UNIVERSITI PUTRA MALAYSIA

ANTIOXIDANT PROPERTIES, BIOACCESSIBILITY AND BIOAVAILABILITY OF POLYPHENOL FROM MANGIFERA INDICA L. (WATER LILY VAR.) USING IN VITRO MODEL

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By

MARINA ZULKIFLI

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

November 2018

DEDICATION

This thesis is dedicated to:

My lovely husband

Whose love, understanding and sacrificial care for me and our children

My three brilliant children

Whose always be my pillar of strength

My beloved father and mother

Whose support and prays of day and night

Along with all respected Supervisory Committee

All made it possible for me to complete this PhD journey.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

ANTIOXIDANT PROPERTIES, BIOACCESSIBILITY AND BIOAVAILABILITY OF POLYPHENOL FROM *Mangifera indica* L. (Water Lily Var.) USING *In Vitro* MODEL

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Chairman : Professor Amin Bin Ismail, PhD
Faculty : Medicine and Health Sciences

The fruit of *Mangifera indica* L. (Water Lily variety) is a mango variety commonly found in Malaysia and Thailand. Its size is about 14 cm length and 7 mm width and a long kidney-shaped. However, limited study done on Water Lily mango pulp related to its quality, digestion and absorption, in which its fate is not totally understand. For the first time, a study on investigating the nutritional composition and physicochemical properties of Water Lily mango pulp were determined. The antioxidant properties of the pulp, together with its polyphenol profile was also evaluated. The bioaccessibility and bioavailability of polyphenol were investigated using an *in vitro* simulation gastrointestinal digestion model and *in vitro* Caco-2 cell model, respectively. The nutritional content of pulp was in the order of moisture > carbohydrate > protein > dietary fibre > ash > fat. For sugar analysis, sucrose found to be the highest sugar followed by fructose and glucose whereas for mineral test, potassium was the greatest amount compared to other elements determined such as calcium, sodium, magnesium and iron. Meanwhile, results on physicochemical characteristics indicated that the pulp had high total soluble solid.

The extract of Water Lily mango pulp has demonstrated to possess high amount of antioxidant constituents such as polyphenols. The antioxidant capacity as well as its polyphenols profile was investigated by using high performance liquid chromatography (HPLC) and liquid chromatography-mass spectroscopy (LC-MS). The antioxidant capacity of Water Lily pulp extract (WLPE) exhibited a good potential as electron donors and radical scavenger, as determined by Ferric Reducing Antioxidant Power (FRAP) and 1,1-diphenyl-2-picrylhydrazyl (DPPH) assays, respectively. Ten polyphenols were identified and quantified in WLPE with descending order; gallic acid > catechin

hydrate > mangiferin > protocatechuic acid > chlorogenic acid > ellagic acid > rutin > myricetin > daidzein > apigenin.

In bioaccessibility study, the *in vitro* simulated gastrointestinal digestion was applied to determine the bioaccessible fraction recovered in two digestion phases; gastric phase and intestinal phase. Among all identified compounds, apigenin was selected as a target compound to be further studied on the bioaccessibility and bioavailability due to its stability in acidic and alkaline environments during gastrointestinal digestion. Results showed that the amount of apigenin after 1 h subjected to acidic gastric condition was significantly reduced ($p<0.05$) from 2.48 mg/100 dry weight (DW) to 0.5 mg/100g DW. After 2 h exposed to mild alkaline condition, the bioaccessible apigenin increased significantly ($p<0.05$) to 1.03 mg/100g DW. The percentage bioaccessibility of apigenin was found to be higher in intestinal digestion than gastric digestion with 41.53% and 20.26%, respectively.

Investigation on bioavailability was carried out by determining the absorption and transport of bioaccessible apigenin into Caco-2 human intestinal cell using the reliable and sensitive analytical method of LC-MS/MS. Results revealed that the concentration of glucuronidated apigenin lower than apigenin. The apigenin was metabolised inside the cells through glucuronidation process, and cross the monolayer to reach the basolateral sides or effluxed back to the apical side. The permeability coefficient of apigenin from apical to basolateral sides and basolateral to apical sides showed a medium permeability as the value was less than 20 $x10^{-6}$ $cm.sec^{-1}$. Since the value of efflux ratio was 1.5, it suggested that the apigenin has been absorbed and transported through the simple diffusion mechanism.

Taken together, the findings of present study highlight the nutritional value of Water Lily mango pulp and its valuable compounds. Although the utilisation of *in vitro* model is not fully responding the physiological and morphological features of human *in vivo* conditions, it can be a useful tool for evaluating the mechanistic effects of phenolic compound released from the food matrix.

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

CIRI ANTIOKSIDAN, BIOAKSESIBILITI DAN BIOAVAILABILITI POLIFENOL DARI *Mangifera indica* L. (Water Lily) MENGGUNAKAN MODEL *In Vitro*

Oleh

MARINA ZULKIFLI

November 2018

Pengerusi : Profesor Amin Bin Ismail, PhD
Fakulti : Perubatan dan Sains Kesihatan

Mangifera indica L. (Water Lily) adalah sejenis buah mangga yang biasanya ditemui di Malaysia dan Thailand. Saiznya adalah 14 cm panjang dan 7 mm lebar dengan bentuk ginjal panjang. Bagaimanapun, kajian yang terhad dilakukan ke atas isi mangga Water Lily terhadap kualiti, penghadaman dan penyerapan, di mana nasibnya tidak difahami sepenuhnya. Untuk pertama kalinya, kajian terhadap komposisi pemakanan dan sifat fizikokimia isi mangga Water Lily ditentukan. Ciri-ciri antioksida isi buah bersama dengan profil polifenolnya juga dinilai. Bioaksesibiliti dan bioavailabiliti polifenol dikaji, masing-masing menggunakan model *in vitro* simulasi penghadaman gastrousus dan *in vitro* model sel Caco-2. Kandungan pemakanan isi mangga dalam urutan kelembapan > karbohidrat > protein > serat diet > abu > lemak. Untuk ujian gula, sukrosa adalah gula yang paling tinggi diikuti dengan fruktosa dan glukosa manakala untuk ujian mineral, kalium adalah kandungan yang paling banyak berbanding dengan elemen lain yang ditentukan seperti kalsium, natrium, magnesium dan besi. Sementara itu, keputusan ciri-ciri fizikokimia menunjukkan bahawa isi mangga Water Lily mempunyai kandungan pepejal terlarut yang tinggi.

Ekstrak isi mangga Water Lily (WLPE) menunjukkan ia mempunyai amaun sebatian antioksida yang tinggi seperti polifenol. Kapasiti antioksida dan profil polifenol dikaji menggunakan kromatografi cecair berprestasi tinggi dan kromatografi cecair spektroskopi jisim. Kapasiti antioksida isi mangga Water Lily menunjukkan potensi penderma elektron dan pemangsa radikal yang baik seperti ditentukan oleh asai Kuasa Antioksida Penurunan Ferik dan 1,1-difenil-2-pikrilhidrazil. Sepuluh polifenol di dalalm WLPE telah dikenalpasti dan dikuantitatifkan dengan susunan menurun; asid galic > katekin hidrat >

mangiferin > asid protokatekuik > asid klorogenik > asid elagik > rutin > myricetin > daidzein > apigenin.

Di dalam kajian bioaksesibiliti, *in vitro* simulasi percernaan gastrousus dilakukan untuk menentukan fraksi bioaksesibiliti yang masih ada dalam dua fasa pencernaan; fasa gastrik dan fasa usus. Di antara semua komponen yang dikenalpasti, apigenin telah dipilih sebagai sebatian sasaran untuk kajian selanjutnya ke atas bioaksesibiliti dan bioavailabiliti disebabkan kestabilannya di dalam persekitaran asid dan alkali semasa percernaan gastrousus. Keputusan menunjukkan bahawa kandungan apigenin selepas 1 jam bergantung kepada keadaan asid gastrik menurun secara signifikan ($p<0.05$) dari 2.48 mg/100 berat kering (jumlah permulaan) kepada 0.5 mg/100g berat kering. Selepas 2 jam terdedah kepada keadaan sedikit beralkali, bioaksesibiliti apigenin meningkat secara signifikan ($p<0.05$) kepada 1.03 mg/100g berat kering. Peratus bioaksesibiliti apigenin didapati meningkat di dalam pencernaan usus dari pencernaan gastrik, masing-masing dengan 41.53% and 20.26%.

Kajian ke atas bioavailabiliti di dalam usus telah dilakukan dengan menentukan penyerapan dan pengangkutan bioaksesibiliti apigenin ke dalam sel Caco-2 usus manusia menggunakan kaedah analisis kromatografi cecair spektroskopi jisim/spektroskopi jisim yang boleh dipercayai dan sensitif. Keputusan mendedahkan bahawa kepekatan apigenin glukuronida adalah lebih rendah berbanding dengan apigenin aglikon. Apigenin telah dimetabolisme di dalam sel melalui proses glukuronidasi, dan melintasi monolapisan untuk sampai ke bahagian basolateral atau kembali efluks ke bahagian apikal. Pekali ketelapan apigenin dari bahagian apikal ke basolateral dan basolateral ke apikal menunjukkan ketelapan medium dengan nilai kurang dari 20 $x10^{-6}$ $cm.sec^{-1}$. Oleh kerana nilai nisbah efluks adalah 1.5, ia dicadangkan bahawa apigenin telah diserap dan diangkut melalui mekanisme pembauran mudah.

Diambil bersama, hasil kajian ini menekankan nilai pemakanan isi mangga Water Lily dan sebatian yang bernilai. Walaupun penggunaan model *in vitro* tidak sepenuhnya menunjukkan ciri-ciri fisiologi dan morfologi keadaan *in vivo* manusia, ia boleh menjadi alat untuk menilai kesan mekanistik komponen fenolik yang dibebaskan dari matrik makanan.

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Declaration by graduate student

I hereby confirm that:

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This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
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LIST OF ABBREVIATIONS

A-3	Appendices of chapter 3
ANOVA	Analysis of variance
AOAC	Association of Official Analytical Chemists
BHT	Butylated hydroxytoluene
cm	Centimetre
CO_2	Carbon dioxide
DAD	Diode array detector
DMEM	Dulbecco's Modified Eagle's Medium
DW	Dry weight
DPPH	1,1- Diphenyl-2-picrylhydrazyl
ESI	ElectroSpray Ionization
FBS	Fetal bovine serum
FRAP	Ferric reducing antioxidant power
FW	Fresh weight
GI	Gastrointestinal
HPLC	High performance liquid chromatography
HBSS	Hank's Balance Salt Solution
IC_{50}	Inhibitory concentration
mm	Millimetre
min	Minute
MRPs	Multidrug resistance-related proteins
MS	Mass spectrometry
°C	Degree Celcius
PBS	Phosphate buffer solution

µl	Microlitre
MW	Molecular weight
RI	Refractive index
Rpm	Route per minute
RSA	Radical scavenging activity
sec	Seconds
SD	Standard deviation
SPSS	Statistical package for the social sciences
TPC	Total phenolic content
WLPE	Water Lily pulp extract

CHAPTER 1

INTRODUCTION

1.1 Research background

Fruits are a good source of many biologically active antioxidant compounds (Kiefer *et al*., 2004). Antioxidants found in fruits such as pomegranate, orange, apple and mango reported to be responsible towards positive health outcomes in preventing many chronic diseases such as cancer, diabetes and cardiovascular disease (Rajendran *et al*., 2014; Yu *et al*., 2005). This effect is thought to be achieved by cumulative biological exposure to antioxidants that are able to quench the proliferation of radical oxygen (ROS) and reactive nitrogen (RNS) species which are implicated in the pathology of these diseases (Valko *et al*., 2007). Numerous studies demonstrated that many fruits exhibited high antioxidant activity when tested using biochemical assays such as Ferric Reducing Antioxidant Power (FRAP), 1,1-diphenyl-2-picrylhydrazyl (DPPH), and Oxygen Radical Absorbance Capacity (ORAC) (Netzel *et al*., 2007; Alam *et al*., 2013).

Food, after consumption is subjected to a gastrointestinal (GI) digestion before being absorbed into the intestine (Antonio *et al*., 2009). The antioxidants and other functional compounds in GI can be converted into other components with different bioaccessibility and biological activity. If they are not released from foods, the original antioxidant potential of compounds will be affected (Cerdá *et al.,* 2004; Cilla *et al.,* 2009). In this sense, numerous studies on effects of *in vitro* digestion on dietary polyphenols in fruit are reported (Bermúdez-Soto *et al.,* 2007; Gil-Izquierdo *et al.,* 2001). Besides, in order to exert their biological activities, the absorption and metabolism of polyphenols should be taken into account because only compounds liberated from food matrix are available to be absorbed into epithelium cells (Cerdá *et al.,* 2005; Saura- Calixto *et al.,* 2007).

Further to these investigations, it is necessary to determine the concentration of ingested polyphenols that available to be utilised in the biological system. The term 'bioavailability' refers to the amount of antioxidants that pass through the cell membrane and available for use within the cell. In order to understand the flavonoid impact on human health, it is important to know the nature of the main polyphenols ingested, their dietary origin, amounts consumed in different diets, bioavailability and the factors controlling their bioavailability.

Mango (*Mangifera indica*) is an important tropical fruit belonging to *Anacardiaceae* family with high nutritional and medicinal values. Morphologically, mango belongs to drupe, in which the pericarp is divided into exocarp (peel), fleshy mesocarp (pulp) and stony endocarp (kernel). A ripe

mango possesses a strong aroma, delicious taste, intense peel colouration, as well as great amount of bioactive compounds like phenolic compounds, minerals, β-carotene and vitamin C (Ma *et al*., 2011; Manthey *et al*., 2009; Ribeiro *et al*., 2008).

Water Lily is one of the mango varieties found in Malaysia. The fruit is originated in Thailand, known as Nam Dok Mai. In Malaysia, it is cultivated commercially in Northern Malaysia, such as Perak and Perlis. The size of fruit could vary with 14 cm length and 7 mm width and a long kidney-shaped. The skin is smooth and pale green, rapidly changing to a yellow colour when ripe, and it normally get matured in 4 to 5 months from flowering. The fruit has a sweet taste, juicy, flavourable and firm texture but sometimes a bit mushy. It is one of the delicious seasonal fruit that generally available between June and August and between November and February.

1.2 Problem statements

Flavonoids are widely distributed in fruits, vegetables and plant-derived products. They have several potential nutritional and health-promoting roles in human body, but limited understanding on its absorption characteristics and metabolic pathways make it hard to understand its poor bioavailability, subsequently has become a great problem. Bioavailability of polyphenols greatly affected by its chemical structure, food matrix, as well as interaction with other compounds. These factors may affect the bioavailability directly or by lowering the polyphenol content in food. Much of the evidence on beneficial effects of mango reported to be due to its polyphenol compounds derived from the test conducted *in vitro* or in animal models. Nevertheless, the information on bioaccessibility and bioavailability of polyphenol in mango is scarce, and even less study on absorption of apigenin stated in the literature, in which their fate is not fully understand.

1.3 Significance of the Study

Fruit is a plant with major dietary sources of various antioxidant phytocompounds for humans. Among fruits, mango can be considered as a great source of dietary antioxidant due to the presence of bioactive compounds such as polyphenols, ascorbic acid and carotenoids. To understand the possible beneficial effects of mango polyphenol, particularly apigenin on human health, it is important to determine its metabolic fate. This compound has attracted both consumers and scientific community due to its health benefits in preventing various human diseases. Study on bioavailability of apigenin from others sources such as articoke and parsley has been done but less attention on its intestinal permeability and transport mechanism. As part of the diet, polyphenols ingested as complex mixtures immersed in a food matrix, which undergo a digestion process in the gut. It is necessary to determine how the digestion process affects the apigenin as this, in turn, will

affect its bioavailability within the cell before it takes an action in bioactivity. Hence, the findings can provide scientific information on the intestinal transport of apigenin across the epithelial cells. The bioaccessibility and bioavailability studies will serve as basis for further investigation on health promoting properties of apigenin *in vivo*. In addition, the present study can also give a valuable knowledge on nutritional values and antioxidant properties of mango from specific crop.

1.4 Objectives

1.4.1 General objective

The general objectives of this work were to study the nutritional quality and antioxidant properties of mango (Water Lily var.) pulp and investigate the bioaccessibility and bioavailability of its polyphenol compound using *in vitro* method, with great emphasis on apigenin.

1.4.2 Specific objectives

The specific objectives were as follows:

I. To determine the nutritional quality, physicochemical attributes and polyphenolic profile of Water Lily mango pulp
II. To evaluate the bioaccessibility of apigenin in Water Lily mango pulp using an *in vitro* gastrointestinal digestion model simulating gastric and intestinal phases.
III. To investigate the intestinal permeability and transport of apigenin across epithelial cell monolayers using a Caco-2 cell culture model.

1.5 Structure of the thesis

The work divided into 6 chapters. This chapter (Introduction) provides the background information of the study and an overview of the research problem. The review of literature related to the present study presented in Chapter 2. The nutritional quality, physicochemical properties and polyphenolic profile of studied Water Lily mango pulp described in Chapter 3. Further works to investigate the bioaccessibility and bioavailability of target compound in Water Lily mango pulp, all data discussed in Chapter 4 and Chapter 5, respectively. The findings of study concluded in Chapter 6, together with the recommendations for future works.

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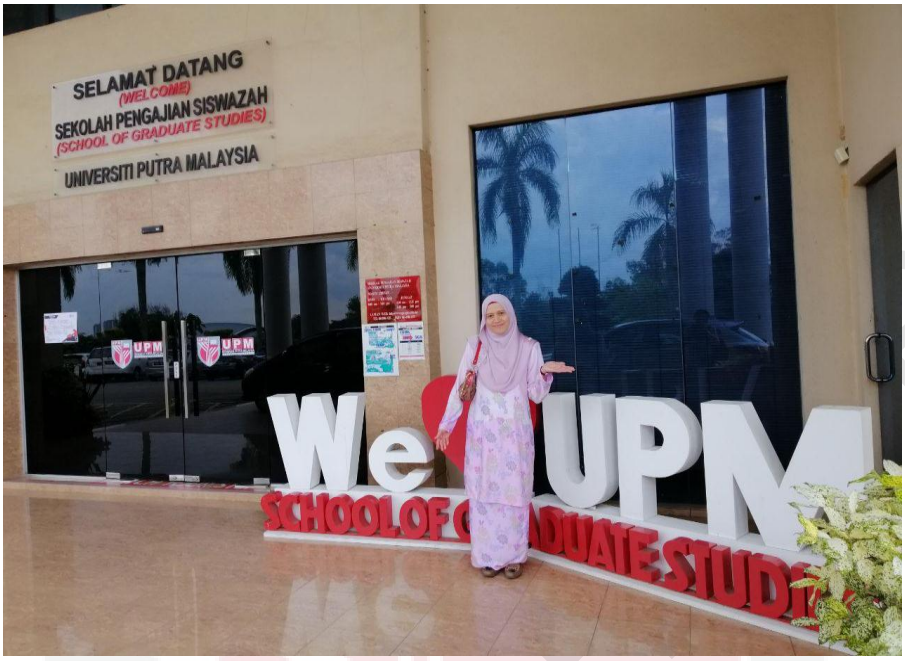

Marina Zulkifli was born in Beseri Jaya, Perlis, in 1983. She completed her primary education at Sekolah Rendah Kebangsaan section 19, Shah Alam, Selangor, in 1995 and secondary education at Sekolah Menengah Kebangsaan Agama Kuala Selangor, Selangor, in 1998 and Maktab Rendah Sains MARA Balik Pulau, Pulau Pinang, in 2000. In 2005, she graduated with second Class Upper Bachelor's Degree (Hons) in Biochemistry from the Faculty of Biotechnology and Biomolecular Sciences, Universiti Putra Malaysia, Selangor. In 2006, she employed in Research Management Centre, Universiti Teknologi Malaysia as Science Officer. In 2010, she received her Master Degree (Research) in Food Antioxidant from Department of Food Science and Technology, Faculty of Applied Sciences, Universiti Teknologi MARA Shah Alam, Selangor. From 2009 until 2014, she joined the Department of Food Science and Technology, as lecturer in Universiti Teknologi MARA, teaching some courses related to her field. She has supervised for more than 30 undergraduate students for final year project as requirement for B.SC degree in UiTM. From 10/2014 to date, she has been doing the requirement for receiving PhD.

LIST OF PUBLICATIONS

Accepted paper

Marina, Z., Amin, I., Loh, S. P., Fadhilah, J., and Kartinee, K. Bioaccessibility of apigenin from *Mangifera indica* (Water Lily var.) during *in vitro* gastrointestinal digestion. Date of submission: 25th October 2018. Manuscript ID: IFRJ181419

Submitted paper

Marina, Z., Amin, I., Loh, S. P., Kartinee, K., and Fadhilah, J. Qualitative and quantitative determination of polyphenolic compounds in mango (*Mangifera indica* cv. Water Lily) by HPLC-DAD tandem mass spectrometric, and evaluation its antioxidant capacity. Date of submission: 6th November 2019. Manuscript ID: 28832 (Under review)

Proceeding paper

Nutritional properties and mineral composition of mango (*Mangifera Indica* var. Water Lily) fruit. Paper presented at Symposium of Malaysian Society of Applied Biology (MSAB) on 29-31st May, 2016 in Swiss-Garden Hotel and Resedences Malacca, Malaysia.

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