UNIVERSITI PUTRA MALAYSIA

ANTIOXIDANT ACTIVITIES AND INHIBITORY EFFECTS OF Mikania micrantha Kunth (SELAPUT TUNGGUL) AGAINST KEY ENZYMES INVOLVED IN HYPERLIPIDEMIA AND HYPERTENSION IN VITRO

AMIRAH HAZIYAH BINTI ISHAK

FPSK(M) 2018 38

ANTIOXIDANT ACTIVITIES AND INHIBITORY EFFECTS OF *Mikania micrantha* Kunth (SELAPUT TUNGGUL) AGAINST KEY ENZYMES INVOLVED IN HYPERLIPIDEMIA AND HYPERTENSION *IN VITRO*

By

AMIRAH HAZIYAH BINTI ISHAK

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

April 2018

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

ANTIOXIDANT ACTIVITIES AND INHIBITORY EFFECTS OF *Mikania micrantha* Kunth (SELAPUT TUNGGUL) AGAINST KEY ENZYMES INVOLVED IN HYPERLIPIDEMIA AND HYPERTENSION *IN VITRO*

By

AMIRAH HAZIYAH BINTI ISHAK

April 2018

Chairman : Nurul Husna Shafie, PhD
Faculty : Medicine and Health Sciences

Mikania micrantha Kunth, locally known as 'Selaput tunggul' in Malaysia, is a plant that traditionally used to reduce the risk of diabetes, hypercholesterolemia, and hypertension. This study was aimed to investigate the antioxidant capacities and inhibitory activities of various extracts of the leaves and stems of *M. micrantha* on key enzymes related to hyperlipidemia and hypertension *in vitro*.

Total phenolic content (TPC) and total flavonoid content (TFC) were determined using the Folin-Ciocalteu and aluminium chloride colorimetric assays, respectively. The antioxidant capacities were determined using 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging, 2,2'-azinobis-3-ethylbenzothiazoline-6-sulphonic acid (ABTS), ferric reducing antioxidant power (FRAP), phosphomolybdenum antioxidative power (PAP), and β-carotene bleaching (BCB) assays. The inhibitory activities of *M. micrantha* on pancreatic lipase (PL), lipoprotein lipase (LPL), HMG-CoA reductase (HMGR), and angiotensin-converting enzyme (ACE) were evaluated *in vitro* using the spectrophotometric method. In addition, the chemical profiling of the selected extracts was determined using gas chromatography-mass spectrometry (GC-MS).

The results demonstrated the ethyl acetate stems (EAS) and leaves (EAL) extracts of *M. micrantha* had significantly ($p < 0.05$) greatest TPC (141±0.51 mg gallic acid equivalent/g) and TFC (70.1±0.92 catechin equivalent/g), respectively, compared to samples extracted by other solvents. The EAS extract had also significantly greatest antioxidant capacities using DPPH (EC_{50}=324±61.4 µg/mL), ABTS (0.53±0.01 mmol trolox equivalent/g), FRAP

(1.28±0.05 mmol Fe^{2+}/g), PAP (219±7.03 mg ascorbic acid equivalent/g), and BCB (108±2.23%) assays.

The ethanol stems (ETS) extract exhibited the highest PL inhibitory activity (IC_{50}=4.49±2.50 µg/mL) followed by hot water leaves (HWL; IC_{50}=4.56±0.07 µg/mL) and ethanol leaves (ETL; IC_{50}=8.02±1.56 µg/mL). These extracts also showed no significant ($p > 0.05$) difference between each other and orlistat (IC_{50}=0.31±0.01 µg/mL). The ethanol leaves (ETL) extract showed the highest LPL inhibitory activity (IC_{50}=1.42±0.48 µg/mL), however, the difference was found not significant ($p > 0.05$) between all extracts and orlistat (IC_{50}=1.98±1.22 µg/mL). ETL also showed the highest inhibitory activity against HMG-CoA reductase (50.12±3.44% inhibition), but not significant ($p > 0.05$) when compared to other extracts except hot water stems (HWS) extract. HWS extract showed the least inhibitory activity against PL, LPL, and HMG-CoA reductase. However, HWS extract showed the greatest ACE inhibition (97.47±1.19%), but not significantly ($p > 0.05$) different when compared to other extracts and captopril (98.42±0.93%). Overall, all extracts exhibited remarkable inhibitory activity against PL, LPL, HMGR, and ACE.

GC-MS analysis of EAL and EAS extracts showed the presence of sesquiterpenes (18.74% and 30.46%, respectively), phenol (14.74% and 16.38%, respectively), and alkane hydrocarbons (26.7% and 10.45%, respectively) which might contribute to its antioxidant and enzyme inhibitory activities. In conclusion, this study indicates the potential of ethyl acetate stems, ethanol leaves, and ethanol stems extracts as antioxidant, anti-hyperlipidemic and anti-hypertensive agents. Results from this study provide baseline knowledge and evidence of the traditional uses of *M. micrantha* which could be the guidance for future development of nutraceuticals from *M. micrantha* for hyperlipidemia and hypertension.

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

AKTIVITI ANTIOKSIDAN DAN KESAN PPERENCATAN *Mikania micrantha* Kunth (SELAPUT TUNGGUL) TERHADAP ENZIM UTAMA YANG TERLIBAT DALAM HIPERLIPIDEMIA DAN HIPERTENSI *IN VITRO*

Oleh

AMIRAH HAZIYAH BINTI ISHAK

April 2018

Pengerusi : Nurul Husna Shafie, PhD
Fakulti : Perubatan dan Sains Kesihatan

Mikania micrantha Kunth, yang dikenali sebagai 'Selaput tunggul' di Malaysia, merupakan sejenis tumbuhan yang digunakan secara tradisional untuk mengurangkan risiko diabetes, hiperkolesterolemia, dan hipertensi. Kajian ini bertujuan untuk mengkaji keupayaan antioksidan dan aktiviti perencatan pelbagai ekstrak daripada bahagian daun dan batang pokok *M. micrantha* terhadap enzim utama yang terlibat dalam hiperlipidemia dan hipertensi secara *in vitro*.

Jumlah kandungan fenolik (TPC) dan jumlah kandungan flavonoid (TFC) masing-masing ditentukan menggunakan kaedah Folin-Ciocalteu dan aluminium klorida kolorimetri. Kapasiti antioksidan telah ditentukan menggunakan kaedah perencatan radikal 2,2-difenil-1-pikrilhidrazil (DPPH), asid 2,2'-azinobis-3-etilbenzothiazoline-6-sulfonat (ABTS), kuasa antioksidan penurunan ferik (FRAP), kuasa antioksidatif phosphomolybdenum (PAP) dan pelunturan β-karotena (BCB). Aktiviti perencatan *M. micrantha* pada lipase pankreas (PL), lipase lipoprotein (LPL), HMG-CoA reduktase (HMGR), dan enzim penukar angiotensin (ACE) telah dinilai secara *in vitro* menggunakan kaedah spektrofotometri. Sebagai tambahan, profil kimia dari ekstrak yang dipilih ditentukan menggunakan gas kromatografi-spektrometri jisim (GC-MS).

Hasil kajian menunjukkan ekstrak etil asetat daripada batang (EAS) dan daun (EAL) *M. micrantha* mempunyai kandungan TPC (141±0.51 mg setara asid galik/g) dan TFC (70.1±0.92 mg setara catechin/g) yang ketara ($p < 0.05$) tinggi berbanding dengan sampel yang diekstrak meggunakan pelarut lain. Ekstrak EAS juga mempunyai kapasiti antioksidan tertinggi apabila diukur menggunakan kaedah DPPH (EC_{50}=324±61.4 µg/mL), ABTS (0.53±0.01 mmol

setara trolok/g), FRAP (1.28±0.05 mmol Fe^{2+}/g), PAP (219±7.03 mg setara asid askorbik/g), dan BCB (108 ± 2.23%).

Ekstrak etanol daripada batang (ETS) menunjukkan aktiviti perencatan PL tertinggi (IC_{50}=4.49±2.50 µg/mL) diikuti oleh ekstrak air panas daripada daun (HWL; IC_{50}=4.56±0.07 µg/mL) dan etanol daun (ETL; IC_{50}=8.02±1.56 µg/mL). Ektrak ini juga menunjukkan tiada perbezaan ketara ($p > 0.05$) di antara satu sama lain dan juga orlistat (IC_{50}=0.31 ± 0.01 µg/mL). Ekstrak etanol daripada daun (ETL) menunjukkan aktiviti perencatan LPL tertinggi (IC_{50}=1.42±0.48 µg/mL), bagaimanapun, perbezaan di antara semua ekstrak dan orlistat (IC_{50}=1.98±1.22 µg/mL) adalah tidak ketara. ETL juga menunjukkan aktiviti perencatan tertinggi terhadap HMG-CoA reduktase (50.12±3.44%), tetapi tiada perbezaan ketara berbanding ekstrak yang lain kecuali ekstrak air panas daripada batang (HWS). Ekstrak HWS menunjukkan aktiviti perencatan yang terendah terhadap PL, LPL, dan HMG-CoA reduktase. Namun begitu, ekstrak HWS menunjukkan perencatan ACE yang tertinggi, walaupun tiada perbezaan ketara berbanding ekstrak lain dan juga captopril (98.42±0.93%). Keseluruhannya, semua ekstrak menunjukkan aktiviti perencatan menentang PL, LPL, HMGR, dan ACE.

Analisis GC-MS ekstrak EAL dan EAS menunjukkan kehadiran seskuiterpena (18.74% dan 30.46%, masing-masing), fenol (14.74% dan 16.38%, masing-masing), dan hidrokarbon alkana (26.7% dan 10.45%, masing-masing) yang mungkin menyumbang kepada aktiviti antioksidan dan perencatan enzim bagi ekstrak tersebut. Kesimpulannya, kajian ini menunjukkan potensi ektrak pokok *M. micrantha* iaitu etil asetat bahagian batang, etanol bahagian daun, dan etanol bahagian batang sebagai agen antioksidan, anti-hiperlipidemik dan anti-hipertensi. Hasil kajian ini dapat memberikan pengetahuan asas dan membuktikan penggunaan tradisional *M. micrantha* yang boleh dijadikan panduan bagi penghasilan nutraseutikal untuk hiperlipidemia dan hipertensi pada masa hadapan.

ACKNOWLEDGEMENT

Alhamdulillah, all praise to Allah S.W.T., for giving me the guidance, strength, and endurance to finish this study and completed the thesis. I would like to express my deepest gratitude to my supervisor, Dr. Nurul Husna Shafie, who has supported me throughout this study without failed. I am blessed enough to have her as my supervisor – thank you Dr. Husna for your invaluable guidance, advice, encouragement, positive thoughts, confidence and all your trust for me, which helped me a lot throughout this journey. A million thanks to my co-supervisors, Assoc. Prof. Dr. Norhaizan Mohd Esa and Dr. Hasnah Bahari for their helpful suggestion, insights, and comments.

Sincerest appreciation and gratefulness are also extended to the laboratory staffs of Nutrition Laboratory (Mr. Eddy, Mr. Hasbullah, and Mdm. Maznah) and Pharmacotherapeutic Laboratory (Miss Ruhaidah) for their assistance. I would also like to thank the Minister of Higher Education (MoHE) Malaysia for My Master scholarship, and Universiti Putra Malaysia for Project Grant funding (GP-IPS/2016/9489400) and Graduate Research Fellowship (GRF).

Finally, deep thanks to my parents, Ishak bin Hussin and Halimah binti Ahmad who had encouraged me and always pray for me throughout my entire life. Without their support and blessing, I would not be able to reach this step. Last but not least, I would like to say thank you to all my friends and lab mates for their help, unfailing support, advice, and encouragement to finish my lab work. To those that I might not mention you here – thank you for your love, prayers, wishes, and endless support.

I certify that a Thesis Examination Committee has met on 19 April 2018 to conduct the final examination of Amirah Haziyah binti Ishak on her thesis entitled "Antioxidant Activities and Inhibitory Effects of *Mikania micrantha* Kunth (Selaput Tunggul) Against Key Enzymes Involved in Hyperlipidemia and Hypertension *In Vitro*." in accordance with the Universities and University Colleges Act 1971 and the Consultation of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master of Science.

Members of the Thesis Examination Committee were as follows:

Loh Su Peng, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairman)

Azrina Azlan, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Internal Examiner)

Zulkhairi Hj Amom, PhD
Professor
Universiti Teknologi MARA
Malaysia
(External Examiner)

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

Date: 28 June 2018

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 the Supervisory Committee were as follows:

Nurul Husna Shafie, PhD
Senior Lecturer
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairman)

Norhaizan Mohd Esa, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

Hasnah Bahari, PhD
Senior Lecturer
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

_____
ROBIAH BINTI YUNUS, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

Date:

Declaration by graduate student

I hereby confirm that:

- this thesis is my original work;
- quotations, illustrations and citations have been duly referenced;
- this thesis has not been submitted previously or concurrently for any other degree at any other institutions;
- intellectual property from the thesis and copyright of thesis are fully-owned by Universiti Putra Malaysia, as according to the Universiti Putra Malaysia (Research) Rules 2012;
- written permission must be obtained from supervisor and the office of Deputy Vice-Chancellor (Research and Innovation) before thesis is published (in the form of written, printed or in electronic form) including books, journals, modules, proceedings, popular writings, seminar papers, manuscripts, posters, reports, lecture notes, learning modules or any other materials as stated in the Universiti Putra Malaysia (Research) Rules 2012;
- there is no plagiarism or data falsification/fabrication in the thesis, and scholarly integrity is upheld as according to the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) and the Universiti Putra Malaysia (Research) Rules 2012. The thesis has undergone plagiarism detection software.

Signature: _____ Date: _____

Name and Matric No.: Amirah Haziyah binti Ishak (GS43869)

Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

Signature : _____
Name of Chairman of
Supervisory Committee : Dr. Nurul Husna Shafie

Signature : _____
Name of Member of
Supervisory Committee : Assoc. Prof. Dr. Norhaizan Mohd Esa

Signature : _____
Name of Member of
Supervisory Committee : Dr. Hasnah Bahari

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AAE	Ascorbic acid equivalent
ABTS	2,2'-azinobis-3-ethylbenzothiazoline-6-sulphonic acid
ACE	Angiotensin-I converting enzyme
Ang I	Angiotensin I
Ang II	Angiotensin II
ANOVA	Analysis of variance
ARB	Angiotensin receptor blocker
BC	Beta carotene/β-carotene
BCB	β-carotene bleaching
BHA	Butylated hydroxyanisole
BHT	Butylated hydroxytoluene
BP	Blood pressure
CAT	Catalase
CCB	Calcium channel blocker
CE	Catechin equivalent
CHD	Coronary heart disease
CVD	Cardiovascular diseases
CWL	Cold water leaves
CWS	Cold water stems
dH_2O	Distilled water
DMSO	Dimethyl sulfoxide
DPPH	2,2-diphenyl-1-picrylhydrazyl
EAL	Ethyl acetate leaves
EAS	Ethyl acetate stems
ETL	Ethanol leaves
ETS	Ethanol stems
FRAP	Ferric reducing antioxidant power
GAE	Gallic acid equivalent
GC-MS	Gas chromatography-mass spectrometry
GSH	Glutathione
GSHPx	Glutathione peroxidase
HA	Hippuric acid
HAT	Hydrogen atom transfer
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HHL	Hippuryl-histidyl-leucine
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HMGR	HMG-CoA reductase
HPLC	High-performance liquid chromatography
HWL	Hot water leaves
HWS	Hot water stems
HXL	Hexane leaves
HXS	Hexane stems
IDL	Intermediate density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LPL	Lipoprotein lipase
M. micrantha	*Mikania micrantha*

MW	Molecular weight
NCD	Non-communicable diseases
NHMS	National Health Morbidity Survey
NO	Nitric oxide
OGTT	Oral glucose tolerance test
ox-LDL	Oxidized low-density lipoprotein
PAP	Phosphomolybdenum antioxidative power
PL	Pancreatic lipase
p-NPB	*p*-nitrophenylbutyrate
PPL	Porcine pancreatic lipase
ppm	Part per million
RAAS	Renin-angiotensin-aldosterone system
RAS	Renin-angiotensin system
ROS	Reactive oxygen species
RT	Retention time
SEM	Standard error of mean
SMC	Smooth muscle cell
SOD	Superoxide dismutase
TE	Trolox equivalent
TEAC	Trolox equivalent antioxidant capacity
TFC	Total flavonoid contents
TG	Triglycerides
TPC	Total phenolic contents
VLDL	Very low-density lipoprotein
VLDL-C	Very low-density lipoprotein cholesterol
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Research background

The importance of plants to human life can be seen in its diverse utilization in medicine and food as nutraceuticals. Plants are a large source of new bioactive molecules with therapeutic potentials and they have increasingly become attractive alternatives to prevent or reduce risk factors of cardiovascular diseases (CVD) such as hyperlipidemia and hypertension (Nasri *et al*., 2014). Phytomedicines may benefit the human healthcare systems since they contain many free radical scavenging molecules such as phenolic compounds, nitrogen compounds, vitamins, terpenoids and other compounds that exhibit antioxidant properties (Chetan *et al*., 2012). The bioactive compounds of the plants will contribute to their medicinal value which produces definite physiological actions on the human body (Hasmida *et al*., 2014). Moreover, there is evidence suggesting that natural antioxidants from plant extracts are safe and they may reduce the risk of non-communicable diseases (NCD) without any side effects (Chetan *et al*., 2012).

Dyslipidemia refers to an abnormal amount of cholesterol and triglycerides level in the blood. Hyperlipidemia, hypertriglyceridemia, and hypercholesterolemia are the types of dyslipidemia resulting from the elevation of both cholesterol and triglycerides (Moor *et al*., 2017). Hypercholesterolemia and hypertension are the important components of metabolic syndromes and risk factors for CVD. The presence of these two risk factors could lead to the development of atherosclerosis and consequently to CVD (Dalal *et al*., 2012). Hypercholesterolemia is a disease condition that is characterized by an abnormally increased level of plasma lipoproteins; particularly the low-density lipoprotein cholesterol (LDL-C). The deposition of LDL-C in the lining of vascular wall will develop atherosclerotic plaque thus narrowing the diameter of the blood vessel (Alinde *et al*., 2012). Moreover, oxidized LDL inhibits endothelial nitric oxide (NO) formation, which contributes to artery stiffening, thereby causing hypertension (Sander & Giles, 2002). Hypertension is defined as persistent elevation of systolic and diastolic blood pressure (BP) that exceeds 140 and 90 mmHg, respectively. Angiotensin II, a hormone which is strongly related to hypertension, triggers endothelial dysfunction in hypertensive patients (John & Schmieder, 2003).

A combination of different strategies is used to treat and manage hyperlipidemia and hypertension. Common therapeutic strategies are generally directed at lowering the serum LDL-C levels and prevention of angiotensin II formation through the inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and angiotensin-I converting enzyme (ACE) which are

the key enzymes of hypercholesterolemia and hypertension, respectively (Ademosun *et al*., 2015; Saravanan & Ignacimuthu, 2015; Martinello *et al*., 2006). Other strategies include the inhibition of pancreatic lipase (PL) and lipoprotein lipase (LPL) which are the key enzymes in lipid metabolism responsible for hydrolysis of dietary fats in the intestine and lipolysis of triglycerides in lipoprotein, respectively (Li *et al*., 2014). Inhibition of both PL and LPL can help to reduce dietary triglycerides absorption, hence, decrease the absorption of dietary cholesterol.

There are reports of established lipases, HMG-CoA reductase and ACE inhibitors such as orlistat (Alqahtani *et al*., 2015), statins (Chogtu *et al*., 2015), and captopril (Weber *et al*., 2014), respectively. Lipase inhibitor drug such as orlistat decreases the absorption of dietary cholesterol by inhibition of intestinal lipases (Alqahtani *et al*., 2015). However, orlistat gives side effects such as steatorrhoea, bloating, oily spotting, faecal urgency, faecal incontinence and even caused subacute liver failure (Drew *et al*., 2007; Thurairajah *et al*., 2005). Modern drugs such as statins, fibrates, nicotinic acid, and resins have been used to lower blood cholesterol level by inhibiting the endogenous synthesis or by lowering the cholesterol absorption from the intestine (Saravanan & Ignacimuthu, 2015). However, the high cost for synthetic drugs and the remaining side effects such as distal muscle weakness, headache, acute renal failure, polyneuropathy, memory loss, sleep disturbances, impotence, and pancreatitis lead to the findings for low cost remedies from natural resources (Lin *et al*., 2015; Djerrou, 2014). Statins have been widely used for the treatment of hypercholesterolemia but it was found that they could also slightly increase the potential risk of type 2 diabetes (Sattar *et al*., 2010), necessitating the search for more options of no or less adverse effects of hypercholesterolemia treatments. Meanwhile, ACE inhibitors such as captopril give side effects such as proteinuria, skin rashes, altered taste (Atlas, 2007) and also cough (Sweitzer, 2003).

Nowadays, there are increasing interests for substitution of modern medicine with traditional plants and some natural component in the plants for treatment of hyperlipidemia and hypertension. According to Cheurfa and Allem (2015), plant-derived products are commonly considered to be less toxic, with few or no side effect than their synthetic equivalents. *Mikania micrantha* Kunth (Asteraceae or Compositae) is a perennial creeping vine and widely distributed in South and North America and can also be found in Africa, Pacific Islands and Southeast Asia, including Southern China and Malaysia (Day *et al*., 2016; Tripathi *et al*., 2012). This plant is known as American rope, Chinese creeper, mile-a-minute, '*Chhagalbati*' or '*Japanilata*' (West Bengal), '*Selaput tunggul*' (Malaysia) and '*Sembung rambat*' (Indonesia) (Saha *et al*., 2015; Haisya *et al*., 2013; Nornasuha & Ismail, 2013). In agriculture, *M. micrantha* is known as a weed plant that can reduce the growth and productivity of several crops such as rubber, oil palm, and cocoa plantation in Malaysia which cost 8-10 million dollars per annum to control its growth (Sankaran, 2008). This is due to its fast-growing habit and production of allelopathic substances (Day *et al*., 2016; Nornasuha & Ismail, 2013; Sankaran, 2008). However, this plant is used

traditionally to treat insect bites and stop minor external bleeding (Facey *et al*., 2010) or consumed as a juice as an alternative to reduce glucose, cholesterol, and high blood pressure.

M. micrantha has demonstrated many health benefits, such as antimicrobial (Chetia *et al*., 2014; Chetan *et al*., 2012; Facey *et al*., 2010), anti-diabetic (Wan Nurhayati *et al*., 2013), anti-dermatophytic (Jyothilakshmi *et al*., 2015), anti-stress (Sibi & Sajid, 2014), anti-inflammatory (Pérez-Amador *et al*., 2010), anti-proliferative (Ríos *et al*., 2014), and anti-cancer (Matawali *et al*., 2016; Dou *et al*., 2014) activities. In fact, *M. micrantha* is rich in phytochemicals such as terpenoids (sesquiterpene lactones), alkaloids, flavonoids, steroids, reducing sugars, saponins, phenolics, and tannins which have shown significant bioactivities (Dong *et al*., 2017; Dev *et al*., 2015).

In spite of its medicinal benefits as aforementioned, the information of the potential antioxidant agent in this plant is still scarce especially the comparison between different parts and the effect of different solvents which can affect the antioxidant capacities and bioactive compounds in *M. micrantha*. Moreover, the potential of *M. micrantha* as pancreatic lipase, lipoprotein lipase, HMG-CoA reductase and ACE inhibitors which are the key enzymes for hyperlipidemia and hypertension has not yet been investigated. Antioxidant agents are important to prevent oxidative damage-related diseases *i.e*., cancer, cardiovascular diseases, diabetes, etc., (Sharma *et al*., 2014) thus potential health benefits of this plant should be further explored.

1.2 Problem statement

Non-communicable diseases (NCD) status in Malaysia such as CVD is in an alarming condition. This problem has significant implications on healthcare costs and drives increasing demand for relatively expensive treatment and long-term rehabilitative care (Mustapha *et al*., 2014). Hyperlipidemia and hypertension are frequently associated, and they might contribute to the development of atherosclerosis which consequently caused CVD (Dalal et al., 2012). The treatment and management of hyperlipidemia and hypertension include dietary changes and also the use of commercial drugs. However, these oral medications have certain limitations and side effects (Alqahtani *et al*., 2015; Chogtu *et al*., 2015; Weber *et al*., 2014).

Due to the side effects of commercially available drugs, the research on alternative treatment such as the use of medicinal plants needs to be studied. Medicinal plants have been used in traditional healthcare since decades and received much attention in recent years in the search of new therapeutic agents due to the low cost, easy availability, and less or no side effects (Sofowora *et al*., 2013). Based on previous studies, *M. micrantha* has demonstrated the potential therapeutic effects of several diseases including

diabetes, infections, and cancers (Dou *et al*., 2014; Wan Nurhayati *et al*., 2013). Many phytochemicals have been detected from different parts of *M. micrantha* which contribute to the medicinal properties of this plant, especially terpenoids, the major compounds isolated (Nicollier & Thompson, 1981). However, further researches are needed to support the traditional claims and the limited scientific evidence on the health benefit of *M. micrantha*.

1.3 Significance of study

To date, there is limited information about the antioxidant capacities, anti-hyperlipidemic, and anti-hypertensive effects of various extracts of the leaves and stems of *M. micrantha*. Hence, results from this study could provide added values such as information on the best extraction solvent, parts of the plants and the phytochemicals present in *M. micrantha* and scientific evidence to prove the traditional medical uses of *M. micrantha*. In future, findings from the antioxidant and enzymatic inhibitory activities of *M. micrantha* extracts *in vitro* could serve as a basis for future *in vivo* research. *M. micrantha* may be a promising source in the search of new anti-hyperlipidemic and anti-hypertensive agents due to its efficacy and broad phytochemical range.

1.4 Research objectives

The general objective of this study is to determine the antioxidant capacities and potential inhibitory activities of various solvent extracts (hot water, cold water, 70% ethanol, and ethyl acetate) of the leaves and stems of *M. micrantha* on key enzymes related to hyperlipidemia and hypertension *in vitro.*

The specific objectives of the study are:

i. To determine and compare the total phenolic content (TPC), total flavonoid content (TFC), and antioxidant capacities of various solvent extracts of the leaves and stems of *M. micrantha* by 2,2,-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging, 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid (ABTS) radical scavenging, ferric reducing antioxidant power (FRAP), phosphomolybdenum antioxidative power (PAP), and β-carotene bleaching (BCB) assays.
ii. To determine the phytochemicals of the leaves and stems of *M. micrantha* using gas chromatography-mass spectrometry (GC-MS) analysis.
iii. To determine the inhibitory activities of various solvent extracts of the leaves and stems of *M. micrantha* against lipases, *i.e*., pancreatic lipase (PL) and lipoprotein lipase (LPL), HMG-CoA reductase (HMGR) and angiotensin-I converting enzyme (ACE).

iv. To evaluate the correlation between antioxidant contents (TPC and TFC) with antioxidant capacities (DPPH, ABTS, FRAP, PAP, and BCB) and enzymes inhibitory activities (PL, LPL, HMGR, ACE) of *M. micrantha* extracts.

1.4 Null hypotheses

H_O 1: There is no significant difference between the TPC, TFC, and antioxidant capacities of various solvent extracts of the leaves and stems of *M. micrantha*.

H_O 2: There is no significant difference between the phytochemicals present in the leaves and stems of *M. micrantha*.

H_O 3: There is no significant difference between the inhibitory activities of various solvent extracts of the leaves and stems of *M. micrantha* against PL, LPL, HMG-CoA reductase and ACE.

H_O 4: There is no significant correlation between the TPC and TFC with antioxidant and enzymes inhibitory activities of *M. micrantha* extracts.

REFERENCES

Abdul Rahman, H., Saari, N., Abas, F., Ismail, A., Mumtaz, M. W., & Abdul Hamid, A. (2017). Anti-obesity and antioxidant activities of selected medicinal plants and phytochemical profiling of bioactive compounds. *International Journal of Food Properties*, *20*(11).

Abu, F., Mat Taib, C. N., Mohd Moklas, M. A., & Mohd Akhir, S. (2017). Antioxidant properties of crude extract, partition extract, and fermented medium of *Dendrobium sabin* flower. *Evidence-Based Complementary and Alternative Medicine*, *2017*, 1–9.

Adefegha, S. A., Olasehinde, T. A., & Oboh, G. (2017). Essential oil composition, antioxidant, antidiabetic and antihypertensive properties of two Afromomum species. *Journal of Oleo Science*, *66*(1), 51–63.

Ademosun, A. O., Oboh, G., Passamonti, S., Tramer, F., Ziberna, L., Boligon, A. A., & Athayde, M. L. (2015). Phenolics from grapefruit peels inhibit HMG-CoA reductase and angiotensin-I converting enzyme and show antioxidative properties in endothelial EA.Hy 926 cells. *Food Science and Human Wellness*, *4*(2), 80–85.

Afify, A. E. M. R., Shalaby, E. A., & El-Beltagi, H. S. (2011). Antioxidant activity of aqueous extracts of different caffeine products. *Journal of Medicinal Plants Research*, *5*(20), 5071–5078.

Ahmad, I., Yanuar, A., Mulia, K., & Mun'im, A. (2017). Review of angiotensin-converting enzyme inhibitory assay: Rapid method in drug discovery of herbal plants. *Pharmacognosy Review*, *11*(21), 1–7.

Alachaher, F. Z., Dali, S., Dida, N., & Krouf, D. (2018). Comparison of phytochemical and antioxidant properties of extracts from flaxseed (Linum usitatissimum) using different solvents. *International Food Research Journal*, *25*(1), 75–82.

Al Disi, S. S., Anwar, M. A., & Eid, A. H. (2016). Anti-hypertensive herbs and their mechanisms of action: Part I. *Frontiers in Pharmacology*, *6*(323), 1–24.

Alam, M. N., Bristi, N. J., & Rafiquzzaman, M. (2013). Review on *in vivo* and *in vitro* methods evaluation of antioxidant activity. *Saudi Pharmaceutical Journal*, *21*(2), 143–152.

Al Shukor, N., Van Camp, J., Gonzales, G. B., Staljanssens, D., Struijs, K., Zotti, M. J., … Smagghe, G. (2013). Angiotensin-converting enzyme inhibitory effects by plant phenolic compounds: A study of structure activity relationships. *Journal of Agricultural and Food Chemistry*, *61*(48), 11832–11839.

Alinde, O. B. L., Esterhuyse, A. J., & Oguntibeju, O. O. (2012). Role of reactive oxygen species in the pathogenesis of cardiovascular disease. *Scientific Research and Assays*, *7*(49), 4151–4159.

Alqahtani, S., Qosa, H., Primeaux, B., & Kaddoumi, A. (2015). Orlistat limits cholesterol intestinal absorption by Niemann-pick C1- like 1 (NPC1L1) inhibition. *European Journal of Pharmacology*, *762*, 263–269.

Anderson, P. J., Weaver, R. E., Neubig, K. M., Frank, M. S., & Dixon, W. N. (2012). *Which Mikania: Native vine or noxious weed? Florida Department of Agriculture and Consumer Services, Division of Plant Industry* (Vol. 37).

Anwar, F., & Przybylski, R. (2012). Effect of solvents extraction on total

phenolics and antioxidant activity of extracts from flaxseed (*Linum usitatissimum* L.). *Acta Scientiarum Polonorum, Technologia Alimentaria*, *11*(3), 293–302.

Atlas, S. A. (2007). The renin-angiotensin aldosterone system: Pathophysiological role and pharmacologic inhibition. *Journal of Managed Care Pharmacy*, *13*(8), 9–20.

Azmir, J., Zaidul, I. S. M., Rahman, M. M., Sharif, K. M., Mohamed, A., Sahena, F., … Omar, A. K. M. (2013). Techniques for extraction of bioactive compounds from plant materials: A review. *Journal of Food Engineering*, *117*(4), 426–436.

Babbar, N., Oberoi, H. S., Sandhu, S. K., & Bhargav, V. K. (2014). Influence of different solvents in extraction of phenolic compounds from vegetable residues and their evaluation as natural sources of antioxidants. *Journal of Food Science and Technology*, *51*(10), 2568–2575.

Bae, H., Jayaprakasha, G. K., Crosby, K., Jifon, J. L., & Patil, B. S. (2012). Influence of extraction solvents on antioxidant activity and the content of bioactive compounds in non-pungent peppers. *Plant Foods for Human Nutrition*, *67*(2), 120–128.

Balasuriya, B. N., & Rupasinghe, H. V. (2011). Plant flavonoids as angiotensin converting enzyme inhibitors in regulation of hypertension. *Functional Foods in Health and Disease*, *1*(5), 172–188.

Bali, E. B., Acik, L., Akca, G., Sarper, M., Elci, M. P., Avcu, F., & Vural, M. (2014). Antimicrobial activity against periodontopathogenic bacteria, antioxidant and cytotoxic effects of various extracts from endemic *Thermopsis turcica*. *Asian Pacific Journal of Tropical Biomedicine*, *4*(7), 505–514.

Baral, B., Bhattarai, N., & Vaidya, G. S. (2011). Pharmacological and antagonistic potentials of *Mikania micrantha*. *Nepal Journal of Science and Technology*, *12*, 75–84.

Baskaran, G., Salvamani, S., Siti Aqlima, A., Noor Azmi, S., Pattiram, P. D., & Mohd Yunus, S. (2015). HMG-CoA reductase inhibitory activity and phytocomponent investigation of *Basella alba* leaf extract as a treatment for hypercholesterolemia. *Drug Design, Development and Therapy*, *9*, 509–517.

Batra, P., & Sharma, A. K. (2013). Anti-cancer potential of flavonoids: Recent trends and future perspectives. *3 Biotech*, *3*(6), 439–459.

Belguith-Hadriche, O., Bouaziz, M., Jamoussi, K., Simmonds, M. S. J., El Feki, A., & Makni-ayedi, F. (2013). Comparative study on hypocholesterolemic and antioxidant activities of various extracts of fenugreek seeds. *Food Chemistry*, *138*(2–3), 1448–1453.

Benzie, I. F., & Strain, J. J. (1996). The ferric reducing ability of plasma (FRAP) as a measure of "antioxidant power": the FRAP assay. *Analytical Biochemistry*, *239*(1), 70–76.

Birari, R. B., & Bhutani, K. K. (2007). Pancreatic lipase inhibitors from natural sources: Unexplored potential. *Drug Discovery Today*, *12*(19–20), 879–89.

Bradley, K. A. (2009). Universiti of South Florida Herbarium. Retrieved May 15, 2018, from http://swbiodiversity.org/seinet/collections/individual/index.php?occid=19365 61

Bravo-Monzón, A. E., González-Rodríguez, A., & Espinosa-García, F. J.

(2018). Spatial structure of genetic and chemical variation in native populations of the mile-a-minute weed *Mikania micrantha*. *Biochemical Systematics and Ecology*, *76*, 23–31.

Brown, M. S., & Goldstein, J. L. (1983). Lipoprotein metabolism in the macrophage: Implications for cholesterol deposition in atherosclerosis. *Annual Review of Biochemistry*, *52*, 223–261.

Bustanji, Y., Issa, A., Mohammad, M., Hudaib, M., & Tawah, K. (2010). Inhibition of hormone sensitive lipase and pancreatic lipase by *Rosmarinus officinalis* extract and selected phenolic constituents. *Journal of Medicinal Plants Research*, *4*(21), 2235–2242.

But, P. P. H., He, Z. D., Ma, S. C., Chan, Y. M., Shaw, P. C., Ye, W. C., & Jiang, R. W. (2009). Antiviral constituents against respiratory viruses from *Mikania micrantha*. *Journal of Natural Products*, *72*(5), 925–928.

Carek, P. J., & Dickerson, L. M. (1999). Current concepts in the pharmacological management of obesity. *Drugs*, *57*(6), 883–904.

Chan, P. T., Matanjun, P., Yasir, S. M., & Tan, T. S. (2015). Antioxidant activities and polyphenolics of various solvent extracts of red seaweed, *Gracilaria changii*. *Journal of Applied Phycology*, *27*(6), 2377–2386.

Chater, P. I., Wilcox, M., Cherry, P., Herford, A., Mustar, S., Wheater, H., … Pearson, J. (2016). Inhibitory activity of extracts of Hebridean brown seaweeds on lipase activity. *Journal of Applied Phycology*, *28*(2), 1303–1313.

Chaudhary, S. K., De, A., Bhadra, S., & Mukherjee, P. K. (2015). Angiotensin-converting enzyme (ACE) inhibitory potential of standardized *Mucuna pruriens* seed extract. *Pharmaceutical Biology*, *53*(11), 1614–1620.

Chetan, J., Sampath Kumara, K. K., Sekhar, S., & Prakash, H. S. (2012). Antioxidant, antibacterial and DNA protecting activity of selected medicinally important Asteraceae plants. *International Journal of Pharmacy and Pharmaceutical Sciences*, *4*(2), 257–261.

Chetia, J., Upadhyaya, S., & Bora, D. K. (2014). Screening of phytochemicals, antioxidant and antimicrobial activity of some tea garden weeds of Tinsukia, Assam. *International Journal of Pharmaceutical Sciences Review and Research*, *26*(33), 193–196.

Cheurfa, M., & Allem, R. (2015). Study of hypocholesterolemic activity of Algerian *Pistacia lentiscus* leaves extracts *in vivo*. *Revista Brasileira de Farmacognosia*, *25*(2), 142–144.

Chogtu, B., Magazine, R., & Bairy, K. L. (2015). Statin use and risk of diabetes mellitus. *World Journal of Diabetes*, *6*(2), 352.

Colares, M., Muguerza, A., Rosella, M. A., & Consolini, A. E. (2013). Antipasmodic effects of *Mikania micrantha* Kunth and dual gastrointestinal effect of *Mikania cordifoli*a (LF.) Wild (Asteraceae) on isolated rat thin intestine. *Pharmacology Online*, *2*, 1–11.

Cue, B. W., & Zhang, J. (2009). Green process chemistry in the pharmaceutical industry. *Green Chemistry Letters and Reviews*, *2*(4), 193–211.

Cushman, D. W., & Cheung, H. S. (1971). Spectophotometric assay and properties of the angiotensin I-converting enzyme of rabbit lung. *Biochemical Pharmacology*, *20*, 1637–1648.

Dalal, J. J., Padmanabhan, T. N. C., Jain, P., Patil, S., Vasnawala, H., & Gulati, A. (2012). Lipitension: Interplay between dyslipidemia and hypertension. *Indian Journal of Endocrinology and Metabolism*, *16*(2), 240–245.

Das, J., Jha, D. K., Policegoudra, R. S., Mazumder, A. H., Das, M.,

Chattopadhyay, P., & Singh, L. (2012). Isolation and characterization of antidermatophytic bioactive molecules from *Piper longum* L. leaves. *Indian Journal of Microbiology*, *52*(4), 624–629.

Daughtery, A., Lu, H., Rateri, D. L., & Cassis, L. A. (2008). Augmentation of the renin–angiotensin system by hypercholesterolemia promotes vascular diseases. *Future Lipidology*, *3*(6), 625–636.

Day, M. D., Clements, D. R., Gile, C., Senaratne, W. K. A. D., Shen, S., Weston, L. A., & Zhang, F. (2016). Biology and Impacts of Pacific Islands Invasive Species. 13. *Mikania micrantha* Kunth (Asteraceae). *Pacific Science*, *70*(3), 257–285.

Dechakhamphu, A., & Wongchum, N. (2015). Screening for anti-pancreatic lipase properties of 28 traditional Thai medicinal herbs. *Asian Pacific Journal of Tropical Biomedicine*, *5*(12), 1042–1045.

Deo, P., Hewawasam, E., Karakoulakis, A., Claudie, D. J., Nelson, R., Simpson, B. S., … Semple, S. J. (2016). *In vitro* inhibitory activities of selected Australian medicinal plant extracts against protein glycation, angiotensin converting enzyme (ACE) and digestive enzymes linked to type II diabetes. *BMC Complementary and Alternative Medicine*, *16*, 435.

Deori, C., Dutta, G., Das, S., & Phukan, D. (2016). Analgesic activity of ethanolic extract of leaves of *Mikania micrantha* on experimental animal models. *Pharma Science Monitor*, *7*(3), 168–173.

Deori, C., Dutta, G., Das, S., Phukan, D., & Gogoi, G. (2017). To evaluate the anti-inflammatory activity of ethanolic extract of leaves of *Mikania micrantha* on experimental animal models. *Journal of Evolution of Medical and Dental Sciences*, *6*(50), 3818–3821.

Department of Statistics Malaysia. (2017). *Statistics on causes of death, Malaysia, 2017*. Retrieved from https://www.dosm.gov.my

Dev, U. K., Hossain, M. T., & Islam, M. Z. (2015). Phytochemical investigation, antioxidant activity and anthelmintic activity of *Mikania micrantha* leaves. *World Journal of Pharmaceutical Research*, *4*(5), 121–133.

Dhanani, T., Shah, S., Gajbhiye, N. A., & Kumar, S. (2017). Effect of extraction methods on yield, phytochemical constituents and antioxidant activity of *Withania somnifera*. *Arabian Journal of Chemistry*, *10*, S1193–S1199.

Djerrou, Z. (2014). Anti-hypercholesterolemic effect of *Pistacia lentiscus* fatty oil in egg yolk-fed rabbits: A comparative study with simvastatin. *Chinese Journal of Natural Medicines*, *12*(8), 561–566.

Dong, L. M., Jia, X. C., Luo, Q. W., Zhang, Q., Luo, B., Liu, W. B., … Tan, J. W. (2017). Phenolics from *Mikania micrantha* and their antioxidant activity. *Molecules*, *22*(7), 1140.

Dou, X., Zhang, Y., Sun, N., Wu, Y., & Li, L. (2014). The anti-tumor activity of *Mikania micrantha* aqueous extract *in vitro* and *in vivo*. *Cytotechnology*, *66*(1), 107–117.

Drew, B. S., Dixon, A. F., & Dixon, J. B. (2007). Obesity management: Update on orlistat. *Vascular Health and Risk Management*, *3*(6), 817–821.

Facey, P. C., Peart, P. C., & Porter, R. B. R. (2010). The antibacterial activities of mikanolide and its derivatives. *West Indian Medical Journal*, *59*(3), 249–252.

Frandsen, J. R., & Narayanasamy, P. (2018). Neuroprotection through flavonoid: Enhancement of the glyoxalase pathway. *Redox Biology*, *14*, 465–473.

Gangwar, M., Gautam, M. K., Sharma, A. K., Tripathi, Y. B., Goel, R. K., &

Nath, G. (2014). Antioxidant capacity and radical scavenging effect of polyphenol rich *Mallotus philippenensis* fruit extract on human erythrocytes: An *in vitro* study. *The Scientific World Journal*, *2014*, 1–12.

Geetha, D. H., Rajeswari, M., & Jayashree, I. (2013). Chemical profiling of *Elaeocarpus serratus* L. by GC-MS. *Asian Pacific Journal of Tropical Biomedicine*, *3*(12), 985–987.

Ghanbari, R., Zarei, M., Ebrahimpour, A., Abdul Hamid, A., Ismail, A., & Saari, N. (2015). Angiotensin-I converting enzyme (ACE) inhibitory and anti-oxidant activities of sea cucumber (*Actinopyga lecanora*) hydrolysates. *International Journal of Molecular Sciences*, *16*(12), 28870–28885.

Ghosh, A., Das, B. K., Roy, A., Mandal, B., & Chandra, G. (2008). Antibacterial activity of some medicinal plant extracts. *Journal of Natural Medicines*, *62*(2), 259–262.

Goulas, V., Exarchou, V., Kanetis, L., & Gerothanassis, I. P. (2014). Evaluation of the phytochemical content, antioxidant activity and antimicrobial properties of mountain tea (*Sideritis syriaca*) decoction. *Journal of Functional Foods*, *6*(1), 248–258.

Guerrero, L., Castillo, J., Quiñones, M., Garcia-Vallvé, S., Arola, L., Pujadas, G., & Muguerza, B. (2012). Inhibition of angiotensin-converting enzyme activity by flavonoids: Structure-activity relationship studies. *PLoS ONE*, *7*(11), e49493.

Gunathilake, K. D. P. P., & Ranaweera, K. K. D. S. (2016). Antioxidative properties of 34 green leafy vegetables. *Journal of Functional Foods*, *26*, 176–186.

Guo, X., Tresserra-rimbau, A., Estruch, R., Martínez-gonzález, M. A., Medina-remón, A., Castañer, O., … Lamuela-raventós, R. M. (2016). Effects of polyphenol, measured by a biomarker of total polyphenols in urine, on cardiovascular risk factors after a long-term follow-up in the PREDIMED Study. *Oxidative Medicine and Cellular Longevity*, *2016*, 1–11.

Gupta, A. K., Ravussin, E., Johannsen, D. L., Stull, A. J., Cefalu, W. T., & Johnson, W. D. (2012). Endothelial dysfunction: An early cardiovascular risk marker in asymptomatic obese individuals with prediabetes. *British Journal of Medicine and Medical Research*, *2*(3), 413–423.

Gupta, D. (2015). Methods for determination of antioxidant capacity: A review. *International Journal of Pharmaceutical Sciences and Research*, *6*(2), 546–566.

Hadi, H. A. R., Carr, C. S., & Al Suwaidi, J. (2005). Endothelial dysfunction: cardiovascular risk factors, therapy, and outcome. *Vascular Health and Risk Management*, *1*(3), 183–198.

Haisya, N. B. S., Latifah, A. R., Suratno, R. P., Sa'diah, S., & Afiff, U. (2013). Sembung rambat (*Mikania micrantha* H.B.K.) as natural alternative antibacterial and its study against bacterial common as causative agent in cattle mastitis in Indonesia. In *6th Conference of Indonesian Students Association in Korea* (pp. 6–7).

Hakimoğlu, F., Kizil, G., Kanay, Z., Kizil, M., & Isi, H. (2007). The effect of ethanol extract of *Hypericum lysimachioides* on lipid profile in hypercholesterolemic rabbits and its *in vitro* antioxidant activity. *Atherosclerosis*, *192*(1), 113–122.

Hasmida, M. N., Nur Syukriah, A. R., Liza, M. S., & Mohd Azizi, C. Y. (2014). Effect of different extraction techniques on total phenolic content and antioxidant activity of *Quercus infectoria* galls. *International Food*

Research Journal, *21*(3), 1075–1079.
Henness, S., & Perry, C. M. (2006). Orlistat: A review of its use in the management of obesity. *Drugs*, *66*(12), 1625–1656.
Hildgate, G. A., Ward, W. H. J., & McTaggart, F. (2003). Molecular mechanism for inhibition of 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase by rosuvastatin. *Biochemical Society Transactions*, *31*, 528–531.
Hoon, L. Y., Choo, C., Watawana, M. I., Jayawardena, N., & Waisundara, V. Y. (2015). Evaluation of the total antioxidant capacity and antioxidant compounds of different solvent extracts of Chilgoza pine nuts (*Pinus gerardiana*). *Journal of Functional Foods*, *18*, 1014–1021.
Hossain, M. A., & Shah, M. D. (2015). A study on the total phenols content and antioxidant activity of essential oil and different solvent extracts of endemic plant *Merremia borneensis*. *Arabian Journal of Chemistry*, *8*(1), 66–71.
Huang, H., Ye, W., Wu, P., Lin, L., & Wei, X. (2004). New sesquiterpene dilactones from *Mikania micrantha*. *Journal of Natural Products*, *67*(4), 734–736.
Huang, W. Y., Davidge, S. T., & Wu, J. (2013). Bioactive natural constituents from food sources - Potential use in hypertension prevention and treatment. *Critical Reviews in Food Science and Nutrition*, *53*(6), 615–630.
Huggins, K. W., Camarota, L. M., Howles, P. N., & Hui, D. Y. (2003). Pancreatic triglyceride lipase deficiency minimally affects dietary fat absorption but dramatically decreases dietary cholesterol absorption in mice. *The Journal of Biological Chemistry*, *278*(44), 42899–42905.
Hussain, F., Islam, A., Bulbul, L., Moghal, M. R., & Hossain, M. S. (2014). *In vitro* thrombolytic potential of root extracts of four medicinal plants available in Bangladesh. *Ancient Science of Life*, *33*(3), 162–164.
Iloki-Assanga, S. B., Lewis-Lujan, L. M., Lara-Espinoza, C. L., Gil-Salido, A. A., Fernandez-Angulo, D., Rubio-Pino, J. L., & Haines, D. D. (2015). Solvent effects on phytochemical constituent profiles and antioxidant activities, using four different extraction formulations for analysis of *Bucida buceras* L. and *Phoradendron californicum*. *BMC Research Notes*, *8*(1), 396.
Institute for Public Health (IPH). (2015). *Non-communicable diseases, risk factors & other health problems*. *National Health and Morbidity Survey 2015*.
Iqbal, D., Khan, M. S., Khan, A., Khan, M. S., Ahmad, S., Srivasta, A. K., & Bagga, P. (2014). *In vitro* screening for β-hydroxy-β-methylglutaryl-CoA reductase inhibitory and antioxidant activity of sequentially extracted fractions of *Ficus palmata* Forsk. *BioMed Research International*, *2014*, 1–10.
Iqbal, S., Younas, U., Sirajuddin, Chan, K. W., Sarfraz, R. A., & Uddin, M. K. (2012). Proximate composition and antioxidant potential of leaves from three varieties of mulberry (Morus sp.): A comparative study. *International Journal of Molecular Sciences*, *13*(6), 6651–6664.
Istvan, E. (2003). Statin inhibition of HMG-CoA reductase: A 3-dimensional view. *Atherosclerosis Supplements*, *4*(1), 3–8.
Jeong, H. U., Kwon, S. S., Kong, T. Y., Kim, J. H., & Lee, H. S. (2014). Inhibitory effects of cedrol, β-cedrene, and thujopsene on cytochrome P450 enzyme activities in human liver microsomes. *Journal of Toxicology and Environmental Health*, *77*(22–24), 1522–1532.

John, S., & Schmieder, R. E. (2003). Potential mechanisms of impaired endothelial function in arterial hypertension and hypercholesterolemia. *Current Hypertension Reports*, *5*(3), 199–207.

Jyothilakshmi, M., Jyothis, M., & Latha, M. S. (2015). Antidermatophytic activity of *Mikania micrantha* Kunth: An invasive weed. *Pharmacognosy Research*, *7*(Suppl 1), 20–25.

Kalita, P., Barman, T. K., Pal, T. K., & Kalita, R. (2013). Estimation of total flavonoids content (TFC) and antioxidant activities of methanolic whole plant extract of *Biophytum sensitivum* Linn. *Journal of Drug Delivery & Therapeutics*, *3*(4), 33–37.

Kersten, S. (2014). Physiological regulation of lipoprotein lipase. *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids*, *1841*(7), 919–933.

Khan, R. A., Khan, M. R., Sahreen, S., & Ahmed, M. (2012). Assessment of flavonoids contents and *in vitro* antioxidant activity of *Launaea procumbens*. *Chemistry Central Journal*, *6*(1), 43.

Khatun, R., Roy, S., & Abdur Rahman, M. A. (2017). *In vitro* comparative evaluation of anti-inflammatory and thrombolytic activity of three Mikania species available in Bangladesh. *Journal of Pharmacognosy and Phytochemistry*, *6*(5), 1007–1011.

Kim, Y. S., Lee, Y., Kim, J., Sohn, E., Kim, C. S., Lee, Y. M., … Kim, J. S. (2012). Inhibitory activities of *Cudrania tricuspidata* leaves on pancreatic lipase *in vitro* and lipolysis *in vivo*. *Evidence-Based Complementary and Alternative Medicine*, *2012*, 1-8.

Kong, K. W., Mat-Junit, S., Aminudin, N., Ismail, A., & Abdul-Aziz, A. (2012). Antioxidant activities and polyphenolics from the shoots of *Barringtonia racemosa* (L.) Spreng in a polar to apolar medium system. *Food Chemistry*, *134*(1), 324–332.

Kumar, S., & Pandey, A. K. (2013). Chemistry and biological activities of flavonoids: an overview. *The Scientific World Journal*, *2013*, 1–16.

Laurella, L. C., Frank, F. M., Sarquiz, A., Alonso, M. R., Giberti, G., Cavallaro, L., … Sülsen, V. P. (2012). *In vitro* evaluation and antiprotozoal and antiviral activities of extracts from Argentinean Mikania species. *The Scientific World Journal*, *2012*, 1–6.

Lee, S. Y., Mediani, A., Nur Ashikin, A. H., Azliana, A. B. S., & Abas, F. (2014). Antioxidant and α-glucosidase inhibitory activities of the leaf and stem of selected traditional medicinal plants. *International Food Research Journal*, *21*(1), 165–172.

Li, Y., He, P. P., Zhang, D. W., Zheng, X. L., Cayabyab, F. S., Yin, W. D., & Tang, C. K. (2014). Lipoprotein lipase: From gene to atherosclerosis. *Atherosclerosis*, *237*(2), 597–608.

Li, Y., Li, J., Li, Y., Wang, X. X., & Cao, A. C. (2013). Antimicrobial constituents of the leaves of Mikania micrantha H.B.K. *PLoS ONE*, *8*(10), 1–10.

Liang, G., Kou, H., Wang, T., Guo, Y., Ping, J., & Wang, H. (2015). Optimization, validation and application of spectrophotometric assay for 3-Hydroxy-3-methylglutaryl-coenzyme A reductase activity. *Tropical Journal of Pharmaceutical Research*, *14*(4), 671–677.

Lim, S. M., Goh, Y. M., Kuan, W. Bin, & Loh, S. P. (2014). Effect of germinated brown rice extracts on pancreatic lipase, adipogenesis and lipolysis in 3T3-L1 adipocytes. *Lipids in Health and Disease*, *13*(1), 169.

Limberger, R. P., Aboy, A. L., Bassani, V. L., Moreno, P. R. H., Ritter, M. R., &

Henriques, A. T. (2001). Essential oils from four Mikania species (Asteraceae). *Journal of Essential Oil Research*, *13*(4), 225–228.

Lin, S. H., Chang, D. K., Chou, M. J., Huang, K. J., & Shiuan, D. (2015). Peptide inhibitors of human HMG-CoA reductase as potential hypocholesterolemia agents. *Biochemical and Biophysical Research Communications*, *456*(1), 104–109.

Liscum, L. (2002). Cholesterol biosynthesis. In D. E. Vance & J. E. Vance (Eds.), *Biochemistry of lipids, lipoproteins and membranes(4th Edn.)* (pp. 409–431). Elsevier Science B.V.

Lobo, V., Patil, A., Phatak, A., & Chandra, N. (2010). Free radicals, antioxidants and functional foods: Impact on human health. *Pharmacognosy Review*, *4*(8), 118–26.

Loh, S. P., & Hadira, O. (2011). *In vitro* inhibitory potential of selected Malaysian plants against key enzymes involved in hyperglycemia and hypertension. *Malaysian Journal of Nutrition*, *17*(1), 77–86.

Loizzo, M. R., Marrelli, M., Pugliese, A., Conforti, F., Nadjafi, F., Menichini, F., & Tundis, R. (2016). Crocus cancellatus subsp. damascenus stigmas: chemical profile, and inhibition of α-amylase, α-glucosidase and lipase, key enzymes related to type 2 diabetes and obesity. *Journal of Enzyme Inhibition and Medicinal Chemistry*, *31*(2), 212–218.

Loizzo, M. R., Said, A., Tundis, R., Rashed, K., Statti, G. A., Hufner, A., & Menichini, F. (2007). Inhibition of angiotensin converting enzyme (ACE) by flavonoids isolated from *Ailanthus excelsa* (Roxb) (Simaroubaceae). *Phytotherapy Research*, *21*, 32–36.

Lunagariya, N. A., Patel, N. K., Jagtap, S. C., & Bhutani, K. K. (2014). Inhibitors of pancreatic lipase: State of the art and clinical perspectives. *EXCLI Journal*, *13*, 897–921.

Madhesh, M., & Vaiyapuri, M. (2013). Luteolin a dietary flavonoid attenuates isoproterenol-induced myocardial oxidative stress in rat myocardium: An *in vivo* study. *Biomedicine & Preventive Nutrition*, *3*(2), 159–164.

Mahmoudabady, M., Kazemi, N., Niazmand, S., Rezaee, S. A., Soukhtanloo, M., & Hosseini, M. (2015). The effect of angiotensin-converting enzyme inhibition on inflammatory and angiogenic factors in hypercholesterolemia. *Pharmacological Reports*, *67*(5), 837–841.

Maiolino, G., Rossitto, G., Caielli, P., Bisogni, V., Rossi, G. P., & Calò, L. A. (2013). The role of oxidized low-density lipoproteins in atherosclerosis: The myths and the facts. *Mediators of Inflammation*, *2013*, 1–13.

Maqsood, M., Ahmed, D., Atique, I., & Malik, W. (2017). Lipase inhibitory activity of *Lagenaria siceraria* fruit as a strategy to treat obesity. *Asian Pacific Journal of Tropical Medicine*, *10*(3), 305–310.

Martinello, F., Soares, S. M., Franco, J. J., Santos, a. C., Sugohara, A., Garcia, S. B., … Uyemura, S. a. (2006). Hypolipemic and antioxidant activities from *Tamarindus indica* L. pulp fruit extract in hypercholesterolemic hamsters. *Food and Chemical Toxicology*, *44*(6), 810–818.

Martson, A., & Hostettmann, K. (2005). Separation and quantification of flavonoids. In O. M. Andersen & K. R. Markham (Eds.), *Flavonoids: chemistry, biochemistry and application* (pp. 1–36). New York: CRC Press.

Matawali, A., Chin, L. P., Eng, H. S., Boon, L. H., & Gansau, J. A. (2016). *In-vitro* evaluation of anti-kinase, anti-phosphatase and cytotoxic activities of

Mikania micrantha H.B.K. (Asteraceae) from Malaysia. *Journal of Chemical and Pharmaceutical Sciences*, *9*(2), 696–701.

Matawali, A., Chin, L. P., Eng, H. S., & Gansau, J. A. (2016). Antibacterial and phytochemical investigations of *Mikania micrantha* H.B.K. (Asteraceae) from Sabah, Malaysia. *Transaction on Science and Technology*, *3*(1–2), 244–250.

McCord, J. M. (2000). Evolution of free radicals and oxidative stress. *American Journal of Medicine*, *108*, 652–659.

Mendes, A. A., Oliveira, P. C., & De Castro, H. F. (2012). Properties and biotechnological applications of porcine pancreatic lipase. *Journal of Molecular Catalysis B: Enzymatic*, *78*, 119–134.

Ministry of Health Malaysia. (2013). *Clinical Practice Guideline on Management of Hypertension - 4th Edition*. Retrieved from http://www.moh.gov.my

Mistriyani, Riyanto, S., & Rohman, A. (2018). Antioxidant activities of Rambutan (*Nephelium lappaceum* L) peel in vitro. *Food Research*, *2*(1), 119–123.

Mohamed, S. (2014). Functional foods against metabolic syndrome (obesity, diabetes, hypertension and dyslipidemia) and cardiovasular disease. *Trends in Food Science and Technology*, *35*(2), 114–128.

Mohd Hadzri, H., Che Yunus, M. A., Zhari, S., & Rithwan, F. (2014). The effects of solvents and extraction methods on the antioxidant activity. *Jurnal Teknologi (Sciences & Engineering)*, *68*(5), 47–52.

Moor, V. J. A., Amougou, S. N., Ombotto, S., Ntone, F., Wouamba, D. E., & Nonga, B. N. (2017). Dyslipidemia in patients with a cardiovascular risk and disease at the University Teaching Hospital of Yaoundé, Cameroon. *International Journal of Vascular Medicine*, *2017*, 1–5.

Mustapha, F., Omar, Z., Mihat, O., Md Noh, K., Hassan, N., Abu Bakar, R., … Allotey, P. (2014). Addressing non-communicable diseases in Malaysia: An integrative process of systems and community. *BMC Public Health*, *14*(Suppl 2), S4.

Nakamura, M., Ra, J. H., Jee, Y., & Kim, J. S. (2017). Impact of different partitioned solvents on chemical composition and bioavailability of *Sasa quelpaertensis* Nakai leaf extract. *Journal of Food and Drug Analysis*, *25*(2), 316–326.

Nasri, H., Baradaran, A., Shirzad, H., & Rafieian-Kopaei, M. (2014). New concepts in nutraceuticals as alternative for pharmaceuticals. *International Journal of Preventive Medicine*, *5*(12), 1487–99.

Nicollier, G., & Thompson, A. C. (1981). Essential oil and terpenoids of *Mikania micrantha*. *Phytochemistry*, *20*(11), 2587–2588.

Nimse, S. B., & Pal, D. (2015). Free radicals, natural antioxidants, and their reaction mechanisms. *Royal Society of Chemistry*, *5*(35), 27986–28006.

Nornasuha, Y., & Ismail, B. S. (2013). Comparative allelopathic effects of *Chromolaena odorata* (L.) king & robinson and *Mikania micrantha* H.B.K. on Ageratum conyzoides. In *24th Asian-Pacific Weed Science Society Conference* (pp. 407–411). Asian-Pacific Weed Science Society.

Nurdiana, S., Nur Ajeerah, S., Nur Farhana, A. S., Siti Khairiyah, M. H., & Norashirene, M. J. (2013). Hypoglycaemic, antioxidant and wound healing activities of *Mikania micrantha* leaves extract in normal and alloxan-induced diabetic rats. *Focus and Scope*, *7*(2), 6–10.

Oboh, G., Akinyemi, A. J., Osanyinlusi, F. R., Ademiluyi, A. O., Boligon, A. A., & Athayde, M. L. (2014). Phenolic compounds from sandpaper (*Ficus*

exasperata) leaf inhibits angiotensin 1 converting enzyme in high cholesterol diet fed rats. *Journal of Ethnopharmacology*, *157*, 119–125.

Olkkonen, V. M., Gylling, H., & Ikonen, E. (2017). Plant sterols, cholesterol precursors and oxysterols: Minute concentrations - Major physiological effects. *Journal of Steroid Biochemistry and Molecular Biology*, *169*, 4–9.

Olugbami, J. O., Gbadegesin, M. A., & Odunola, O. A. (2015). *In vitro* free radical scavenging and antioxidant properties of ethanol extract of *Terminalia glaucescens*. *Pharmacognosy Research*, *7*(1), 49.

Othman, A., Ismail, A., Hassan, F. A., Yusof, B. N. M., & Khatib, A. (2016). Comparative evaluation of nutritional compositions, antioxidant capacities, and phenolic compounds of red and green sessile joyweed (*Alternanthera sessilis*). *Journal of Functional Foods*, *21*, 263–271.

Painuli, S., Rai, N., & Kumar, N. (2016). Gas chromatography and mass spectrometry analysis of methanolic extract of leaves of *Rhododendron Arboreum*. *Asian Journal of Pharmaceutical and Clinical Research*, *9*(1), 101–104.

Pak-Dek, M. S., Abdul Hamid, A., Osman, A., & Soh, C. S. (2008). Inhibitory effect of *Morinda citrifolia* L. on lipoprotein lipase activity. *Journal of Food Science*, *78*(8), 595–598.

Pérez-Amador, M. C., Muñoz Ocotero, V., Ibarra Balcazar, R., & García Jiménez, F. (2010). Phytochemical and pharmacological studies on *Mikania micrantha* H.B.K. (Asteraceae). *Phyton-International Journal of Experimental Botany*, *79*, 77–80.

Phatak, R. S., & Hendre, A. S. (2014). Total antioxidant capacity (TAC) of fresh leaves of *Kalanchoe pinnata*. *Journal of Pharmacognosy and Phytochemistry*, *2*(5), 32–35.

Pichandi, S., Pasupathi, P., Raoc, Y. Y., Farook, J., Ambika, A., Ponnusha, B. S., … Virumandye, R. (2011). The role of statin drugs in combating cardiovascular diseases. *International Journal of Current Scientific Research*, *1*(2), 47–56.

Plazonic, A., Males, Z., Mornar, A., Nigovic, B., & Kujundzic, N. (2011). Characterization and quantification of flavonoid aglycones and phenolic acids in the hydrolyzed methanolic extract of *Caucalis platycarpos* using HPLC-DAD-MS/MS. *Chemistry of Natural Compounds*, *47*(1), 27–32.

Pomaro, D. R., Ihara, S. S., Pinto, L. E., Ueda, I., Casarini, D. E., Ebihara, F., … Fonseca, F. A. (2005). High glucose levels abolish antiatherosclerotic benefits of ACE inhibition in alloxan-induced diabetes in rabbits. *Journal of Cardiovascular Pharmacology*, *45*(4), 295–300.

Prieto, P., Pineda, M., & Aguilar, M. (1999). Spectrophotometric quantitation of antioxidant capacity through the formation of a phosphomolybdenum complex : specific application to the determination of vitamin E. *Analytical Biochemistry*, *341*, 337–341.

Rafieian-Kopaei, M., Setorki, M., Doudi, M., & Nasri, H. (2014). Atherosclerosis: Process, indicators, risk factors and new hopes. *International Journal of Preventitive Medicine*, *5*(8), 927–946.

Re, R., Pellegrini, N., Proteggente, A., Pannala, A., Yang, M., & Rice-Evans, C. (1999). Antioxidant activity applying an improved ABTS radical cation decolorization assay. *Free Radical Biology and Medicine*, *26*(9–10), 1231–1237.

Ríos, E., León, A., Chávez, M. I., Torres, Y., Ramírez-Apan, M. T., Toscano, R. A., … Delgado, G. (2014). Sesquiterpene lactones from *Mikania*

micrantha and *Mikania cordifolia* and their cytotoxic and anti-inflammatory evaluation. *Fitoterapia*, *94*, 155–163.

Rizvi, S. M., Shakil, S., Zeeshan, M., Khan, M. S., Shaikh, S., Biswas, D., … Kamal, M. A. (2014). An enzoinformatics study targeting polo-like kinases-1 enzyme: Comparative assessment of anticancer potential of compounds isolated from leaves of *Ageratum houstonianum*. *Pharmacognosy Magazine*, *10*(37), S14-21.

Roh, C., & Jung, U. (2012). Screening of crude plant extracts with anti-obesity activity. *International Journal of Molecular Sciences*, *13*, 1710–1719.

Rufatto, L. C., Gower, A., Schwambach, J., & Moura, S. (2012). Genus Mikania: Chemical composition and phytotherapeutical activity. *Brazilian Journal of Pharmacognosy*, *22*(6), 1384–1403.

Saeed, N., Khan, M. R., & Shabbir, M. (2012). Antioxidant activity, total phenolic and total flavonoid contents of whole plant extracts *Torilis leptophylla* L. *BMC Complementary and Alternative Medicine*, *12*, 221.

Saha, S., Mandal, S. K., & Chowdhury, H. R. (2015). Anato-pharmacognostic studies of *Mikania micrantha* Kunth: A promising medicinal climber of the family Asteraceae. *International Journal of Research in Ayurveda & Pharmacy*, *6*(6), 773–780.

Sakulnarmrat, K., & Konczak, I. (2012). Composition of native Australian herbs polyphenolic-rich fractions and *in vitro* inhibitory activities against key enzymes relevant to metabolic syndrome. *Food Chemistry*, *134*(2), 1011–1019.

Sakulnarmrat, K., Srzednicki, G., & Konczak, I. (2014). Composition and inhibitory activities towards digestive enzymes of polyphenolic-rich fractions of Davidson's plum and quandong. *LWT - Food Science and Technology*, *57*(1), 366–375.

Salvamani, S., Gunasekaran, B., Shukor, M. Y., Shaharuddin, N. A., Sabullah, M. K., & Ahmad, S. A. (2016). Anti-HMG-CoA reductase, antioxidant, and anti-inflammatory activities of *Amaranthus viridis* leaf extract as a potential treatment for hypercholesterolemia. *Evidence-Based Complementary and Alternative Medicine*, *2016*, 1–10.

Sander, G. E., & Giles, T. D. (2002). Hypertension and lipids: Lipid factors in the hypertension syndrome. *Current Hypertension Reports*, *4*(6), 458–463.

Sankaran, K. V. (2008). *Mikania micrantha: Mile-a-minute weed*. [Fact sheet]. Retrived from http://apfisn.net

Santos, M. C. P., & Gonçalves, É. C. B. A. (2016). Effect of different extracting solvents on antioxidant activity and phenolic compounds of a fruit and vegetable residue flour. *Scientia Agropecuaria*, *7*(1), 07–14.

Saraphanchotiwitthaya, A., & Sripalakit, P. (2014). Effect of *Morinda citrifolia* Linn. leaf extracts on *in vitro* lipase activity. *Chiang Mai Journal of Science*, *41*(5–1), 1182–1193.

Saravanan, M., & Ignacimuthu, S. (2015). Hypocholesterolemic effect of Indian medicinal plants - A review. *Medicinal Chemistry*, *5*(1), 40–49.

Sarian, M. N., Ahmed, Q. U., Mat So'ad, S. Z., Alhassan, A. M., Murugesu, S., Perumal, V., … Latip, J. (2017). Antioxidant and antidiabetic effects of flavonoids: A structure-activity relationship based study. *BioMed Research International*, *2017*, 1–14.

Sattar, N., Preiss, D., Murray, H. M., Welsh, P., Buckley, B. M., & de Craen, Anton, J. M. (2010). Statins and risk of incident diabetes: A collaborative

meta-analysis of randomised statin trials. *Revista Portuguesa de Cardiologia*, *29*(6), 1077–1078.
Shafaei, A., Sultan Khan, M., F. A. Aisha, A., Abdul Majid, A., Hamdan, M., Mordi, M., & Ismail, Z. (2016). Flavonoids-rich *Orthosiphon stamineus* extract as new candidate for angiotensin I-converting enzyme inhibition: a molecular docking study. *Molecules*, *21*, 1500.
Shahidi, F., & Ambigaipalan, P. (2015). Phenolics and polyphenolics in foods, beverages and spices: Antioxidant activity and health effects - A review. *Journal of Functional Foods*, *18*, 820–897.
Shahidi, F., & Zhong, Y. (2010). Novel antioxidants in food quality preservation and health promotion. *European Journal of Lipid Science and Technology*, *112*(9), 930–940.
Shao, H., Peng, S., Wei, X., Zhang, D., & Zhang, C. (2005). Potential allelochemicals from an invasive weed *Mikania micrantha* H.B.K. *Journal of Chemical Ecology*, *31*(7), 1657–1668.
Sharifi, N., Souri, E., Ziai, S. A., Amin, G., & Amanlou, M. (2013). Discovery of new angiotensin converting enzyme (ACE) inhibitors from medicinal plants to treat hypertension using an *in vitro* assay. *DARU Journal of Pharmaceutical Sciences*, *21*, 74.
Sharma, C., Al Kaabi, J. M., Nurulain, S. M., Goyal, S. N., Kamal, M. A., & Ojha, S. (2016). Polypharmacological properties and therapeutic potential of β-caryophyllene: A dietary phytocannabinoid of pharmaceutical promise. *Current Pharmaceutical Design*, *22*(21), 3237–3264.
Sharma, G., Prakash, D., & Gupta, C. (2014). Phytochemicals of Nutraceutical Importance: Do They Defend Against Deseases? In D. Prakash & G. Sharma (Eds.), *Phytochemicals of Nutraceutical Importance* (pp. 1–19). United Kingdom: CAB International.
Sibi, P. I., & Sajid, K. P. (2014). Behavioural assessment of *Mikania micrantha* Kunth roots in Wistar albino rats. *Journal of Medicinal Plants Research*, *8*(11), 448–453.
Sofowora, A., Ogunbodede, E., & Onayade, A. (2013). The role and place of medicinal plants in the strategies for disease prevention. *African Journal of Traditional, Complementary and Alternative Medicines*, *10*(5), 210–229.
Sowndhararajan, K., & Kang, S. C. (2013). Free radical scavenging activity from different extracts of leaves of *Bauhinia vahlii* Wight & Arn. *Saudi Journal of Biological Sciences*, *20*(4), 319–325.
Steinberg, D. (2002). Atherogenesis in perspective: hypercholesterolemia and inflammation as partners in crime. *Nature Medicine*, *8*(11), 1211–1217.
Steinberg, D. (2005). Hypercholesterolemia and inflammation in atherogenesis: Two sides of the same coin. *Molecular Nutrition and Food Research*, *49*(11), 995–998.
Sweitzer, N. K. (2003). What is an angiotensin converting enzyme inhibitor? *Circulation*, *108*(3), e16–e18.
Thaxton, C. S., Rink, J. S., Naha, P. C., & Cormode, D. P. (2016). Lipoproteins and lipoprotein mimetics for imaging and drug delivery. *Advanced Drug Delivery Reviews*, *106*, 116–131.
Thurairajah, P. H., Syn, W. K., Neil, D. A. H., Stell, D., & Haydon, G. (2005). Orlistat (Xenical)-induced subacute liver failure. *European Journal of Gastroenterology and Hepatology*, *17*(12), 1437–1438.
Tiwari, V., & Khokhar, M. (2014). Mechanism of action of anti-hypercholesterolemia drugs and their resistance. *European Journal of*

Pharmacology, *741*, 156–170.
Treml, J., & Smejkal, K. (2016). Flavonoids as potent scavengers of hydroxyl radicals. *Comprehensive Reviews in Food Science and Food Safety*, *15*, 720–738.
Trentman, T. L., Avey, S. G., & Ramakrishna, H. (2016). Current and emerging treatments for hypercholesterolemia: A focus on statins and proprotein convertase subtilisin/kexin Type 9 inhibitors for perioperative clinicians. *Journal of Anaesthesiology, Clinical Pharmacology*, *32*(4), 440–445.
Tripathi, R. S., Khan, M. L., & Yadav, A. S. (2012). Biology of *Mikania micrantha* H.B.K.: A Review. In J. R. Bhatt, J. S. Singh, S. P. Singh, R. S. Tripathi, & R. K. Kohli (Eds.), *Invasive Alien Plants : An Ecological Appraisal for the Indian Subcontinent* (pp. 99–107). CAB International.
Ulker, S., Placidi, C., Point, V., Gadenne, B., Serveau-Avesque, C., Canaan, S., … Cavalier, J. F. (2015). New lipase assay using Pomegranate oil coating in microtiter plates. *Biochimie*, *120*, 110–118.
van der Wulp, M. Y. M., Verkade, H. J., & Groen, A. K. (2013). Regulation of cholesterol homeostasis. *Molecular and Cellular Endocrinology*, *368*, 1–16.
Van Rooy, M. J., & Pretorius, E. (2014). Obesity, hypertension and hypercholesterolemia as risk factors for atherosclerosis leading to ischemic events. *Current Medicinal Chemistry*, *21*(19).
Wan Nurhayati, W. H., Norli Arlizan, T., & Nurdiana, S. (2013). Effect of *Mikania micrantha* leaf extract on the level of blood glucose and hepatic glycogen in the normal and alloxan-induced diabetic rats. *Natural Products an Indian Journal*, *9*(10), 398–402.
Wang, J., Geng, S., Wang, B., Shao, Q., Fang, Y., & Wei, Y. (2017). Magnetic nanoparticles and high-speed countercurrent chromatography coupled in-line and using the same solvent system for separation of quercetin-3-O-rutinoside, luteoloside and astragalin from a Mikania micrantha extract. *Journal of Chromatography A*, *1508*, 42–52.
Wang, R. L., Peng, S. L., Zeng, R. S., Ding, L. W., & Xu, Z. F. (2009). Cloning, expression and wounding induction of β-caryophyllene synthase gene from *Mikania micrantha* H.B.K. and allelopathic potential of β-caryophyllene. *Allelopathy Journal*, *24*(1), 35–44.
Ward, M. G., Li, G., Barbosa-Lorenzi, V. C., & Hao, M. (2017). Stigmasterol prevents glucolipotoxicity induced defects in glucose-stimulated insulin secretion. *Scientific Reports*, *7*(1), 1–13.
Weber, M. A., Schiffrin, E. L., White, W. B., Mann, S., Lindholm, L. H., Kenerson, J. G., … Harrap, S. B. (2014). Clinical practice guidelines for the management of hypertension in the community a statement by the American Society of Hypertension and the International Society of Hypertension. *The Journal of Clinical Hypertension*, *16*(1), 14–26.
Wei, X., Huang, H., Wu, P., Cao, H., & Ye, W. (2004). Phenolic constituents from *Mikania micrantha*. *Biochemical Systematics and Ecology*, *32*(11), 1091–1096.
WHO. (2016). Cardiovascular Diseases (CVDs). Retrieved February 3, 2017, from http://www.who.int/mediacentre/factsheets/fs317/en/
WHO. (2017a). Global health observatory data: raised blood pressure. Retrieved December 13, 2017, from http://www.who.int/gho/ncd/risk_factors/blood_pressure_prevalence_text/en/

WHO. (2017b). Global health observatory data: raised cholesterol. Retrieved September 28, 2017, from http://www.who.int/gho/ncd/risk_factors/cholesterol_text/en/

Wu, Y., Zhang, R., & Zhangli, H. (2005). Study on the immunological activity of the secondary metabolite in *Mikania micrantha*. *Natural Product Research and Development*, *17*(3), 313–315.

Xie, Y., & Zhang, W. (2012). Antihypertensive activity of *Rosa rugosa* Thunb. flowers: Angiotensin I converting enzyme inhibitor. *Journal of Ethnopharmacology*, *144*(3), 562–566.

Xu, D. P., Li, Y., Meng, X., Zhou, T., Zhou, Y., Zheng, J., … Li, H. Bin. (2017). Natural antioxidants in foods and medicinal plants: Extraction, assessment and resources. *International Journal of Molecular Sciences*, *18*(1), 20–31.

Xu, Q., Xie, H., Xiao, H., & Wei, X. (2013). Phenolic constituents from the roots of *Mikania micrantha* and their allelopathic effects. *Journal of Agricultural and Food Chemistry*, *61*(30), 7309–7314.

Xu, S., Ogura, S., Chen, J., Little, P. J., Moss, J., & Liu, P. (2013). LOX-1 in atherosclerosis: Biological functions and pharmacological modifiers. *Cellular and Molecular Life Sciences*, *70*(16), 2859–2872.

Yang, J., Chen, C., Zhao, S., Ge, F., & Liu, D. (2014). Effect of solvents on the antioxidant activity of walnut (*Juglans regia* L.) shell extracts. *Journal of Food and Nutrition Research*, *2*(9), 621–626.

Yang, Y. K., Wang, L. P., Chen, L., Yao, X. P., Yang, K. Q., Gao, L. G., & Zhou, X. L. (2015). Coenzyme Q10 treatment of cardiovascular disorders of ageing including heart failure, hypertension and endothelial dysfunction. *Clinica Chimica Acta*, *450*, 83–89.

Yoshikawa, M., Shimoda, H., Nishida, N., & Takada, M. (2002). *Salacia reticulata* and its polyphenolic constituents with lipase inhibitory and lipolytic activities have mild antiobesity effects in rats. *The Journal of Nutrition*, *132*(7), 1819–1824.

Zerbinati, C., & Iuliano, L. (2017). Cholesterol and related sterols autoxidation. *Free Radical Biology and Medicine*, *111*, 151–155.

Zhang, M., Ling, B., Chen, S., Liang, G., & Pang, X. (2004). Repellent and oviposition deterrent activities of the essential oil from *Mikania micrantha* and its compounds on *Plutella xylostella*. *Insect Science*, *11*(1), 37–45.

Zhang, Q. (2015). Effects of extraction solvents on phytochemicals and antioxidant activities of Walnut (*Juglans regia* L.) green husk extracts. *European Journal of Food Science and Technology*, *3*(5), 15–21.