat dan kembali normal, dengan ekstrak daun tembikai dos tinggi lebih baik daripada ubat (Metformin). Analisis histopatologi ke atas buah pinggang dan hati menunjukkan nekrosis tubular dan pembentukan kas hialin pada ginjal tikus diabetes, nekrosis, dan penyusupan leukosit hepatosit, yang juga dipulihkan kembali normal selepas rawatan. Kajian metabolisme pada serum dan urin menunjukkan peningkatan penanda metabolik dalam laluan karbohidrat, asid amino dan lipid yang terganggu pada tikus diabetes. Gangguan kembali normal secara beransur-ansur pada kadar yang perlahan. Rawatan ekstrak daun tembikai dos tinggi juga memberikan keputusan yang lebih baik dalam memulihkan gangguan metabolisme, menunjukkan bahawa ekstrak etanol 60% daun tembikai boleh menjadi pengganti metformin sebagai bahan antidiabetik semula jadi. Kajian ini meramalkan bahawa daun tembikai mungkin mempunyai molekul antidiabetik yang lebih kuat daripada metformin setelah diterokai. Oleh itu, daun tembikai dapat dimanfaatkan sebagai bahan mentah yang berpotensi untuk dibangunkan sebagai makanan berfungsi dan bahan nutraseutikal untuk pengurusan diabetes melitus jenis 2.

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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 Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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1D	One dimensional
^{1}H NMR	Proton nuclear magnetic resonance
2D	Two dimensional
ABTS	2,2′-azino-bis (3-ethylbenzthiazoline-6-sulfonic acid)
AGEs	Advanced glycated end products
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine amino transferase
ANOVA	Analysis of variance
AOPPs	Advanced oxidation protein products
ASCII	American Standard Code for Information Interchange
AST	Aspartate amino transferase
ATP	Adenosine triphosphate
BMI	Body mass index
BW	Body weight
C. lanatus	*Citrullus lanatus*
Ca^{2+}	Calcium ion
cAMP	cyclic Adenosine monophosphate
CAT	Catalase
CD_3OD	Deuterated methanol
Cl^-	Chloride ion
CMC	Carboxymethyl cellulose
d	Doublet

D_2O	Deuterium oxide
dBIL	Direct bilirubin
dd	Doublet of doublet
DCG	Diabetic control group
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
DNS	Dinitrosalicylic
DO	Diabetic obese
DPP-4	Dipeptidylpeptidase 4
DPPH	1,1-diphenyl-2-picryl-hydrazyl
DPX	Dibutyl phthalate xylene
EGCG	Epigallocatechin-3-gallate
ELISA	Enzyme linked immunosorbent assay
ETC	Electron transport chain
FBS	Fasting blood sugar
Fe^{3+}	Iron 3 ion
Fe^{2+}	Iron 2 ion
$Fe_2SO_4.7H_2O$	Iron (II) sulphate solutions heptahydrate
FRAP	Ferric reducing antioxidant power
g	Gram
GGT	Gamma glutamyl transferase
GIP	Glucose dependent insulinotropic peptide
GLP-1	Glucagonlike peptide-1
GLUT	Glucose transporter

SGH	Reduced glutathione
GSH-Px	Glutathione peroxidase
GSSG	Oxidized glutathione
GST	Glutathione-S-transferase
H_2O_2	Hydrogen peroxide
HCA	Hierarchical cluster analysis
HDG	High dose group
HDL	High density lipoprotein
HFD	High-fat diet
HLJDD	Huang-Lian-Jie-Du-Decoction
HMBC	Heteronuclear multiple bond coherence
HMDB	Human metabolome database
HNE	4-hydroxynonenal
Hz	Hertz
IACUC	Institutional Animal Care and Use Committee
IC_{50}	Half maximal inhibitory concentration
IDF	International Diabetes Federation
IGF-1	Insulin-like growth factor 1
IL	Interleukin
IRS	Insulin receptor substrate
IsoLGs	Isolevuglandins
K^+	Potassium ion
K_{ATP}	ATP-sensitive potassium ion
KCl	Potassium chloride

KEGG	Kyoto Encyclopaedia of Genes and Genomes
kg	Kilogram
KH_2PO_4	Potassium dihydrogen phosphate
LBP	*Lycium barbarum* polysaccharides
LBP-X	*Lycium barbarum* purified polysaccharide fraction
LC-MS	Liquid chromatography mass spectrometry
LDG	Low dose group
LDL	Low density lipoprotein
M	Multiplet
MDA	Malondialdehyde
MetPA	MetaboAnalyst pathway analysis
METLIN	Metabolite and Chemical Entity Database
mg	Milligram
MHz	Megahertz
mL	Millilitre
mM	Millimolar
mmol/L	Millimole per litre
MTG	Metformin treated group
MVDA	Multivariate data analysis
Na_2HPO_4	Disodium hydrogen phosphate
Na_2SO_3	Sodium thiosulphate
Na^+	Sodium ion
NaCl	Sodium chloride
NADPH	Reduced nicotinamide dinucleotide phosphate

NaOD	Deuterated sodium hydroxide
NaOH	Sodium hydroxide
NC	Normal control
ND	Not detected
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
ng	Nano gram
NO	Nitric oxide
NOS	Nitric oxide synthase
O_2	Oxygen molecule
O^{2-}	Superoxide radical
$O^{\cdot}$	Oxygen radical
$OH^{\cdot}$	Hydroxyl radical
$ONOO^{\cdot}$	Peroxynitrile radical
OPLS	Orthogonal partial least square
OPLS-DA	Orthogonal partial least square discriminant analysis
oxLDL	Oxidized low density lipoproteins
P. notoginseng	*Panax notoginseng*
Par	Parreto
PBS	Phosphate buffer saline
PC 1	Principal component 1
PC 2	Principal component 2
PCA	Principal component analysis
PDX-1	Pancreas duodenum homeobox-1
pH	Negative log to base 10 of hydrogen ion concentration

PKA	Protein kinase A
PI3-K	Phosphatidylinositol 3-kinase
PKB/Akt	Protein kinase B
PKC-αβII	Protein kinase C alpha beta II
PLS	Partial least square
PLS-DA	Partial least square discriminant analysis
PMQ	Pentamethyl quercetin
PNP	Para-nitrophenol
PNPG	Para-nitrophenyl glucose
ppm	Parts per million
PPRE	Peroxisome proliferator-response element
PTP1B	Protein-tyrosine Phosphatase 1B
Q^2	Predictability of the model
R^2	Goodness of fit
RNA	Ribonucleic acid
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
RXR	Retinoid X receptor
S	Singlet
SD	Standard deviation
SI	Serum insulin
SOD	Superoxide dismutase
SPSS	Statistical package for social sciences
STZ	Streptozotocin

T	Triplet
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TBARs	Thiobarbituric acid reactive substances
tBIL	Indirect bilirubin
TC	Total cholesterol
TG	Triglyceride
TGF-β	Transforming growth factor beta
THP-1	Human acute monocytic leukemia cell line
TNF-α	Tumor necrotic factor alpha
TP	Total protein
TPC	Total phenolics content
TPTZ	2,4,6-tri(2-pyridyl)-s-triazine
TSP	Trimethyllsilyl propionic acid
TZDs	Thiazolidinediones
USDA	United states department of agriculture
VIP	Variable importance to the projection
VLDL	Very low density lipoprotein
WHO	World Health Organization
X_{AA}	Absorbance of ascorbic acid
X_{CL}	Absorbance of watermelon extracts
X_o	Absorbance of blank
α	Alpha
β	Beta

°C	Degree Celsius
δ	Proton NMR signal
µg	Microgram
µL	Microliter
µM	Micro molar
µmol/L	Micromole per litre
%	percent

CHAPTER 1

INTRODUCTION

1.1 Research Background

Diabetes mellitus is a chronic metabolic disorder preceded either by the absence of insulin, insufficient insulin and/or degenerate insulin action (Alberti et al., 2007; American Diabetes Association, 2014; Diabetes, 2019; World Health Organization, 2016). It has several etiologies and characterized by chronic hyperglycemia with perturbed protein, fat, and carbohydrate metabolism (Alberti & Zimmet, 1998; WHO, 2016). Type 2 diabetes (T2D) is differentiated from type 1 diabetes (T1D) by insulin inaction. Uncontrolled hyperglycemia in T2D precipitates malfunctions in the micro- and macro-vascular tissues, causing damages to blood vessels and nerves, prolonged impairments, and failure of the eyes, heart, and kidneys, (Brownlee, 2005; Donaghue et al., 2007; Fateema et al., 2012; Forbes & Cooper, 2013).

Over 90% of diabetic patients worldwide have T2D, and it is preceded by excessive growth or increase in the size of adipose tissue, i.e. overweight and obesity (González-Castejón & Rodriguez-Casado, 2011). There is presently an alarming rate of increase in overweight and obesity (WHO 2016), and thus, they independently contribute to increased diabetes mellitus prevalence. Diabetes mellitus prevalence rate is placed at 8.5% worldwide. Diabetes mellitus caused 1.6 million deaths in 2016, which made it the 7th cause of death in the world (WHO, 2016). According to International Diabetes Federation (IDF), about 425 million adults aged between 20-79 years were living with the disease in 2017, and has caused the death of about 4 million people in the same year (IDF, 2017). Since 352 million people risked having type 2 diabetes, and over 21 million live births (i.e. 1 in 7 births) had congenital diabetes in 2017, it has been estimated that the number of individuals living with diabetes mellitus will increase to 6029 million by the year 2045 (IDF, 2017). The population of diabetic individuals aged 20-70 years in Malaysia currently is about 3.2 million. Based on the Malaysian National Health and Morbidity Survey, the prevalence rate of T2D in individuals aged 30 and above between 2006 and 2015, increased from 11.6% to 17.5%, which was further compounded by undiagnosed T2D with further prevalence rate of 9.2% and its associated factors (Chew et al., 2016; Ismail et al., 2018; Rahim et al., 2020). In Malaysia, T2D and its complications, including nephropathy, stroke, myocardial infarction, heart failure, retinopathy, foot amputation and cataract costed about RM 2.04 billion (USD 47.44 billion) in the year 2011, which is costly to the economy (Mustapha et al., 2017). The quality of life of Malaysians living with diabetes has been negatively affected including their freedom to eat and to live freely (Jannoo et al., 2015).

Insulin treatment in T1D and other oral hypoglycemic agents, like the sulfonylureas e.g. glibenclamide, thiazolidinediones e.g. rosiglitazone, biguanides e.g. metformin, glycosidase inhibitors e.g. acarbose, dipeptidylpeptidase IV inhibitors e.g. saxagliptin, etc. (Baggio & Drucker, 2006; DeFronzoet al., 2014; G. et al., 2007; Green et al, 2007; Inzucchi & McGuire, 2008; Scirica et al., 2013) are the current treatments for diabetes mellitus. These drugs have failed as they are characterized with side effects (Chang et al., 2013; Dey et al., 2002; Hui et al., 2009; Neustadt & Pieczenik, 2008 ; Priyanka & Singh, 2016; Visen et al., 2015; Alberti, & Shaw, 2001). Hence, the search for negligible side effect molecules from the natural flora, for the treatment and management of T2D as proposed by world health organization (WHO) in 2005.

Active phytochemicals are the beneficial attributes of plants to man in traditional medicine. They are effective and less-toxic, have negligible side effects, and thought as brilliant hopefuls for oral antidiabetic treatment (Elujoba et al., 2005; Firdous, 2014; Shokeen et al., 2008; Teoh & Das, 2018). The efficacy of plant phytochemicals is importantly attributed to the synergistic effect of plant extracts, and is considered as a core factor in the concept of herbal medicine (Che et al., 2013; Houghton & Mukherjee, 2009; Williamson, 2001). Watermelon has shown an inherent richness in active phytochemicals with natural healing properties (Abu-Hiamed, 2017; Jibril, et al., 2019; Sulaiman et al., 2020).

Watermelon [Citrullus lanatus (Thumb.) Matsum. & Nakai var *lanatus*] a member of *Cucurbitaceae* family, is rich in both primary and secondary metabolites. Watermelon is reported as the richest in citrulline naturally (Rimando & Perkins-Veazie, 2005; Soteriou et al., 2014; Tarazona-Díaz et al., 2011). It is also rich in ascorbic acid, lycopene, beta carotene, beta-sitosterol, phenolic acids, flavonoids, etc. (Abu-Hiamed, 2017; Choo & Sin, 2012; Huang et al., 2016; Jayaprakasha & Patil, 2016). Citrulline and lycopene are good scavenger of hydroxyl radical and strong antioxidants (Naz et al., 2014; Rimando & Perkins-Veazie, 2005: Tlili et al., 2011a; Tlili et al., 2011b; Waugh et al., 2001). Watermelon is consumed to correct or prevent erectile dysfunction in male individuals, high blood pressure, antiobesity, diuretic, antibacterial, and in lowering high blood glucose (Adunola et al., 2015; Ahn et al., 2011; Figueroa et al., 2011; Sani, 2015; Sathya & Shoba, 2014).

Recently, the antidiabetic and antioxidant effects of yellow-fleshed watermelon seed, flesh, rind and leaf, and their metabolite profiles were studied (Jibril et al., 2019). However, previous literature on the bioactivity and antidiabetic properties of watermelon did not emphasize the active components involved and the biochemical reactions they interacted with at the level of metabolites (Ahn et al., 2011; Bailey et al., 2016; Cutrufello et al., 2015; Etim et al., 2013; Figueroa et al., 2011; Kolawole et al., 2016; Omigie & Agoreyo, 2014; Rahman et al. 2013; Tlili et al., 2011 Yadav et al., 2016). Moreover, watermelon leaf in our understanding, has been underutilized and has poorly documented literature on its bioactivity and medicinal use by metabolomics approach (Ozturk et al., 2018).

Metabolomics as a tool for profiling biomolecules in bio fluids and biological systems, it has been helpful in diagnosing and treating many disease conditions, including diabetes mellitus (Clish, 2015; Guasch-Ferré et al., 2016). It detects, identifies, and differentiates between dynamic, variable, and multiples of metabolic fluctuations in living systems, in both normal and perturbed conditions (Nicholson et al., 2002; Sajak et al., 2017; Clish, 2015). Metabolomics is a committed and objective approach for identifying and quantifying the metabolite composition of an organism or any biological system (Mediani et al., 2016; Putri et al., 2013). As such, the evaluation of systemic responses to the smallest metabolic perturbation either caused by xenobiotic or environment, identification of potential biomarkers and providing insight to the pathogenesis of diseases including diabetes mellitus is possible through metabolomics (Azam et al., 2017; Klein & Shearer, 2016; Sajak, et al., 2017).

Proton nuclear magnetic resonance (^{1}H NMR) as an analytical technique have been used to detect and analyze the metabolic changes in T2D disease conditions. ^{1}H NMR serves as an excellent tool to detect and profile a number of metabolites in biological systems (Abdul Hamid et al., 2017; Mediani et al., 2015). Thus, ^{1}H NMR metabolomics has much use in describing the metabolite changes associated with diabetes mellitus (Sajak et al., 2017; Al-zuaidy et al., 2016; Khoo et al., 2015; Maulidiani et al., 2016; Shen et al., 2016).

1.2 Problem statement

Many pharmaceutical compounds are available for oral treatment of T2D, each have its specific mode of lowering blood glucose depending on the class it belongs. However, these drugs are very costly, with probable side effects such as, severe hypoglycemia, lactic acidosis, idiosyncratic liver cell injury, permanent neurological deficit, digestive discomfort, headache, dizziness and death among others (Guimarães Filho et al., 2015; Marín-Peñalver et al., 2016; Thakare et al., 2017; Zaharenko, 2015). The paradigm shift, of harmless and efficacious treatment of T2D is not attained yet with all the available oral antidiabetic molecules (Marín-Peñalver et al., 2016; Patel et al., 2012). This necessitates the search for new bioactive molecules for safe and effective treatment of diabetes mellitus and its accompanied complications, especially from the plant kingdom. Research on the antidiabetic effects of watermelon, could not point out the active metabolites involved in the observed bioactivity. Complications including end stage renal failure, liver cirrhosis, retinopathy, nephropathy, neuropathy, stroke, myocardial infarction, and heart failure, always accompany diabetes disease (Lipinski, 2001; Marín-Peñalver et al., 2016; IDF, 2014; Rogers, 1973; Zimmet et al., 2001). These may be linked to the perturbed glycolytic, lipid metabolism, β-oxidation, amino acid metabolism, tricarboxylic acid pathway etc. seen in diabetes conditions (Azam et al., 2017; Dong et al., 2016; Heinzmann et al., 2012; Mathew et al., 2019; Maulidiani et al., 2016; Xu et al., 2013). Using ^{1}H NMR metabolomics to study the effects watermelon leaf extracts may exert on these pathways in a T2D model may give an indication on how to arrest these common diabetic complications.

1.3 Research Objectives

This study was embarked to evaluate the medicinal potential of an underutilized part of *C. lanatus* (var Lanatus) plant, to highlight a possible future raw material for functional food in the treatment of T2D and improving its metabolic complications. The main objective of this research was to evaluate the effects of *C. lanatus* (var Lanatus) leaf extracts in T2D rat model using ^{1}H NMR-based metabolomics. To achieve this all-important goal, four specific objectives were defined as follows:

1. To determine and compare the α-amylase and α-glucosidase inhibitory and antioxidant activities of different *C. lanatus* (Thumb.) flesh, rind, and leaf extracts.
2. To profile the compounds in *C. lanatus* (Thumb.) flesh, rind, and leaf extracts and correlate them with their biological activities using ^{1}H NMR-based metabolomics.
3. To evaluate the antidiabetic effect of the most active *C. lanatus* (Thumb.) leaf extract in high-fat diet-fed streptozotocin (HFD-STZ)-induced T2D in rats, by assaying their fasting blood sugar, fasting serum insulin and lipid profile, and kidney and liver histology.
4. To evaluate the metabolic changes in the serum and urine composition of T2D rats treated with *C. lanatus* (Thumb.) leaf extract using ^{1}H NMR-based metabolomics.

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