PHYTOCHEMICALS, ANTIOXIDANTS AND ACETYLCHOLINESTERASE INHIBITION PROPERTIES OF SELECTED UNDERUTILIZED FRUITS OF SABAH

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INSTITUTE FOR TROPICAL BIOLOGY AND CONSERVATION

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ABSTRACT

Sabah tropical rainforest consist of a rich biodiversity of fruits and vegetables which still remain underutilized. Fruits which have antioxidant properties are frequently related to anti-Alzheimer's potential. Acetylcholinesterase is an enzyme known to break down the neurotransmitter acetylcholine which leads to Alzheimer's disease. The aims of the present study was to determine the phytochemical content (total phenolic, total flavonoid, total anthocyanin and total carotenoid), antioxidant activity and acetylcholinesterase inhibition effect of five selected fruits of Sabah namely pengolaban (*Litsea garciae*), pidada (*Sonneratia caseolaris*), kembayau (*Canarium odontophyllum*), asam kandis (*Garcinia parvifolia*) and tamarillo (*Cyphomandra betacea*). All samples were separated into different parts (i.e edible and non-edible part) and extracted by using 80% methanol and distilled water. First, determination of total phenolic, flavonoid, anthocyanin and carotenoid contents were done spectrophotometrically. The total phenolic and flavonoid content for 80% methanolic and aqueous extract were significantly highest in the flesh of unripe *S. caseolaris* with the values of 67.67 ± 0.10 mg GAE/g and 37.06 ± 0.30 mg RE/g, respectively while the lowest phenolic was observed in the flesh of *C. betacea* (80% methanol) and peel of *G. parvifolia* (aqueous) with the values of 2.61±0.12 and 1.78±0.15 mg/g, respectively. The lowest flavonoid content were observed in the flesh of *L. garciae* (80% methanol) and flesh of *C. betacea* (aqueous) with the values of 2.05±0.21 and 1.15±0.01 mg/g, respectively. The flesh of *C. odontophyllum* displayed highest anthocyanin content while there was no anthocyanin detected in all parts of *S. caseolaris*. The flesh of *C. betacea* showed highest carotenoid content while the seed of *C. odontophyllum* displayed lowest carotenoid content in both extract. Evaluation of antioxidant activity was conducted using DPPH free radical scavenging assay, radical scavenging ABTS and ferric reducing power (FRAP) assay. Highest scavenging activity was found in unripe flesh *S. caseolaris* with the values of 98.32 ± 0.28% for DPPH, 91.24 mg AA/g in terms of AEAC (ascorbic acid equivalent antioxidant capacity) and 67.72 ± 0.74 mmol/g for FRAP assay. For acetylcholinesterase inhibition activity, the enzyme inhibition method and galanthamine was used as positive control. All the samples demonstrate dose dependant inhibition activity. Unripe flesh of *S. caseolaris* displayed highest acetylcholinesterase inhibition activity (47.18 ± 0.68% and 7.80 ± 0.94%) when tested at 250 µg/mL for both 80% methanol and aqueous extracts. As a conclusion, it might provide protection against oxidative damage in body and having a potential as acetylcholinesterase inhibitor.

ABSTRAK

FITOKIMIA, ANTIOKSIDA DAN PERENCATAN ENZIM ASETILKOLINESTERAS DALAM BUAH-BUAHAN SABAH YANG TERPILIH

Hutan hujan tropika Sabah memiliki biodiversiti buah-buahan dan sayur-sayuran yang masih belum diterokai. Buah-buahan yang mengandungi antioksida selalu dikaitkan dengan kebolehan mencegah penyakit Alzheimer. Asetilkolinesteras merupakan enzim yang bertindak merencatkan aktiviti neurotransmitter asetilkolin dan menyebabkan penyakit Alzheimer's. Objektif kajian ini dijalankan adalah untuk mengkaji kandungan fitokimia (fenolik, flavonoid, antosianin, karoten), aktiviti antiokisda dan kebolehan merencatkan kesan enzim asetilkolinesteras bagi lima buah-buahan Sabah yang terpilih iaitu pengolaban (Litsea garciae), pidada (Sonneratia caseolaris) kembayau (Canarium odontophyllum), asam kandis (Garcinia parvifolia) dan tamarillo (Cyphomandra betacea). Semua sampel diasingkan kepada bahagian yang berbeza (boleh dan tidak boleh dimakan) dan diekstrak menggunakan 80% metanol dan air suling. Pertama, penentuan kandungan fenolik, flavonoid, antosianin dan karoten dijalankan menggunakan kaedah spektrofotometrik. Kandungan fenolik dan flavonoid bagi ekstrak 80% metanol dan akueus tertinggi (secara signifikan) pada isi tidak ranum S. caseolaris dengan nilai 67.67 ± 0.10 mg GAE/g dan 37.06 ± 0.30 mg RE/g sementara isi C. betacea menunjukkan kandungan fenolik terendah (80% methanol) dan kulit G. parvifolia (akueus) masing-masing dengan nilai 2.61±0.12 dan 1.78±0.15 mg/g. Isi L. garciae (80% metanol) dan isi C. betacea (akueus) menunjukkan kandungan flavonoid terendah masing-masing dengan nilai 2.05±0.21 dan 1.15±0.01, mg/g. Kandungan antosianin tertinggi dapat dilihat pada isi C. odontophyllum manakala tiada antosianin dikesan pada keseluruhan bahagian S. caseolaris. Isi C. betacea menunjukkan kandungan karoten yang tertinggi manakala tiada karoten dikesan pada biji C. odonthophylllum pada kedua-dua ekstrak. Penentuan aktiviti antioksida dijalankan menggunakan ujian penghapusan radikal bebas DPPH, ujian penghapusan ABTS dan ujian penurunan ferik kepada ferus (FRAP). Aktiviti penghapusan radikal bebas tertinggi dilihat pada isi (tidak ranum) S. caseolaris dengan nilai 98.32 ± 0.28% untuk DPPH, 91.24 mg AA/g (AEAC) (ascorbic acid equivalent capacity) dan 67.72 ± 0.74 mmol/g untuk ujian FRAP. Untuk ujian perencatan kesan asetilkolinesteras, kaedah perencatan enzim digunakan dan galantamin digunakan sebagai kawalan positif. Penambahan kepekatan sampel menunjukkan penambahan aktiviti perencatan asetilkolinesterase pada kesemua sampel. Isi (tidak ranum) S. caseolaris menunjukkan perencatan kesan asetilkolinesteras yang tinggi (47.18 ± 0.68% dan 7.80 ± 0.94%) pada kepekatan 250 µg/mL untuk 80% metanol dan akueus. Kesimpulannya, isi (tidak ranum) S. caseolaris berpotensi untuk mengelak proses pengoksidaan di dalam tubuh dan serta berupaya menghentikan kesan enzim asetilkolinesteras.

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LIST OF ABBREVIATIONS

%	Percent
µg	Microgram
µL	Microliter
cm	Centimeter
h	Hour
mm	Milimeter
nm	Nanometer
mg	Miligram
M	Molar
Min	Minute(s)
mL	Mililiter
mM	Milimolar
ABTS	2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid)
AChE	Acetylcholinesterase
AD	Alzheimer's Disease
AMD	Age-related Macular Degeneration
BHA	Butylated Hydroyanisole
BHT	Butylated Hydroxytoluene
BChE	Butyrylcholinesterase
DPPH	2,2-diphenyl-1-picrylhydrazyl
DNA	Deoxyribonucleic acid
FRAP	Ferric Reducing Ability of Plasma
HeLa	Cervical Cancer Cell
HT-29	Colorectal Cancer Cell

FAO	Food and Agriculture Organization
LDL	Low Density Lipoprotein
MCF-7	Human Breast Cancer Cell
MDA	Malondialdehyde
MDG	Millenium Development Organization
NCD	Non-communicable Disease
NG108-15	Neuroblastoma cell line
OFR	Oxygen Free Radicals
ORAC	Oxygen Radical Absorbance Capacity
Pa	Pascal (unit of pressure)
PC12	Phaeochromocytoma cell line
PC-3	Prostate Cancer Cell
PUFA	Polyunsaturated Fatty Acid
RNS	Reactive Nitrogen Species
ROS	Reactive Oxygen Species
SET	Single Electron Transfer
SOD	Superoxide Dismutase
SPGE	Sweet Potato Green Extract
TEAC	Trolox Equivalent Capacity
UV	Ultraviolet

CHAPTER 1

INTRODUCTION

1.1 Background of the Study

Southeast Asia especially Malaysia possesses a rich diversity and variety of commercial fruits such as durian (*Durio sp.*), rambutan (*Nephelium lappaceum*), ciku (*Manilkara zapota*), papaya (*Carica papaya*) and banana (*Musa sp.*). Sabah itself have many indigenous fruits such as tarap (*Artocarpus odorotissimus*), bambangan (*Mangifera pajang*), salak (*Salacca zalacca*), belunu (*Mangifera caesia*) and durian sukang (*Durio oxleyanus*). Fruits from the tropical and sub-tropical climates such as Malaysian fruits are often associated with many medicinal health benefits. Most of them were use as remedies to treat coughs, intestinal bleeding and diarrhea (Morton, 1987). Ciku and salak from Malaysia were classified as contained high Ascorbic Acid Equivalent Capacity (AEAC), followed by mangosteen, papaya, rambutan, pineapple and cempedak as having middle AEAC and coconut, tomato and watermelon were classified as low AEAC (Leong and Shui, 2002).

However, there are also fruits that are commercialized locally but remain underutilized. These fruits have lack of promotion, minimal planting area and not fully explored but still possess economic potential (Chai *et al.,* 2008). These underutilized fruits might also contribute to human health. Since the synthetic antioxidants such as butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) is suspected to be carcinogenic to human, many epidemiological studies have been performed on natural antioxidants in fruits, vegetables, seeds, cereals, aromatic plants, teas and wines (Hsu *et al.,* 2006). The antioxidant in plants especially fruit have been shown to prevent atherogenesis and cellular damage which act as an anti-tumor, anti-inflammatory and anti-allergy agents (Crozier *et al.,* 2009).

Non-communicable diseases (NCDs) such as cardiovascular disease, type II diabetes mellitus, hypertension and cancer are increasing every year. It is projected that by 2020, seven out of ten deaths might be caused due to NCDs in developing countries (Habib and Saha, 2010). The main cause of the NCDs disease is the excess of free radical in the body and hence a diet with high antioxidant found to be effective to suppress the damaged cause by free radical imbalance in human body (Uttara *et al.,* 2009). Fruits and vegetables have been found to contained high antioxidant properties that can inhibit the free radical in the body (Leong and Shui, 2002), contain phytochemicals with cytotoxic activity towards cancer cells (Rao and Rao, 2007) and induce apoptosis in cancer cell lines (Saiko *et al.,* 2008). Thus, fruits and vegetable have been suggested to be consumed as a "disease preventing" diet.

Therefore, scientists nowadays are looking towards the suitable fruits and vegetables that may provide high antioxidant and phytochemicals as a part of disease preventing diet as many studies have shown that the fruits and vegetables have antioxidant properties. The natural antioxidant in fruits and vegetables found to have a potential to treat and prevent many serious diseases such as cancer, heart disease, stroke as well as Alzheimer's disease.

Hence, this research is carried out to investigate selected underutilized fruits of Sabah that might have potential health benefits such as Pidada (*Sonneratia caseolaris*), Pengolaban (*Litsea garciae*), Kembayau (*Canarium odontophyllum*), Tamarillo (*Cyphomandra betacea*) and Asam Kandis (*Garcinia parvifolia*). Fruits with high phytochemical content display a wide range of bioactivity which could be recommended as disease preventing fruits targeted especially to the low and middle income group of population as the death rate cause by NCDs usually high among people in low income and middle income group of population (Habib and Saha, 2010). In addition to that, this study was also aimed to provide and gathered the basic scientific data about the fruit of Sabah that remain underutilized. With the finding of this study, it is expected that these fruits may increase socio-economic potential to the state and nation.

1.2 PROBLEM STATEMENTS

The mortality due to degenerative diseases such as cancer, heart disease and Alzheimer's disease are increasing (Liu, 2003). Although many medicines are available to treat and cure the mentioned diseases, but they were found to have side effects after being consume for a long period. Hence, many scientists have conducted research to search for alternative therapy and medicine to cure and treat these diseases.

The synthethic antioxidant (such as BHA and BHT) were found to be carcinogenic and have been withdrawn from use in all foods because of their possible adverse side effects on the kidney and liver as well as lung tissues of rat (Siman and Eriksson, 1996). Therefore, the natural phytochemicals with antioxidant from fruits and vegetables should be study extensively to replace the use of synthetic antioxidants that are dangerous to human.

As the prevalence of NCDs are increasing, more research on alternative prevention or research treatment such as plants with anti free radical related diseases and anti-Alzheimer's disease need to be further studied. The cholinergic deficit in the brains of Alzheimer's disease patients is one of the hypotheses contributing the Alzheimer's disease. The shortage of the acetylcholine as neurotransmitter resulting the degeneration of neuron cells. Inhibition of acetylcholinesterase (AChE) enzyme that causing the break down of acetylcholine into acetate and choline form will reduce the incidence of Alzheimer's disease due to acetylcholinesterase shortage (Orhan, 2013). Drugs such as galanthamine, donepezil and rivastigmine are the cholinesterase inhibitors and used to treat Alzheimer's disease patients (Hansen *et al.,* 2008). However, these drugs showed adverse effect such as nausea, vomiting, diarrhea, dizziness and severe weight loss (Hansen *et al.,* 2008). The potential of plants as natural acetylcholinestrase inhibitor were reported from previous study (Vinutha *et al.,* 2007; Zhao *et al.,* 2013; Haque *et al.,* 2012).

Some fruits of Sabah such as bambangan (*Mangifera pajang*) and tarap (*Artocarpus odoratisimus*) have been shown to display diverse health benefit properties including cancer chemopreventive and chemotherapeutic activity (Abu Bakar *et al.,* 2009). However, there a no current research on the potential of fruits of Sabah as an anti-alzheimer agent. Hence, the current research intends to investigate the phytochemicals and potential health benefits of selected underutilized fruits of Sabah such as *Litsea garciae, Sonneratia caseolaris, Canarium odontophyllum, Garcinia parvifolia and Cyphomandra betacea*.

1.3 OBJECTIVES

1.3.1 Main objective

To investigate the phytochemical contents, antioxidants and anti-acetylcholinesterase properties of selected underutilized fruits of Sabah namely *Sonneratia caseolaris* (Pidada), *Litsea garciea* (Pengolaban), *Canarium odontophyllum* (Kembayau), *Garcinia parvifolia* (Asam kandis) and *Cyphomandra betacea* (Tamarillo).

1.3.2 Specific objectives

i. To determine the phytochemicals components (total phenolic, total flavonoid, total anthocyanins and total carotenoid content) of selected underutilized fruits of Sabah.

ii. To investigate the antioxidant properties of selected underutilized fruits of Sabah.

iii. To study the acetylcholinesterase inhibition activity of selected underutilized fruits of Sabah.

1.3.3 Justification of Study

The selected underutilised fruits of Sabah (*Sonneratia caseolaris* (Pidada), *Litsea garciea* (Pengolaban), *Canarium odontophyllum* (Kembayau), *Garcinia parvifolia* (Asam kandis) and *Cyphomandra betacea* (Tamarillo) fruits are popular among the people in some area of Sabah which covered Sipitang, Weston, Penampang and Kota Belud however it remains unpopular among the people in other regions of Sabah. Previously, there are no studies about the selected underutilised fruits of Sabah. Hence, this study intends to provide scientific data on the selected underutilised fruits which might have a great potential to the health benefits.

1.3.4 Hypothesis of Study

Selected underutilized fruits of Sabah have a potential health benefits with phytochemicals compounds (total phenolic, total flavonoid, total anthocyanin and total carotenoid contents) and natural antioxidants as well as acetylcholinesterase inhibitor.

CHAPTER 2

LITERATURE REVIEW

2.0 Fruits and Vegetables

2.1 General benefit of fruits and vegetables

Phytochemicals in fruits and vegetables are shown to have potent antioxidant and health benefits. The combination of phytochemicals from fruits and vegetables was proposed to be responsible for the potent antioxidant activity in human body (Sun *et al.,* 2002).

Recent studies showed that high consumption of fruits and vegetables as well as whole grains have been associated to decrease the risk of many chronic and serious diseases such as cancer (Southon, 2000), cardiovascular diseases (Saiko *et al.,* 2008) and Alzheimer's disease (Mani and Milind, 2007). In addition, for cosmoceutical purposes, previous study showed that fruits and vegetables are associated in delaying the aging process in humans (Kusnindar and Mitri, 2003). The ability of the fruit to reduce the risk of some chronic diseases such as cancer and atherosclerosis has been proposed in the United States of America. By increasing the intake of fruits in the diet, one third of the cancer death can be avoided (Liu, 2004). In addition to that, fruits and vegetable juices play an important role in delaying the onset of Alzheimer's disease especially among those who are at high risk for the disease (Qi *et al.,* 2006).

Different species and varieties of fruits, vegetables and grains have different phytochemicals profiles (Chu *et al.,* 2002). For example, the total antioxidant activity of phytochemicals in 1 g of apples with peel is equivalent to 83.3 µmol of vitamin C. In the other words, the antioxidant in 100 g of apples with peel is equivalent to 1500mg Vitamin C (Eberhardt *et al.,* 2000). Although there is only less than 0.4% vitamin C in apples, it still shows high antioxidant activity due to the

occurrence of other phytochemicals in apples that contributes to the antioxidant activity. Thus, the natural combination of phytochemicals in fruits and vegetables is responsible for its potent antioxidant activity.

Eberhardt *et al.,* (2000) also reported that apple extract contains bioactive compounds that inhibit tumor cell growth *in vitro*. Phytochemicals in apples (without peel) suppress the growth of colon cancer by 29%. However, the inhibition of the growth of the colon cancer is increased by 43% by the apples with peel. Thus, it showed that the different combination of the phytochemicals in different parts of one fruit gives different antioxidant activity.

A study by Pedraza-Chaverri *et al.,* (2008) has demonstrated that extracts of *Garcinia mangostana* displayed anti-inflammatory, antibacterial, antioxidant, antitumoral, antiallergic, and antiviral properties. The pericarp of *G. mangostana* is a source of xanthones and other bioactive substances. Xanthones (i.e a-, b-, and c-mangostins, garcinone E, 8- deoxygartanin, and gartanin) that were isolated from pericarp, whole fruit, heartwood, and leaves of *G. mangostana* have been associated with the biological properties. A study by Yoshikawa *et al.,* (1994) found that the methanolic extract of *G. mangostana* hulls showed potent DPPH free radical scavenging activity. α- and γ- mangostins (isolated from *G. mangostana* hulls) showed antioxidant activity as assessed using the ferric thiocyanate method. In the other study by Williams *et al.,* (1995) found that α-mangostins decreases the oxidation of human low density lipoproteins (LDL). α-mangostin also found to prolong lag time of conjugated dienes in a dose-dependent manner, diminished thiobarbituric reactive substances (TBARS) production. Consistently, Mahabusarakam *et al.,* (2000) also found that α-mangostin and their synthetic derivatives reduce LDL oxidation.

On the other hand, Weecharangsan *et al.,* (2006) studied the antioxidant and neuroprotective properties of four extracts obtained from mangosteen fruit pericarp by using different types of solvents such as water, 50% ethanol, 95% ethanol and ethyl acetate. The antioxidant capacity was evaluated by the DPPH method using various concentration starting at 1, 10, 50 and 100 g/mL of each

extract. Water and 50% ethanolic extracts showed high antioxidant capacity (inhibitory concentration at 50% (IC_{50}) = 34.98 ± 2.24 and 30.76 ± 1.66 g/mL, respectively). The antioxidant capacity of these extracts was tested on a neuroblastoma cell line (NG108-15) exposed to hydrogen peroxide (H_2O_2). Both extracts exhibited neuroprotective activity when they used concentration of 50 g/mL. Furthermore, Haruenkit *et al.*, (2007) showed that mongosteen displayed high antioxidant activity as measured with DPPH and ABTS assays. In addition, rats fed with basal diet supplemented with 1% of cholesterol plus 5% of mangosteen showed an increase in antioxidant activity in plasma (Haruenkit *et al.,* 2007).

Until today, research on fruit of Sabah is lacking. For example, *Litsea garciae* or locally known as Pengolaban which is endemic to Borneo island. Kutoi *et al.,* (2012) reported that *L. garciae* bark extract showed moderate cytotoxic activity against Human Breast Cancer (MCF-7) and Human Colorectal Cancer (HT-29) cell lines. The leaf extract of *L. garciae* however is inactive against Cervical Cencer (HeLa) and weak towards Human Breast Cancer cell lines. Meanwhile, for the HT-29 cell line, the leaves extract exhibited moderate cytotoxic activity with IC_{50} value of 73 g/ml.

In the same study by Kutoi *et al.,* (2012) all methanolic crude extracts of *L. garciae* from Sarawak demonstrated low anti-inflammatory properties. For the lipoxygenase assay, all the barks, leaves and fruits extracts showed a low inhibition ranging from 1.20% to 9.42% while these extracts showed slightly higher inhibitory activity ranging from 9.51-27.70% in Hyaluronidase assay. Both of the barks and leaves extracts showed a weak antigout property in the Xanthine oxidase assay with 2.19% and 2.26% inhibitory activity respectively. However, the fruits extracts were found to be inactive towards this activity.

Sweet potato (*Ipomoea batatas*) leaves are extensively consumed as a vegetable in Africa and Asia. Sweet potato is one of vital source of dietary polyphenols such as anthocyanin and phenolic acids. Sweet Potato Green Extract (SPGE) perturbed cell cycle progression, reduced clonogenic survival, modulated cell cycle and apoptosis regulatory molecules and induced apoptosis in human