UNIVERSITI PUTRA MALAYSIA

ANTIDIABETIC ACTIVITY OF BIOACTIVE FRACTIONS FROM Lepisanthes fruticosa (Roxb.) Leenh. FRUITS IN STREPTOZOTOCIN-INDUCED DIABETIC RATS

MIRFAT BT HJ AHMAD HASAN SALAHUDDIN

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**Thesis Submitted to the School of Graduate Studies,
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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

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Chairman: Prof. Amin bin Ismail, PhD
Faculty: Medicine and Health Sciences

Lepisanthes fruticosa (Roxb.) Leenh. or locally known as *ceri Terengganu* is an underutilised fruit species from the family Sapindaceae. The species was previously identified as a potent antioxidant source, but scientific information of the fruit species is still lacking and limited to *in vitro*. Therefore, the present study focused on both *in vitro* and *in vivo* evaluations of antioxidant and antidiabetic activities of *L. fruticosa* fruit extracts along with phytochemical profiling using liquid chromatography mass spectrometry (LC-MS/MS) approach. The different parts of the unripe fruits were successively extracted with hexane, chloroform, ethyl acetate and ethanol. Ethanolic seed crude extract was the most potent due to the strongest radical scavenging (IC_{50} 0.178 ± 0.001 mg/mL), β-carotene bleaching (71%), α-glucosidase inhibition (IC_{50} 1.873 ± 0.421 µg/mL) and highest total phenolic content (363.515 ± 46.296 mg GAE/g) ($P<0.05$). Bioassay-guided fractionation of the ethanolic seed crude extract showed fraction M4 as the most active due to the remarkable radical scavenging (IC_{50} 0.128 ± 0.004 mg/mL), β-carotene bleaching (87%), α-glucosidase inhibition (IC_{50} 0.341 ± 0.094 µg/mL) and greatest amount of total phenolic (1045.6 mg GAE/g) ($P<0.05$). Further LC-MS/MS analysis of the ethanolic seed crude extract and fraction M4 showed the presence of putative phytochemicals from various classes. Among the dominant compounds with notable antioxidant and antidiabetic properties were soyacerebroside II, α-kojibiose, genistein-7,4'-di-O-β-D-glucoside, daturametelin J and actinidioionoside which were detected in negative mode interface. The MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) assay revealed that *L. fruticosa* ethanolic extracts showed no cytotoxic effect against 3T3 (mouse embryonic fibroblast) cells up to concentration of 500 µg/mL. To investigate the *in vivo* antidiabetic effect of *L. fruticosa* ethanolic seed extract (LFSE) in Sprague Dawley rats, a combination of high fat diet (HFD) and low dose streptozotocin (STZ) (35 mg/kg body weight) was used. After 8 weeks of obesity induction, the STZ-induced diabetic rats were orally treated with 300 and 600 mg/kg body weight LFSE for 4 weeks. At the end of the experiment, significant ($P<0.05$) differences in body weight, water and energy intake between normal and diabetic groups were observed. There were no significant variations in the relative organ weights of heart,

liver, lung and spleen of all diabetic groups as compared to normal control group. The LFSE treatment (600 mg/kg body weight) showed a more pronounced effect in anti-hyperglycaemic activities in both long-term (4 weeks) and short-term (2 hours) studies as assessed by oral glucose tolerance test (OGTT). The reduction of blood glucose level was comparable to metformin-treated group. The glucose lowering ability of LFSE (600 mg/kg body weight) was supported by its improved serum insulin level (32%) as compared to diabetic control. The treatment group also resulted in a significant ($P<0.05$) increase in plasma superoxide dismutase (SOD) (23%) and catalase (CAT) (75%) activities. Treatment with LFSE (600 mg/kg body weight) led to a significant ($P<0.05$) increase in the high density lipoprotein-cholesterol (HDL-c) (25%) when compared to diabetic control. The HDL-c level was also higher than all other groups at the end of study. Besides, LFSE (600 mg/kg body weight)-treated group exhibited a lower levels of aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP) than diabetic control group. No significant changes were seen in other liver and kidney functions. The findings may suggest that LFSE has potentials in reducing hyperglycaemia and oxidative stress-related biomarkers in HFD/STZ-induced diabetic rats. Although the underlying mechanisms remain elusive, the presence of various compounds could possibly be the key to the synergistic effects. Therefore, it can be concluded that *L. fruticosa* may be considered as a new potential therapeutic agent for diabetes management and its related complications.

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

AKTIVITI ANTIDIABETIK FRAKSI BIOAKTIF DARIPADA BUAH *Lepisanthes fruticosa* (Roxb.) Leenh. DALAM TIKUS DIABETIK DIARUH STREPTOZOTOCIN

Oleh

MIRFAT BT HJ AHMAD HASAN SALAHUDDIN

April 2021

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Lepisanthes fruticosa (Roxb.) Leenh. atau nama amnya ceri Terengganu adalah spesies buah nadir daripada keluarga Sapindaceae. Spesies buah ini telah dikenalpasti sebagai sumber antioksidan yang berpotensi, namun kajian saintifik masih kurang dijalankan dan terhad secara *in vitro*. Oleh itu, kajian ini dijalankan untuk menilai aktiviti antioksidan dan antidiabetik ekstrak buah *L. fruticosa* secara *in vitro* dan *in vivo*, serta mengenalpasti profil fitokimia menggunakan kaedah kromatografi cecair spektrometri jisim (LC-MS/MS). Bahagian buah muda yang berbeza diekstrak secara berperingkat menggunakan heksana, kloroform, etil asetat dan etanol. Ekstrak kasar etanol daripada bahagian biji menunjukkan aktiviti pemusnahan radikal (IC_{50} 0.178 ± 0.001 mg/mL), pelunturan β-karotena (71%), perencatan enzim *α-glucosidase* (IC_{50} 1.873 ± 0.421 µg/mL) dan jumlah kandungan fenolik (363.515 ± 46.296 mg GAE/g) yang paling tinggi ($P<0.05$). Ujian biologi pemeringkatan terarah ekstrak kasar etanol daripada bahagian biji menunjukkan fraksi M4 sebagai fraksi yang paling aktif berdasarkan aktiviti pemusnahan radikal (IC_{50} 0.128 ± 0.004 mg/mL), pelunturan β-karotena (87%), perencatan enzim *α-glucosidase* (IC_{50} 0.341 ± 0.094 µg/mL) dan jumlah kandungan fenolik (1045.6 mg GAE/g) yang paling tinggi ($P<0.05$). Analisis LC-MS/MS mendapati ekstrak etanol daripada bahagian biji dan fraksi M4 mengandungi sebatian fitokimia yang dicadangkan daripada pelbagai kelas. Antara sebatian utama yang dikenalpasti mempunyai aktiviti antioksidan dan antidiabetik adalah *soyacerebroside II*, *α-kojibiose, genistein-7,4'-di-O-β-D-glucoside, daturametelin J* dan *actinidioionoside* yang diperoleh daripada analisis mod negatif. Ujian kesitotoksikan MTT (3-[4,5-dimetilthiazol-2-yl]-2,5-diphenyltetrazolium bromida) membuktikan ekstrak etanol *L. fruticosa* adalah tidak toksik kepada sel 3T3 (fibroblast embrio mencit) pada kepekatan sehingga 500 µg/mL. Seterusnya, untuk mengkaji kesan antidiabetik ekstrak etanol daripada bahagian biji *L. fruticosa* (LFSE) terhadap tikus *Sprague Dawley,* kombinasi diet tinggi lemak (HFD) dan dos *streptozotocin* (STZ) yang rendah (35 mg/kg berat badan) telah digunakan. Selepas 8 minggu induksi obesiti, tikus diabetik aruhan-STZ diberikan rawatan 300 dan 600 mg/kg berat badan LFSE secara oral selama 4 minggu. Di akhir eksperimen, terdapat perbezaan signifikan ($P<0.05$) pada berat badan tikus, pengambilan air dan tenaga di

antara kumpulan tikus normal dan diabetik. Tiada perbezaan signifikan pada berat organ relatif jantung, hati, paru-paru dan limpa bagi semua kumpulan diabetik dibandingkan dengan kumpulan kawalan normal. Dos rawatan LFSE (600 mg/kg berat badan) menunjukkan kesan yang lebih baik bagi aktiviti anti-hiperglisemik bagi kedua-dua tempoh masa yang panjang (4 minggu) dan pendek (2 jam) yang ditentukan dengan kaedah ujian oral toleransi glukosa (OGTT). Penurunan paras glukosa ini adalah setanding dengan kumpulan rawatan metformin. Keberkesanan LFSE (600 mg/kg berat badan) dalam menurunkan paras gluokosa disokong dengan kenaikan paras insulin serum (32%). Kumpulan rawatan ini juga meningkatkan paras enzim plasma *superoxide dismutase* (SOD) (23%) dan *catalase* (CAT) (75%). Kesemua aktiviti signifikan ($P<0.05$) ini dibandingkan dengan kumpulan kawalan diabetik. Selain itu, LFSE (600 mg/kg berat badan) menunjukkan peningkatan yang signifikan ($P<0.05$) dalam paras kolesterol-lipoprotein ketumpatan tinggi (HDL-c) (25%) dibandingkan dengan kumpulan kawalan diabetik. Paras HDL-c di akhir eksperimen juga menunjukkan kenaikan yang paling tinggi berbanding kumpulan tikus yang lain. Kumpulan rawatan LFSE (600 mg/kg berat badan) menunjukkan paras *aspartate transaminase* (AST), *alanine transaminase* (ALT) and *alkaline phosphatase* (ALP) yang lebih rendah berbanding kumpulan kawalan diabetik. Tiada perbezaan signifikan didapati pada fungsi hati dan buah pinggang yang lain. Hasil kajian ini mencadangkan LFSE mempunyai potensi dalam mengurangkan hiperglisemia dan penanda bio yang berkaitan tekanan oksidatif dalam tikus diabetik aruhan-HFD/STZ. Walaupun mekanisme di sebalik aktiviti-aktiviti ini sukar difahami, kehadiran pelbagai sebatian kimia mungkin telah menyumbang kepada kesan sinergistik aktiviti tersebut. Kesimpulannya, spesies buah *L. fruticosa* boleh dipertimbangkan sebagai agen terapeutik berpotensi yang baharu untuk pengurusan diabetes dan komplikasi-komplikasi yang berkaitan.

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Date: 08 July 2021

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LIST OF ABBREVIATIONS

ADMET	Absorption, distribution, metabolism, excretion and toxicology
ADP	Adenosine diphosphate
AGE	Advanced glycation end products
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AMPK	AMP-activated protein kinase
amu	Atomic mass unit
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the curve
cAMP	Cyclic adenosine monophosphate
BHA	Butylated hydroxyanisole
BHT	Butylated hydroxytoluene
BMI	Body mass index
CC	Column chromatography
DM	Diabetes mellitus
DMPK	Drug metabolism and pharmacokinetics
DPP-IV	Dipeptidyl peptidase-IV
DPPH	2,2-diphenyl-1-picrylhydrazyl
ELISA	Enzyme-linked immunosorbent assay
ESI	Electrospray ionisation
FBPase	Fructose-1,6-biphosphatase
FFA	Free fatty acid

FRAP	Ferric reducing antioxidant power
G6P	Glucose-6-phosphate
G6Pase	Glucose-6-phosphatase
GAE	Gallic acid equivalent
GK	Glucokinase
GLP-1	Glucagon-like peptide-1
GLUT	Glucose transporter
GPx	Glutathione peroxidase
GSH	Reduced glutathione
GSSG	Oxidized glutathione
GST	Glutathione-S-transferase
GR	Glutathione reductase
H_2O_2	Hydrogen peroxide
HAT	Hydrogen atom transfer
Hb	Haemoglobin
Hct	Haematocrit
HFD	High fat diet
HRP	Horseradish peroxidase
HPLC	High performance liquid chromatography
HRP	Horseradish Peroxidase
IC_{50}	Inhibitory concentration 50%
IDDM	Insulin dependent diabetes mellitus
IDF	International Diabetes Federation
LC-MS	Liquid chromatography-mass spectrometry
M	Molar

MDA	Malondialdehyde
MPO	Myeloperoxidase
MRM	Multiple reaction monitoring
MS	Mass spectrometry
MTT	3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide
MUFA	Monounsaturated fatty acids
m/z	Mass-to-charge ratio
NADPH	Nicotinamide adenine dinucleotide phosphate
NCD	Non-communicable disease
NHMS	National Health and Morbidity Survey
NIDDM	Non-insulin dependent diabetes mellitus
NOS	Nitric oxide synthase
OGTT	Oral glucose tolerance test
PEPCK	Phosphoenolpyruvate carboxykinase
PKC	Protein kinase C
pNPG	*p*-nitrophenyl α-D-glucoside
PPAR-γ	Peroxisome proliferator-activated receptor gamma
PUFA	Polyunsaturated fatty acids
QTOF	Quadrupole time-of-flight
RDA	Retro-Diels–Alder reaction
RE	Rutin equivalent
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
RT	Retention time
SET	Single electron transfer

SGLT	Sodium-coupled glucose transporters
SOD	Superoxide dismutase
STZ	Streptozotocin
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TBARS	Thiobarbituric acid reactive substances
TIC	Total ion chromatogram
TLC	Thin layer chromatography
TPC	Total phenolic content
UHPLC	Ultra high pressure liquid chromatography
UV	Ultraviolet
WHO	World Health Organisation

CHAPTER 1

INTRODUCTION

1.1 Research Background

Diabetes mellitus (DM) is a deadly disease with increasing prevalence throughout the world. The metabolic disorder is characterised by a persistent hyperglycaemia associated with disturbances of carbohydrate, fat and protein metabolism that results from absolute or relative deficiency of insulin secretion, action or combination of both (Nanjan et al., 2018; Rathore et al., 2014). World Health Organisation (WHO) has projected that around 422 million people worldwide are diabetics (Zhang et al., 2016a) and the numbers are expected to rise over 650 million by the year 2040 (Tang et al., 2017). The disease has also been considered to be one of the top leading causes of death worldwide (Nain et al., 2012), with the highest rates of prevalence and mortality in both developed and developing countries (Vahid et al., 2017). In 2017, the occurrence was found to be the highest in China (110 million diabetics), followed by India (70 million) and the US (30 million) (Shettar et al., 2017). It is anticipated to affect South East Asia region with 145 million diabetics by 2025. Based on the National Health and Morbidity Survey (NHMS) 2015, the prevalence of diabetes in Malaysia was similar to other countries in the Asia-Pacific Region such as Japan, Brunei Darussalam, Singapore and Republic of Korea (Tee and Yap, 2017).

A recent NHMS reported that the diabetes prevalence in Malaysia has increased from 13.4% in 2015 to 18.3% in 2019. The NHMS 2019 has also found that about 3.9 million Malaysians aged 18 years and above suffers from diabetes, higher than 3.5 million in 2015. Furthermore, Malaysia is described to have the highest prevalence of type 2 DM in South East Asia (Lasano et al., 2019). Type 2 is the most common condition which accounts for nearly 95% of all the DM cases (Chinsembu, 2018; Irondi et al., 2015). It typically occurs when the body produces enough insulin but fails to utilise it effectively due to impaired insulin secretion and/or insulin resistance (Wang and Zhu, 2016).

Several complications have been associated with DM that result in significant morbidity and mortality if left untreated. Hyperglycaemia-mediated oxidative stress produces free radicals which plays a major role in the development of diabetic complications. Almost all organisms possess antioxidant defences and repair systems to protect them against the harmful free radicals. However, in diabetic situation, antioxidant defence systems are compromised due to the imbalance in the free radicals production and scavenging ability of antioxidants (Tang et al., 2017). The excessive production of free radicals may trigger oxidative stress which causes cellular damage by altering macromolecules such as proteins, lipids, carbohydrates and DNA leading to disturbances in most metabolic processes (Ceriello et al., 2016; Martín and Ramos, 2016). If uncontrolled, this condition may result in the pathogenesis of various chronic diseases such as cancers, neurodegenerative and cardiovascular diseases (CVD) (Martín and Ramos, 2016).

According to WHO recommendations, antidiabetic agents from natural plant origin have drawn much attention for their potential uses in the treatment and prevention of type 2 DM. Natural products have been considered as effective antidiabetic agents owing to the presence of notable phytochemicals such as polyphenols which exert antioxidant and hypoglycaemic effects (Tang et al., 2017). Phenolic compounds have increasingly gained popularity due to their excellent health benefits that are mostly ascribed to their free radical scavenging and antioxidant activity, and thereby contribute to the alleviation of various oxidative stress associated diseases such as cancer and diabetes (Passo Tsamo et al., 2015). In addition to phenolics, terpenes, saponins and alkaloids have been reported to be the bioactive antidiabetic principles (Hu and Jia, 2018; Muhd Sani, 2015).

In the present study, *Lepisanthes fruticosa* (Roxb.) Leenh., an underutilised fruit species from Sapindaceae family was evaluated. The species can be found in Malaysia, Myanmar, Thailand, Indonesia and the Philippines, and has long been used as food source and traditional remedy by rural folks (Mirfat et al., 2017). Wetwitayaklung et al. (2012) reported that *L. fruticosa* root has anti-pyretic properties and the ripe fruit has anti-diarrhoea effect. It was also discovered that *L. fruticosa* fruit was a promising source of antioxidant in comparison to a number of underutilised fruits and some popular fruits such as guava, mango and orange (Mirfat and Salma, 2015). Its formulated drink showed stronger antioxidant activity (83%) than commercially available antioxidant drink powerberries (acai berry, blueberry, cranberry, mulberry, raspberry) and blackcurrant (Mirfat et al., 2012a). However, the antioxidant properties of *L. fruticosa* showed a significant decrease with fruit maturation. The antioxidant activity and total phenolic content of the fruit pulp were found the highest at the unripe stage (Mirfat et al., 2017). *In vitro* antidiabetic study of aqueous extract of the unripe fruit pulp showed that *L. fruticosa* possessed strong α-glucosidase inhibition and insulin secretion activity (Mirfat et al., 2018). A preliminary phytochemical profiling using high performance liquid chromatography (HPLC) found the presence of 4-hydroxybenzoic acid in the ripe fruit pulp extracts which was previously reported to possess free radical scavenging activity (Nur Yuhasliza et al., 2018). In an *in silico* modelling, 5,6,7,4'-Tetrahydroxyflavanone6,7-diglucoside, 5,7,4'-Trihydroxy3,6,8,2',5'-pentamethoxyflavone, distemonatin, quercetin 3-galactoside-7-xyloside and cyanidin-3-O-rutinoside were suggested as promising compounds with medicinal benefits (Lina et al., 2018).

1.2 Problem Statements

Diabetes mellitus has been a global health concern causing significant mortality and morbidity. Even more alarming, DM has now reached epidemic proportions and the prevalence is expected to increase in the foreseeable future. This deadly disease is the most common non-communicable disease (NCD) posing a substantial economic burden on human health worldwide. Sustainable Development Goal 3 (SDG 3) has projected the cumulative economic losses to low- and middle-income countries from cardiovascular diseases, cancers, chronic respiratory diseases and diabetes to exceed USD 7 trillion by 2025. Based on the NHMS 2015, estimates by the US place the management costs of the chronic diseases at around three-quarters of the total national health expenditure. In some European countries, diabetes accounts for 2% to 15% of the national health expenditure. In Malaysia, management of NCD complications is also difficult and costly, which

further contributes to the increasing burden of NCDs in the country. International Diabetes Federation (IDF) reported that in 2013, about USD 548 billion was spent on DM management alone (Irondi et al., 2015). Data from the IDF showed that the healthcare expenditure has significantly increased from USD 232 billion in 2007 to USD 727 billion in 2017. This economic burden is projected to rise to USD 776 billion by 2045 (Hu and Jia, 2018).

Despite the huge capital investment, DM remains a major global health and economic burdens, having no reasonable effective therapy in modern medicine in terms of safety and efficacy. Even though there are various antidiabetic agents are available to reduce, control and manage DM, there are some disadvantages of these synthetic drugs such as low efficacy, high secondary failure rates, undesirable side effects and being expensive to most of the people (Rashid and Sil, 2017). In addition, the carcinogenic properties and adverse side effects have also been reported for some synthetic antioxidants making them less acceptable. Some of the currently used synthetic antioxidants are butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT), which are suspected of being carcinogenic and causing liver damage (Barchan et al., 2014).

Considering the chronic nature of DM, high management cost and the limitations of current therapies, particularly for rural populations, there remains a consensus for the need to explore new dietary constituents from natural sources as an alternative treatment for diabetes management. According to WHO, natural sources are excellent candidates for oral therapy as they are effective, non-toxic, and have low or no side effects (Gargouri et al., 2016). Antidiabetic drugs from natural origin also counter the high cost and poor availability of the existing antidiabetic drugs especially in low income countries. However, the potential to discover new antidiabetic drugs from plants is still untapped. It has been postulated that more than 800 plants used in the management of DM have a great clinical potential, but only 30% of plants used in folk medicines have been scientifically validated which may support their substitution for the current therapies (Chinsembu, 2018).

Underutilised fruits are usually maintained by cultural preferences and traditional practices, that some of them have been largely neglected in research and conservation. They have not been comprehensively investigated for their biological activities as compared to commercial fruits. This could be due to the lack of knowledge of their potential values and also promotional campaigns. *Lepisanthes fruticosa* is an underutilised fruit which has not received much attention from scientific research. Previous research involved only *in vitro* with the ripe edible portion (pulp) being the most commonly studied. The i*n vitro* study, nevertheless, cannot be simply extrapolated to the *in vivo* situation. *In vitro* assays only serve as preliminary steps or important indicator for further biological studies particularly, *in vivo*. Hence, supplementation with *in vivo* assays is vital to complement *in vitro* investigations and therefore assess the full potential of the extract.

1.3 Significance of Study

Malaysia possesses a rich diversity of underutilised fruits grown in orchards, home gardens and some can be found in the wild of Peninsular Malaysia, Sabah and Sarawak. These underutilised fruits are excellent sources of food and nutrition especially for rural and farm communities, which improve the quality of diets and nutrition of the communities. The diversity of the fruit species does not only provide nutritionally balanced diets, but also more importantly, secures household income, and thus leads to the improvement of the livelihood. This is in line with SDG2 which aims to end hunger, achieve food security, improve nutrition and promote sustainable agriculture. In addition, SDG3 is concerned with ensuring health and well-being, including a bold commitment to achieve universal health coverage and provide access to safe and effective medicines by 2030.

The present study is critical to generate useful data and produce supporting information for antidiabetic medication. Since scientific information of *L. fruticosa* is still scarce, this study provides a greater insight on the potential of the fruit species as an antidiabetic agent. The data obtained from the study also serve as a guideline for prioritisation of further use of *L. fruticosa* fruit, as part of the diet, in disease prevention and health promotion, based on the active compounds and its antidiabetic effects. In addition, the findings add valuable information to the current knowledge of health and nutritional properties of underutilised fruit species. From this, better understanding of the nutraceutical and functional product potential of the underutilised fruit can be developed which is important for the enhancement of the fruit species. This will create new income generation opportunities and new market niche in the future. The value of *L. fruticosa* fruit species will further be increased to help enhance the preservation and sustainable use of these neglected species in strengthening food and nutrition security, and health wellbeing.

1.4 Objectives of Study

The overall aim of this study was to investigate the antidiabetic effects of *L. fruticosa* fruit. The hypothesis of the study was that *L. fruticosa* would ameliorate hyperglycemia and oxidative stress-related biomarkers in diabetic rats induced with streptozotocin (STZ) that could be attributed to the synergistic actions of various phytochemicals. Therefore, to test this hypothesis the following specific objectives were investigated:

1.4.1 To determine the *in vitro* antioxidant and antidiabetic activities of *L. fruticosa* various extracts.

1.4.2 To identify and characterise the chemical constituents from *L. fruticosa* active extracts using LC-MS/MS approach.

1.4.3 To evaluate the *in vivo* effects of *L. fruticosa* active extracts on hyperglycaemia and oxidative stress-related biomarkers in streptozotocin-induced diabetic rats.

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