

## **UNIVERSITI PUTRA MALAYSIA**

ANTIOXIDANT AND FUNCTIONAL COSMECEUTICAL PROPERTIES OF LEAVES OF THREE MELASTOMATACEAE SPECIES IN NANOEMULSION SYSTEM FOR TOPICAL APPLICATIONS

NUR FAUWIZAH BINTI AZAHAR

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By

## NUR FAUWIZAH BINTI AZAHAR

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

September 2019

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

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#### NUR FAUWIZAH BINTI AZAHAR

September 2019

# Chairman: Associate Professor Siti Salwa Abd Gani, PhDFaculty: Halal Products Research Institute

Melastomataceae commonly known as "Senduduk" has been recognized for its potential for the treatment of various ailments. The leaves of Melastoma malabathricum L., Clidemia hirta (L.) D. Don and Melastoma malabathricum varr. *alba* were studied for their antioxidant and functional cosmeceuticals properties. The levels of total antioxidant activities were evaluated using multiple assay and the result shows the correlation and cluster analysis (CA) were found that different antioxidant assays significantly correlated at (P<0.05). The high total antioxidant assay can be seen mainly from the ethyl acetate and methanolic extract of three *Melastoma* species. The functional cosmetic properties such as sun protection factor (SPF), anti-tyrosinase (whitening activity) and anti-microbial test were noticed to be influenced by the more polar solvents. The simplex centroid mixture design was found to be the best tools and was successfully developed the optimal ratio composed of 30:40:30 mixtures. The leaves of Melastoma leaves species exhibited positive result for tannin/polyphenolic, flavonoids and also saponin. Terpenes, terpenoids, hydrocarbon, fatty acid derivatives, phenol and carbohydrate (amino acids) were significant bioactive compounds identified in the Melastoma leaves using GCMS. Rutin and quercetin of flavonoid compounds were also detected using HPLC. The highlights of the development and characterization of nanoemulsion formulation revealed that the cream has smooth and silky texture and exhibited Melastoma nanoemulsion can act as natural photoprotective agents and natural inhibitors for elastase and collagenase activity on skin. The in vivo results showed Melastoma nanoemulsion can be used significantly as good moisturizing cream as it increases the hydration level and reduce the rate of transpiration (TEWL) after 30 minutes of application and presents as a good anti-wrinkles properties after four weeks of applications. Hence, the innovations of nanoemulsion of plant based materials containing active extract of Melastoma leaves yield good and effective cosmeceutical products particularly for improving skin conditions and ready to be utilized as one of the cosmeceutical ingredients.



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

## ANTIOKSIDA DAN SIFAT-SIFAT FUNGSI KOSMETIK DARIPADA TIGA JENIS SPESIS DAUN MELASTOMATACEAE DALAM SISTEM NANOEMULSI UNTUK APLIKASI TOPIKAL

Oleh

#### NUR FAUWIZAH BINTI AZAHAR

September 2019

Pengerusi Fakulti : Profesor Madya Siti Salwa Abd Gani, PhD : Institut Penyelidikan Produk Halal

Melastomataceae yang lazimnya dikenali sebagai "Senduduk "telah mendapat perhatian atas potensinya untuk merawat pelbagai jenis penyakit. Daun spesies senduduk ungu, senduduk bulu dan senduduk putih dikaji untuk unsur-unsur antioksida dan sifat-sifat kosmetik. Tahap jumlah aktiviti antioksida diukur dengan menggunakan pelbagai kaedah dan statistik korelasi dan kluster hirarki (CA) analisis mendapati variasi antioksida menghasilkan korelasi (P<0.05). Sifat-sifat kosmetik dalam daun Melastoma seperti faktor perlindungan matahari (SPF), anti-tyrosinase (aktiviti pemutihan) dan ujian anti-mikrob juga dipengaruhi oleh pelarut yang lebih cenderung polar. Reka bentuk campuran (MDE) "simplex centroid" telah berjaya digunakan sebagai alat terbaik untuk menentukan nisbah optimum antioksida iaitu 30:40:30. Analisis fitokimia, menunjukkan bahawa keseluruhan daun Melastoma positif terhadap tannin/polifenol, flavonoid dan juga saponin. Sebatian bioaktif seperti terpenes, terpenoid hidrokarbon, derivatif asid lemak, fenol dan juga karbohidrat (amino acid) telah dikenalpasti melalui GCMS. Rutin dan guercetin dari sebatian flavonoid dapat dikesan dalam optimum campuran daun Melastoma. Pembangunan produk nanoemulsi dengan menggunakan campuran tiga jenis daun Melastoma sebagai bahan aktif mendapati bahawa krim yang telah dihasilkan mempunyai tekstur licin dan kajian in vitro menunjukkan, krim nanoemulsi Melastoma berpotensi bertindak sebagai agen pelindung matahari semulajadi dan agen perencat untuk aktiviti elastase dan kollagenase pada kulit. Keputusan in vivo menunjukkan, krim nanoemulsi Melastoma dapat meningkatkan tahap penghidratan dan pengurangan kadar transpirasi (TEWL) selepas 30 minit penggunaannya dan menunjukkan anti-kedutan selepas minggu penggunaan. sifat-sifat 4 Kesimpulannya, melalui hasil kajian, tumbuhan semulajadi dari krim nanoemulsi Melastoma dapat memberikan kesan yang terbaik terutamanya dalam memperbaiki kesihatan kulit hasil daripada sebatian bioaktif antioksida yang terdapat dalam campuran daun *Melastoma* serta sedia digunakan sebagai salah satu bahan formulasi untuk produk kosmetik.



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## LIST OF ABBREVIATIONS

AA	Ascorbic acid
ABTS	2,2'- azino-bis (3-ethylbenzothiazoline-6-sulfonic acid
ANOVA	Analysis of variance
BHT	Butylated hydroxytoluene
C. hirta	Clidemia hirta (L.) D. Don
DPPH	1,1-diphenyl-2-picryhdrazyl assay
FRAP	Ferric reducing antioxidant power
GCMS	Gas chromatography- mass spectrometry
M.M Linn	Melastoma malabathricum Linn
M.M var. alba	Melastoma malabathrium var. alba
nm	Nanometer
o/w	Oil in water
PDI	Polydispersity index
SPF	Sun protection factor
TAC	Total anthocyanin content
тсс	Total carotenoid content
TFC	Total flavonoid content
TPA	Total phosphomolybdate assay
TPC	Total phenolic content
TEM	Transmission electron microscopy
TEWL	Transepidermal water loss
UV	Ultraviolet radiation

## CHAPTER 1

## **INTRODUCTION**

## 1.1 Research Background

Cosmetics are essentials products used throughout the world for maintaining and enhancing the general appearance of face and other parts of the body. They include creams, lotions, moisturizers, face mask, shampoo, hair oil, nail polish and conditioners. A financial analysis reported by a French-based company estimated that the cosmetic industry has an annual turnover of US\$170 billion and its indicated that it will continue to grow exponentially (Wang et al., 2015). As the cosmetic industry grows, more studies are done to improve products to fulfil consumer's satisfaction by using natural ingredients and innovate on the most effective delivery system.

Over the years, plant-based materials have been increasingly used due to safety concerns as they are less toxic as compared to synthetic drugs and chemicals. Moreover, according to Niziol-ŁukaszewskaNizio et al. (2018) nowadays, industry demands multifunctional cosmetic ingredients primarily in natural origins as their complex bioactive and chemical compositions are able to deliver multi-faceted activity towards problematic skin conditions such as moisturizing, soothing, and nourishing effects using just one active ingredients. Research done by Ya et al. (2015) showed that several chemicals isolated from plants can be used as whitening agents which control the overproduction of melanin synthesis. This is due to the fact that plants can synthesize major chemical compounds which can be sorted by their chemical class, functional groups and biosynthetic origin into primary and secondary metabolites (Ahirrao et al., 2011). For instance, there are a number of compounds extracted from plants such as phenols, flavones, alkaloid, and tannin that have shown antioxidant properties against unwanted radical species. A study done by Mansur et al. (2016) revealed that plant extract incorporated with antioxidant properties are of utmost interest in the phyto-cosmetic field as they provide molecules that could inactivate radical oxygen species (ROS) by restoring skin homeostasis therefore, preventing premature aging of the skin. Moreover, the biological function of the skin will be improved and in turn will improve the appearance, radiance and texture of the skin from the application of natural ingredients (Taofiq et al., 2016).

Melastomataceae are widely distributed in tropical and subtropical areas of the world and comprises 170 genera and 4600 species in total (Costa et al., 2015). The genus of *M. malabathricum linn, Clidemia. hirta and M. malabathricum var. alba* are popularly known in Malays community as "senduduk ungu, senduduk bulu and senduduk putih" respectively. They can be found growing in mountain forests, lowland, and also on cleared land such as roadsides. This plant can be differentiated by the colour of the flower petals which are light-pink magenta, dark-purple magenta and white (Haron et al., 2015). Traditionally, these plants are used by old folks to treat various diseases such as inflamed wounds, diarrhea, pox scars, bleeding, dysentery, gastric ulcers, epilepsy, and remedy for skin infections (Jamalnasir et al., 2013; Lopez et al., 2016; Zakaria et al., 2011). Various pharmacological activities were also reported from *M. malabathricum Linn, C. hirta* and *M. malabathricum var. alba* such as antioxidant, antiulcer, antimicrobial and anticancer activities (Basu et al., 2016; Danladi et al., 2015; Hamid et al., 2018; Ismail et al., 2017 and Zabidi et al., 2012).

Recently, nano research has been exploited with the increasing use of engineered nanoparticles (ENPs) in numerous industries such as analytical, cosmeceuticals, pharmaceuticals and others (Soriano et al., 2018). This is because the revolution of the application of nanotechnology can improve the analytical properties of results, analytical processes, and produce high ends products. For example, pharmaceutical technology, especially nanomedicines have higher capability to deliver effectively to the targeted site. Nanotechnology (nanomedicines) remains to be the most suitable approach due to the small size of the droplets which are in the nano range of 100-600 nm (Zainol et al., 2015). Moreover, it has been proven that nanomaterials are the most efficient and reliable delivery systems as they can elevate the solubility, absorption and bioavailability (Alexander et al., 2016).

Nano-emulsion or nanocream has been an active cosmeceutical, pharmaceuticals and personal care product for topical formulations and a tool to enhance the delivery of active ingredients to problematic skin. For instance, there is a number of developed nano-emulsion formulations containing various plants extract applied topically. One of them is dogwood fruits (*Cornus mas*) berries which is an active ingredients in cosmetic emulsions (Nizioł-ŁukaszewskaNizio et al., 2018). Alexander et al. (2016) cited that many researchers and scientists have used the nanomedicines as the delivery system of plant bioactive or herbal extracts into the problematic organs. This shows that the application of cosmeceutical and pharmaceutical nanotechnology from natural sources grows tremendously among the researchers.

Hence, the aim of the present study was to develop a nanoemulsion containing mixtures of extract from the leaves of Melastomataceae family species (*M. malabathricum Linn, Clidemia hirta* and *M. malabathricum var. alba*). To this end, the *in vitro* and *in vivo* evaluation of the efficacy and safety of this formulation as well as assessment of therapeutic properties of these plants were studied for its antioxidant and functional cosmetic properties.

## 1.2 Problem Statement

Despite the erratic progresses in conventional cosmeceutical products in the last 20 vears, to date available products for the treatment of various skin related diseases were often limited in efficacy and could triggered many unwanted side effects such as itching, rashes, dehydrated skin, peeling skin and many more. In order to response to these circumstances, scientists all over the world were eager working in the area of new cosmeceutical discovery to identify new sources of agents with highest potential in the treatment of skin illness. Usage of medicinal plant is one of the alternative treatments which play an important role and can be exploited into discovering novel cosmeceuticals or pharmaceutical drugs since plant- based or natural drugs have less or no negative side effects or toxicity. The therapeutic value of medicinal plant had been identified for many decades by traditional healers and old-folk practices. For instance, some medicinal plants able to treat wounds, eczema, sinuses, lowering blood pressure, constipation and stimulate the reproductive organs. Moreover, due to remarkable and therapeutic values in some of medicinal plant, they can synthesizes numerous of active agent where they are used to combat all sorts of pathogens and other substances in the human body. Thus, researcher all around the world believed that plants have great biomedical potential and possessed wide range of bioactive chemical compounds via secondary metabolites that can be used to treat various human illness and other degenerative diseases especially in the area of cosmeceuticals for not only enhancing human beauty but at the same time able to encounter and treat problematic skin.

## 1.3 Objectives

i.

The general objective of this study was to investigate the phytochemical of three different Melastomataceae family species namely (*M. malabathricum Linn*, *Clidemia hirta* and *M. malabathricum var. alba*) for its antioxidants and functional cosmeceuticals activities and its efficacy as nanoemulsion system for stratum corneum applications.

The specific objectives are as follow:

- To compare the three different *Melastoma* species (*M. malabathricum Linn*, *Clidemia hirta* and *M. malabathricum var. alba*) using different solvent polarity.
- ii. To determine the antioxidant activities and functional cosmeceutical properties of three different *Melastoma* leaves extract.
- iii. To develop and optimize *Melastoma* leaves mixture based cosmeceutical formulation by using mixture design expert (MDE).

- iv. To evaluate the preliminary and phytochemical analysis of optimized *Melastoma* leaves mixture and its bioactive compounds via spectrophotometric method.
- v. To evaluate the efficacy of active mixture of *Melastoma* leaves based nanocosmeceuticals via *in vitro* and *in vivo* studies for stratum corneum applications.

## 1.4 Significance of Study

This study will explore the antioxidant capacity and its functional cosmeceutical properties in three *Melastoma* species (*M. malabathricum linn, Clidemia hirta and M. malabathricum var. alba*) or locally known as "senduduk ungu, senduduk bulu and senduduk putih" respectively. The therapeutic values on these plants will be benefit to human beings for cosmeceutical applications related to skin aging and other degenerative diseases. In addition, it will help to increase the economic value of the abundant natural plant sources to achieve a sustainable and environmentally production and utilization. Therefore, this study is proposed to be the new potential cosmetic ingredients from botanical sources and environmental friendly to consumers.

## 1.5 Scope of Study

This study is outlined into five phases in exploring the three *Melastoma* species (M. malabathricum linn, Clidemia Hirta and M. malabathricum var. alba) extract as alternative active ingredients in a nanoemulsion cosmeceuticals formulations. The first phase is the extraction of three different *Melastoma* species using three different solvent extraction of hexane, ethyl acetate and methanol. In second phase, the antioxidant potential of three different Melastoma species were discovered where multiple of antioxidant assays were used to define its level and activities. In addition, the potential of three different Melastoma species were subjected into various functional cosmeceutical assay such as sun protection factor (SPF), anti-microbial and whitening effects. In third phase, the three different Melastoma leaves species with highest antioxidant activity were subjected into mixture design experiment (MDE) for its optimization study. Next, the preliminary phytochemicals and identification of bioactive compounds in the mixture of Melastoma leaves extracts were screened. Finally, the nanoemulsion formulation was developed containing an active from the mixture of Melastoma leaves extracts and their physicochemical properties as well as its efficacy were evaluated via in vitro and in vivo studies.

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## **BIODATA OF STUDENT**



Nur Fauwizah binti Azahar was born on 29<sup>th</sup> October 1991 in Muar, Johor. She received her early education at Sekolah Kebangsaan Sri Serdang, Selangor from standard 1 to standard 6. Then she continued her secondary education at Sekolah Menengah Kebangsaan Sri Indah, Selangor and Sekolah Menengah Sains Seri Puteri, Kuala Lumpur from form 1-3 and form 4-5, respectively. After completing her Sijil Pelajaran Malaysia (SPM), she continued her studies at Matriculation level under Ministry of Education, Malaysia at Matriculation College Malacca in the year 2009/2010. After completing her matriculation level, she gained her Bachelor of Science majoring Chemistry with honours at Universiti Teknologi Mara (UiTM) and graduated in 2014.

Nur Fauwizah served as Food Technologist Researcher in private sector for one year then she continued her Master Degree programme at Universiti Putra Malaysia (UPM) majoring in Halal Products Development. Upon completion of Master, She served as Research Assistant at Halal Products Research Institute, Universiti Putra Malaysia (UPM) under special project with Jabatan Kemajuan Islam Malaysia (JAKIM) for about one year then she continued her Doctor of Philosophy at Universiti Putra Malaysia (UPM) under supervision of Assoc Prof Dr. Siti Salwa binti Abd Gani. During her study, she attended a mobility (Outbound) Program at Universiti Islam Sultan Sharif Ali, Brunei Darussalam for two weeks as an exchange student. She also was awarded a Graduate Research Fellowship (GRF) and gained experiences as laboratory demonstrator for organic chemistry at Centre of Foundation Studies for Agricultural Science, UPM.

## LIST OF PUBLICATIONS

#### **Research Papers**

- Nur Fauwizah Azahar, Siti Salwa Abd Gani, Uswatun Hasanah Zaidan and Paiman Bawon (2018). Photo-Protective and Anti-Oxidative Potential in the Leaves of Three Different Melastomataceae Family Species. *International Journal of Advanced and Applied Sciences- (Accepted)*
- Nur Fauwizah Azahar, Siti Salwa Abd Gani, Uswatun Hasanah Zaidan and Paiman Bawon (2018). In Vitro Whitening Properties and Antioxidative Potentials of The Extracts of Three Melastoma Leaves Species (*M. malabathricum*, *M. hirta* and *M. decemfidum*). Journal of Applied Sciences Research – (Accepted)
- Nur Fauwizah Azahar, Siti Salwa Abd Gani, Uswatun Hasanah Zaidan, Paiman Bawon and Mohd Izuan Effendi Halmi. The Effects of the Leaves Extract of Melastomataceae Family Species (*M. malabathricum*, *M. hirta* and *M. decemfidum*) on Antioxidant Activity and Growth of Pathogenic Bacteria. *Malaysian Applied Biology Journal. – (Accepted)*
- Nur Fauwizah Azahar, Siti Salwa Abd Gani, Uswatun Hasanah Zaidan and Paiman Bawon (2018). Melastomataceae family species (Melastoma Malabathricum L. Smith, Melastoma Malabathricum var. alba and Clidemia hirta (L.) D. Don): A review of their ethnomedicinal, chemical constituents and pharmacological properties – *Applied Science and Technology- (Accepted)*
- Nur Fauwizah Azahar, Siti Salwa Abd Gani, Uswatun Hasanah Zaidan, Paiman Bawon and Mohd Izuan Effendi Halmi. *In vitro* anti-elastase and anticollagenase activities from the optimum antioxidants extracts of three Melastomataceae leaves species. *BMC Complementary Alternatives Medicines – (Submitted, Under review)*
- Nur Fauwizah Azahar, Siti Salwa Abd Gani, Uswatun Hasanah Zaidan, Paiman Bawon and Mohd Izuan Effendi Halmi. The efficacy of mixture *Melastoma* leaves extract (*M. Malabathricum (L), C. hirta* and *M. Malabathricum var. alba*) as sunscreen lotion and anti-aging cream. **RSC Advances- (Submitted)**
- Nur Fauwizah Azahar, Siti Salwa Abd Gani, Uswatun Hasanah Zaidan, Paiman Bawon and Mohd Izuan Effendi Halmi. Development and characterization of the extracts of mixture Melastoma leaves extract (*M. Malabathricum (L), C. hirta* and *M. Malabathricum var. alba*) nanoemulsion for topical application. *Industrial Crops and Products- (In preparation)*

## List of Conferences, Awards And Mobility Program

## Conferences

- Nur Fauwizah Azahar, Siti Salwa Abd Gani, Uswatun Hasanah Zaidan and Paiman Bawon. Melastomataceae Family Species (Melastoma Malabathricum L. Smith, Melastoma Malabathricum var. alba and Clidemia Hirta L. D. Don): a review of their ethnomedicinal, chemical constituents and pharmacological properties. The 6<sup>th</sup> International Conference of Applied Science and technology (ICAST 2019), 11-13 November 2019. Kyoto, Japan.
- Nur Fauwizah Azahar, Siti Salwa Abd Gani, Uswatun Hasanah Zaidan, Paiman Bawon and Mohd Izuan Effendi Halmi. The Effects of the Leaves Extract of Melastomataceae Family Species (*M. malabathricum*, *M. hirta* and *M. decemfidum*) on Antioxidant Activity and Growth of Pathogenic Bacteria. 2<sup>nd</sup> International Conference on Recent Advancements in Science and Technology, 28-30 October 2019, Kuala Lumpur, Malaysia.
- Nur Fauwizah Azahar, Siti Salwa Abd Gani, Uswatun Hasanah Zaidan and Paiman Bawon (2018). In Vitro Whitening Properties and Antioxidative Potentials of The Extracts of Three *Melastoma* Leaves Species (*M. malabathricum*, *M. hirta* and *M. decemfidum*). 5<sup>th</sup> International Conference on Chemical Industry and Science 2019, 1-3 February 2019, Kuching, Malaysia.
- Nur Fauwizah Azahar, Siti Salwa Abd Gani, Uswatun Hasanah Zaidan and Paiman Bawon (2018). Photo-Protective and Anti-Oxidative Potential in the Leaves of Three Different Melastomataceae Family Species. 3<sup>rd</sup> Current Research on Information Technology, Mathematics, Sciences, Science and Technology (CRIMSTIC 2018). 27-29<sup>th</sup> April 2018, Melaka, Malaysia,

## Awards

- Nur Fauwizah Azahar, Siti Salwa Abd Gani, Uswatun Hasanah Zaidan, Ramya Vijayakumar, Nur Royhaila Mohammad and Paiman Bawon (2018). The unexplored botanical extracts: A new horizon in skin anti-aging formulation. *SILVER AWARDS*. International Eureka Innovation Exhibition 2018, 29<sup>th</sup> 31<sup>st</sup> October 2018, Universiti Kuala Lumpur Malaysia Spanish Institute (UniKL MSI), Kulim Hitecch Park, Kedah.
- Nur Fauwizah Azahar, Siti Salwa Abda Gani, Ramya Vijayakumar and Asiah Abdullah. The unexplored botanical extracts: A new horizon in skin anti-aging formulation. *SILVER AWARDS*. International Invention & Innovative Competition (InnIIC Series 2/2019), 2 November 2019, Palace of the Golden Horses, Selangor.

## **Mobility Program**

Mobility Program (Outbound) at Universiti of Sultan Sharif Ali Islamic (UNISSA), Brunei Darussalam on 22<sup>nd</sup> October 2018 – 5<sup>th</sup> November 2018.

