PHYTOCHEMICAL, ANTIOXIDANT AND CYTOTOXIC ACTIVITIES OF WHITE MULBERRY (*Morus alba* L.) FROM KAMPUNG TUDAN, RANAU, SABAH

CENTHYEA

FACULTY OF FOOD SCIENCE AND NUTRITION
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THESIS SUBMITTED IN FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE

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ABSTRACT

Morus alba Linnaeus (*M. alba*), also commonly known as white mulberry, belongs to the genus *Morus* of the Moraceae family. *M. alba* has been widely reported for its abundant phytochemical components and promising biological activities, including antioxidant and anticancer activities. However, the variation of maturity levels, and extraction solvents could influence their phytochemicals and pharmacological activities. Regrettably, Sabah-cultivated *M. alba* is mainly consumed as fruits without knowing its antioxidant activity, phytochemical components, and anticancer activity. All of these have critically hindered its nutraceutical potential as antioxidant agent and pharmaceutical potential as anticancer agent against breast cancer that is the highest death-causing cancer in Sabah, Malaysia and Worldwide. Therefore, the antioxidant activity, phytochemical components and anticancer activity of Sabah-cultivated *M. alba* under the influence of maturity levels and extraction solvents was studied. Sabah-grown *M. alba* fruits (brackish black fully and ripe red mature) and leaves (young and mature) were picked as samples. They were freeze-dried before extracted in 70% (v/v) methanol (MeOH), 60% (v/v) ethanol (EtOH), and 65% (v/v) acetone. Samples were analysed for their antioxidant activity, phytochemical components' values, and cell viability activity against the human breast cancer cell line (MCF-7). As a result, data from fruits demonstrated maturity-dependent increment for antioxidant activities, total phenolic content (TPC), total flavonoids content (TFC), and total anthocyanin content (TAC). This was indicated by the higher values in brackish black fully ripe fruits than in red mature fruits. The overview from principal component analysis (PCA) of fruits displayed brackish black fully ripe fruits in 65% (v/v) acetone as the best source of antioxidants, phenolics, and flavonoids, whereas their 60% (v/v) EtOH was the best anthocyanin source. While the red mature fruits in 65% (v/v) acetone were the best chlorogenic acid source, and their 70% (v/v) MeOH was the best rutin source. Moreover, the cytotoxicity of fruits against MCF-7 decreased across fruit maturity as the red mature fruits in 70% (v/v) MeOH exerted the strongest cytotoxicity (IC_{50} = 26.83 mg/mL). In leaves, data revealed maturity-dependent decrements for antioxidant activities, TPC, TFC, chlorogenic acid, and rutin. This was shown by their higher values in young leaves than in mature leaves. The overview of PCA of leaves presented young leaves in 65% (v/v) acetone as the best antioxidant sources as well as phenolics, flavonoids, and rutin sources. Though its 60% (v/v) EtOH is the best source of chlorogenic acid. Conversely, the cytotoxicity of leaves showed a maturity-dependent increment as mature leaves in 60% (v/v) EtOH possessed the strongest cytotoxicity against MCF-7 (IC_{50} = 2.45 mg/mL). Overall, Sabah-grown *M. alba* possesses significant antioxidant activity, a high amount of phytochemical components, and cytotoxic activities, which are significantly influenced by maturity levels and extraction solvents. This suggests its potential use in the functional food and pharmaceutical industries. Future studies should be focused on the screening and isolation of compounds responsible for the antioxidant and anticancer activities of *M. alba* fruit and leaves. Also, the cytotoxicity of the fruit and leaves should be tested on normal breast cell including the luminal epithelial cells and myoepithelial cells of breast to ensure the non-toxicity of *M. alba* towards them before moving on to *in vivo* and clinical trials.

ABSTRAK

AKTIVITI ANTIOKSIDAN DAN ANTIKANSER BUAH DAN DAUN MULBERI (Morus alba **L.***)*

Morus alba Linnaeus *(M. alba), juga dikenali sebagai mulberi putih, tergolong dalam genus Morus daripada keluarga Moraceae. M. alba telah dilaporkan secara meluas untuk sebatian fitokimia yang banyak dan aktiviti biologi yang menjanjikan, termasuk aktiviti antioksidan dan antikanser. Walau bagaimanapun, variasi tahap kematangan, dan pelarut pengekstrakan boleh mempengaruhi fitokimia dan aktiviti farmakologinya. Malangnya, M. alba yang ditanam di Sabah kebanyakannya hanya dimakan sebagai buah-buahan tanpa mengetahui aktiviti antioksidan, komponen fitokimia dan aktiviti antikansernya. Kesemua ini telah secara kritikal menghalang potensi nutraseutikalnya sebagai agen antioksidan dan potensi farmaseutikalnya sebagai agen antikanser untuk melawan kanser payudara yang merupakan kanser penyebab kematian tertinggi di Sabah, Malaysia dan Seluruh Dunia. Oleh itu, aktiviti antioksidan, komponen fitokimia dan aktiviti antikanser M. alba yang ditanam Sabah dengan pengaruh tahap kematangan dan pelarut pengekstrakan telah dikaji. Buah M. alba Sabah (hitam masak sepenuhnya dan merah matang) dan daun M. alba Sabah (muda dan matang) telah dipilih sebagai sampel. Sampel telah dikering beku sebelum diekstrak dalam 70% (v/v) metanol (MeOH), 60% (v/v) etanol (EtOH), dan 65% (v/v) aseton. Sampel dianalisis untuk aktiviti antioksidan, nilai komponen fitokimia, dan aktiviti daya maju sel terhadap sel kanser payudara manusia (MCF-7). Hasilnya, data daripada buah menunjukkan peningkatan yang bergantung kepada kematangan untuk aktiviti antioksidan, jumlah kandungan fenolik (TPC), jumlah kandungan flavonoid (TFC), dan jumlah kandungan antosianin (TAC). Ini dibuktikan oleh nilai mereka yang lebih tinggi dalam buah hitam yang masak sepenuhnya daripada buah merah matang. Gambaran keseluruhan dari analisis komponen utama (PCA) buah menunjukkan bahwa buah hitam yang masak sepenuhnya dalam 65% (v/v) aseton adalah sumber terbaik untuk antioksidan, fenolik dan flavonoid, sedangkan 60% (v/v) EtOH-nya adalah sumber antosianin terbaik. Manakala, buah merah matang dalam 65% (v/v) aseton adalah sumber asid klorogenik terbaik dan 70% (v/v) MeOH-nya adalah sumber rutin terbaik. Selain itu, sitotoksisiti buah terhadap MCF-7 menunjukkan penurunan yang merentasi tahap kematangan kerana buah merah matang dalam 70% (v/v) MeOH menunjukkan sitotoksisiti terkuat (IC_{50} = 26.83 mg/mL). Untuk sampel daun, data mendedahkan pengurangan yang bergantung kepada kematangan bagi aktiviti antioksidan, TPC, TFC, asid klorogenik, dan rutin. Ini ditunjukkan oleh nilai mereka yang lebih tinggi dalam daun muda berbanding daun matang. Gambar keseluruhan PCA daun memperlihatkan daun muda dalam 65% (v/v) aseton sebagai sumber antioksidan, fenolik, flavonoid dan rutin terbaik. Manakala, 60% (v/v) EtOH-nya sebagai sumber asid klorogenik terbaik. Sebaliknya, sitotoksisiti daun menunjukkan kenaikan yang bergantung kepada kematangan kerana daun matang dalam 60% (v/v) EtOH mempunyai sitotoksisiti terkuat terhadap MCF-7 (IC_{50} = 2.45 mg/mL). Secara keseluruhannya, M. alba Sabah mempunyai aktiviti antioksidan yang ketara, jumlah komponen fitokimia yang tinggi, dan aktiviti antikanser yang dipengaruhi oleh tahap kematangan dan pelarut pengekstrakan. Ini menunjukkan potensi*

penggunaan M. alba Sabah dalam industri makanan berfungsi dan farmaseutikal. Kajian masa depan harus ditumpukan kepada saringan sebatian yang bertanggungjawab atas aktiviti antioksidan dan antikanser dalam buah dan daun M. alba. Selain itu, sitotoksisiti buah dan daun perlu diuji pada sel payudara normal termasuk sel epitelium luminal dan sel mioepitelial di payudara untuk memastikan ketidak toksikan M. alba terhadapnya sebelum beralih kepada ujian in vivo dan klinikal.

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LIST OF SYMBOLS

%	-	Percentage
λ	-	Wavelength
>	-	More than
<	-	Less than
° C	-	Degree Celsius
°	-	Degree of angle

LIST OF ABBREVIATIONS

M. alba	-	*Morus alba*
BF	-	Brackish black fully ripe fruits
RF	-	Red mature fruits
YL	-	Young leaves
ML	-	Mature leaves
MeOH	-	Methanol
EtOH	-	Ethanol
v/v	-	Volume/Volume
m/v	-	Mass/Volume
DW	-	Dry weight
IC_{50}	-	Half maximal inhibitory concentration
TPC	-	Total Phenolics Content
TFC	-	Total Flavonoids Content
TAC	-	Total Anthocyanins Content
HPLC	-	High Performance Liquid Chromatography
UHPLC	-	Ultra High Performance Liquid Chromatography
DPPH	-	2, 2-Diphenyl-1-picrylhydrazyl Free Radical
ABTS	-	2, 2′-Azino-bis (3-ethylbenzthiazoline)-6-sulphonic acid
$ABTS^{\bullet+}$	-	Stable ABTS free radicals
FRAP	-	Ferric Reducing Antioxidant Power
MCF-7	-	Human-derived breast cancer cell line

MTT	-	3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide
SET	**-**	Single Electron Transfer
HAT	-	Hydrogen Atom Transfer
KMO	**-**	Kaiser–Meyer–Olkin
PCA	-	Principal Component Analysis
ANOVA	**-**	Analysis of variance

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CHAPTER 1

INTRODUCTION

1.1 Background

Morus alba Linnaeus (*M. alba*), commonly known as white mulberry, is a deciduous tree belonging to the genus *Morus* in the Moraceae family (Ercisli & Orhan, 2007). It is a native China plant whose high adaptability to various topographies, soil conditions, and climates has allowed its wide cultivation. Eventually, *M. alba* has been cultivated in various countries, including Korea, Japan, Europe, America, Thailand, and even Malaysia (Angki et al., 2018; Ning et al., 2005). *M. alba* fruits are commonly consumed fresh and after being processed as jam, wine, or juice. The leaves are the silkworm larvae's feed material. *M. alba* possesses a therapeutic effect which allows its incorporation into many traditional and Ayurvedic medication systems (Devi et al., 2013). Their traditional usage ranges from simple illnesses such as stomach discomfort, dyspepsia, constipation, sore throat, and cough (Gryn-Rynko et al., 2016; Chan et al., 2016; Venkatesh Kumar & Chauhan, 2008), up to serious diseases such as anaemia, jaundice, diabetes, high blood pressure, and liver problems (Yang et al., 2010; Liu et al., 2008; Bae & Suh, 2007).

In 1993, *M. alba* leaves were recognised by the Ministry of Health of the People's Republic of China as consumable medicinal substances (Cui et al., 2019). Later, the multi-functionality of *M. alba* was documented in the Chinese Pharmacopoeia and the British Herbal Pharmacopoeia, including its fruits, leaves, roots, branches, and barks (He et al., 2018; Younus et al., 2016; Khan et al., 2013). Further studies reported its high content of carbohydrates, protein, fibre, and vitamins but low amounts of calories and lipids, making *M. alba* an ideal diet food (Yuan & Zhao, 2017; Jiang & Nie, 2015). *M. alba* also contains an abundant quantity of polyphenol classes, including phenolics, alkaloids, flavonoids, anthocyanins, flavonols, terpenes, and vitamins (Xu et al., 2020; Sánchez-Salcedo et al., 2015a). Compounds including chlorogenic acid, rutin, quercetin, gallic acid, apigenin, ferulic, protocatechuic acids, and others have also been validated (Chen et al., 2021; Hussain et al., 2017). These polyphenols are natural contributors to the biological properties of *M. alba*, including its antioxidative, anti-tumour, anti-hepatoxic, anti-inflammatory, anti-microbial, anti-diabetic, hypolipidemic, neuroprotective, and immunomodulatory effects (Hussain et al., 2017; Alam et al., 2016).

Free radicals impose oxidative stress on lipids, proteins, carbohydrates and deoxyribonucleic acid (DNA), causing damage to the body system and inducing chronic diseases, including cancers (Ríos-Arrabal et al., 2013). Cancer is the second-leading cause of death worldwide and is the top four principal causes of death in Malaysia (The Health Ministry of Malaysia, 2021). Reactive oxygen species (ROS) and reactive nitrogen species (RNS) damage DNA molecules and alter signalling pathways (Ríos-Arrabal et al., 2013). Subsequently, they induce the progression of various cancers, including lung, breast, prostate, liver, brain, colon, and ovary (Saha et al., 2017). According to Malaysia Global Cancer Incidence, Mortality and Prevalence (GLOBOCAN) 2020, breast cancer accounts for the highest 17.3% of all new cases. This value corresponded to 32.9% of new breast cancer cases in Malaysian females (The Global Cancer Observatory, 2021). Several drugs and treatments have been established to treat cancer patients, but their high cost and severe side effects are huge disadvantages to patients' overall health. Free radicals can be scavenged by antioxidants. Endogenous antioxidants inhibited the oxidation that occurred in the human body (Ríos-Arrabal et al., 2013). Nevertheless, the production of extra ROS and RNS induced by external stimuli such as cigarette smoke, toxins, alcohol, and radiation can overwhelm the oxidising capacity of endogenous antioxidants (Li et al., 2015). As a result, exogenous antioxidants are needed to enhance the body's anti-oxidant level, mitigate the damage caused by oxidative stress, and inhibit the instigation or commencement of oxidative chain reactions (Baiano & Del Nobile, 2016). In addition, the toxicological and carcinogenesis reports on synthetic antioxidants have led to the option of more natural-based antioxidants (Shah et al., 2014). Hence, the increasing interest in the exploration and utilisation of plant-based antioxidative compounds throughout the years.

Among the plants, *M. alba* has been validated to contain a high amount of antioxidative polyphenols. The anticancer and cytotoxicity of *M. alba* have also been tested on various cancer cell lines, including breast, colon, cervical, liver, stomach, prostate, hepatocellular, and others (Ramis et al., 2018; El-Baz et al., 2017). All of these have proven the antioxidative and anticancer potential of *M. alba*. The cultivation of *M. alba* plant has also reached Malaysia but studies were centred on west (Peninsular) Malaysia-cultivated *M. alba* while the east Malaysia-cultivated *M. alba* has been overlooked. In Sabah, the East of Malaysia, there exist a three hectares *M. alba* plantation at Tudan village in Tuaran. The *M. alba* plantation was started by Mr. Marius samin upon his finding of *M. alba* seedling in a weekly morning market in Penampang, Sabah in 2002 (Inus, 2017). However, over the years, this Sabah-cultivated *M. alba* remains mainly sold as fresh fruits, or made into jam, wine and tea for own consumption, despite the reported biological benefits of *M. alba* from various countries. Accordingly, the phytochemicals, biological properties, and pharmacological potency of plants could be remarkably influenced by cultivars, species, maturity stages, cultural practices, geographical location, soil, and environmental conditions (Wulandari et al., 2019; Jha et al., 2018; Lee & Hwang, 2017; Calín-Sánchez et al., 2013). They are also significantly affected by the choice of extraction solvents and processing parameters due to the selective nature of solvents towards compounds (Boeing et al., 2014). For that reason, the properties of Sabah-cultivated *M. alba* cannot be fully determined based on previous studies. Therefore, this study focuses on the exploitation of Sabah-grown *M. alba* fruit and leaves by analysing the effects of different maturity levels (Fruits: Brackish black fully ripe and Red mature; Leaves: Young and Mature) and extraction solvents (70% (v/v) methanol (MeOH); 65% (v/v) acetone; 60% (v/v) ethanol (EtOH)) on the plant's antioxidant activity, phytochemical components, and cytotoxicity activity towards breast cancer (MCF-7). The antioxidant activity will be analysed through 2.2-Dyphenyl-1-Pikrilhidrazil (DPPH), 2, 2′-Azino-bis (3-ethylbenzthiazoline-6-sulphonic acid) (ABTS) and Ferric Reducing Antioxidant Power (FRAP) assays. The phytochemical components will be analysed through total phenolic content (TPC), total flavonoids content (TFC), total anthocyanin content (TAC) (fruits only) and quantification of chlorogenic acid and rutin via UHPLC system. The cytotoxicity activity against MCF-7 cell will be analysed through 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay. It is expected that this Borneo-cultivated *M. alba* fruit and leaves will contain strong antioxidant activity, high value of phytochemical components and potent cytotoxicity against MCF-7. Also, all of these will be significantly affected by their level of maturities and type of extraction solvents used. The obtained results will lead to a deeper understanding of the functional properties of Sabah-cultivated *M. alba*, the optimum maturity levels of fruit and leaves, and the best solvents for the extraction. This will be a preliminary step toward the production of mulberry-based functional foods, nutraceutical products, and pharmaceutical products from *M. alba* grown in Sabah.

1.2 Problem Statement

Exogenous antioxidants is needed in human body to support endogenous antioxidants in their role of scavenging free radicals and inhibiting oxidative damage that leads to illnesses such as cancers (Baiano & Del Nobile, 2016). *Morus alba* Linnaeus (*M. alba*) is a white mulberry plant widely reported for its rich amounts of natural antioxidative phytochemicals including phenolic acids, anthocyanins, flavonoids, chalcones, coumarins, and tannins. Their richness has made them to be known as one of the best exogenous antioxidants to be attained (Chen et al., 2021; Xu et al., 2020; Hussain et al., 2017; Sánchez-Salcedo et al., 2015a). Nevertheless, the chemical composition, phytochemicals and biological activities of plants can significantly differ and vary due to the influence of plants' species, organs, development level, cultivation location, and environment as well as handling and processing techniques (Li et al., 2020; Lee & Hwang, 2017; Radojkovića et al., 2012). Thus, it unfeasible to assume the same presence of phytochemical groups and biological activities in plants from different country or plantations, despite their same species and genus

Despite their fame, *M. alba* cultivated in Malaysia has received little attention and analysis. Before 2014, Malaysia-cultivated *M. alba* was mainly studied for its nutritive potential as animal feedstuffs (Sheikhlar et al., 2014; Simol et al., 2012; Jelan, 2010; Saddul et al., 2005), and limited studies have been focused on their nutrient content (Sadia et al., 2014) and biological activity (Wahab et al., 2020; Salih et al., 2015; Eric et al., 2012). Besides, these studies were centred on west (Peninsular) Malaysia-cultivated *M. alba* while the east Malaysia-cultivated *M. alba* has been overlooked. In Sabah, a state located in the East of Malaysia, a three hectares *M. alba* main plantation has been grown in Tudan village in Tuaran. Nevertheless, the nutraceutical potential of this *M. alba* is undeveloped because instead of being utilised as functional foods and dietary supplements, it remains mostly sold as fresh fruits or made into jams and wines for their own consumption. In 2017, Sabah-cultivated *M. alba* was successfully innovated into locally commercialised tea, chilled mulberry drink, Ready to Drink (RTD) (Angki et al., 2018), hand-made skin whitening lotion and soap (Chan, 2017). However, these advances could not reach a large scale and nation or international levels due to the lack of scientific study to support the biological properties of Sabah-cultivated *M. alba*. Eventually, the desertion of this Sabah-cultivated *M. alba* has critically hindered the expanse of its nutraceutical, pharmaceutical, and especially its economic potential that is greatly needed by the locals.

Cancer is the second-leading cause of death in the world and is the top four cause of death in Malaysia (The Health Ministry of Malaysia, 2021; Azizah et al., 2019). An increasing cancer-related death from 9.54% in 2004 to 12.18% in 2019 was reported in Malaysia (The Health Ministry of Malaysia, 2021). In Sabah, 45.4% cancer incidence for males and 54.6% for females was recorded in the Malaysia National Cancer Registry (MNCR) (2012-2016) (Azizah et al., 2019). Among all of the cancers, breast cancer is the highest occurrence in Sabah which amounts to 13.8% from the total of 8,818 Sabah-cancer cases. Breast cancer has 99% occurred in Sabahan women with late stage