PROTEIN EXPRESSION PROFILING OF *Orthosiphon aristatus* (Blume) Miq AND MOLECULAR DYNAMICS SIMULATION OF TRANSKETOLASE WITH ANTIDIABETIC POTENTIAL

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DEDICATION

This thesis is dedicated to my father, who always give me motivation, support and believed that I can do it whatever I want to. It is also dedicated to my beloved late mother, who always give me strength to accomplish all the tasks I have.

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ABSTRACT

Orthosiphon aristatus (Blume) Miq is a well-known medicinal plant widely commercialized especially as tea product to promote health. However, to date, the proteome of *O. aristatus* has never been studied. Hence, this study used four approaches; one-dimensional (1D) and two-dimensional (2D) proteomics, antidiabetic assay and bioinformatics to analyze the leaves proteome of *O. aristatus*. Protein from fresh and dried leaves (microwave-drying, halogen oven-drying and freeze-drying) was extracted using phenol/sodium dodecyl sulphate (SDS) buffer with three preliminary washes and separated by sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE) to check the quality. Subsequently, antioxidant assays; ferric reducing antioxidant power (FRAP) and 2,2-diphenyl-1-picrylhydrazyl (DPPH) were performed on the protein to identify a suitable drying method with minimum effect on plant's beneficial content as it is highly consumed as tea product. Microwave-drying was the most suitable drying method for *O. aristatus* as it produced better protein quality (859.49 ± 5.98 µg/mL, 14 protein bands detected) with high antioxidant activity (71.5% free radical scavenging activity, 1426.13 Fe^{2+}mM/g). Thus, only fresh and microwave-dried leaves protein were further used for subsequent study. Over 1000 proteins were identified from fresh and dried leaves using Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS) with 43 proteins found to be similar for both samples. The profiled proteins were obviously affected by heat stress, where proteins with known anticancer property such as thioredoxin were only present in fresh leaves whereas myrosinase and glutathione were only extracted from dried leaves. Protein expression profile of fresh and dried leaves using 2D approach was analyzed with PDQuest software. Fresh and dried leaves have 202 and 106 spots of different distribution pattern on 2D gel respectively. Via PDQuest analysis, 32 distinct spots were detected from fresh leaves but not dried leaves and 12 spots with 2-fold expression detected from both types of leaves. Fresh and dried leaves protein also showed potential antidiabetic activity from inhibitions of glucose diffusion, α-amylase and α-glucosidase. Subsequently, one of the identified proteins, Transketolase (TKT) which plays a crucial role in preventing diabetes complications, was studied further in terms of its thermostability using molecular dynamics (MD) simulation at different temperature (310 K, 368 K, 373 K, 423 K, 453 K and 473 K) and interaction with its ligand, thiamine diphosphate (TPP) via Autodock Vina. The MD results indicated that TKT is a thermostable protein but TKT and TKT-TPP complex may start to denature when exposed to temperature beyond boiling point. Gln237, Ser242, Cys246, Arg283 and Phe284 were identified as the possible TPP binding sites. Taken together, the findings provide a snapshot of fresh and dried leaves proteome of *O. aristatus* showing that the plant protein exhibited antioxidant and antidiabetic activities. The protein expression profile of *O. aristatus* could also be used for quality control purpose as a biomarker for *O. aristatus*. TKT bioinformatics information provided pharmacological insight that can accelerate drug design process.

ABSTRAK

Orthosiphon aristatus (Blume) Miq merupakan tumbuhan perubatan terkenal dikomersialkan secara meluas terutamanya sebagai produk teh untuk meningkatkan kesihatan. Walaubagaimanapun, sehingga kini, maklumat proteom *O. aristatus* masih belum pernah dikaji. Oleh itu, kajian ini menggunakan empat pendekatan; proteomik 1-dimensi (1D) dan 2-dimensi (2D), asai antidiabetik dan bioinformatik untuk menganalisa proteom daun *O. aristatus*. Protein daripada daun segar dan kering (pengeringan gelombang mikro, pengeringan ketuhar halogen dan pengeringan beku) telah diesktrak menggunakan penimbal fenol/sodium dodesil sulfat (SDS) dengan tiga pembersihan awal dan dipisahkan menggunakan electrophoresis gel sodium dodesil sulfat-poliakrilamida (SDS-PAGE) untuk pemeriksaan kualiti. Seterusnya, ujian antioksida; *ferric reducing antioxidant power* (*FRAP*) dan 2,2-difenil-1-pikrilhidrazil (DPPH) dilakukan ke atas protein untuk mengenalpasti kaedah pengeringan yang sesuai dengan kesan minimum pada kandungan bermanfaat tumbuhan kerana ia digunakan sebagai produk teh. Pengeringan gelombang mikro adalah cara pengeringan yang paling sesuai untuk *O. aristatus* kerana menghasilkan kualiti protein yang lebih baik (859.49 ± 5.98 µg/mL, 14 jalur protein dikesan) dengan aktiviti antioksida yang tinggi (71.5% aktiviti skavengan radikal bebas, 1426.13 $Fe^{2+}mM/g$). Oleh itu, hanya protein daun segar dan dikeringkan melalui gelombang mikro digunakan untuk kajian selanjutnya. Lebih 1000 protein telah dikenalpasti daripada daun segar dan kering menggunakan Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS) dengan 43 protein adalah sama bagi kedua-dua sampel. Protein terprofil didapati terjejas oleh haba, di mana protein yang diketahui bersifat antikanser seperti tioredoksin hanya terdapat dalam daun segar manakala mirosinase dan glutation hanya diesktrak daripada daun kering. Profil pengekspressan protein daun segar dan kering menggunakan kaedah 2D telah dianalisa menggunakan perisian PDQuest. Daun segar dan kering masing-masing mempunyai 202 dan 106 titik protein dengan corak sebaran atas 2D yang berbeza. Melalui analisis PDQuest, 32 titik dikesan pada daun segar tetapi tidak pada daun kering dan 12 bintik dengan pengekspresan dua kali ganda dikesan pada kedua-dua jenis daun. Protein daun segar dan kering juga menunjukkan potensi aktiviti antidiabetik melalui perencatan sebaran glukosa, α-amilase dan α-glukosidase. Salah satu protein yang dikenalpasti, transketolase (TKT) yang diketahui memainkan peranan penting dalam pencegahan komplikasi diabetes, telah dikaji lebih lanjut dari segi termostabiliti menggunakan simulasi dinamik molekul (MD) pada suhu yang berbeza (310 K, 368 K, 373 K, 423 K, 453 K and 473 K) dan interaksi dengan ligannya, tiamin difosfat (TPP) melalui Autodock Vina. Keputusan MD menunjukkan TKT adalah protein stabil-suhu tetapi TKT dan juga kompleks TKT-TPP mungkin mula dinyahasli apabila terdedah kepada suhu di atas paras didih. Gln237, Ser242, Cys246, Arg283 and Phe284 telah dikenalpasti berkemungkinan menjadi tapak pengikatan TPP. Kesimpulannya, hasil kajian memberi gambaran proteom daun segar dan kering *O. aristatus* dan menunjukkan protein tumbuhan ini mempunyai bioaktiviti antioksida dan antidiabetik. Profil ekspresi protein *O. aristatus* juga boleh digunakan sebagai biopenanda untuk pengawalan kualiti. Maklumat bioinformatik TKT memberi pandangan fakmakologi yang dapat mempercepatkan proses reka bentuk ubat.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

1D	-	One-dimensional
1-DE	-	One-dimensional Gel Electrophoresis
2D		Two-dimensional
2-DE		Two-dimensional Gel Electrophoresis
3D	-	Three-dimensional
ABTS	-	2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonc acid)
ACE	-	Angiotensin-converting Enzyme
APS	-	Ammonium Persulfate
AtBRCA2	-	*Arabidopsis* Breast Cancer 2 Like 2A Protein
BRCA2	-	Breast Cancer 2 Like 2A Protein
BSA	-	Bovine Serum Albumin
CBB-R	-	Coomassie Brilliant Blue-Red
DAG-PKC	-	Diacylglycerol-Protein Kinase C
DIGE	-	Difference Gel Electrophoresis
DPP-4	-	Dipeptidyl Peptidase-4
DPPH	-	1,1-diphenyl-2-picrylhydrazyl
DTT	-	Dithiothreitol
FeSO4.7H2O	-	Iron (II) Sulphate Heptahydrate
FRAP	-	Ferric Reducing Antioxidant Power
GO	-	Gene Ontology
GROMACS	-	Groningen Machine for Chemical Simulations
GRX	-	Glutaredoxin
GST	-	Glutathione S-transferase
HMGB1	-	High Mobility Group Box-1
HSOS	-	Hepatic Sinusiodal Obstruction Syndrome
HSP	-	Heat Shock Protein
HTKT	-	Human TKT
IAA	-	Iodoacetamide
IEF	-	Isoeletric Focusing
IPG	-	Immobilized pH Gradient

I-TASSER	-	Iterative Threading Assembly Refinement
ITCs	-	Isothiocyanates
LC-MS/MS	-	Liquid Chromatography Tandem Mass Spectrometry
MD	-	Molecular Dynamics
MS	-	Mass Spectrometry
MS/MS	-	Tandem Mass Spectrometry
MTKT	-	Maize TKT
MW	-	Molecular Weight
NADPH	-	Nicotinamide Adenine Dinucleotide Phospahte
NCBI	-	National Center for Biotechnology Information
NF-κB	-	Nuclear Factor kappa B
NMR	-	Nuclear Magnetic Resonance
OATKT	-	TKT from *O. aristatus*
PDB	-	Protein Data Bank
PPP	-	Pentose Phosphate Pathway
PRX	-	Peroxidase
Rg	-	Radius of Gyration
RMSD	-	Root Mean Square Deviation
RMSF	-	Root Mean Square Fluctuation
ROS	-	Reactive Oxygen Species
RSA	-	Radical Scavenging Activity
S.D	-	Standard Deviation
SDS	-	Sodium Dodecyl Sulphate
SDS-PAGE	-	Sodium Dodecyl Sulphate Polyacrylamide Gel Electrophoresis
SEM	-	Standard Error Mean
SM	-	Secondary Metabolism
SPC	-	Simple Point Charge
SPC/E	-	Extended Simple Point Charge
TEMED	-	Tetramethylethylenediamine
TIP3P	-	Transferable Intermolecular Potential 3P
TIP4P	-	Transferable Intermolecular Potential 4P
TKT	-	Transketolase

TPC	-	Total Phenolic Content
TPP	-	Thiamine Diphosphate
TPTZ	-	2,4,6-tri(2-pyridyl)-s-triazine
Tris-HCl	-	Tris Hydrochloride
UTM		Universiti Teknologi Malaysia
WHO	-	World Health Organization
YASARA	-	Yet Another Scientific Artificial Reality Application

LIST OF SYMBOLS

α		Alpha
Å	-	Angstorm
β		Beta
°C	-	Degree Celsius
<	-	Less than
%	-	Percent
Cl^-	-	Chloride ion
•OH	-	Hydroxyl Radical
Da	-	Dalton
IC_{50}	-	Half of the Inhibition Concentration
K	-	Kelvin
K^+	-	Potassium ion
kDa	-	Kilodalton
M	-	Moles
µg	-	Microgram
µL	-	Microlitre
µm	-	Micrometre
mM	-	Millimoles
mmHg	-	Manometric Unit of Pressure
m/z	-	Mass/Charge
Na^+	-	Sodium ion
ng	-	Nanogram
nL	-	Nanolitre
nm	-	Nanometer
ns	-	Nanosecond
pI	-	Isoelectric Point
rpm	-	Revolution per Minute
U	-	Unit
V	-	Voltage
v/v	-	Volume per Volume

w/v	-	Weight per Volume

LIST OF APPENDICES

CHAPTER 1

INTRODUCTION

1.1 Background of Study

In today's world, the medicinal plants have attracted scientists' interest to employ the bioactive compounds as primary sources for early drug discovery (Veeresham, 2012) due to the side effect of synthetic drugs. In recent years, there is a breakthrough in medical field where researchers found that protein or peptides from natural products could be used as therapeutic agent to treat diseases as they exhibit potent pharmacological activities such as plant protein and peptides possess anti-tumor activity (Tepkeeva *et al*., 2008). At the same time, there is rapid growth in the consumption of herbal products as primary health care globally since public perceived herbal products as safe because they are naturally occurring and used for treatment from decades ago (Liu *et al.*, 2016). Thus, comprehensive authentication of herbs' components such as bioactive compounds and protein is necessary in order to ensure the quality of the medicines produced.

Orthosiphon aristatus (Blume) Miq is one of the famous traditional medicinal plants in Malaysia which is widely used as folk medicines for the treatment of many diseases such as diabetes and kidney problems (Chin *et al.*, 2008). Most of the studies related to the plant was mainly focused on its phytochemical content. The first paper of *O. aristatus* was published in 1973, focusing flavonoid (Matsuura *et al*., 1973). Alshawsh *et al.* (2011) reported that the most important constituents from *O. aristatus* are nine lipophilic flavones, two flavonol glycosides and nine caffeic acid derivatives. The presence of phytochemical contents such as phenolic compounds were attributed to the pharmacological activities of the plant including diuretic, antidiabetic, antioxidant, anti-inflammatory, antihypertensive, antiobesity and antitumor activities (Adnyana *et al.*, 2013). Thus, the leaves of the plant had been commercialized as herbal product especially tea product aiming to benefit human health as people

awareness about the health benefits of herbal tea is increasing. Drying process is the common practice applied to the commercialized products in order to extend the products' shelf life. Despite of it, the drying process may cause side effect on food quality if improper drying technique was applied. Although many compounds from this plant have been isolated and studied, detailed proteomics study on both *O. aristatus* fresh and dried leaf remains unknown.

Proteomics can be defined as a large scale protein analysis from any organism, tissue or cell and now it becomes a powerful tool in the field of biology research as it is able to reveal details about how the protein function, regulation and the interaction of proteins (Mirzaei *et al.*, 2016). Until now, many proteome of medicinal plants' have been studied using two dimensional gel electrophoresis (2-DE) and tandem mass spectrometry including *Gynura procumbens* (Hew and Gam, 2011), *Piper sarmentosum* (Shim and Gam, 2012), *Clematis chinensis* (Ishtiaq *et al*., 2014), *Gingko biloba* (Uvackova *et al*., 2014), *Phyllanthus niruri* (Nail and Zin, 2015) and *Withania somnifera* (Singh *et al*., 2017). The two-dimensional (2-DE) result or protein spot distribution pattern can be used as a reference map for quality control of different herbal drugs (Ishtiaq, 2013). Meanwhile, mass spectrometry analysis is able to explore the complete proteome of the plant. Usually, the main focus will be the defense and stress-related proteins as they may also contribute to the plant's medicinal value such as antibacterial and antioxidant activities (Shim and Gam, 2012).

Antioxidant sources are gaining high demands in market as many reports suggested that antioxidant compounds is able to eliminate free radicals or reactive oxygen species (ROS) in the body and thus can prevent oxidative damage-related diseases such as coronary heart disease, cancer, aging and Alzheimer's disease (Szymanska *et al*., 2016). Antioxidant can be defined as any compound which can prevent, eliminate or delays oxidative damage in cells (Halliwell, 2007) through donation of proton or electron (Aruoma *et al*., 1993). Diabetes is one of the diseases without cure even in today's world and the worst thing is the current treatments for diabetes such as insulin injection and antidiabetic drugs will cause side effects on human health. For example, metformin may cause gastrointestinal problems (Chaudhury *et al*., 2017) and deficiency of vitamin B12 and folic acid that leading to

anemia and neuropathy (Fogelman *et al*., 2017). Meanwhile, insulin injection may cause lipoatrophy and lipohypertrophy at sites of injection and allergy reaction (Chaudhury *et al*., 2017). Hence, the researchers are trying to find alternative therapeutic approach from natural sources. To date, there are many antidiabetic proteins or peptides have been reported (Rajasekhar *et al*., 2010; Mendes *et al*., 2014; Admassu *et al*., 2018). For instance, catalase and trehalose phosphorylase are the identified proteins from grey oyster mushroom that may associate in combating diabetes (Wahab *et al*., 2014) as catalase is able to enhance insulin secretion and sentization whereas trehalose phosphate plays a crucial role in starch, sucrose and glucose metabolism (Christian and Nidetzky, 1999). Besides, bean peptide from Pinto bean (Ngoh and Gan, 2016) and LAPSLPGKPKPD peptide from egg yolk protein (Zambrowicz *et al*., 2015) are considered as antidiabetic peptides due to its possible role in inhibiting α-amylase and α-glucosidase respectively. Nevertheless, the potential of *O. aristatus* protein in combating diabetes is still not yet known.

Bioinformatics is gaining popularity in plant proteome studies in order to obtain detailed understanding of protein three-dimensional (3D) structure, protein-protein interaction and protein-ligand interaction. Molecular dynamics (MD) simulation analysis is always being used to study the behaviour of the protein at varied conditions. For example, MD simulation is able to reveal the structural flexibility of malate dehydrogenase from marine molluscs and how the protein can adapt to the different temperature conditions (Dong *et al*., 2017). Transketolase (TKT) protein from *O. aristatus* is of particular interest because we believed that TKT may be a useful protein that can be used to prevent the side effects of diabetes based on its function which can inhibit three biochemical pathways implicated in the pathogenesis of hyperglycemia induced-vascular damage (hexosamine pathway, advanced glycation end product formation pathway and diacylglycerol-protein kinase c pathway) by converting fructose-6-phosphate and glyceraldehyde-3-phosphate into pentose-5-phosphate and other sugars (Hammes *et al*., 2003). Nevertheless, the properties of TKT little known.

1.2 Problem Statement

O. aristatus is a plant known for its medicinal properties from both the traditional background and scientific research and is commonly known as Java tea. In Malaysia, *O. aristatus* has been used as traditional medicine especially the leaves in diabetes, urinary lithiasis, edema, hypertension, diuretic, inflammation, jaundice, eruptive fever, hepatitis, rheumatism, and as a remedy for kidney stones (Shafaei *et al.*, 2015). Due to its pharmacological properties, the plant has been widely produced as herbal products to maintain human health. To date, lots of studies have been done on the plant, majorly on its phytochemical contents and many chemical compounds especially the secondary metabolites of the plant were isolated and identified. Many studies reported that the pharmacological activities of the plant are associated with the presence of the phytochemical compounds (Arafat *et al*. 2008; Mohamed *et al*., 2011; Al-Suede *et al*., 2012; Ripin *et al*., 2018). Nevertheless, protein is arising as a therapeutic source to treat human diseases nowadays because protein is able to be engineered to enhance its functionality, half-life and drug efficacy (Lutz, 2010; Tobin *et al*., 2014). According to Lagasse *et al*. (2017), certain therapeutic protein drugs have been approved as therapies for the patients. Thus, it is important to explore the potent proteins' bioactivity especially protein from medicinal plants as the protein may be associated with its medicinal value. Yet, the information of *O. aristatus* protein is lacking although many studies have been done on the plant. It is worth to explore the *O. aristatus* protein due to the fact that protein can become an alternative source in producing medicines for diseases. Moreover, it is necessary to know the drying effect on *O. aristatus* protein since it has been highly produced as products in dry form.

1.3 Significance of Work

Through this study, protein profiling and protein expression profile of fresh and dried leaf were provided. It is valued to study the protein of *O. aristatus* because protein is the direct product from central dogma and involved in all the biological process as all the enzymes are protein. From the protein profiling of fresh and dried leaf, it can provide knowledge on the plant growth and development process and how

the plant cope with heat stress. In addition, the protein profile could also be useful for finding proteins with potent beneficial property and the expression profile could be used as a reference map for drug quality control. Besides, the antioxidant and antidiabetic activity of *O. aristatus* fresh and dried leaf protein were explored in this study using *in vitro* study. The results obtained were very crucial as it is revealed that proteins from *O. aristatus* also attributed to therapeutic value besides its phytochemical compounds. At the same time, it also provides insight that the antioxidant and antidiabetic activity of the protein was affected by drying process. Furthermore, potential protein with antidiabetic activity from the plant was studied further using bioinformatics analysis to explore its thermostability and docking mechanism with the ligand because the plant had been claimed to be effective in alleviate diabetes. This kind of insight may give a great impact in pharmaceutical industries as it could reveal the properties of the protein and thus can save time for the whole process of drug design.

1.4 Objectives of Research

The objectives of this study were:

(a) To profile the protein of *O. aristatus* from fresh and manually dried leaf for further comparison of 2-DE expression.

(b) To determine the antidiabetic activity of fresh and manually dried leaf protein from *O. aristatus*.

(c) To predict thermostability and docking mechanism of selected protein with antidiabetic potential from profiled protein.

1.5 Scope of Research

The scope of this study is to profile and analyse protein of *O. aristatus* fresh and dried leaf. In this study, the protein from fresh and dried leaf (microwave-dried, freeze-dried and halogen oven-dried) were used for extraction by using modified phenol/SDS buffer with three preliminary washes. The protein obtained was quantified using Bradford assay and the quality was checked via sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE) where its electrophoretic pattern was determined. Furthermore, the protein from fresh and dried leaf was further used to quantity antioxidant activity via 1,1-diphenyl-2-picrylhydrazyl (DPPH) and ferric reducing antioxidant power (FRAP) assays in order to determine the antioxidant activity of the protein. Then, the most suitable drying method for the leaf was chosen based on the protein quantity, quality and its antioxidant activity. After that, the protein from fresh and the best dried leaf was tryptic-digested and sent for liquid chromatography tandem mass spectrometry (LC-MS/MS). Spectral results obtained from LC-MS/MS was analyzed and searched against National Center for Biotechnology Information (NCBI) database. After that, the identified proteins were classified based on functional categorization of gene ontology (GO). To compare 2-DE expression pattern of fresh and dried leaf, the protein from fresh and dried leaf was run using 17 cm IPG strip, pH 4-7, 8000 focusing voltage. The number of protein spots and the expression level of the protein in fresh and dried leaf were compared using PDQuest software (Biorad, CA, USA). Apart from that, the antidiabetic activity of the fresh and dried leaf protein was determined in the study through *in vitro* studies via glucose diffusion, α-amylase and α-glucosidase inhibition. Lastly, TKT as one of the identified proteins with potential antidiabetic property was selected to perform molecular simulation at different temperatures (310 K, 368 K, 373 K, 423 K, 453K and 473 K) using GROningen MAChine for Chemical Simulations (GROMACS) software version 5.0.4 to determine its thermostability as well as molecular docking with its ligand, TPP using Autodock in order to know the protein-ligand interaction.

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LIST OF PUBLICATIONS

Journal with Impact Factor

1. **Ng, M. L**., Shahir, M. S. & Zaidah, R. (2019). Molecular modeling and simulation of transketolase from *Orthosiphon stamineus*. Current Computer-Aided Drug Design. 10.2174/1573409914666181022141753. **(Q4, IF: 0.77)**

Non-Indexed Conference Proceedings

1. **Ng, M. L**., Usman, K. & Zaidah, R. (2016). Leaf proteome and simulation of transketolase from *Orthosiphon stamineus*. In *International Conference on Biosciences & Medical Engineering* (pp. 125). ICBME2016.

2. **Ng, M. L**., Shahir, M. S & Zaidah, R. (2017). Molecular docking and simulation of transketolase from *Orthosiphon stamineus*. In *International Postgraduate Symposium in Biotechnology 2017* (pp. 1-5). Universiti Teknologi Malaysia.

3. **Ng, M. L**., Shahir, M. S & Zaidah, R. (2018). Optimization of two-dimensional gel electrophoresis for *Orthosiphon stamineus* leaf proteome analysis. In *7th International Graduate Conference of Engineering, Science and Humanities* (pp.482-484). Universiti Teknologi Malaysia.

4. **Ng, M. L.**, Shahir, M. S. & Zaidah, R. (2019). Effect of hot and cold infusion of *Orthosiphon stamineus* on the antioxidant activity. In *2nd International Conference on Biosciences and Medical Engineering* (pp. 15). Universiti Teknologi Malaysia.

Book Chapter

1. **Ng, M. L**. & Zaidah, R. (2018). Impact of various drying methods on plant nutrient. In *Plant Science and Its Application* (167-190). Universiti Teknologi Malaysia.