UNIVERSITI PUTRA MALAYSIA

PHYTOCHEMICALS FROM THE STEM BARK OF Mesua hexapetala (HOOK. F.) P.S. ASHTON., Mesua beccariana (BAILL.) KOSTERM. AND Garcinia mangostana LINN. AND THEIR BIOLOGICAL ACTIVITIES

THIRUVENTHAN A/L KARUNAKARAN

FS 2017 78

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By

THIRUVENTHAN A/L KARUNAKARAN

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

September 2017

DEDICATION

This thesis is dedicated to my beloved family, Professor, supervisory committee and friends

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

PHYTOCHEMICALS FROM THE STEM BARK OF *Mesua hexapetala* (HOOK. F.) P.S. ASHTON., *Mesua beccariana* (BAILL.) KOSTERM. AND *Garcinia mangostana* LINN. AND THEIR BIOLOGICAL ACTIVITIES

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THIRUVENTHAN A/L KARUNAKARAN

September 2017

Chairman : Professor Gwendoline Ee Cheng Lian, PhD
Faculty : Science

Phytochemical constituents isolated from the Calophyllaceae and Clusiaceae family of plants have gained impressive attention recently due to their amazing potencies in biological activities such as anti-inflammatory, cytotoxicity and anti-bacterial. Coumarins and xanthones discovered from this family have exhibited potent biological activities and some of these compounds have been proposed as lead compounds for drug discovery processes. Nitric oxide plays a vital role in the key molecular signaling constituent involved in inflammatory processes and mass production of NO is one of the main factors that contribute towards chronic degenerative diseases such as cancer and arthritis. It is necessary to find an alternative sources from natural products such as plants as its offer greater hope in the identification of bioactive compounds, less adverse effects and their development into drugs for the treatment of inflammatory diseases. Phytochemical studies such as extraction, isolation and structure elucidation of the isolated compounds with the aid FTIR, GCMS, HRESIMS and NMR were performed on the stem bark of two selected species from the family of Calophyllaceae which are *Mesua hexapetala* and *Mesua beccariana* as well on the stem bark of species from the Clusiaceae family which is *Garcinia mangostana* afforded twenty secondary metabolites, three of which were identified as new compounds.

Phytochemical investigation on the stem bark of *Mesua hexapetala* yielded one new coumarin derivative, hexapetarin (**143**) together with 1,3,7-trihydroxy-2,4-di (3-methyl-2-butenyl)xanthone (**144**), trapezifolixanthone (**96**), cudraxanthone G (**19**), stigmasterol (**7**), β-sitosterol (**65**) and γ-sitosterol (**145**). These findings are considered novel as no previous reports nor research have been conducted on *Mesua hexapetala.* Meanwhile, from the stem bark of *Mesua beccariana*, a new xanthone derivative,

beccarixanthone T (**146**) and a new coumarin derivative, beccamarin T (**147**) were successfully isolated together with mesuarianone (**1**), mesuasinone (**2**), 1,5-dihydroxyxanthone (**57**), euxanthone **(20)** and four common triterpenoids, friedelin (**8**), **7**, **65** and **145**. The chemical constituents isolated from *Garcinia mangostana* were α-mangostin (**14**), β-mangostin (**88**), mangostenol (**137**), garcinone D (**132**) fuscaxanthone C (**148**), dulcisxanthone F (**94**) and **7**.

Moreover, the semi-synthesis reaction of β-mangostin which were acetylation and *O*-alkylation afforded six derivatives in which four are new derivatives, 6-monoacetate β-mangostin (**149**), 6-*O*-methyl β-mangostin (**148**), 6-*O*-benzyl β-mangostin (**150**), 6-*O*-*n*-hexyl β-mangostin (**151**), 6-*O*-*n*-butyl β-mangostin (**152**) and 6-*O*-*sec*-butyl β-mangostin (**153**). All extracted plant crude extracts, seven selected natural product compounds and four semi-synthetic derivatives of β-mangostin were evaluated for cell based cytotoxicity and nitric oxide inhibition assay. Nitric oxide inhibition activities indicated that four compounds **143**, **144**, **14** and **88** exhibited very significant activity towards inhibition of LPS/IFN-γ stimulated RAW 264.7 macrophages with IC_{50} value of 30.79 ± 2.68, 12.41 ± 0.89, 29.81 ± 0.77 and 11.72 ± 1.16 μM respectively. The ethyl acetate extract of *G.mangostana* and the *n*-hexane extract of *M.hexapetala* showed very potent activities. Structure-activity relationship studies of pure compounds and semisynthetic derivatives of β-mangostin towards anti-inflammatory activity demonstrated the importance of hydroxyl groups in their structure which influence bioactivity.

Anti-*Bacillus* tests were conducted on seven types of pure compounds - **145**, **146**, **147**, **144**, **14** and **88** as well as with all the plant extracts against four types *Bacillus* bacteria - *Bacillus subtilis*, *B.cereus*, *B.megaterium* and *B.pumilus*. Hexapetarin (**145**) showed potential anti-*bacillus* activities while the *n*-hexane and chloroform extract of *M.hexapetala* (MHH and MHC) gave good inhibitive activity towards these four bacteria. Thus, it can be summarized that the newly discovered coumarin derivative from *M.hexapetala*, hexapetarin (**145**), n-hexane crude extract of *M.hexapetala* and ethyl acetate crude extract of *G.mangostana* showed very significant nitric oxide inhibition and anti-*Bacillus* activity while compound **144**, **14** and **88** portrayed very potent nitric oxide inhibition activities. These compounds can be further developed into anti-inflammatory agents.

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

SEBATIAN FITOKIMIA DARIPADA BATANG KULIT KAYU *Mesua hexapetala* (HOOK. F.) P.S. ASHTON., *Mesua beccariana* (BAILL.) KOSTERM. DAN *Garcinia mangostana* LINN., DAN AKTIVITI BIOLOGIKALNYA

Oleh

THIRUVENTHAN A/L KARUNAKARAN

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Pengasingan sebatian fitokimia daripada genus pokok keluarga Calophyllaceae dan Clusiaceae telah mendapat perhatian yang mengagumkan pada masa kini disebabkan potensinya terhadap akiviti-aktiviti farmakologi seperti anti-radang, sitotoksik, anti-mikrobial, anti-diabetik dan anti-oksida. Kumarin dan xanton yang dijumpai daripada keluarga pokok ini didapati menunjukkan aktiviti biologikal yanag sangat bagus, malah ada sesetengah sebatian semula jadi telah pun dicadangkan untuk dijadikan sampel ubat bagi proses penemuan ubat. Nitrik oksida memainkan peranan penting dalam menjadi kunci isyarat utama sebatian molekul terhadap proses keradangan dan produksi NO secara besar-besaran yang menjadi salah satu faktor yang menyumbang kearah penyakit degeneratif kronik seperti kanser dan arthritis. Adalah menjadi keperluan untuk mencari sumber alternatif daripada hasil semulajadi seperti pokok kerana ia memberikan harapan yang tinggi dalam mengenal pasti sebatian bioaktif, impak negatif yang kurang dan pembangunannya dalam menjadikan ubat untuk mengubati penyakit berkaitan anti-radang. Kajian fitokimia seperti pengekstrakan, pengasingan dan mengenal pasti bentuk sebatian hasil semulajadi dengan bantuan FTIR, GCMS, HRESIMS dan NMR telah dijalankan keatas batang kulit kayu, dua spesis keluarga pokok Calophyllaceae iaitu *Mesua hexapetala* dan *Mesua beccariana* serta satu spesis daripada keluarga pokok Clusiaceae iaitu *Garcinia mangostana* yang telah memberi dua puluh metabolit sekunder, tiga daripadanya telah dikenal pasti sebagai sebatian baru.

Kajian fitokimia terhadap batang kulit kayu *Mesua hexapetala* telah menghasilkan penemuan sebatian kumarin yang baru, hexapetarin (**143**) bersama-sama dengan 1,3,7-trihidroksi-2,4-di(3-methil-2-butenil)xanton (**144**), trapezifolixanton (**96**),

kudraxanton G (**19**), stigmasterol (**17**), β-sitosterol (**65**) dan γ-sitosterol (**145**). Tiada penyelidikan dan laporan kajian yang dilaporkan terhadap pokok ini. Di samping itu, melalui kajian terhadap batang kulit kayu, *Mesua beccariana*, xanton baru, bekarixanton T (**146**) dan kumarin baru, bekamarin T (**147**) telah berjaya diasingkan bersama-sama dengan mesuarianon (**1**), mesuasianon (**2**), 1,5-dihidroksixanton (**57**), euxanton (**20**) dan empat triterpenoids biasa, fridelin (**8**), stigmasterol (**7**), β-sitosterol (**65**) dan γ -sitosterol (**145**). Daripada pokok *Garcinia mangostana*, sebatian kimia yang diasingkan ialah α-mangostin (**14**), β-mangostin (**88**), mangostenol (**137**), garcinon D (**132**), fuskaxanton C (**148**), dulsisxanton F (**94**) dan **7**.

Malah, reaksi semi-sintesis terhadap β-mangostin iaitu asetilasi dan *O*-alkilasi yang memberikan hasil enam penerbitan β-mangostin dimana empat penerbitan merupakan penerbitan baru, 6-monoasetat β-mangostin (**149**), 6-*O*-methil β-mangostin (**148**), 6-*O*-benzil β-mangostin (**150**), 6-*O*-*n*-hexil β-mangostin (**151**), 6-*O*-*n*-butil β-mangostin (**152**) and 6-*O*-*sek*-butil β-mangostin (**153**). Kesemua ekstrak pokok dan juga tujuh sebatian semulajadi serta empat semi-sintetik β-mangostin telah dipilih untuk dinilai terhadap cerakin nitrik oksida dan sitotoksik berasaskan sel. Aktiviti anti-radang telah mengenal pasti empat sebatian iaitu **145**, **144**, **14** dan **88** telah menunjukkan aktiviti yang sangat ketara terhadap penyekatan RAW 264.7 makrofaj yang dirangsangkan oleh LPS/IFN-γ dengan nilai IC_{50} 30.79 ± 2.68, 12.41 ± 0.89, 29.81 ± 0.77 and 11.72 ± 1.16 μM masing-masing. Ekstrak etil asetat *G.mangostana* dan ekstrak n-hexana *M.hexapetala* menunjukkan aktiviti yang sangat berpotensi .Kajian terhadap hubungan struktur-aktiviti sebatian tulen dan penerbitan semi-sintetik β-mangostin terhadap anti-radang menunjukkan kepentingan kewujudan kumpulan hidroksil dalam sruktur sebatian yang mempengaruhi bioaktiviti sebatian tersebut.

Ujian anti-*Bacillus* yang dijalankan terhadap tujuh jenis sebatian tulen iaitu **145**, **146**, **147**, **144**, **2**, **14** dan **88** dengan semua ekstrak pokok daripada pokok-pokok yang dikaji terhadap empat jenis bakteria *Bacillus*. Hexapetarin (**143**) telah menunjukkan aktiviti anti-*Bacillus* yang sangat berpotensi terhadap empat jenis bakteria *Bacillus* - *Bacillus subtilis*, *B.cereus*, *B.megaterium* dan *B.pumilus*. Tuntasnya, boleh disimpulkan bahawa penemuan penerbitan baru kumarin, hexapetarin (**143**), ekstrak pokok n-hexana *M.hexapetala* dan ekstrak etil asetat pokok *G.mangostana* menunjukkan aktiviti anti-radang yang yang sangat signifikan terhadap anti-*Bacillus* sementara itu, **144**, **14** dan **88** mempamerkan aktiviti anti-radang yang sangat berpotensi dimana boleh diperkembangkan sebagai ejen anti-radang di masa hadapan.

ACKNOWLEDGEMENTS

First and foremost, I would like to express my deepest gratitude and appreciation to my beloved supervisor, YBhg. Prof. Dr. Gwendoline Ee Cheng Lian for giving me the chance to carry out my PhD studies under her guidance and supervision with great patience, as well as giving me many opportunities to gain knowledge in the field of organic chemistry, especially in phytochemistry, spectroscopic chemistry as well as in pharmacology. Her guidance has helped me throughout my research and writing of this thesis. I cannot imagine having a better advisor and mentor for my PhD study.

I would like to express my gratitude to my co-supervisor, Assoc. Prof Dr. Intan Safinar Ismail for giving me the chance to explore the world of biology and pharmacology under her guidance as well as for the motivation she has supplied me with along the way. I would also like to thank her for allowing me to use the facilities and equipment in her Laboratory of Natural Products (LHS), Institute of Bioscience. I would also like to thank my co-supervisor from the field of organic synthesis, Dr. Siti Mariam Mohd Nor, for her guidance and help in my semi-synthesis work. Special thanks goes to fellow researchers from LHS - Dr. Leong Sze Wei, Dr. Ramesh Kumar Santhanam, Assoc. Prof Dr. Yaya Rukayadi, Miss Kalaivani Palachandran and Miss Hong Xia - for their guidance and motivation in my biological work, which is a new field explored by me.

Not forgetting my friends who have always given me encouragement, motivation as well as helped me to face difficult situations during my PhD studies, Mr. Mahashanon Arumugam (PutraCAT, UPM), Miss Annushiah Vasanthakumar (USM), Mr. Kumar Arumgam (Jasin, Melaka), Dr. Shaari Daud (UiTM), Miss Naveena Reddy Kalidass (LHS, IBS, UPM), Miss Arthy Surendran (INTROP, UPM), Miss Pireya Arulu (Biotech, UPM), Mr. Yugesh Gannason (UCSI), Mrs. Guhan Uthayakumar (Ulsan, Korea), Mr. Fadzly Salleh (Vet, UPM), Dr. Raghunath Parayani (LHS, IBS, UPM), Dr. Karthivashan Govindasamy (Seoul, Korea), Dr. Peter Waziri (Nigeria) and others who were with me during these challenging times.

I would also like to express my gratitude to all my lab mates from the Chemistry Department, Faculty of Science, UPM, as well as lab mates from the Laboratory of Natural Products (LHS), Miss Nor Hisham Zamakshshari, Dr. Irene See, Mr. Lee Kar Wei, Dr. Teh Soek Sin, Mr. Ahmad Azri Fitri, Mr. Muniandy, Mr Wong Ka Woong, Mr. Lim Wui Zhuan, Mr. Taufiq Astifa, Miss Ashikin, Miss Kayne Lee, Miss Khaleeda, Mrs Ilya Iryani, Miss Amalina Azam, Miss Foong Yen Lum, Mrs Asila Mazlan, Mr. Abdel Ghani, Mr. Tee Keng Hong and Miss Ashkwinie Siramaloo, for their willingness to help and share their knowledge with me as well as being good listeners when I needed someone to talk to. All of them have made an awesome working environment for me which united us all as one team. I am really happy to have been blessed the opportunity to work with them all.

Special thanks goes to science officers Ms. Shareena Safiai (NMR) and Mr. Johadi Iskandar (NMR) in their guidance for using the NMR instrument. I am also grateful to Mr. Zainal Abidin Kassim (GCMS), Mrs. Rusnani Amirudin (FTIR), Mrs. Noriza Atan (UV-Vis), Mrs. Nurul Huda (Bioassay Lab, LHS) and Mr. Azizul Isha (Phyto Lab, LHS) for giving me the chance to analyze all my compounds for GCMS, IR, UV-Vis and biological analysis. I am highly indebted to Dr. Vivian Jong Yi Mian and Prof Dr. Jegak Uli for collection of plant samples.

My deepest appreciation goes to my beloved mother who has always given her moral support and wisdom in guiding me towards righteousness in the absence of my father in my life. Special thanks to my sister, Sharvina Karunakaran and relatives for their kindness and thoughtfulness. Moreover, I would like to express my appreciation to individuals around me for their beneficial advices and critics that have impacted my research methods and myself, which have indirectly led to the completion of my PhD studies successfully. Last but not least, my greatest and deepest gratitude to God Almighty who has always been beside me and answered all of my prayers. God Almighty has given me the courage to face all of the obstacles and difficulties that I have faced throughout my PhD journey and with His blessing and grace, I would be able to finish my PhD journey successfully.

I certify that a Thesis Examination Committee has met on 14 September 2017 to conduct the final examination of Thiruventhan a/l Karunakaran on his thesis entitled "Phytochemicals from the Stem Bark of *Mesua hexapetala* (Hook. F.) P.S. Ashton., *Mesua beccariana* (Baill.) Kosterm. and *Garcinia mangostana* Linn. and their Biological Activities" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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This thesis was submitted to the Senate of the Universiti Putra Malaysia and has been accepted as fulfillment of requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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δ	Chemical shift in ppm
λ_{max}	Wavelength maxima in nm
˚C	Degree celcius
^{1}H	Proton
^{13}C	Carbon-13
CHX	Chlorhexidine
Cm	centimeter
D	Doublet
D	Deuterated proton
DMEM	Dulbecco's Modified Eagle's medium
DMSO	Dimethyl sulfoxide
ESI	Electrospray Ionization
FBS	Fetal Bovine Serum
FTIR	Fourier Transform Infra-Red
G	Gram
GC-MS	Gas chromatography-mass spectroscopy
HIV	Human immunodeficiency virus
HPLC	High performance liquid chromatography
Hz	Hertz
IC_{50}	Initial Concentration to kill 50% of cells
IR	Infra-Red
IFN- γ	Interferon gamma
J	Coupling constant
LPS	Lipopolysaccharides
m	meter
[M]+	Molecular ion
MBC	Minimal Bactericidal Concentration
MIC	Minimal Inhibitory Concentration

Mg	Milligram
MHA	Mueller Hinton Agar
MHB	Mueller Hinton Broth
MHz	Megahertz
m.p.	Melting point
MS	Mass spectrometry
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide
m/z	Mass per charge
NMR	Nuclear Magnetic Resonance
NO	Nitric oxide
s	Singlet
d	Doublet
dd	Doublet of doublet
t	Triplet
q	Quartet
m	Multiplet
TLC	Thin layer chromatography
TMS	Tetramethylsilane
TSB	Tryptic Soybean Broth
µg	microgram
µM	Micro molar
UATR	Universal attenuated total reflection
UV	Ultraviolet
ν_{max}	Wavenumber maxima in cm^{-1}
γ	gamma
α	alpha
β	beta

CHAPTER 1

INTRODUCTION

1.1 General Introduction

Natural products from flora and fauna have become the essential source for discovery of new drugs based on the new chemical compounds found through the studies conducted by researchers around the globe. Throughout the ages, since ancient times, natural products have played a vital role in the daily life of human beings especially in traditional medicine. It is known as the source of active ingredients of medicine used to treat various diseases. Historically, most of the new drugs discovered from natural products and compounds derived from it. Most bioactive natural products are discovered from sources like plants, bacteria and fungi. It has become the main source of active ingredients for medicines that been used to treat various diseases (Harvey, 2008).

The usage of natural products in the medicinal world can be traced from the ancient civilization such as Egyptian medicine which dates from 1500 BC. It was found in the Egyptian pharmaceutical record known as "Ebers Papyrus" that more than 700 drugs were mostly from plants, animal organs and natural minerals used during the civilization for medicinal purpose to treat various disease. In the eastern civilization like the Chinese and Indian traditional medicine, the Chinese *Materia Medica* and Indian *Ayurveda* scripts documented the usage of over 800 drugs from natural products especially from plants for various diseases dating from 1000 BC (Newman et al., 1999).

Bioactive natural products especially the secondary metabolites isolated from bioactive samples, including plants, microbes and animals and also semisynthetically derived compounds showed that a great diversity of chemical structures are used in a wide range of therapeutic medicinal applications such as anti-cancer, anti-inflammatory, anti-biotic, anti-diabetic and neurological disorders. Moreover, most of these natural products are found to obey the Lipinski's Rule of Five for orally available compounds indicating that natural product drugs have good absorbance properties compared to synthetic drugs (Harvey, 2008).

Plants have been used as drugs for thousands of years. Phytochemistry is the study of chemistry of plants which concentrates on the phytochemical constituents. Phytochemical constituents consist of primary and secondary metabolites produced by plants through biosynthesis. Phytochemical studies focused more on the isolation, structural identification and application of the secondary metabolites as these compounds have the potency to be developed as lead for various types of diseases and application. Phytochemistry is mainly focused on the secondary metabolites. Secondary metabolites are made up of molecules from reactions which are not

common to all life forms, but occur in certain species only. Secondary metabolism is of most interest to organic chemists. The structures of secondary metabolites are extraordinarily complex and their biosynthesis have been studied by organic chemists and biochemists to understand how plants system in produce phytochemicals. Secondary metabolism produces products that aid the growth and development of plants but are not required by the plants to survive. Secondary metabolism facilitates the primary metabolism in plants. Most of the phytochemicals discovered have been reported to be active towards human biology. Throughout the ages, plants have become the foundation for traditional medicine systems in eastern countries like China and India.

The field of phytochemistry has helped to explore and understand the world of traditional and herbal medicine. There is no proper documentation on the chemistry of drugs used in traditional and herbal medicine prescriptions since ancient times till the 1900s. Phytochemical studies have enabled researchers to identify bioactive lead compounds responsible for the medicinal properties with the aid from analytical chemistry and spectroscopic techniques. Moreover, the field of phytochemistry studies are required to expose the fourteen myths of traditional medicine which been argued by the synthetic chemists and pharmacist over the years. The fourteen myths are listed below (Cordell, 2014).

- Safety and effectiveness of traditional medicine eventhough it has been used for thousands of years.
- Using the "correct" plant is adequate.
- The biological effects are the same for different parts of plants.
- The biological effects are the same irrespective of the origin of the plants.
- The biological effects are the same irrespective of the plants preparation.
- Older plant material is less effective (or more toxic).
- ''Wild''-collected plants are more active than cultivated plants.
- All of the materials in a complex prescription are necessary for effectiveness.
- Complex mixtures of plants cannot be standardized.
- This medicinal plant product is already well-regulated.
- Medicinal plants are safer than synthetic drugs.
- Medicinal plant will always be available.
- Traditional knowledge will always be there.
- Traditional medicines are not effective, and are therefore not worth considering as a part of a contemporary health care system.

Phytochemicals can be divided into six main groups which are phenolics, terpenoids, alkaloids, glycosides, tannins and saponins.

1.2 Problem Statements

Natural products or natural product derived compounds represent great structural diversity, which is not commonly seen in synthetic compounds. It can be concluded that natural products play a vital role in the discovery of leads for to be developed into drugs for treating human diseases. Natural products offer great hope in the identification of bioactive compounds and their development into drugs for the treatment many types of diseases. Besides that, plants have been the source for many traditional medicine systems throughout the world for thousands of years and continue to provide mankind with new remedies (Harvey, 2008). There is no proper documentation on the chemistry of drugs used in traditional and herbal medicine prescriptions since times till the 1900s (Newman et al., 1999).

Phytochemical studies have enabled researchers to identify bioactive hit compounds responsible for medicinal properties with the aid of analytical and spectroscopic chemistry techniques. Through phytochemical studies, researchers can prove the effectiveness of plant based medicines which have been used since ancient civilzations as well as the safety of plant based medicines compared to available synthetic drugs (Cordell, 2014). Moreover, it is necessity to explore alternative sources of medicinal plants rather than depend on available plants especially cultivated plants. Wild plants especially new species that have never been explored by any researchers should be starting point in the phytochemical and biological studies so as to provide new sources in the medicinal world hence enable medicinal supplies and stock which will continue to support the human needs.

There are several records in traditional medicine focusing on relief from pain and inflammation. Since ancient time, people suffering from inflammation were treated with phytochemicals, which is evident from the discovery of the first analgesic drug aspirin. The discovery of aspirin was based on the known analgesic and antipyretic properties of the bark of willow tree since 400 BC by the Greeks and Romans. Nitric oxide plays a vital role in the key molecular signaling constituent involved in inflammatory processes. Mass production of NO is one of the main factors that contribute towards chronic degenerative diseases such as cancer, arthritis, neurodegenerative and cardiovascular disorder (Leong et al. 2015; Leong et al. 2014). Biological interference of phytochemicals with NO production and bacterial inhibition are necessities in developing potent leads for anti-inflammatory and anti-bacterial related diseases.

From the previous researches on species such as *Mesua* and *Garcinia*, there are lot of potential secondary metabolites mostly xanthones, coumarins and flavonoids that have been isolated recently with high bioactivities especially in anti-inflammatory especially in nitric oxide inhibition and anti-bacterial activities. In a nutshell, it is pivotal for chemists with the aid from the field of phytochemistry, analytical chemistry, spectroscopic chemistry and biological studies to continue the search for potential bioactive phytochemicals from plants in order to find an alternative source

of medicinal plants as well as do proper documentation of the chemistry of drugs present in the plants studied.

1.3 Objectives of Study

The research project is designed to isolate, purify and identify the structures of phytochemical compounds from *Mesua hexapetala*, *Mesua beccariana* and *Garcinia mangostana*. Structural modification will be carried out on the major constituents from the plants and the structural activity relationship study will be studied. The main purpose of this research is to study the phytochemistry of a new plant species *Mesua hexapetala* as well as the two other species *Mesua beccariana* and *Garcinia mangostana* and their potential bioactivities. Hence, the specific objectives of the research are:

1. To extract, isolate and elucidate the structures of the chemical constituents from *Mesua hexapetala, Mesua beccariana* and *Garcinia mangostana* using various chromatographic techniques and spectroscopic methods including IR, GCMS, UV-VIS, HRESIMS, and NMR.

2. To carry out structural modifications of β-mangostin isolated from *Garcinia mangostana* with simple synthesis method.

3. To determine cytotoxicity, nitric oxide inhibition and anti-*bacillus* test on the isolated compounds and plant extracts of *Mesua hexapetala, Mesua beccariana* and *Garcinia mangostana* as well as the semi-synthetic derivatives of β-mangostin and study the structure activity relationship on anti-inflammatory activities between natural and semi-synthesized compound.

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