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CHEMICAL PROFILING OF Cosmos caudatus Kunth POSSESSING ANTIOXIDANT AND α-GLUCOSIDASE INHIBITORY ACTIVITY

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By

WAN NADILAH ADIBAH W. AHMAD

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

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Chairman : Professor Khozirah Shaari, PhD
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Herbs and medicinal plants are major ingredients in traditional medicine systems or folk medicines for many countries of the world, including Malaysia. The present study aimed to evaluate their antioxidant and antidiabetic potential of some herbs used in Malaysia, and to select the most bioactive amongst the tested plants for further metabolomics study towards identifying their bioactive metabolites. The aqueous ethanolic extracts of five medicinal plant species, i.e *Cosmos caudatus*, *Leucaena leucocephala*, *Momordica charantia*, *Pereskia bleo* and *Averrhoa bilimbi* were assayed using DPPH radical scavenging activity, α-glucosidase inhibitory activity and total phenolic contents. *C. caudatus* gave the highest DPPH radical scavenging activity with IC_{50} value of 272.46 ± 8.98 µg/mL, and the highest total phenolic content with a value of 0.263 ± 0.02 g GAE/g DW. Meanwhile, the most potent α-glucosidase inhibitory activity was demonstrated also by the leaves of *C. caudatus* with IC_{50} of 21.90 ± 3.60 µg/mL, followed by *L. leucocephala* with IC_{50} value of 30.80 ± 2.50 µg/mL. The inhibitions were significantly more potent than the positive control, quercetin, with IC_{50} value of 109.30 ± 4.30 µg/mL. Based on these properties, *C. caudatus* was selected for further investigation in which the (i) influence of varying the polarity of the extraction solvents, and the (ii) harvesting age of the cultivated herb were correlated to its biological activities (DPPH free radical scavenging and α-glucosidase inhibition activity). An NMR-based metabolomics approach in combination with multivariate data analysis (MVDA) were used to analyse the correlation, while identification of the bioactive metabolites utilized both 2D NMR spectroscopy and LCMS/MS profiling.

An EtOH:water (80:20) solvent system was found to be the more preferred extraction solvent for obtaining *C. caudatus* with significant biological activities. The DPPH free radical scavenging (235.11 ± 29.92 µg/mL), α-glucosidase inhibitory activity (39.18 ± 5.80 µg/mL), and the total phenolic content (0.79 ± 0.09 g GAE/g) of the EtOH:water (80:20) extract were the highest among the *C. caudatus* leaf extracts. Based on the correlations observed in the NMR metabolomics and detailed NMR spectroscopy and LCMS analysis, were shown to comprise of quercetin derivatives (rutin, quercetin 3-

O-glucoside, quercetin 3-*O*-xyloside, quercetin 3-*O*-arabinofuranoside and quercetin 3-*O*-rhamnoside). Meanwhile fatty acid, chlorogenic acid, proline, acetic acid and catechin were the main metabolites present in other, less bioactive *C. caudatus* leaf extracts.

The investigation on how age affected the biological activity of the plant, *C. caudatus* harvested at different stages of growth, spanning from the 6th to the 14th weeks after planting were subjected to the metabolomics study. The results showed that the best quality of plant material, based on biological activities and total phenolic content, was after 10 weeks of growth. Cluster analysis, using PCA, of the EtOH:water (80:20) extracts prepared from various ages of *C. caudatus*, separated the 10, 12 and 14 weeks samples from the younger 6 and 8 weeks samples by PC1. Meanwhile, an analysis using PLS, showed strong correlation between 10, 12 and 14 weeks old samples with the and DPPH free radical scavenging and α-glucosidase inhibition activities, as well as the phenolic contents, which formed the basis of the conclusion that the best quality *C. caudatus* material is obtainable after 10 weeks of growth. The differentiating factors of the discriminative analysis were the chemical shifts for quercetin derivatives and rutin, which were found to be higher in the 10, 12 and 14 weeks old samples. This was further supported by the relative quantification of the metabolites, where higher concentrations of quercetin derivatives including rutin were detected in the 10 weeks old plants, while the levels were observed to decrease as the plant aged to the 12nd and up to the 14th weeks. Relatively lower concentrations were reported for other components such as fatty acid, chlorogenic acid, proline, acetic acid and catechin. Further support for the identification of bioactive metabolites was obtained using LCMS analysis.

For the analysis, the EtOH:water (80:20) leaf extract was first solvent partitioned and tested for bioactivity. The EtOAc and BuOH fractions of the *C. caudatus* extract showed the highest bioactivities with TPC (0.72 g GAE/g DW and 0.60 g GAE/g DW), DPPH radical scavenging activity (255.20 µg/mL and 257.61 µg/mL) and α-glucosidase inhibitory activity (40.90 µg/mL and 74.84 µg/mL), respectively. Both fractions were found to be bioactive and further metabolite profiling using LCMS/MS revealed the presence of six phenolic compounds were detected in EtOAc fraction i.e rutin, quercetin 3-*O*-galactoside, quercetin 3-*O*-glucoside, quercetin 3-*O*-xyloside, quercetin 3-*O*-arabinofuranoside and quercetin 3-*O*-rhamnoside. The same metabolites, except for quercetin 3-*O*-galactoside, were also detected in the BuOH fraction. It's showed that the flavonoids glycosides were the responsible compounds that contribute to the free radical scavenging and lowering the glucose effects of *C. caudatus* leaves. Interestingly, in the present study, quercetin 3-*O*-xyloside in *C. caudatus* extracts was reported for the first time.

On the overall, the results of the current study showed that the EtOH:water (80:20) are the best extraction solvent system for obtaining *C. caudatus* with significant biological activities. Meanwhile, the 10th weeks old plant (before the flowering stage) was the best harvesting age to yield potentially valuable of antioxidant and α-glucosidase inhibitory activities in *C. caudatus*. Hence, this plant can be suggested as a potential natural source of antioxidant and antidiabetic compounds for the prevention or the treatment of diabetes and its complications. However, the use of this plant as an alternative remedy for diabetes requires more extensive studies and isolation of the bioactive compounds and its safety and efficacy evaluation on human subjects.

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

PROFIL KIMIA BAGI *Cosmos caudatus* Kunth YANG MENGANDUNGI ANTIOKSIDAN DAN AKTIVITI PERENCATAN α-GLUKOSIDASE

Oleh

WAN NADILAH ADIBAH W. AHMAD

Julai 2017

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Herba-herba dan tumbuh-tumbuhan berubat adalah perkara utama di dalam sistem perubatan tradisional atau perubatan setempat bagi banyak negara di dunia, termasuk Malaysia. Kajian ini dijalankan untuk menentukan potensi antioksidan dan antidiabetik beberapa herba di Malaysia. Seterusnya kajian diteruskan menggunakan pendekatan metabolomik untuk menentukan metabolit bioaktif yang terdapat pada tumbuhan tersebut. Lima ekstrak akueus etanol tumbuhan berubat iaitu *Cosmos caudatus*, *Leucaena leucocephala*, *Momordica charantia*, *Pereskia bleo* dan *Averrhoa bilimbi* telah diuji dengan aktiviti perencatan radikal DPPH, α-glukosidase aktiviti dan jumlah kandungan fenolik. *C. caudatus* memberi nilai perencatan radikal DPPH tertinggi dengan nilai IC_{50} sebanyak 272.46 ± 8.98 µg/mL, dan jumlah kandungan fenolik tertinggi iaitu 0.263 ± 0.02 g GAE/g DW. Sementara itu, perencatan aktiviti α-glukosidase paling berkesan turut dilaporkan di dalam daun *C. caudatus* dengan nilai IC_{50} sebanyak 21.90 ± 3.60 µg/mL, diikuti dengan *L. leucocephala* dengan nilai IC_{50} sebanyak 30.80 ± 2.50 µg/mL. Perencatan ini adalah ketara lebih berkesan berbanding kawalan positif, kuersetin iaitu mencatat nilai IC_{50} sebanyak IC_{50} 109.30 ± 4.30 µg/mL. Berdasarkan ciri-ciri ini, *C. caudatus* telah dipilih untuk meneruskan kajian menerusi (i) kesan pelarut pengekstrakan yang berbeza polariti dan (ii) umur penuaian tumbuhan yang ditanam yang telah dikaitkan dengan aktiviti-aktiviti biologi (perencatan α-glukosidase dan perencatan radikal DPPH). Pendekatan metabolomik berasaskan NMR yang digabungkan dengan analisis data multivariat (MVDA) telah digunakan untuk menganalisis korelasi, sementara pengenalpastian metabolit bioaktif telah menggunakan kedua-dua spektroskopi 2D NMR dan pemprofilan menggunakan LCMS/MS.

Sistem pelarut EtOH:air (80:20) merupakan pelarut pengekstrakan yang telah dipilih kerana keupayaannya untuk mendapatkan *C. caudatus* dengan aktiviti-aktiviti biologi yang ketara. Aktiviti perencatan radikal bebas DPPH (235.11 ± 29.92 µg/mL) and jumlah kandungan fenolik (0.79 ± 0.09 g GAE/g) serta aktiviti perencatan α-glukosidase (39.18 ± 5.80 µg/mL) daripada ekstrak EtOH:air (80:20) adalah tertinggi di kalangan ekstrak-ekstrak daun *C. caudatus*. Berdasarkan korelasi yang diperhatikan

dalam NMR metabolomik dan analisis LCMS yang lebih terperinci, menunjukkan ianya terdiri daripada derivatif kuersetin (rutin, kuersetin 3-*O*-glukosida, kuersetin 3-*O*-xilosida, kuersetin 3-*O*-arabinofuranosida dan kuersetin 3-*O*-rhamnosida). Sementara itu asid lemak, asid klorogenik, prolin, asid asetik dan katekin adalah metabolit utama di dalam ekstrak-ekstrak lain daun *C. caudatus* yang kurang aktif.

Kajian untuk menunjukkan bagaimana umur memberi kesan kepada aktiviti biologi sesuatu tumbuhan telah dilakukan dengan menuai *C. caudatus* pada peringkat pertumbuhan yang berbeza, bermula dari minggu ke-6 sehingga minggu ke-14 selepas penanaman tumbuhan tersebut, kemudian diteruskan untuk kajian metabolomik terhadapnya. Hasil kajian menunjukkan kualiti yang terbaik pada tumbuhan, berdasarkan aktiviti-aktiviti biologi dan jumlah kandungan fenolik, adalah selepas minggu ke-10 penanaman. Analisis kelompok menggunakan PCA, menunjukkan ekstrak EtOH:air (80:20) daripada tumbuhan *C. caudatus* yang dituai daripada pelbagai umur, menunjukkan minggu ke-10, 12 dan 14 terasing daripada sampel-sample minggu ke-6 dan 8 menerusi PC1. Sementara itu, analisis menggunakan PLS menunjukkan korelasi yang kuat di antara minggu ke-10, 12 dan 14 dengan perencatan radikal bebas DPPH dan perencatan α-glukosidase, begitu juga dengan kandungan fenolik, yang menjadi asas kesimpulan iaitu kualiti terbaik adalah *C. caudatus* yang dituai adalah selepas 10 minggu pertumbuhan. Faktor-faktor yang membezakan analisis diskriminatif adalah anjakan kimia bagi derivatif kuersetin termasuk rutin, yang didapati lebih tinggi dalam sampel yang dituai pada minggu ke-10, 12 dan 14. Ini turut disokong oleh kuantifikasi relatif metabolit, di mana kepekatan yang lebih tinggi dikesan di dalam derivatif kuersetin termasuk rutin pada minggu ke-10, manakala mengalami pengurangan pada minggu ke-12 sehingga minggu ke-14. Kepekatan yang agak rendah dikesan bagi komponen lain seperti asid lemak, asid klorogenik, prolin, asid asetik dan katekin. Sokongan lanjut untuk mengenalpasti metabolit bioaktif telah diperolehi dengan menggunakan analisis LCMS. Untuk analisis, ekstrak EtOH:air (80:20) adalah pelarut pertama yang diuji untuk bioaktiviti. Kedua-dua pecahan EtOAc dan butanol mengandungi bioaktif dan kajian lanjut untuk profil metabolit menggunakan LCMS/MS menunjukkan kehadiran enam sebatian fenolik iaitu rutin, kuersetin 3-*O*-galaktosida, kuersetin 3-*O*-glukosida, kuersetin 3-*O*-xilosida, kuersetin 3-*O*-arabinofuranosida dan kuersetin 3-*O*-rhamnosida. Metabolit yang sama kecuali kuersetin 3-*O*-galaktosida turut dikesan di dalam pecahan pelarut BuOH. Ini menunjukkan glikosida flavonoid adalah sebatian yang menyumbang kepada perencatan radikal bebas dan merendahkan kandungan glukos. Lebih menarik, kuersetin 3-*O*-xilosida dalam ekstrak *C. caudatus* kajian ini adalah pertama kali dilaporkan.

Secara keseluruhannya, keputusan hasil kajian ini menunjukkan EtOH:air (80:20) adalah sistem pengekstrakan pelarut terbaik untuk mendapatkan *C. caudatus* dengan aktiviti-aktiviti biologi yang ketara. Manakala, minggu ke-10 (sebelum peringkat berbunga) adalah umur terbaik untuk dituai untuk mendapatkan potensi antioksidan dan perencatan α-glukosidase yang bernilai di dalam tumbuhan *C. caudatus.* Maka, tumbuhan ini boleh dicadangkan sebagai sumber semulajadi untuk antioksidan dan antidiabetik untuk langkah pencegahan atau rawatan diabetis dan kesan-kesannya. Bagaimanapun, penggunaan tumbuhan ini sebagai rawatan alternatif untuk diabetis memerlukan kajian lanjut dan pengasingan sebatian bioaktif untuk keselamatan dan penilaian ke atas manusia perlu dilakukan.

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

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^{1}H NMR	Proton Nuclear Magnetic Resonance
PCA	Principal Component Analysis
PLS-DA	Partial Least Square Discriminant Analysis
OPLS-DA	Orthogonal Least Square Discriminant Analysis
PC	Principal Component
SIMCA	Soft Independent Modelling of Class Analogy
TPC	Total Phenolic Content
d	Doublet
MVDA	Multivariate Data Analysis
LCMS	Liquid Chromatography Mass Spectroscopy
GAE	Gallic Acid Equivalent
HMBC	Heteronuclear Multiple Bond Correlation
HSQC	Heteronuclear Single Quantum Coherence
DPPH	Dipenylpicylhydrazyl
Hz	Hertz
MHz	MegaHertz
m/z	Mass to charge
ppm	Part per million
IC_{50}	Inhibition concentration at 50 percent
UV	Ultraviolet
VIP	Variable Important in the Projection
J	Coupling constant in Hz
DW	Dry weight
MeOH	Methanol
EtOH	Ethanol
BuOH	Butanol
EtOAc	Ethyl acetate
δ	Chemical shift in ppm
°C	Degree in Celsius
m	Multiplet
s	Singlet
dd	Doublet of doublet
DM	Diabetes mellitus
ANOVA	Analysis of Variance
PNPG	p-nitrophenyl-α-D-glucopyranose
NaOD	Sodium Deuterium Oxide
D_2O	Deuterium Oxide
CD_3OD	Methanol-d_4
KH_2PO_4	Potassium Dihydrogen Phosphate
CH_3OH-d_4	Deuterated Methanol-d_4
USDA	United State America
IDF	International Diabetes Federation
WHO	World Health Organization
MOH	Ministry of Health Malaysia

CHAPTER 1

INTRODUCTION

Diabetes mellitus (DM) is a serious, debilitating disease that has become an increasing health burden to most of its sufferers. This metabolic disorder is characterized by loss of glucose homeostasis with disturbances of carbohydrate, fats and protein metabolism resulting from defects in insulin secretion, insulin action or both (WHO, 1999; Pietropolo, 2001; DeFronzo, 2004). Without having enough insulin, body tissues, particularly the liver, muscle and adipose tissues, fail to take and utilize glucose for blood circulation. Subsequently, this could increase the blood glucose level, a condition known as hyperglycaemia. If the blood glucose level remains high for long periods of time, it could damage the organs in our body such as the kidneys, eyes, nerves, heart and blood vessels. Complications arising from such organ failures could also lead to death (Brownlee, 2001; Weiss and Sumpio, 2006).

According to the International Diabetes Federation (IDF) (2011), about 366 million people worldwide, had diabetes. This number is expected to rise to 522 million by 2030. The present trend indicated that more than 60% of the world's diabetic population will be from Asia (Yang *et al.*, 2010). In Malaysia alone, an alarming 3.6 million adults of greater than 18 years old, were estimated to be affected by diabetes (The Star, 2013). About 2 100 patients were diagnosed in the year 2000 and this number had increased to 4 000 in 2012. A National Health and Morbidity Survey indicated that the prevalence of diabetes among adults has increased from 11.6% in 2006 to 15.2% in 2011. The diabetes clinical audit also showed that the usage of α-glucosidase inhibitors as a method of treatment has increased, with 4.7%, 5.9% and 6.5% for 2009, 2010 and 2011, respectively (Ministry of Health Malaysia, 2012).

Two forms of DM are recognized, namely Type 1 and Type 2 DM. Type 1 insulin-dependent diabetes mellitus (T1DM), which accounted for 5 - 10% of the total number of diabetes patients, is a condition in which the body does not produce any insulin, mostly occurring in children and young adults. People with T1DM must take insulin injection daily to survive. Type 2 non-insulin dependent diabetes mellitus (T2DM) is the most common type of diabetes, accounting for 90 - 95% of cases. This type of DM occurs when the body does not produce enough insulin, or is unable to use the insulin. The main cause of T2DM is diet mismanagement, usually involving high contents of sugar (Li *et al.*, 2008). Therefore, people with T2DM can sometimes manage their condition with lifestyle measures alone, but oral drugs are often required, and less frequently insulin, in order to achieve good metabolic control (Bailey, 2000).

Despite the vast understanding of its epidemiology, there are no effective therapies to cure diabetes (Maiti *et al.*, 2004) and a define solution for its prevention and causes are still not forthcoming (Zhang *et al.*, 2008). Acarbose, miglitol, voglibose and nateglinide are drugs used alone or together with insulin to treat this disease. Unfortunately, these medications can cause side effects and high secondary failure rates (Bailey, 2000; Erasto *et al.,* 2005; Dey *et al.*, 2007). Furthermore, due to their high costs, these drugs cannot be afforded by a majority of people living in the rural communities of developing countries such as South Africa (Bailey, 2000). This failure leads to a greater demand for alternative therapies, particularly safer and more effective antidiabetic agents. Many studies have focused on the exploration of herbal remedies as treatment of DM, since this natural method of treatment promises lesser side effects and lower costs than using modern, synthetic drugs (Pushparaj *et al.*, 2000; Gupta *et al.*, 2005; Kim *et al.*, 2005; Sohn *et al.*, 2010; Petchi *et al.*, 2014).

Metabolomics is an approach used for the qualitative and quantitative analysis of all metabolites of the living organism (Fiehn, 2002). Metabolomics utilizes advanced and data rich analytical tools such as Nuclear Magnetic Resonance (NMR)-Spectroscopy and Liquid Chromatography-Mass Spectrometry (LCMS), combined with multivariate data analysis (MVDA). Between these two instrumental platforms, NMR is the preferable choice in non-targeted plant metabolomics study because it is robust, rapid, has high reproducibility and is capable of classifying the plants according to their total chemical composition (Bailey *et al.*, 2002; Defernez and Colquhoun, 2003; Wang *et al.*, 2004; Choi *et al.*, 2006; Verpoorte *et al.*, 2007; Son *et al.*, 2008; 2009; Georgiev *et al.*, 2011). Research involving metabolomics has been published as early as in the 1970s, for example the research by Devaux *et al.* (1971), and Horning and Horning (1970; 1971a; 1971b). Among the many examples of its application, metabolomics has been successfully used to monitor plant metabolic changes due to external factors such as harvesting time, seasons, handling and storage (Abdel-Farid *et al.*, 2007; Shuib *et al.*, 2011).

In a typical plant metabolomics study, the NMR spectral pattern and intensity of the plant metabolome are recorded, and then statistically compared. Their features were compared and analysed for the relevant spectral characteristics that discriminate sample classes. Identification technique usually involved unsupervised clustering (Principal Component Analysis or PCA), or supervised classification (Partial Least Square Discriminant Analysis or PLS-DA and Orthogonal Partial Least Square Discriminant Analysis or OPLS-DA) (Cozzolino *et al.*, 2011; Lee *et al.*, 2011). Subsequent identification of the plant's marker metabolites is further established via LCMS, often combined, when necessary, with chromatographic separation and structural elucidation by 1D and 2D NMR spectroscopy.

The use of α-glucosidase inhibitors is a therapeutic approach to reduce postprandial hyperglycaemia in diabetic patients. It works by retarding the absorption of carbohydrate and glucose (Ortiz-Andrade *et al.*, 2007). The α-glucosidase enzyme is located in the brush border membrane of the small intestine. Its function is to break down carbohydrates to form the more absorbable monosaccharides. Alpha-glucosidase inhibitors delay and reduce the postprandial glucose and insulin levels (Stuart *et al.*, 2004). Thus, inhibition of carbohydrate-hydrolyzing enzyme using α-glucosidase inhibitors is a plausible pathway to combat DM (Krentz and Bailey, 2005; Jong-Anurakkun *et al.*, 2007; Bhandari *et al.*, 2008). In recent years, there have been numerous investigations carried out on the α-glucosidase inhibitory activity of various plant extracts in the hope of discovering new or more potent α-glucosidase inhibitors (Abesundara *et al.*, 2004; Yuhao *et al.*, 2005; Önal *et al.*, 2005).

More than 1 000 plants have been claimed to be used as an alternative treatment for diabetes ever since the first medical text was reported on DM over 2000 years ago (Teschke and Eickhoff, 2015). However, only a small fraction of these valuable plants have received adequate scientific scrutiny (Eidi *et al.*, 2005). This is rather ironic since about 80% of the world population is using herbal medicines as part of their primary healthcare, as estimated by the World Health Organization (Cragg *et al.*, 1999; Narins, 2000). In the United States, approximately 20% of the population have been reported to use herbal products, in one form or another (Bent, 2008). Malaysia is also one of many countries that favour the use of herbal medicine for primary healthcare. This dependence on plants for medicinal applications is not surprising since Malaysia's biodiversity is the twelfth largest in the world, with about 12 000 flowering plants reported to have potential health promoting properties (Noridayu *et al.,* 2011). From these, only 1 300 species have been properly identified for medicinal purposes (Jamal *et al.,* 2010). Although knowledge on the chemical constituents of these plants are increasing, information on the mode of action and clinical pharmacology of the bioactive principles are still limited or non-existent, which limits practical efforts in their proper standardization, evaluation and further utilization (Ma *et al.*, 2008). Examples of tropical plants that are traditionally used for treating diabetes by Malaysian traditional healers and herbalist include *Averrhoa bilimbi* L. (belimbing buluh), *Leucaeana leucocephala* (petai belalang), *Momordica charantia* (peria katak), *Pereskia bleo* (jarum tujuh bilah) and *Cosmos caudatus* (ulam raja), among many others. Despite their popular use as herbal remedies for DM, the effects of *A. bilimbi*, *L. leucocephala*, *M. charantia*, *P. bleo* and *C. caudatus* on α-glucosidase are still not known or fully understood. The plants should thus be re-evaluated for possible inhibitory action on the enzyme glucose degrading enzyme. Once this information is established, studies may then be carried out to obtain a better understanding of their potential as therapeutic modalities for DM.

Among the five herbs, mentioned in the previous paragraph, *C. caudatus* Kunth (Asteracecae) is an interesting and popular medicinal plant in Southeast Asian countries, particularly Indonesia and Malaysia. In Malaysia, the plant is a popular vegetable known as "*ulam raja*" and is recommended for use against diabetes, high blood pressure, arthritis and fever (Burkill, 1966; Abas *et al.,* 2003; Rasdi *et al.*, 2010) as well as for several other health uses such as longevity and aiding digestion (Ong and Norzalina, 1999; Bunawan *et al.*, 2014). It has also been reported to have excellent antioxidant properties (Shui *et al.*, 2005). The major chemical constituents of *C. caudatus* have been investigated and reported in the scientific literature. Some compounds, for example the phenolics, have been shown to exert antioxidant and antidiabetic activities (Kerem *et al.,* 2006; Mai *et al.*, 2007; Ranilla *et al.,* 2010; Kunyanga *et al.,* 2012). Although, there have been various studies on the antidiabetic and antioxidant activities of *C. caudatus*, more studies that can help to further understand the therapeutic value of the plant would still be beneficial.

An area of particular importance for the plantation crop and herbal industries alike, are the influence of a crop's age on the potency of a particular property or bioactivity, and what are the responsible or contributing chemical constituents. For the herbal industry in particular, these aspects are very important in standardization and quality control of the herbal produce, either in the upstream or the downstream stages. For example, the choice of solvent is an important aspect to consider in ensuring plant extracts of certain chemical quality and biological activity. Solubility of the different classes of chemical constituents in the plant metabolome would also vary based on the polarity of the extracting solvent. To ensure that the plant's natural therapeutic value is not lost, it is important to determine the best solvent for the optimum extraction of the bioactive chemical constituents of the plant. Another crucial factor in assuring the potency of the biological or pharmacological effect of the final plant extract is the harvesting age. This is due to the fact that different metabolites are biosynthesized and may be present at different ages of the plant's growth.

Therefore, with the above scenario as a background, the present study aims to evaluate the antioxidant (DPPH free radical scavenging activity) and α-glucosidase inhibitory activity as well as total phenolic content of the highlighted herbs. Once their bioactivities are established, the herb showing the highest bioactivity, specifically the DPPH free radical scavenging activity and α-glucosidase inhibitory activity, will be selected for further study to, first, understand the influence of solvent polarity on the bioactivity, and then, to identify the potentially bioactive constituents through the use of NMR spectroscopy and tandem mass spectrometry (LCMS^n). Then, the influence of variation on different harvesting ages was carried out. An NMR-based metabolomics approach will be adopted so as to obtain a more holistic view of the changes in the metabolite profiles due to difference in choice of extracting solvents, and harvesting age.

Thus, the four objectives of the study are:

1. to determine the total phenolic content, DPPH free radical scavenging activity and α-glucosidase inhibitory activity of ethanolic extracts of *Cosmos caudatus*, *Leucaena leucocephala*, *Momordica charantia*, *Pereskia bleo* and *Averrhoa bilimbi.*
   (Note: In the screen, *C. caudatus* was identified as having the strongest bioactivity and was thus selected for further study).

2. to determine the best solvent for optimal extraction of bioactive metabolites of *C. caudatus*. Selection of solvent systems for evaluation, include 100% EtOH, a series of EtOH:water systems (i.e 80:20, 60:40, 40:60, 20:80) and 100% water.

3. to determine the best harvesting age for *C. caudatus* on the basis of its bioactive metabolite composition identified. Selection of harvesting age for analysis, include 6, 8, 10, 12 and 14 weeks.

4. to identify the chemical constituents of *C. caudatus* which are responsible and/or contributed to the antioxidant and α-glucosidase inhibitory activities.

REFERENCES

Abas, F., Shaari, K., Lajis, N. H., Israf, D. A. and Kalsom, Y. U. (2003). Antioxidative and radical scavenging properties of the constituents isolated from *Cosmos caudatus* Kunth. *Natural Product Sciences*, 9 (4), 245-248.

Abas, F., Lajis, N. H., Israf, D. A, Shaari, K. and Kalsom, Y. U. (2006). Antioxidant and nitric oxide inhibition activities of selected Malay traditional vegetables. *Food Chemistry*, 95, 566-573.

Abdel-Farid, I. B., Hye, K. K., Young, H. C. and Verpoorte, R. (2007). Metabolic characterization of *Brassica rapa* leaves by NMR spectroscopy. *Journal of Agricultural and Food Chemistry*, 55 (19), 7936-7943.

Abdille, M. H., Singh, R. P., Jayaprakasa, G. K. and Jens, B. S. (2005). Antioxidant activity of the extracts from *Dillenia indica* fruits. *Food Chemistry*, 90, 891-896.

Ablat, A., Mohamad, J., Awang, K., Jamil, A., Shilpi and Arya, A. (2014). Evaluation of antidiabetic and antioxidant properties of *Brucea javanica* seed. *The Scientific World Journal*, 786130, 2-10.

Abesundara, K. J., Matisui, T. and Matsumoto, K. (2004). Alpha-glucosidase inhibitory activity of some Sri Lanka plant extracts, one of which, *Cassia auriculata*, exerts a strong antihyperglycemic effects in rats comparable to therapeutic drug acarbose. *Journal of Agricultural and Food Chemistry*, 52, 2541-2545.

Adewole, S. O., Caxton-Martins, E. A. and Ojewole, J. A. O. (2006). Protective effect of quercetin on the morphology of pancreatic β-cells of streptozotocin-treated diabetic rats. *African Journal of Traditional, Complementary and Alternative Medicine*, 4, 64-74.

Ado, M. A., Abas, F., Ismail, I. S., Ghazali, H. M. and Shaari, K. (2014). Chemical profile and antiacetylcholinesterase, antityrosinase, antioxidant and α-glucosidase inhibitory activity of *Cynometra cauliflora* L. leaves. *Journal of the Science of Food and Agriculture*, 95 (3), 635-642.

Ahmed, I., Lakhani, M. S., Gillett, M., John, A. and Raza, H. (2001). Hypotriglyceridemic and hypocholesterolemic effects of anti-diabetic *Momordica charantia* (karela) fruit extract in streptozotocin-induced diabetic rats. *Diabetes Research and Clinical Practice*, 51, 155-161.

Akowuah, G. A., Ismail, Z., Norhayati, I. and Sadikun, A. (2005). The effects of different extraction solvents of varying polarities of polyphenols of *Orthosiphon stamineus* and evaluation of the free radical-scavenging activity. *Food Chemistry*, 93, 311-317.

Alexiou, P. and Demopoulus, V. J. (2010). Medicinal plants used for the treatment of diabetes and its long-term complications. *Plants in Traditional and Modern Medicine: Chemistry and Activity*, 69-175.

Ali, I., Azad Khan, A. and Hassan, Z. (1995). Characterization of the hypoglycaemic effects of *Trigonella foenum-graecum* seed. *Planta Medica*, 61, 358-360.

Ali, Z. M., Chin, L. -H. and Lazan, H. (2004). A comparative study on wall degrading enzymes, pectin modifications and softening during ripening of selected tropical fruits. *Plant Science*, 167 (2), 317–327.

Ali, K., Maltese F., Fortes A. M., Pais, M. S., Verpoorte, R. and Choi, Y.H. (2011). Pre-analytical for NMR-based grape metabolic fingerprinting and chemometrics. *Analytica Chimica Acta*, 703, 179-186.

Allwood, J. W., Ellis, D. I. and Goodacre, R. (2008). Metabolomic technologies and their application to the study of plants and plant-host interactions. *Physiologia Plantarum*, 132, 117-135.

Allwood, J. W. and Goodacre, R. (2010). An introduction to liquid chromatography-mass spectrometry instrumentation applied in plant metabolomics analyses. *Phytochemical Analysis,* 21, 33-47.

Almey, A. A., Ahmed Jalal Khan, C., Syed Zahir, I., Mustapha Suleiman, K., Aisyah, M. R. and Kamarul Rahim, K. (2010). Total phenolic content and primary antioxidant activity of ethanolic and ethanolic extracts of aromatic plants' leaves. *International Food Research Journal*, 17, 1077-1084.

Amalia, L., Anggadiredja, K., Sukrasno, I., Fidrianny and Inggriani, R. (2012). Antihypertensive potency of wild cosmos (*Cosmos caudatus* Kunth, asteraceae) leaf extract. *Journal of Pharmacology and Toxicology,* 7(8), 359-368.

Amrizal, M. (2002). Treatment cost of diabetes mellitus, preeclampsia and neonatal jaundice in HUSM, Kelantan. Community Medicine, Universiti Sains Malaysia. Master Dissertation.

Andarwulan, N., Batari, R., Sandrasari, D. A., Bolling, B. and Wijaya, H. (2010). Flavonoid content and antioxidant activity of vegetables from Indonesia. *Food Chemistry,* 121, 1231-1235.

Andarwulan, N., Kurniasih, D., Apriady, R. A., Rahmat, H., Roto, A. V. and Bolling, B. W. (2012). Polyphenols, carotenoids and ascorbic acid in underutilized medicinal vegetables. *Journal of Functional Foods,* 4, 339-347.

Andrade-Cetto, A., Becerra-Jiménez, J. and Cárdenas-Vázquez, R. (2008). Alfa-glucosidase -inhibiting activity of some Mexican plants used in the treatment of type 2 diabetes. *Journal of Ethnopharmacolgy,* 116, 27-32.

Ani, V. and Naidu, K. A. (2008). Antihyperglycemic activity of polyphenolic components of black/bitter cumin *Centratherum anthelminticum* (L.) Kuntze seeds. *European Food Research and Technology,* 226 (4), 897-903.

Anjaneyulu, M. and Chopra, K. (2004). Quercetin, an anti-oxidant bioflavonoid, attenuates diabetic nephropathy in rats. *Clinical and Experimental Pharmacology and Physiology,* 31, 244-248.

Anwar, F., Jamil, A., Iqbal, S. and Sheikh, M. A. (2006). Antioxidant activity of various plant extracts under ambient and accelerated storage of sunflower oil. *Grasas Aceites Sevilla,* 57, 189-197.

Apostolidis, E., Kwon, Y-I. and Shetty, K. (2007). Inhibitory potential of herb, fruit, and fungal-enriched cheese against key enzymes linked to type 2 diabetes and hypertension. *Innovative Food Science and Emerging Technologies,* 8, 46-54.

Art, I. C. and Hollman, P. C. (2005). Polyphenols and disease risk in epidemiologic studies. *The American Journal of Clinical Nutrition,* 81 (1), 317-325.

Asano, N. (2009). Sugar-mimicking glycosidase inhibitors: bioactivity and application. *Cellular and Molecular Life Sciences,* 66, 1479-1492.

Azura, N. A. Z. (2007). *Ulam Traditional Malaysia*. Retrieved 2014/9/23, from http://kebunwarisan.blogspot.com/2007/12/ulam-traditional-malaysia.html

Babish, J. G., Pacioretty, L. M., Bland, J. S., Minich, D. M., Hu, J. and Tripp, M. L. (2010). Antidiabetic screening of commercial botanical products in 3T3-L1 adipocytes and db/db mice. *Journal of Medical Foods*, 13, 535-547.

Bachok, M. F., Yusof, B. N. M., Ismail, A. and Hamid, A. A. (2014). Effectiveness of traditional Malaysian vegetables (ulam) in modulating blood glucose levels. *Asia Pacific of Journal Clinical Nutrition,* 23 (3), 369-376.

Bailey, C. J. (2000). Potential new treatments for type 2 diabetes. *Trends in Pharmacological Sciences,* 21 (7), 259-265.

Bailey, N. J. C., Sampson, P. J., Hylands, P. J., Nicholson, J. K. and Holmes, E. (2002). Multi-component metabolic classification of commercial feverfew preparations via high-field ^{1}H-NMR spectroscopy and chemometrics. *Planta Medica*, 68, 734-738.

Bailey, N. J., Oven, M., Holmes, E., Nicholson, J. K. and Zenk, M. H. (2003). Metabolomic analysis of the consequences of cadmium exposure in *Silene cucubalus* cell cultures via ^{1}H-NMR spectroscopy and chemometrics. *Phytochemistry,* 62, 851-858.

Bansal, P., Paul, P., Mudgal, J., Nayak, P. G., Panakal, S. T., Priyadarsini, K. I. And Unnikrishnan, M. K. (2012). Antidiabetic, antihyperlipidemic and antioxidant effects of the flavonoid rich fraction of *Pilea microphylla* (L.) in high fat diet/streptozotocin-induced diabetes in mice. *Experimental and Toxicologic Pathology,* 64 (6), 651-658.

Bent, S. (2008). Herbal medicine in the United States: Review of efficacy, safety, and regulation. *Journal of General Internal Medicine,* 23 (6), 854-859.

Bertram, H. C., Weisbjerg, M. R., Jensen, C. S., Pedersen, M. G., Didion, T., Petersen, B. O., Duus, J., Larsen, M.K. and Nielsen, J. H. (2010). Seasonal changes in the metabolic fingerprint of 21 grass and legume cultivars studied by nuclear magnetic resonance-based metabolomics. *Journal of Agricultural and Food Chemistry,* 58, 4336-4341.

Bhandari, M. R., Nilubon, J. A., Gao, H. and Kawabata, J. (2008). α-glucosidase and α-amylase inhibitory activities of Nepalese medicinal herb Pakhanbhed (*Bergenia ciliate* Haw.). *Food Chemistry,* 106, 247-252.

Boccard, J., Grata, E., Thiocone, A., Gauvrit, J. Y., Lantéri, P. and Carrupt, P. A. (2007). Multivariate data analysis of rapid LC-TOF/MS experiments from *Arabidopsis thaliana* stressed by wounding. *Chemometrics and Intelligent Laboratory Systems,* 86 (2), 189-197.

Bolling, B. W., Dolnikowski, G., Blumberg, J. B. and Chen, C. Y. (2010). Polyphenol content and antioxidant activity of California almonds depend on cultivar and harvest year. *Food Chemistry,* 122 (3), 819-825.

Bonoli, M., Verardo, V., Marconi, E. and Caboni, M. F. (2004). Antioxidant phenols in barley (*Hordeum vulgare* L.) flour: comparative spectrophotometric study among extraction methods of free and bound phenolic acids. *Journal of Agricultural and Food Chemistry,* 52, 5195-5200.

Bravo, L. (1998). Polyphenols: chemistry, dietary sources, metabolism, and nutritional significance. *Nutrition Reviews,* 56 (11), 317-33.

Bressler, R. and Johnson, D. (1992). New pharmacological approaches to therapy of NIDDM. *Diabetes Care,* 15, 792-805.

Brownlee, M. (2001). Biochemistry and molecular biology of diabetic complications. *Nature,* 414, 813-820.

Bunawan, H., Baharum, S. N., Bunawan, S. N., Amin, N. A. and Noor, N. M. (2014). *Cosmos caudatus* Kunth: A traditional medicinal herb. *Global Journal of Pharmacology,* 8 (3), 420-426.

Burkill, I. H. (1966). A Dictionary of the Economic Products of the Malay Peninsula, Vol. 1 and 2, Kuala Lumpur, Malaysia: Ministry of Agriculture Cooperative.

Cai, Y., Luo, Q., Sun, M. and Corke, H. (2004). Antioxidant activity and phenolic compounds of 112 Chinese medicinal plants associated with anticancer. *Life Sciences*, 74, 2157-2184.

Chatha, S. A. S., Anwar, F., Manzoor, M. and Bajwa, J. R. (2006). Evaluation of the antioxidant activity of rice bran extracts using different antioxidant assays. *Grasas Aceites Sevilla*, 57, 328-335.

Chaturvedi, P. (2012). Antidiabetic potentials of *Momordica charantia*: multiple mechanisms behind the effects. *Journal of Medicinal Food*, 15 (2), 101-107.

Chen, H., Qu, Z., Fu, L., Dong, P. and Zhang, X. (2009). Physicochemical properties and antioxidant capacity of 3 polysaccharides from green tea, oolong tea, and black tea. *Journal of Food Science*, 74 (6), 469-474.

Chen, H., Lu, X., Qu, Z., Wang, Z. and Zhang, L. (2010). Glycosidase inhibitory activity and antioxidant properties of a polysaccharide from the mushroom *Inonotus obliquus*. *Journal of Food Biochemistry*, 34 (1), 178-191.

Cheng, S. H., Ismail, A., Anthony, J., Ng, O. C., Hamid, A. A. and Barakatun-Nisak, M. Y. (2015). Eight Weeks of *Cosmos caudatus* (Ulam Raja) Supplementation Improves Glycemic Status in Patients with Type 2 Diabetes: A Randomized Controlled Trial. *Evidence-Based Complementary and Alternative Medicine*, 2015, 405615-405622.

Chiasson, J. L. and Rabasa-Lhoret, R. (2004). Prevention of type 2 diabetes: insulin resistance and beta-cell function. *Diabetes*, 53 (3), 34-38.

Chin, W. Y. (1992). A guide to medicinal plants. Singapore Science Centre, Singapore pp. 21.

Choi, H. K, Kim, K. H., Kim, Y. S., Lee, M. W. and Whang, W.K. (2006). Metabolomic differentiation of deer antlers of various origins by ^{1}H NMR spectrometry and principal components analysis. *Journal of Pharmaceutical and Biomedical Analysis*, 41 (3), 1047-1050.

Coen, M., Holmes, E., Lindon, J. C. and Nicholson, J. K. (2008). NMR based metabolic profiling and metabonomic approaches to problems in molecular toxicology. *Chemical Research in Toxicology*, 21 (1), 9-27.

Collins, R. A., Ng, T. B., Fong, W. P., Wan, C. C. and Yeung, H. W. (1997). Inhibition of glycohydrolase enzymes by aqueous extracts of Chinese medicinal herbs in a microplate format. *IUBMB Life*, 42 (6), 1163-1169.

Conforti, F., Statti, G. A. and Menichini, F. (2007). Chemical and biological variability of hot pepper fruits (*Capsicum annuum var. accuminatum* L.) in relation to maturity stage. *Food Chemistry*, 102 (4), 1096-1104.

Constantino, L., Rastelli, G. and Gamberini, M. C. (1999). 1-Benzopyran-4-one antioxidants and aldose reductase inhibitors. *Journal of Medicinal Chemistry*, 42 (11), 1881-1893.

Coskun, O., Kanter, M., Korkmaz, A. and Oter, S. (2005). Quercetin, a flavonoid antioxidant, prevents and protects streptozotocin-induced oxidative stress and β-cell damage in rat pancreas. *Pharmacological Research*, 51 (2), 117-123.

Cozzolino, D., Cynkar, W. U., Shah, N. and Smith, P. (2011). Multivariate data analysis applied to spectroscopy: Potential application to juice and fruit quality. *Food Research International*, 44 (7), 1888-1896.

Cragg, G. M., Boyd, M. R., Khanna, R., Kneller, R., Mays, T. D., Mazan, K. D., Newman, D. and Sausville, J. E. A. (1999). International collaboration in drug discovery and development: the NCI experience. *Pure and Applied Chemistry*, 71 (9), 1619-1633.

Crozier, A., Burns, J., Aziz, A. A., Stewart, A. J., Rabiasz, H. S. and Jenkins, G. I. (2000). Antioxidant flavonols from fruits, vegetables and beverages: Measurements and bioavailability. *Biological Research*, 33, 79-88.

Cutler, G. J., Nettleton, J. A., Ross, J. A., Harnack, L. J., Jacobs, D. R., Scrafford, C. G., Barraj, L. M., Mink, P. J. and Robien, K. (2008). Dietary flavonoid intake and risk of cancer in postmenopausal women: The Iowa Women's Health Study. *International Journal Cancer*, 123 (3), 664-671.

Dai, J. and Mumper, R. J. (2010). Plant phenolics: Extraction, analysis and their antioxidant and anticancer properties. *Molecules,* 15 (10), 7313-7352.

Dans, A. M. L., Villarruz, M. V. C., Jimeno, C. A., Javelosa, M. A. U., Chua, J. and Bautista, R. (2007). The effect of *Momordica charantia* capsule preparation on glycemic control in type 2 diabetes mellitus needs further studies. *Journal of Clinical Epidemiology,* 60 (6), 554-559.

De Moraes, S. L., Gregório, L. E., Tomaz, J. C. and Lopes, N. P. (2009). Rapid screening and identification of polar constituents from Brazilian Arnica *Lychnophora* sp. by LC-UV/DAD-ESI-MS and LC-UV/DAD-ESI-MS/MS analysis. *Chromatographia,* 69, 157-165.

De Souza Schmidt Goncalves, A. E., Lajolo, F. M. and Genovese, M. I. (2010). Chemical composition and antioxidant/antidiabetic potential of Brazilian native fruits and commercial frozen pulps. *Journal of Agricultural and Food Chemistry,* 58 (8), 4666-4674.

Defernez, M. and Colquhoun, I. J. (2003). Factors affecting the robustness of metabolite fingerprinting using ^{1}H NMR spectra. *Phytochemistry*, 62 (6), 1009-1017.

DeFronzo, R. A. (2004). Pathogenesis of type 2 diabetes mellitus. *Medical Clinics,* 88 (4), 787-835.

Dehghan, H., Sarrafi, Y. and Salehi, P. (2016). Antioxidant and antidiabetic activities of 11 herbal plants from Hyrcania region. *Iran Journal of Food and Drug Analysis,* 24, 179-188.

Dehghan-Kooshkghazi, M. and Mathers, J. C. (2004). Starch digestion, large-bowel fermentation and intestinal mucosal cell proliferation in rats treated with the α-glucosidase inhibitor acarbose. *British Journal of Nutrition,* 91, 357-365.

Deutschländer, M. S., Van de Venter, M., Roux, S., Louw, J. and Lall, N. (2009). Hypoglycaemic activity of four plant extracts traditionally used in South Africa for diabetes. *Journal of Ethnopharmacology,* 124 (3), 619-624.

Devaux, P. G., Horning, M. G. and Horning, E. C. (1971). Benzyloxime derivatives of steroids. A new metabolic profile procedure for human urinary steroids human urinary steroids. *Analytical Letters,* 4 (3), 151-160.

Dey, L., Anoja, M. D. and Attele, S. (2007). Alternative therapies for type 2 diabetes. *Alternative Medicinal Review,* 7, 56-57.

Dian-Nashiela, F., Noriham, A., Nooraain, H. and Azizah, A. H. (2015). Antioxidant activity of herbal tea prepared from *Cosmos caudatus* leaves at different maturity stages. *International Food Research Journal,* 22 (3), 251-264.

Do, Q. D., Angkawijaya, A. E., Tran-Nguyen, P. L., Huynh, L. H., Soetaredjo, F. E., Ismadji, S. and Yi-Hsu, J. (2014). Effect of extraction solvent on total phenol content, total flavonoid content, and antioxidant activity of *Limnophila aromatic. Journal of Food and Drug Analysis,* 22 (3), 296-302.

Domon, B. and Costello, C. E. (1988). A systematic nomenclature for carbohydrate fragmentations in FAB-MS/MS spectra of glycoconjugates. *Glycoconjugate Journal*, 5 (4), 397-409.

Du, W. Q., Shi, X. F. and Qiu, M. Y. (2005). Progress in treatment of diabetes drugs. *Chinese Pharmaceutical Journal*, 25, 67-69.

Dutta, A. K., Gope, P. S., Makhnoon, S., Siddiquee, M. A. and Kabir, Y. (2012). Effect of solvent extraction on phenolic content, antioxidant and α-amylase inhibition activities of *Swertia chirata*. *International Journal of Drug Development and Research,* 4 (4), 317-325.

Drazkiewicz, M. and Baszynski, T. (2005). Growth parameters and photosynthetic pigments in leaf segments of *Zea mays* exposed to cadmium, the related to protection mechanisms. *Journal of Plant Physiology*, 162, 1013-1021.

Eidi, M., Eidi, A. and Zamanizadeh, H. (2005). Effect of *Salvia officinalis* leaves on serum glucose and insulin in healthy and streptozotocin-induced diabetic rats. *Journal of Ethnopharmacology,* 100 (3), 310-313.

Erasto, P., Adebola, P. O., Grierson, D. S. and Afoloyan, A. J. (2005). An ethnobotanical study of plants used for the treatment of diabetes in the Eastern Cape Province, South Africa. *African Journal Biotechnology,* 4 (12), 1458-1460.

Erikkson, L., Johansson, E., Kettaneh-Wold, N., Wold, S., Trygg, J. and Wikstrom, C. (2006). Multi and Megavariate Data Analysis Part 1: Basic Principles and Applications (2nd edn). Umetrics Academy, Götoborg, Sweden, pp. 39-62.

Farnsworth, N. R. (1993). Biological approaches to the screening and evaluating of natural products. In: Rasoanaivo, P and Ratsimamanga-Urverg, S. (Eds.). Biological evaluation of plants with reference to the Malagasy flora, monograph from the IFS-NAPRECA Workshop on Bioassays, Madagaskar, pp. 25-43.

Fatimah, A. M. Z., Norazian, M. H. and Rashidi, O. (2012). Identification of carotenoid composition of selected 'ulam' or traditional vegetables in Malaysia. *International Food Research Journal*, 19 (2), 527-530.

Fatin, R. J, Wahab, R., Daud, J. M., Sudin, M., Rasat, M. S. and Sulaiman, O. (2012). Study on methanol extracts of *Nauclea subdita* (Korth) Steud. heartwood parts for the total phenolic contents and free radical scavenging activities. *Current Research Journal of Biological Sciences,* 4 (5), 600-607.

Fiehn, O., Kopka, J., Dörmann, P., Altmann, T., Trethewey, R. N. and Willmitzer, L. (2000). Metabolite profiling for plant functional genomics. *Nature Biotechnology,* 18, 1157-1161.

Fiehn, O. (2002). Metabolomics – the link between genotypes and phenotypes. *Plant Molecular Biology,* 48 (1), 155-171.

Flora of North America Editorial Committee, eds. (1993). Flora of North America North of Mexico. 16 vols. New York and Oxford.

Fuzzati, N., Sutarjadi, Dyatmiko, W., Rahman, A. and Hostettmann, K. (1995). Phenylpropane derivatives from roots of *Cosmos caudatus*. *Phytochemistry,* 39, 409-412.

Gao, X., Ohlander, M., Jeppsson, N., Björk, L. and Trajkovski, V. (2000). Changes in antioxidant effects and their relationship to phytonutrients in fruits of sea buckthorn (*Hippophae rhamnoides* L.) during maturation. *Journal of Agricultural and Food Chemistry,* 48 (5), 1485-1490.

Geleijnse, J. M., Launer, L. J., Hofman, A., Pols, H. A. and Witteman, J. C. (1999). Tea flavonoids may protect against atherosclerosis: The Rotterdam study. *Archives of Internal Medicine,* 159 (18), 2170-2174.

Georgiev, M. I., Ali, K., Alipieva, K., Verpoorte, R. and Choi, Y. H. (2011). Metabolic differentiations and classification of *Verbascum* species by NMR-based metabolomics. *Phytochemistry,* 72 (16), 2045-2051.

Gerich, J. E. (2003). Clinical significance, pathogenesis, and management of postprandial hyperglycemia. *Archives of Internal Medicine,* 163, 1306-1316.

Ghasemzadeh, A., Jaafar, H. Z. and Rahmat, A. (2010). Identification and concentration of some flavonoid components in Malaysian young ginger (*Zingiber officinale* Roscoe) varieties by a high performance liquid chromatography method. *Molecules*, 15 (9), 6231-6243.

Goh, S. H., Chuah, C. H., Mok, J. S. L. and Soepadmo, E. (1995). Malaysian medicinal plants for the treatment of cardiovascular disease. Pelanduk Publication, Malaysia, pp. 162.

Goh, K.L. (2000). Malaysian Herbaceous Plants Millennium. 1st Edn., Advanco Press, Malaysia.

Goodacre, R., Vaidyanathan, S., Dunn, W. B., Harrigan, G. G. and Kell, D. B. (2004). Metabolomics by numbers: Acquiring and understanding global metabolite data. *Trends Biotechnology*, 22, 245–252.

Groot, H. D. and Rauen, U. (1998). Tissue injury by reactive oxygen species and the protective effects of flavonoids. *Fundamental and Clinical Pharmacology*, 12 (3), 249-255.

Gruz, J., Ayaz, F. A., Torun, H. and Strnad, M. (2011). Phenolic acid content and radical scavenging activity of extracts from medlar (*Mespilus germanica* L.) fruit at different stages of ripening. *Food Chemistry*, 124 (1), 271-277.

Guanghou, S., Lai, P. L. and Shih, P. W. (2005). Rapid screening and characterisation of antioxidants of *Cosmos caudatus* using liquid chromatography coupled with mass spectrometry. *Journal of Chromatography*, 827, 127-138.

Guendouzi, A. and Mekelleche, S. M. (2012). Prediction of the melting points of fatty acids from computed molecular descriptors: A quantitative structure–property relationship study. *Chemistry and Physics of Lipids*, 165 (1), 1-6.

Gulfraz, M., Waheed, A., Mehmood, S. and Ihtisham, M (2006). Extraction and purification of various organic compounds in selected medicinal plants of Kotli Sattian, district Rawalpindi, Pakistan. *Ethnobotanical Leaflets*, 10, 13-23.

Gupta, R., Gabrielsen, B. and Ferguson, S. M. (2005). Nature's medicines: traditional knowledge and intellectual property management. Case studies from the National Institutes of Health (NIH), USA. *Current Drug Discovery Technologies*, 2 (4), 203-219.

Güçlü-Üstündağ, Ö. and Mazza, G. (2007). Saponins: properties, applications and processing. *Critical Reviews in Food Science and Nutrition*, 47 (3), 231-258.

Hagel, J. M. and Facchini, P. J. (2008). Plant metabolomics: analytical platforms and integration with functional genomics. *Phytochemistry Reviews*, 7 (3), 479-497.

Hanefeld, M., Fischer, S., Julius, U., Schulze, J., Schwanebeck, U., Schmechel, H., Ziegelasch, H. J. and Lindner, J. (1996). Risk factors for myocardial infarction and death in newly detected NIDDM: The Diabetes Intervention Study, 11-year follow-up. *Diabetologia*, 39 (12), 1577-1583.

Haraguchi, H., Saito, T., Ishikawa., Date, H., Kataoka, S., Tamura, Y. and Mizutani, K. (1996). Antiperoxidative components in *Thymus vulgaris. Planta Medicine*, 62, 217-221.

Hassan, S. A., Mijin, S., Yusoff, U. K., Ding, P. and Wahab, P. E. M. (2012). Nitrate, ascorbic acid, mineral and antioxidant activities of *Cosmos caudatus* in response to organic and mineral-based fertilizer rates. *Molecules*, 17 (7), 7843-7853.

Hassanbaglou, B., Hamid, A. A., Roheeyati, A. M., Saleh, N. M., Abdulamir, A., Khatib, A. and Sabu, M. C. (2012). Antioxidant activity of different extracts of leaves of *Pereskia bleo* (Cactaceae). *Journal of Medicinal Plants Research*, 6 (15), 2932-2937.

Hatipoğlu, G., Sökmen, M., Bektaş, E., Daferera, D., Sökmen, A., Demir, E. and Şahin, H. (2013). Automated and standard extraction of antioxidant phenolic compounds of *Hyssopus officinalis* L. ssp. angustifolius. *Industrial Crops and Products*, 43, 427-433.

Hayouni, A., Abedrabba, M., Bouix, M. and Hamdi, M. (2007). The effects of solvents and extraction method on the phenolic contents and biological activities in vitro of *Tunisian quercuscoccifera* L. and *Juniperusphoenicea* L. fruit extracts. *Food Chemistry*, 105 (3), 1126-1134.

Hertog, M. G., Sweetnam, P. M., Fehily, A. M., Elwood, P. C. and Kromhout, D. (1997) Antioxidant flavonols and ischemic heart disease in a Welsh population of men: The Caerphilly Study. *The American Journal of Clinical Nutrition*, 65 (5), 1489-1494.

Holmes, E., Nicholls, A. W. and Lindon, J. C. (2000). Chemometric models for toxicity classification based on NMR spectra of biofluids. *Chemical Research in Toxicology*, 13, 471-478.

Hong, Y. S., Bong-Kuk, K. O., Hyuk-Jin, A. H. N., van Den Berg, F. and Lee, C. H. (2009). Metabolomic insight into soy source through ^{1}H NMR spectroscopy. *Journal of Agricultural and Food Chemistry*, 57 (15), 6862-6870.

Horning, E. C. and Horning, M. G. (1970). Metabolic profile: chromatographic methods for isolation and characterization of a variety of metabolites in man. In: Olson, R.E. (Ed.), Methods in Medical Research. Year Book Medical Publishers, Chicago, pp. 369.

Horning, E. C. and Horning, M. G. (1971a). Human metabolic profiles obtained by GC and GC/MS. *Journal of Chromatographic Science*, 9, 129-140.

Horning, E. C. and Horning, M. G. (1971b). Metabolic profiles: gas-phase methods for analysis of metabolites. *Clinical Chemistry*, 17, 802-809.

Houshyani, B., Kabouw, P., Muth, D., De Vos, R. C. H., Bino, R. J. and Bouwmeester, H. J. (2012). Characterization of the natural variation in *Arabidopsis thaliana* metabolome by the analysis of metabolic distance. *Metabolomics*, 8, 131-145.

Hsu, B., Coupar, I. M. and Ng, K. (2006). Antioxidant activity of hot water extract from the fruit of the Doum palm, *Hyphaene thebaica*. *Food Chemistry*, 98 (2), 317-328.

Huang, D., Ou, B. and Prior, R. L. (2005). The chemistry behind antioxidant capacity assays. *Journal of Agricultural and Food Chemistry*, 53 (6), 1841-1856.

Huda-Faujan, N., Noriham, A., Norrakiah, A. S. and Babji, A. S. (2007). Antioxidative activities of water extracts of some Malaysian herbs. *ASEAN Food Journal*, 14 (1), 61-68.

Huda-Faujan, N., Noriham, A., Norrakiah, A. S. and Babji, A. S. (2009). Antioxidant activity of plants methanolic extracts containing phenolic compounds. *African Journal of Biotechnology*, 8 (3), 484-489.

Hyun, T.K., Hyoun-Chol, K. and Ju-Sung, K. (2014). Antioxidant and antidiabetic activity of *Thymus quinquecostatus* Celak. *Industrial Crops and Products*, 52, 611- 616.

Hyun, T.K., Hyoun-Chol, K., Yeong-Jong, K. and Ju-Sung, K. (2016). Antioxidant, α-glucosidase inhibitory and anti-inflammatory effects of aerial parts extract from Korean crowberry (*Empetrum nigrum var. japonicum*). *Saudi Journal of Biological Sciences*, 23, 181-188.

International Diabetes Federation (2003). IDF Atlas 2nd edition. Brussels, Belgium. Retrieved 29 June 2015, from: http:www.idf.org/sites/default/files/IDF_Diabetes_Atlas_2ndEd.pdf.

International Diabetes Federation (2011). IDF Atlas 5th edition. Brussels, Belgium. Retrieved 29 June 2015, from : http://www.idf.org/diabetesatlas.

Ishikawa, A., Yamashita, H., Hiemori, M., Inagaki, E., Kimoto, M., Okamoto, M., Tsuji, H., Memon, A. N., Mohammadio, A. and Natori, Y. (2007). Characterization of inhibitors of postprandial hyperglycemia from the leaves of *Nerium indicum*. *Journal of Nutritional Science and Vitaminology,* 53 (2), 166-173.

Ismail, S. (2000). Sayuran traditional ulam dan penyedap rasa. Malaysia. Universiti Kebangsaan Malaysia.

Iwashina, T. (2000). The structure and distribution of the flavonoids in plants. *Journal of Plant Research,* 113, 287-299.

Jamal, P., Barkat, A. A. and Amid, A. (2010). Distribution of phenolics in various Malaysian medicinal plants. *Journal of Applied Science*, 10, 2658-2662.

Jansen, J. J., Allwood, J. W., Marsden-Edwards, E., Putten, W. H., Goodacre, R. and Dam, N. M. (2009). Metabolomic analysis of the interaction between plants and herbivores. *Metabolomic,* 5, 150-161.

Javadi, N., Abas, F., Hamid, A. A., Simoh, S., Shaari, K., Ismail, I. S., Mediani, A. and Khatib, A. (2014). GC-MS-based metabolite profiling of *Cosmos caudatus* leaves possessing alpha-glucosidase inhibitory activity. *Journal of Food Science*, 79 (6), 1130-1136.

Javadi, N., Abas, F., Mediani, A., Hamid, A. A., Khatib, A., Simoh, S. and Shaari, K. (2015). Effect of storage time on metabolite profile and alpha-glucosidase inhibitory activity of *Cosmos caudatus* leaves-GCMS based metabolomics approach. *Journal of Food and Drug Analysis*, 23 (3), 433-441.

Ji-Hye, K., Min-Jung, K., Ha-Neul, C., Soo-Mi, J., Young-Min, L. and Jung-In, K. (2011). Quercetin attenuates fasting and postprandial hyperglycemia in animal models of diabetes mellitus. *Nutrition Research and Practice*, 5 (2), 107-111.

Johnson, M. H., Lucius, A., Meyer, T. and de Mejia, E. G. (2011). Cultivar evaluation and effect of fermentation on antioxidant capacity and in vitro inhibition of α-amylase and α-glucosidase by highbush blueberry (*Vaccinium corymbosum*). *Journal of Agricultural and Food Chemistry*, 59, 8923-8930.

Jo, S. H., Ka, E. H., Lee, H. S., Apostolidis, E., Jang, H. D. and Kwon, Y. I. (2009). Comparison of antioxidant potential and rat intestinal α-glucosidases inhibitory activities of quercetin, rutin and isoquercetin. *International Journal of Applied Research in Natural Products,* 2 (4), 52-60.

Jong-Anurakkun, N., Bhandari, M. R. and Kawabata, J. (2007). α-glucosidase inhibitors from Devil tree (*Alstonia scholaris*). *Food Chemistry,* 103 (4), 1319-1323.

Jung, M., Park, M., Lee, H. C., Kang, Y. H., Kang, E. S. and Kim, S. K. (2006). Antidiabetic agents from medicinal plants. *Current Medicinal Chemistry,* 13 (10), 1203-1218.

Kähkönen, M. P., Hopia, A. I., Vuorela, H. J., Rauha, J., Pihlaja, K., Kujala, T. S. and Heinonen, M. (1999). Antioxidant activity of plant extracts containing phenolic compounds. *Journal of Agricultural and Food Chemistry,* 47 (10), 3954-3962.

Kamalakkannan, N. and Prince, P. S. M. (2006). Antihyperglycaemic and antioxidant effect of rutin, a polyphenolic flavonoid, in streptozotocin-induced diabetic Wistar Rats. *Basic and Clinical Pharmacology and Toxicology,* 98 (1), 97-103.

Kang, J., Choi, M. Y., Kang, S., Kwon, H. N., Wen, H. and Lee, C. H. (2008). Application of a ^{1}H nuclear magnetic resonance (NMR) metabolomics approach combined with orthogonal projections to latent structure- discriminant analysis as an efficient tool for discriminating between Korean and Chinese herbal medicine. *Journal of Agriculture and Food Chemistry*, 56, 11589-11595.

Karananayake, E. H. and Tennekoon, K. H. (1993). Search of novel hypoglycaemic agents from medicinal plants. In: Diabetes mellitus and its complications, An update. Sharma, A. K. (Editor-in-chief), Macmillan India Ltd.

Keli, S. O., Hertog, M. G., Freskens, E. J. and Kromhout., D. (1996). Dietary flavonoids, antioxidant vitamins and incidence of stroke: The Zutphen study. *Archives of Internal Medicine,* 156, 637-642.

Kemsley, E. K., Le Gall, G., Dainty, J. R., Watson, A. D., Harvey, L. J. and Tapp, H. S. (2007). Multivariate techniques and their application in nutrition: a metabolomics case study. *British Journal of Nutrition,* 98 (1), 1-14.

Kerem, Z., Bilkis, I., Flaishman, M. A. and Sivan, L. (2006). Antioxidant activity and inhibition of α-glucosidase by trans-resveratrol, Piceid, and a novel trans-stilbene from the roots of Israeli *Rumex bucephalophorus* L. *Journal of Agricultural and Food Chemistry,* 54 (4), 1243-1247.

Ketchi, D. O. and Kuiper, P. J. C. (1979). Fatty acid levels in apple leaves of different age as affected by temperature. *Physiologia Plantarum,* 46 (2), 93-96.

Khan, M. H. and Yadava, P. S. (2010). Antidiabetic plants used in Thoubal district of Manipur, Northeast India. *Indian Journal of Traditional Knowledge,* 9 (3), 510-514.

Kim, Y. M., Jeong, Y. K., Wang, M. H., Lee, W. Y. and Rhee, H. I. (2005). Inhibitory effects of pine bark extract on alpha-glucosidase activity and postprandial hyperglycemia. *Nutrition,* 21, 756-761.

Kim, H. K. and Verpoorte, R. (2010a). Sample preparation for plant metabolomics. *Phytochemical Analysis,* 21 (1), 4-13.

Kim, H. K., Choi, Y. H. and Verpoorte, R. (2010b). NMR-based metabolomic analysis of plants. *Nature Protocols,* 5 (3), 536-549.

Kim, J., Yang, J. and Kim, M. (2011). Alpha glucosidase inhibitory effect, anti-microbial activity and UPLC analysis of *Rhus verniciflua* under various extract conditions. *Journal of Medicinal Plants Research,* 5 (5), 778-783.

King, H. A. R. and Herman, W. H. (1998). Global burden of disease 1999-2025: Prevalence, numerical estimates and projection. *Diabetes Care,* 21, 1414-1431.

Knekt, P., Kumpulainen, J., Järvinen, R., Rissanen, H., Heliövaara, M., Reunanen, A., Hakulinen, T. and Aromaa, A. (2002). Flavonoid intake and risk of chronic diseases. *The American Journal of Clinical Nutrition,* 76 (3), 560-568.

Kobori, M., Masumoto, S., Akimoto, Y. and Takahashi, Y. (2009). Dietary quercetin alleviates diabetic symptoms and reduces streptozotocin-induced disturbance of hepatic gene expression in mice. *Molecular Nutrition and Food Research,* 53 (7), 859-868.

Krentz, A. J. and Bailey, C. J. (2005). Oral antidiabetic agent’s current roles in type-2 diabetes mellitus. *Drugs,* 65, 385-411.

Kunyanga, C. N., Imungi, J. K., Okoth, M. W., Biesalski, H. K. and Vadivel, V. (2012). Total phenolic content, antioxidant and antidiabetic properties of methanolic extract of raw and traditionally processed Kenyan indigenous food ingredients. *LWT-Food Science and Technology,* 45 (2), 269-276.

Kwon, Y. I. I., Vattem, D. A. and Shetty, K. (2006). Evaluation of clonal herbs of Lamiaceae species for management of diabetes and hypertension. *Asia Pacific Journal of Clinical Nutrition*, 15 (1), 107-118.

Lawal, U., Mediani, A., Maulidiani, H., Shaari, K., Ismail, I. S., Khatib, A. and Abas, F. (2015). Metabolite profiling of *Ipomoea aquatica* at different growth stages

in correlation to the antioxidant and α-glucosidase inhibitory activities elucidated by ^{1}H NMR-based metabolomics. *Scientia Horticulturae*, 192, 400-408.
Lebovitz, H. E. (1998). Postprandial hyperglycaemic state: importance and consequences. *Diabetes Research and Clinical Practice,* 40, 27-28.
Lee, T. K. and Vairappan, C. S. (2011). Antioxidant antibacterial and cytotoxic activities of essential oils and ethanol extracts of selected South East Asian herbs. *Journal of Medicinal Plant Research,* 5 (21), 5284-5290.
Lee, J., Lee, B., Chung, J., Shin, H., Lee, S. and Lee, C. (2011). ^{1}H NMR-based metabolomic characterization during green tea (*Camellia sinensis*) fermentation. *Food Research International*, 44 (2), 597-604.
Lee, S. Y., Mediani, A., Nur Ashikin, A. H., Azliana, A. B. S. and 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.
Legrand, P. and Rioux, V. (2015). Specific roles of saturated fatty acids: Beyond epidemiological data. *European Journal of Lipid Science and Technology,* 117 (10), 1489-1499.
Lesniak, A. P. and Liu, E. H. (1981). Biological properties of *Leucaena leucocephala* (lmk) DeWit seed galactomannans. *Leucaena Reports,* 2, 77-78.
Li, Y., Guo, C., Yang, J., Wei, J., Xu, J. and Cheng, S. (2006). Evaluation of antioxidant properties of pomegranate peel extract in comparison with pomegranate pulp extract. *Food Chemistry,* 96, 254-260.
Li, C., Barker, L., Ford, E. S., Zhang, X., Strine, T. W. and Mokdad, A. H. (2008). Diabetes and anxiety in US adults: findings from the 2006 Behavioural Risk Factor Surveillance System. *Diabetic Medicine,* 25 (7), 878-881.
Li, Y. Q., Zhou, F. C., Gao, F., Bian, J. S. and Shan, F. (2009). Comparative evaluation of quercetin, isoquercetin and rutin as inhibitors of α-glucosidase. *Journal of Agricultural and Food Chemistry,* 57 (24), 11463-11468.
Li, L. and Seeram, N. P. (2011). Further investigation into maple syrup yields 3 new lignans, a new phenylpropanoid, and 26 other phytochemicals. *Journal of Agricultural and Food Chemistry,* 59, 7708-7716.
Lim, S. T., Jimeno, C. A., Razon-Gonzales, E. B. and Velasquez, E. N. (2010). The MOCHA DM study: The effect of *Momordica charantia* tablets on glucose and insulin levels during the postprandial state among patients with type 2 diabetes mellitus. *Philippine Journal of Internal Medicine,* 48, 19-25.
Lindon, J. C. and Nicholson, J. K. (1997). Recent advances in high-resolution NMR spectroscopic methods in bioanalytical chemistry. *Trends in Analytical Chemistry,* 16, 190-200.
Lindon, J. C., Holmes, E. and Nicholson, J. K. (2006). Metabonomics techniques and applications to pharmaceutical research and development. *Pharmaceutical Research,* 23, 1075-1088.
Liu, S., Yu, Z., Zhu, H., Zhang, W. and Chen, Y. (2016). In vitro α-glucosidase inhibitory activity of isolated fractions from water extract of Qingzhuan dark tea. *BMC Complementary and Alternative Medicine,* 16 (1), 378.
Loh, S. P. and 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.
Lu, Y. and Foo, L. Y. (1997). Identification and quantification of major polyphenols in apple pomace. *Food Chemistry,* 59 (2), 187-194.

Ma, C., Wang, H., Lu, X., Xu, G. and Liu, B. (2008). Metabolic fingerprinting investigation of *Artemisia annua* L. in different stages of development by gas chromatography and gas chromatography-mass spectrometry. *Journal of Chromatography A*, 1186 (1), 412-419.

Mai, T. T., Thu, N. N., Tien, P. G. and Chu Yen, N. V. (2007). Alpha-glucosidase inhibitory and antioxidant activities of Vietnamese edible plants and their relationships with polyphenol contents. *Journal of Nutritional Science and Vitaminology*, 53 (3), 267-276.

Maiti, R., Jana, D., Dan, U. and Ghosh, D. (2004). Antidiabetic effect of aqueous extract of the seed of *Tamarindus indica* in streptozotin-induced diabetic rats. *Journal of Ethnopharmacology*, 92 (1), 85-91.

Maizura, M., Aminah, A. and Wan Aida, W. M. (2011). Total phenolic content and antioxidant activity of kesum (*Polygonum minus*), ginger (*Zingiber officinale*) and turmeric (*Curcuma longa*) extract. *International Food Research Journal*, 18 (2), 529-534.

Manaharan, T., Palanisamy, U. D. and Ming, C. H. (2012). Tropical plant extracts as potential antihyperglycemic agents. *Molecules*, 17, 5915-5923.

Markham, K. R., Ternai, B., Stanley, R., Geiger, H. and Mabry, T. J. (1978). Carbon-13 NMR studies of flavonoids- III. *Tetrahedron*, 34, 1389-1397.

Markom, M., Hasan, M., Daud, W., Sigh, H. and Jahim, J. M. (2007). Extraction of hydrolysable tannins from *Phyllanthus niruri* Linn. Effects of solvents and extraction methods. *Separation and Purification Technology*, 52, 487-496.

Mata, R., Cristians, S., Escandón-Rivera, S., Juárez-Reyes, K. and Rivero-Cruz, I. (2013). Mexican antidiabetic herbs: valuable sources of inhibitors of α-glucosidases. *Journal of Natural Products*, 76 (3), 468-483.

Maulidiani, H., Khatib, A., Shaari, K., Abas, F., Shitan, M., Kneer, R., Neto, V. and Lajis, N. H. (2012). Discrimination of three pegaga (*Centella*) variaties and determination of growth-lighting effects on metabolites content based on the chemometry of ^{1}H nuclear magnetic resonance spectroscopy. *Journal of Agricultural and Food Chemistry*, 60 (1), 410-417.

Mediani, A., Abas, F., Khatib, A., Maulidiani, H., Shaari, K., Choi, Y. H. and Lajis, N. H. (2012a). ^{1}H-NMR-based metabolomics approach to understanding the drying effects on the phytochemicals in *Cosmos caudatus*. *Food Research International*, 49 (2), 763-770.

Mediani, A., Abas, F., Ping, T. C., Khatib, A. and Lajis, N. H. (2012b). Influence of growth stage and season on the antioxidant constituents of *Cosmos caudatus*. *Plant Foods for Human Nutrition*, 67, 344-350.

Mediani, A., Abas, F., Khatib, A. and Tan, C. P. (2013). *Cosmos caudatus* as a potential source of polyphenolic compounds: Optimisation of oven drying conditions and characterisation of its functional properties. *Molecules*, 18 (9), 10452-10464.

Mediani, A., Abas, F., Khatib, A., Ping, T. C., Ismail, I. S., Shaari, K., Ismail, A. and Lajis, N. H. (2015). Phytochemical and biological features of *Phyllanthus niruri* and *Phyllanthus urinaria* harvested at different growth stages revealed by ^{1}H NMR-based metabolomics. *Industrial Crops and Products*, 77, 602-613.

Menichini, F., Tundis, R., Bonesi, M., Loizzo, M. R., Conforti, F., Statti, G., Cindio, B. D., Houghton, P. J. and Menichini, F. (2009) The influence of fruit ripening on the phytochemical content and biological activity of *Capsicum chinense* Jacq. cv Habanero. *Food Chemistry*, 114 (2), 553-560.

Michalak, A. (2006). Phenolic compounds and their antioxidant activity in plants growing under heavy metal stress. *Polish Journal of Environmental Studies*, 15 (4), 523-530.

Ministry of Health Malaysia (MOH). (2012). The future of diabetes in Malaysia.

Moco, S., Vervoort, J., Bino, R. J., De Vos, R. C. and Bino, R. (2007). Metabolomics technologies and metabolite identification. *Trends in Analytical Chemistry*, 26 (9), 855-866.

Moein, M. R., Moein, S. and Ahmadizadeh, S. (2008). Radical scavenging and reducing power of *Salvia mirzayanii* subfractions. *Molecules*, 13, 2804-2813.

Mohamed, N., Sahhugi, Z., Ramli, E. S. M. and Muhammad, N. (2013). The effects of *Cosmos caudatus* (ulam raja) on dynamic and cellular bone histomorphometry in ovariectomized rats. *BMC Research Notes*, 6 (1), 239.

Mohamed, N. S., Khee, G. S. K., Shuid, A. N., Muhammad, N., Suhaimi, F., Othman, F., Babji, A. S. and Soelaiman, I. N. (2012). The effects of *Cosmos caudatus* on structural bone histomorphometry in ovariectomized rats. *Evidence-based Complementary and Alternative Medicine*, 2012, 817814.

Mossa, A. and Nawwar, G. (2011). Free radical scavenging and antiacetylcholinesterase activities of *Origanum majorana* L. essential oil. *Human and Experimental Toxicology*, 30 (10), 1501-1513.

Moure, A., Cruz, J. M., Franco, D., Dominguez, J. M., Sineiro, J. and Dominguez, H. (2001). Natural antioxidants from residual sources. *Food Chemistry*, 72 (2), 145-171.

Mun'im, A., Andriani, A., Mahmudah, K. F. and Mashita, M. (2013). Screening of α-glucosidase inhibitory activity of some Indonesian medicinal plants. *International Journal of Medicinal and Aromatic Plants*, 3 (2), 144-150.

Mushtaq, M. Y., Choi, Y. H., Verpoorte, R. and Wilson, E. G. (2014). Extraction for metabolomics: access to the metabolome. *Phytochemical Analysis*, 25 (4), 291-306.

Mustafa, R. A., Hamid, A. A., Mohamed, S. and Bakar, F.A. (2010). Total phenolic compounds, flavonoids and radical scavenging activity of 21 selected tropical plants. *Journal of Food Science*, 75 (1), 28-35.

Nabilla, A. S., Dzaki, M. S., Zainal, A. O., Ismail, M. S., Fatanah, I., Azah, N. D., Anis, S. K., Ishak, J., Rushidi, R., Roslina, N. M. and Rohaizan, J., (2003). Direct costs of diabetes in an outpatient setting in Malaysia. *NCD Malaysia*, 2 (1), 19-27.

Nadzirah, K. Z., Zainal, S., Noriham, A., Normah, I., Siti Roha, A. M. and Nadya, H. (2013). Physico-chemical properties of pineapple variety N36 harvested and stored at different maturity stages. *International Food Research Journal*, 20 (1), 225-231.

Narins, B. (2000). World of Health. Gale Group, Farmington Hills, U.S.

Nicholson, J. K., Connelly, J., Lindon, J. C. and Holmes, E. (2002). Metabolomics: A platform for studying drug toxicity and gene function. *Nature Reviews Drug Discovery*, 1 (2), 153-161.

Noridayu, A. R., Hii, Y. F., Faridah, A., Khozirah, S. and Lajis, N. (2011). Antioxidant and antiacetylcholinesterase activities of *Pluchea indica* Less. *International Food Research Journal*, 18 (3), 925-929.

Noriham, A., Dian-Nashiela, F., Kherni Hafifi, B., Nooraain, H. and Azizah, A. H. (2015). Influences of maturity stages and extraction solvents on antioxidant activity of *Cosmos caudatus* leaves. *International Journal of Research Studies in Biosciences*, 3 (12), 1-10.

Nguyen, Q. H., Talou, T., Cerny, M., Evon, P. and Merah, O. (2015). Oil and fatty acid accumulation during coriander (*Coriandrum sativum* L.) fruit ripening under organic cultivation. *The Crop Journal*, 3 (4), 366-369.

Omar, M. H. (2013) Analysis of phytochemical in a Malaysian medicinal plant and the bioavailability of dietary hydroxycinnamates. PhD thesis.

Ong, H. C. and Norzalina, J. 1999. Malay herbal medicine in Gemencheh, Negeri Sembilan, Malaysia. *Fitoterapia,* 70 (1), 10-14.

Ortiz-Andrade, R. R., Garcia-Jiménez, S., Castillo-Espãna, P., Raminez-Āvila, G., Villalobos-Monila, R. and Estrada-Soto, S. (2007). α-glucosidase inhibitory activity of the methanolic extract from *Tournefortia hartwegiana*: An anti-hyperglycemic agent. *Journal of Ethnopharmacology*, 109, 48-53.

Önal, S., Timmur, S., Okuttucu, B. and Zihnioglu. (2005). Inhibition of α-glucosidase by aqueous extracts of some potent antidiabetic medicinal herbs. *Preparative Biochemistry and Biotechnology,* 35, 29-36.

Öztürk, M., Fatma, A. O., Mehmet, E. D. and Gülacti, T. (2007). Antioxidant activity of stem and root extracts of Rhubarb (*Rheum ribes*): an edible medicinal plant. *Food Chemistry*, 103 (2), 623-630.

Paixào, N., Perestrelo, R., Marques, J. C. and Câmara, J.S. (2007). Relationship between antioxidant capacity and total phenolic content of red, rose and white wines. *Food Chemistry,* 105 (1), 204-214.

Pandey, K. B. and Rizvi, S. I. (2009). Plant polyphenols as dietary antioxidants in human health and disease. *Oxidative Medicine and Cellular Longevity,* 2 (5), 270-278.

Pandeya, K. B., Tripathi, I. P., Mishra, M. K., Dwivedi, N., Pardhi, Y., Kamal, A., Gupta, P., Dwivedi, N. and Mishra, C. (2013). A critical review on traditional herbal drugs: An emerging alternative drugs for diabetes. *International Journal of Organic Chemistry*, 3 (1), 1-22.

Parejo, I., Viladomat, F., Bastida, J., Rosas-Romero, A., Flerlage, N., Burillo, J. and Codina, C. (2002). Comparison between the radical scavenging activity and antioxidant activity of six distilled and non-distilled Mediterranean herbs and aromatic plants. *Journal of Agricultural and Food Chemistry*, 50 (23), 6882-6890.

Patel, D. K., Prasad, S. K., Kumar, R. and Hemalatha, S. (2012). An overview on antidiabetic medicinal plants having insulin mimetic property. *Asian Pacific Journal of Tropical Medicine,* 2 (4), 320-330.

Pietropolo, M. (2001). Pathogenesis of diabetes: our current understanding. *Clinical Cornerstone Diabetes*, 4 (2), 1-21.

Pietta, P. G. (2000). Flavonoids as antioxidants. *Journal of Natural Products,* 63 (7), 1035-1042.

Pietta, P. G., Gardana, C. and Pietta, A. M. (2002). Analytical methods for quality control of propolis. *Fitoterapia*, 73, 7-20.

Pinto, M. D. S., Kwon, Y. I., Apostolidis, E., Lajolo, F. M., Genovese, M. I. and Shetty, K. (2009). Potential of *Ginkgo biloba* L. leaves in the management of hyperglycemia and hypertension using in vitro models. *Bioresource Technology,* 100 (24), 6599-6609.

Peschel, W., Sanchez-Rabaneda, F., Dn, W., Plescher, A., Gartzia, I., Jimenez, D., Lamuela-Raventos, R., Buxaderas, S. and Condina, C. (2006). An industrial approach in the search of natural antioxidants from vegetable and fruit wastes. *Food Chemistry*, 97 (1), 137-150.

Petchi, R., Vijaya, C. and Parasumaran, S. (2014). Antidiabetic activity of polyherbal formulation in streptozotocin-nicotinamide induced diabetic wistar rats. *Journal of Traditional Complementary Medicine,* 4 (2), 108-117.

Platel, K. and Srinivasan, K. (1997). Plants foods in the management of diabetes mellitus: vegetables as potential hypoglycemic agents. *Nahrung,* 41 (2), 68-74.

Playford, R. J., Pither, C. and Gao, R. (2013). Use of the α-glucosidase inhibitor acarbose in patients with 'Middleton syndrome': normal gastric anatomy but with accelerated gastric emptying causing postprandial reactive hypoglycemia and diarrhoea. *Canadian Journal of Gastroenterology and Hepatology,* 27 (7), 403-404.

Pushparaj, P., Tan, C. H. and Tan, B. K. H. (2000). Effects of a *Averrhoa bilimbi* on blood glucose and lipids in streptozotocin-diabetic rats. *Journal of Ethnopharmacology,* 76, 2827-2839.

Pullins, E. (2000). *Why is organic produce generally smaller in size?* Retrieved 15 July 2017, from http://www.ecoglobe.org/nz/index.htm

Proestos, C., Chorianopoulos, N., Nychas, G. -J. E. and Komaitis, M. (2005). RP-HPLC analysis of the phenolic compounds of plant extracts. Investigation of their antioxidant capacity and antimicrobial activity. *Journal of Agricultural and Food Chemistry,* 53 (4), 1190-1195.

Qu, J., Liang, Q., Luo, G. and Wang, Y. (2004). Screening and identification of glycosides in biological samples using energy-gradient neutral loss scan and liquid chromatography tandem mass spectrometry. *Analytical chemistry,* 76 (8), 2239-2247.

Rafat, A., Philip, K. and Muniandy, S. (2010). Antioxidant potential and phenolic content of ethanolic extract of selected Malaysian plants. *Research Journal of Biotechnology,* 5 (1), 16-19.

Ramachandra, R., Shetty, A. K. and Salimath, P. V. (2005). Quercetin alleviates activities of intestinal and renal disaccharides in streptozotocin-induced diabetic rats. *Molecular Nutrition and Food Research,* 49 (4), 355-360.

Ramirez, T., Daneshian, M., Kamp, H., Bois, F. Y., Clench, M. R., Coen, M., Donley, B., Fischer, S. M., Ekman, D. R., Fabian, E., Guillou, C., Heuer, J., Hogberg, H. T., Jungnickel, H., Keun, H. C., Krennrich, G., Krupp, E., Luch, A., Noor, F., Peter, E., Riefke, B., Seymour, M., Skinner, N., Smirnova, L., Verheij, E., Wagner, S., Hartung, T., van Ravenzwaay, B. and Leist, M. (2013). Metabolomics in toxicology and preclinical research. *ALTEX,* 30 (2), 209-225.

Ranilla, L. G., Kwon, Y., Apostolidis, E. and Shetty, K. (2010). Phenolic compounds, antioxidant activity and in vitro inhibitory potential against key enzymes relevant for hyperglycemia and hypertension of commonly used medicinal plants, herbs and spices in Latin America. *Bioresource Technology,* 101 (12), 4676-4689.

Rasdi, N. H. M., Samah, O. A., Sule, A. and Ahmed, Q. U. (2010). Antimicrobial studies of *Cosmos caudatus* Kunth. (Compositae). *Journal of Medicinal Plant Research,* 4 (8), 669-673.

Razak, M. F., Yong, P. K., Shah, Z. M., Abdullah, L. C., Yee, S. S. and Yaw, T. C. S. (2012). The effects of varying solvent polarity on extraction yield of *Orthosiphon stamineus* leaves. *Journal of Applied Sciences,* 12, 1207-1210.

Rehman, Z. U. (2006). Citrus peel extract- A natural source of antioxidant. *Food Chemistry,* 99, 450-454.

Reihani, S. F. S. and Azhar, M. E. (2012). Antioxidant activity and total phenolic content in aqueous extracts of selected traditional Malay salads (ulam). *International Food Research Journal*, 19 (4), 1439-1444.

Robertson, D. G., Watkins, P. B. and Reily, M. D. (2011). Metabolomics in toxicology: Preclinical and clinical applications. *Toxicological Sciences,* 120 (1), 146-170.

Robya, M. H., Sarhan, M. A., Selim, K. A. and Khalel, K. I. (2013). Evaluation of antioxidant activity, total phenols and phenolic compounds in thyme (*Thymus vulgaris* L.), sage (*Salvia officinalis* L.), and marjoram (*Origanum majorana* L.) extracts. *Industrial Crops and Products,* 43, 827-831.

Ryu, H. W., Cho, J. K., Curtis-Long, M. J., Yuk, H. J., Kim, Y. S., Jung, S., Kim, Y. S., Lee, B. W. and Park, K. H. (2011). α-Glucosidase inhibition and antihyperglycemic activity of prenylated xanthones from *Garcinia mangostana*. *Phytochemistry,* 72, 2148-2154.

Samy, J., Sugumaran, M. and Lee, K. L. W. (2005). Herbs of Malaysia: An introduction to the medicinal, culinary, aromatic and cosmetic use of herbs. (ed) Wong, K.M., Times Editions, pp. 82-83.

Sanchez-Sampedro, A., Kim, H. K., Choi, Y. H., Verpoorte, R. and Corchete, P. (2007). Metabolomic alterations in elicitor treated *Silybum marianum* suspension cultures monitored by nuclear magnetic resonance spectroscopy. *Journal Biotechnology,* 130, 133-142.

Sasidharan, S., Chen, Y., Saravanan, D., Sundram, K. M. and Latha, L. Y. (2011). Extraction, isolation and characterization of bioactive compounds from plants' extracts. *African Journal of Traditional, Complementary and Alternative Medicines*, 8 (1), 1-10.

Schripsema, J. (2010). Application of NMR in plant metabolomics: Techniques, problems and prospects. *Phytochemical Analysis,* 21, 14-21.

Schweiggert, R. M., Steingass, C. B., Heller, A., Esquivel, P. and Carle, R. (2011) Characterization of chromoplasts and carotenoids of red- and yellow- fleshed papaya (*Carica papaya* L.). *Planta,* 234, 1031-1044.

Seagle, C., Christie, M. A., Winnike, J. H., McClelland, R. E., Ludlow, J. W., O'Connell, T. M., Gamcsik, M. P. and Macdonald, J. M. (2008). High-throughput nuclear magnetic resonance metabolomics foot printing for tissue engineering. *Tissue Engineering,* 14, 107-118.

Seeram, N. P. and Nair, M. G. (2002). Inhibition of lipid peroxidation and structure-activity-related studies of the dietary constituents anthocyanins, anthocyanidins, and catechins. *Journal of Agricultural and Food Chemistry,* 50 (19), 5308-5312.

Seeram, N. P., Lee, R., Scheuller, H. S. and Heber, D. (2006). Identification of phenolic compounds in strawberries by liquid chromatography electrospray ionization mass spectroscopy. *Food Chemistry,* 97, 1-11.

Selmar, D. and Kleinwächter, M. (2013). Influencing the product quality by deliberately applying drought stress during the cultivation of medicinal plants. *Industrial Crops and Products,* 42, 558-566.

Shahidi, F. (1997). Natural antioxidants: chemistry, health effects, and applications. Champaign: The American Oil Chemists Society.

Shai, L. J., Masoko, P. and Mokgotho, M. P. (2010). Yeast alpha glucosidase inhibitory and antioxidant activities of six medicinal plants collected in Phalaborwa, South Africa. *South African Journal of Botany,* 76 (3), 465-470.

Shan, B., Cai, Y. Z., Sun, M. and Corke, H. (2005). Antioxidant capacity of 26 spice extracts and characterization of their phenolic constituents. *Journal of the Agricultural and Food Chemistry,* 53, 7749-7759.

Shaw, J. E., Sicree, R. A. and Zimmet, P. Z. (2010). Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Research and Clinical Practice*, 87 (1), 4-14.
Shetty, K. (1997). Biotechnology to harness the benefits of dietary phenolics; focus on Lamiaceae. *Asia Pacific Journal of Clinical Nutrition*, 6, 162-171.
Shetty, K. and Wahlqvist, M. (2004). A model for the role of the proline linked pentose phosphate pathway in phenolic phytochemicals biosynthesis and mechanism of action for human health and environment applications. *Asia Pacific Journal of Clinical Nutrition,* 13, 1-24.
Shetty, A. K., Rashmi, R., Rajan, M. G. R., Sambaiah, K. and Salimath, P. V. (2004). Antidiabetic influence of quercetin in streptozotocin-induced diabetic rats. *Nutrition Research*, 24 (5), 373-381.
Shobana, S., Sreerama, Y. N. and Malleshi, N. G. (2009). Composition and enzyme inhibitory properties of finger millet (*Eleusine coracana* L.) seed coat phenolics: Mode of inhibition of α-glucosidase and pancreatic amylase. *Food Chemistry,* 115 (4), 1268-1273.
Shui, G., Leong, L. P. and Wong, S. P. (2005). Rapid screening and characterisation of antioxidants of *Cosmos caudatus* using liquid chromatography coupled with mass spectrometry. *Journal of Chromatography B,* 827 (1), 127-138.
Shuib, N. H., Shaari, K., Khatib, A., Maulidiani, Kneer, R. and Zareen, S. (2011). Discrimination of young and mature leaves of *Melicope ptelefolia* using ^{1}H NMR and multivariate data analysis. *Food Chemistry,* 126 (2), 640-645.
Shukri, M., Mirfat, A., Erny Sabrina, M., Razali, M. and Salma, I. (2011a). Nutritional value and potential of Malaysian underutilised fruits and traditional vegetables. *In II International Symposium on Underutilized Plant Species: Crops for the Future-Beyond Food Security,* 979, 173-185.
Shukri, M., Alan, C. and Noorzuraini, A. S. (2011b). Polyphenols and antioxidant activities of selected traditional vegetables. *Journal of Tropical Agriculture and Food Science,* 39 (1), 69-83.
Siddhuraju, P. and Becker, K. (2003). Antioxidant properties of various solvent extracts of total phenolic constituents from three different agro climatic origins of drumstick tree (*Moringa oleifera* Lam.) leaves. *Journal of Agricultural and Food Chemistry*, 5 (8), 2144-2155.
Siddiqui, M. W., Momin, C. M., Acharya, P., Kabir, J., Debnath, M. K. and Dhua, R. S. (2013). Dynamics of changes in bioactive molecules and antioxidant potential of Capsicum chinense Jacq. cv. Habanero at nine maturity stages. *Acta Physiologiae Plantarum,* 35, 1141-1148.
Singh, J., Cumming, E., Manoharan, G., Kalasz, H. and Adeghate, E. (2011). Medicinal chemistry of the anti-Diabetic effects of *Momordica charantia*: Active constituents and modes of actions. *The Open Medicinal Chemistry Journal*, 5, 70-77.
Sohn, E., Kim, J., Kim, C., Kim, Y., Jang, D. and Kim, J. (2010). Extract of the aerial parts of *Aster koraiensis* reduced development of diabetic nephropathy via anti-apoptosis of pedocytes in streptozotocin-induced diabetic rats. *Biochemical and Biophysical Research Communications,* 391 (1), 733-738.
Solanky, K. S., Bailey, N. J. C., Beckwith-Hall, B. M., Davis, A., Bingham, S. and Holmes, E. (2003). Application of bio fluid ^{1}H-nuclear magnetic resonance-based metabonomic techniques for the analysis of the biochemical effects of dietary isoflavones on human plasma profile. *Analytical Biochemistry*, 323 (2), 197-204.

Son, H., Ki, M. K., Van Den Berg, F., Hwang, G., Park, W. and Lee, C. (2008). ^{1}H nuclear magnetic resonance-based metabolomic characterization of wines by grape varieties and production areas. *Journal of Agricultural and Food Chemistry*, 56 (17), 8007-8016.

Son, H., Hwang, G., Ahn, H., Park, W., Lee, C. and Hong, Y. (2009). Characterization of wines from grape varieties through multivariate statistical analysis of ^{1}H NMR spectroscopic data. *Food Research International*, 42 (10), 1483-1491.

Song, J., Kwon, O., Chen, S., Daruwala, R., Eck, P., Park, J. B. and Levine, M. (2002). Flavonoid inhibition of sodium-dependent vitamin C transporter 1 (SVCT1) and glucose transporter isoform 2 (GLUT2), intestinal transporters for vitamin C and glucose. *Journal of Biological Chemistry*, 277 (18), 15252-15260.

Soobrattee, M. A., Neergheen, V. S., Luximon-Ramma, A., Aruoma, O. I. and Bahorun, T. (2005). Phenolics as potential antioxidant therapeutic agents: Mechanism and actions. *Mutation Research- Fundamental and Molecular Mechanisms of Mutagenesis*, 579 (1-2), 200-213.

Spratlin, J. L., Serkova, N. J. and Eckhardt, S. G. (2009). Clinical applications of metabolomics in oncology. *Clinical Cancer Research*, 15 (2), 431-440.

Sreelatha, S. and Padma, P. R. (2009). Antioxidant activity and total phenolic content of *Moringa oleifera* leaves in two stages of maturity. *Plant Foods for Human Nutrition*, 64 (4), 303-311.

St-Onge, M. P. and Jones, P. J. (2002). Physiological effects of medium-chain triglycerides: potential agents in the prevention of obesity. *The Journal of Nutrition*, 132 (3), 329-332.

Standl, E. and Schnell, O. (2012). Alpha-glucosidase inhibitors cardiovascular considerations and trial evaluation. *Diabetes and Vascular Disease Research*, 9 (3), 163-169.

Stobiecki, M., Malosse, C., Kerhoas, L., Wojlaszele, P. and Einhorn, J. (1999). Detection of isoflavonoids and their glycosides by liquid chromatography/electrospray ionization mass spectrometry in root extracts of lupin (*Lupinus albus*). *Phytochemical Analysis*, 10 (4), 198-207.

Stobiecki, M. (2000). Application of mass spectrometry for identification and structural studies of flavonoid glycosides. *Phytochemistry*, 54 (3), 237-256.

Stoilova, I., Krastanov, A., Stoyanova, A., Denev, P. and Gargova, S. (2007). Antioxidant activity of a ginger extract (*Zingiber officinale*). *Food Chemistry*, 102, 764-770.

Stuart, A. R., Gulve, E. A. and Wang, M. (2004). Chemistry and biochemistry of type 2 diabetes. *Chemical Reviews*, 104, 1255-1282.

Subramanian, R., Asmawi, M. Z. and Sadikun, A. (2008). In vitro alpha-glucosidase and alpha-amylase enzyme inhibitory effects of *Andrographis paniculata* extract and andrographolide. *Acta Biochimica Polonica*, 55 (2), 391-398.

Sugiwati, S., Setiasih, S. and Afifah, E. (2009). Antihyperglycemic activity of the mahkota dewa *Phaleria macrocarpa* (scheff.) boerl. leaf extracts as an alpha-glucosidase inhibitor. *Makara Journal of Health Research*, 13 (2), 74-78.

Suhaj, M. (2006). Spice antioxidants isolation and their antiradical activity: a review. *Journal of Food Composition and Analysis*, 19 (6), 531-537.

Sukrasno, S., Fidriany, I., Anggadiredja, K., Handayani, W. A. and Anam, K. (2011). Influence of drying method on flavonoid content of *Cosmos caudatus* (Kunth) leaves. *Research Journal of Medicinal Plant,* 5 (2), 189–195.

Sukri, N. A. (2012). Effect of different types of solvent on extraction of phenolic compounds from *Cosmos caudatus* (Doctoral dissertation, UMP).

Sultana, B., Anwar, F. and Ashraf, M. (2009). Effect of extraction solvent/ technique on the antioxidant activity of selected medicinal plant extracts. *Molecules,* 14 (6), 2167-2180.

Sumazian, Y. A., Syahida, M., Hakiman and Maziah, M. (2010). Antioxidant activities, flavonoids, ascorbic acid and phenolic contents of Malaysia vegetables. *Journal of Medicinal Plants Research*, 4 (10), 881-890.

Sumner, L. W., Mendes, P. and Dixon, R. A. (2003). Plant metabolomics: Large-scale phytochemistry in the functional genomics era. *Phytochemistry*, 62, 817-836.

Sun, C., Wu, Z., Wang, Z. and Zhang, H. (2015). Effect of ethanol/water solvents on phenolic profiles and antioxidant properties of Beijing propolis extracts. *Evidence-Based Complementary and Alternative Medicine*, 2015, 595393-595402.

Surveswaran, S., Cai, Y., Corke, H. and Sun, M. (2007). Systematic evaluation of natural phenolic antioxidants from 133 Indian medicinal plants. *Food Chemistry,* 102 (3), 938-953.

Syamsudin, Sumarny, R. and Simanjuntak, P. (2010). Antidiabetic activity of active fractions of *Leucaena Leucocephala* (lmk) DeWit seeds in experimental model. *European Journal of Scientific Research,* 43, 384-391.

Tahir, N. I., Shaari, K., Abas, F., Parveez, G. K. A., Ishak, Z. and Ramli, U. S. (2013). Characterization of apigenin and luteolin derivatives from oil palm (*Elaeis guineensis* Jacq.) leaf using LC–ESI-MS/MS. *Journal of Agricultural and Food Chemistry,* 60 (45), 11201-11210.

Tarachiwin, L., Ute, K., Kobayashi, A. and Fukusaki, E. (2007). ^{1}H NMR based metabolic profiling in the evaluation of Japanese green tea quality. *Journal of Agricultural and Food Chemistry*, 55 (23), 9330-9336.

Teschke, R. and Eickhoff, A. (2015). Herbal hepatotoxicity in traditional and modern medicine: actual key issues and new encouraging steps. *Frontier in Pharmacology,* 6, 72.

The Star, (2013). *Number of diabetic in Malaysia is alarming.* Retrieved 29 June 2015, from http://www.thestar.com.my/News/Nation/2013/06/14/Nunber=of-diabetics-in-Malaysia-alarming/html.

Theoharides, T. C. and Bielory, L. (2004). Mast cells and mast cell mediators as targets of dietary supplements. *Annals of Allergy, Asthma and Immunology, 93 (2),* 24-34.

Thoo, Y. Y., Ho, S. K., Liang, J. Y., Ho, C. W. and Tan, C. P. (2010). Effects of binary solvent extraction system, extraction time and extraction temperature on phenolic antioxidants and antioxidant capacity from mengkudu (*Morinda citrifolia*). *Food Chemistry, 120 (1),* 290-295.

Trygg, J., Holmes, E. and Lundstedt, T. (2007). Chemometrics in metabonomics. *Journal of Proteome Research,* 6 (2), 469-479.

Tugizimana, F., Steenkamp, P. A., Piater, L. A. and Dubery, I. A. (2012). Ergosterol-induced sesquiterpenoid synthesis in tobacco cells. *Molecules,* 17, 1698-1715.

Turkmen, N., Sari, F. and Velioglu, Y. S. (2006). Effects of extraction solvents on concentration and antioxidant activity of black and black mate tea polyphenols determined by ferrous tartrate and Foline-Ciocalteu methods. *Food Chemistry*, 99, 835-841.

van Der Kooy, F., Maltese, F., Choi, Y. H., Kim, H. K. and Verpoorte, R. (2009). Quality control of herbal material and phytopharmaceuticals with MS and NMR based metabolic fingerprinting. *Planta Medica*, 75, 763-775.

Vattem, D. A., Ghaedian, R. and Shetty, K. (2005). Enhancing health benefits of berries through phenolic antioxidant enrichment: Focus on cranberry. *Asia Pacific Journal of Clinical Nutrition*, 14, 120-130.

Viant, M. R., Rosenblum, E. S. and Tjeerdema, R. S. (2003). NMR-based metabolomics: A powerful approach for characterizing the effects of environmental stressors on organism health. *Environmental Science and Technology,* 37, 4982-4989.

Verpoorte, R., Choi, Y. H. and Kim, H. K. (2007). NMR-based metabolomics at work in phytochemistry. *Phytochemistry Reviews*, 6 (1), 3-14.

Waisundara, V. Y., Hsu, A., Tan, B. K. and Huang, D. (2009). Baicalin reduces mitochondrial damage in streptozotocin-induced diabetic Wistar rats. *Diabetes/Metabolism Research and Reviews*, 25 (7), 671-677.

Wan, C., Yuan, T., Cirello, A. L. and Seeram, N. P. (2012). Antioxidant and α-glucosidase inhibitory phenolics isolated from highbush blueberry flowers. *Food Chemistry*, 135, 1929-1937.

Wang, M., Shao, Y., Li, J., Zhu, N., Rangarajan, M., La Voie, E. J. and Ho, C. (1999). Antioxidative phenolic glycosides from sage (*Salvia officinalis*). *Journal of. Natural Products*, 62 (3), 454-456.

Wang, Y., Tang, H., Nicholson, J. K., Hylands, P. J., Sampson, J., Whitcombe, I., Stewart, C. G., Caiger, S., Oru, I. and Holmes, E. (2004). Metabolomic strategy for the classification and quality control of phytomedicine: A case study of chamomile flower (*Matricaria recutita* L.). *Planta Medica*, 70 (3), 250-255.

Wang, Y., Tang, H., Nicholson, J. K., Hylands, P. J., Sampson, J. and Holmes, E. (2005). A metabolomics strategy for the detection of the metabolite effects of chamomile (*Matricaria recutita* L.) ingestion. *Journal of Agricultural and Food Chemistry*, 53 (2), 191-196.

Wang, H., Du, Y.J. and Song, H. C. (2010). α-Glucosidase and α-amylase inhibitory activities of guava leaves. *Food Chemistry*, 123 (1), 6-13.

Wang, H., Liu, T. and Huang, D. (2013). Starch hydrolase inhibitors from edible plants. *Advance in Food and Nutrition Research*, 70, 103-136.

Ward, J. L., Forcat, S., Beckmann, M., Bennett, M., Miller, S. J. and Baker, J. M. (2010). The metabolic transition during disease following infection of *Arabidopsis thaliana* by *Pseudomonas syringae* pv. tomato. *The Plant Journal*, 63 (3), 443- 457.

Waszkowiak, K. and Gliszczyńska-Świgło, A. (2016). Binary ethanol–water solvents affect phenolic profile and antioxidant capacity of flaxseed extracts. *European Food Research and Technology*, 242 (5), 777-786.

Wei, L., Liao, P., Wu, H., Li, X., Pei, F., Li, W. and Wu, Y. (2008). Toxicological effects of cinnabar in rats by NMR-based metabolic profiling of urine and serum. *Toxicology and Applied Pharmacology*, 227 (3), 417-429.

Wei, X. H., Yang, S. J., Liang, N., Hu, D. Y., Jin, L. H., Xue, W. and Yang, S. (2013). Chemical constituents of *Caesalpinia decapetala* (Roth) Alston. *Molecules*, 22 (1), 1325-1326.

Weiss, J. and Sumpio, B. (2006). Review of prevalence and outcome of vascular disease in patients with diabetes mellitus. *European Journal of Vascular and Endovascular Surgery,* 31 (2), 143-150.
Weljie, A. M., Newton, J., Mercier, P., Carlson, E. and Slupsky, C. M. (2006). Targeted Profiling: Quantitative Analysis of ^{1}H NMR Metabolomics Data. *Analytical Chemistry,* 78 (13), 4430-4442.
Wijekoon, M. M. J. O., Bhat, R. and Karim, A. A. (2011). Effect of extraction solvents on the phenolic compounds and antioxidant activities of bunga kantan (*Etlingera elatior* Jack) inflorescence. *Journal of Food Composition and Analysis,* 24 (4), 615-619.
Wiklund, S., Johansson, E., Sjöström, L., Mellerowicz, E. J., Edlund, U., Shockcor, J. P., Gottfries, J., Moritz, T. and Trygg, J. (2008). Visualization of GC/TOF-MS-based metabolomics data for identification of biochemically interesting compounds using OPLS class models. *Analytical Chemistry,* 80 (1), 115-122.
Wishart, D. S. (2008). Metabolomics: Applications to food science and nutrition research. *Trends in Food Science and Technology,* 19 (9), 482-493.
Wong, C.-C., Li, H.-B., Cheng, K.-W. and Chen, F. (2006). A systematic survey of antioxidant activity of 30 Chinese medicinal plants using the ferric reducing antioxidant power assay. *Food Chemistry,* 97, 705-711.
World Health Organization (WHO). (1999). Definition, diagnosis and classification of diabetes mellitus and its complication, department of non-communicable diseases surveillance Geneva, Part 1 Diagnosis and classification of diabetes mellitus:2.
Wresdiyati, T., Sa'diah, S., Winarto, A. and Febriyani, V. (2015). Alpha-glucosidase inhibition and hypoglycemic activities of *Sweitenia mahagoni* seed extract. *HAYATI Journal of Biosciences,* 22 (2), 73-78.
Wu, W., Yan, C., Li, L., Liu, Z. and Liu, S. (2004). Studies on the flavones using liquid chromatography-electrospray ionization tandem mass spectrometry. *Journal of Chromatography A,* 1047 (2), 213-220.
Wyzgoski, F. J., Paudel, L., Rinaldi, P. L., Reese, R. N., Ozgen, M. and Tulio, A. Z. (2010). Modelling relationships among active components in black raspberry (*Rubus occidentalis* L.) fruit extracts using high-resolution ^{1}H nuclear magnetic resonance (NMR) spectroscopy and multivariate statistical analysis. *Journal of Agricultural and Food Chemistry,* 58 (6), 3407-3414.
Xiao, J., Kai, G., Yamamoto, K. and Chen, X. (2013). Advance in dietary polyphenols as α-glucosidases inhibitors: a review on structure–activity relationship aspect. *Critical Reviews in Food Science and Nutrition,* 53 (8), 818-836.
Xu, Y., Muhamadali, H., Sayqal, A., Dixon, N. and Goodacre, R. (2016). Partial Least Squares with Structured Output for Modelling the Metabolomics Data Obtained from Complex Experimental Designs: A Study into the *Y*-Block Coding. *Metabolites,* 6 (4), 38.
Yang, W., Lu, J., Weng, J., Jia, W., Ji, L., Xiao, J., Shan, Z., Liu, J., Tian, H., Ji, Q., Zhu, D., Ge, J., Lin, L., Chen, L., Guo, X., Zhao, Z., Li, Q., Zhou, Z., Shan, G. and He, J. (2010). Prevalence of diabetes among men and women in China. *New England Journal of Medicine,* 362 (12), 1090-1101.
Yin, Z., Zhang, W., Feng, F., Zhang, Y. and Kang, W. (2014). α-Glucosidase inhibitors isolated from medicinal plants. *Food Science and Human Wellness,* 3, (3-4), 136-174.

You, Q., Chen, F., Wang, X., Jiang, Y. and Lin, S. (2012). Anti-diabetic activities of phenolic compounds in muscadine against alpha-glucosidase and pancreatic lipase. *Food Science and Technology,* 46, 164-168.

Yuhao, L., Wen, S., Prasad-Kota, B., Peng, G., Qian-Li, G., Yamahara, J. and Roufogalis, B. D. (2005). *Punica granatum* flower extract, potent α-glucosidase inhibitors, improves postprandial hyperglycemia in Zucker diabetic fatty rats. *Journal of Ethnopharmacology,* 99, 239-244.

Yusoff, N. A. H., Sanuan, F. M. and Rukayadi, Y. (2015). *Cosmos caudatus* Kunth. extract reduced number of microflora in oyster mushroom (*Pleurotus ostreatus*) *International Food Research Journal*, 22 (5), 1837-1842.

Zainudin, M. A. M., Hamid, A. A, Anwar F., Osman, A. and Saari, N. (2014). Variation of bioactive compounds and antioxidant activity of carambola (*Averrhoa carambola* L.) fruit at different ripening stages. *Scientia Horticulturae,* 172, 325-331.

Zawiah, D. (2007). Direct costs of treating diabetic foot in orthopaedic ward, Hospital Universiti Sains Malaysia, Department of Community Medicine, Universiti Sains Malaysia, Kelantan. Master Dissertation.

Zewdie, Y. and Bosland, P. W. (2000). Evaluation of genotype, environment, and genotype by-environment interaction for capsaicinoids in *Capsicum annuum* L. *Euphytica,* 111 (3), 185-190.

Zhang, Q., Zhang, J., Shen, J., Silva, A., Dennis, D. A. and Barrow, C. J. (2006). A simple 96-well microplate method for estimation of total polyphenol content in seaweeds. *Journal of Applied Phycology*, 18 (3), 445-450.

Zhang, Z. S., Li, D., Wang, L. J., Ozkan, N., Chen, X. D., Mao, Z. H. and Yang, H. Z. (2007). Optimization of ethanol–water extraction of lignans from flaxseed. *Separation and Purification Technology,* 57 (1), 17-24.

Zhang, J., Wider, B., Shang, H., Li, X. and Ernst, E. (2008). Quality of herbal medicines: challenges and solutions. *Complementary Therapies in Medicine,* 20, 100-106.

Zheng, W. and Wang, S. (2001). Antioxidant activity and phenolic composition in selected herbs. *Journal of Agricultural and Food Chemistry,* 49, 5165-5170.

Zin, Z. M., Hamid, A. A. and Osman, A. (2002). Antioxidative activity of extracts from mengkudu (*Morinda citrifolia* L.) root, fruit and leaf. *Food Chemistry*, 78 (2), 227-231.