UNIVERSITI PUTRA MALAYSIA

CHEMICAL CONSTITUENTS AND BIOLOGICAL ACTIVITIES OF ARTOCARPUS ELASTICUS REINW EX BLUME

FAIQAH BINTI RAMLI

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FAIQAH BINTI RAMLI

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CHEMICAL CONSTITUENTS AND BIOLOGICAL ACTIVITIES OF *ARTOCARPUS ELASTICUS* REINW EX BLUME

By

FAIQAH BINTI RAMLI

Thesis submitted to the School of Graduate studies, Universiti Putra Malaysia in fulfilment of requirements for the degree of Master in Science

May 2013

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Abstract of thesis presented to the senate of Universiti Putra Malaysia in fulfilment of requirements for the degree of Master of Science

CHEMICAL CONSTITUENTS AND BIOLOGICAL ACTIVITIES OF *ARTOCARPUS ELASTICUS* REINW. EX BLUME

By

FAIQAH BINTI RAMLI

May 2013

Chairman: Professor Mawardi Rahmani, PhD

Faculty : Science

Detailed phytochemical investigation has been carried out on leaves and bark of *Artocarpus elasticus* (Moraceae) collected from two separate locations, Gunung Nuang, Selangor and Sarawak. Various chromatography techniques such as thin layer chromatography (TLC), gravity column chromatographic, vacuum column chromatography, and chromatotron have been used to isolate several compounds of different classes, such as triterpenes, chalcones, flavone, and dihydrobenzoxanthones. Structural elucidations of the pure compounds were carried out using spectroscopic techniques such as UV, IR, NMR, MS and also by comparison with published data. The crude extracts and some isolated compounds were screened for antioxidant activity using 2, 2-diphenyl-1-picrylhydrazyl assay, cytotoxicity by using microculture tetrazolium salt assay and antimicrobial activity using disc diffusion assay. The cell lines used in the cytotoxic assay were human estrogen receptor (ER+) positive breast cancer (MCF-7), human estrogen receptor (ER-) negative (MDA-MB 231), human hepatocarcinoma (HepG2), and normal human cell (WLR-68). For the antimicrobial activity samples were tested against

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Bacillus ATCC, Bacillus cereus, Bacillus subtilis, Staphylococcus aureus ATCC, Staphylococcus aureus IMR, Staphylococcus pyogenes, Staphylococcus epidermidis, S1211 IMR, Pseudomonas aeruginosa, Klebsiella sp., Pseudomonas multocida, Enterobacter cloacae and *Escherichia coli.*

Isolation work on leaves of *Artocapus elasticus* collected from Gunung Nuang, Selangor, Malaysia has led to the isolation and identification of three new dihydrochalcones [elastichalcone A **(105)**, elastichalcone B **(109)**, elastichalcone C **(107)**], cycloartocarpesin **(111)** along with stigmasterol **(96**) and *p*-hydroxybenzoic acid **(112)**. In contrast, detailed study on the bark of *Artocarpus elasticus* collected from Sarawak afforded one new flavone, elastixanthone **(113)**, together with the known cycloartobiloxanthone **(15)**, artobiloxanthone **(79)** and artonin E **(80).**

All compounds isolated showed interesting biological activity towards certain bioassays. However, five of the prenylated flavonoids, cycloartobiloxanthone **(15)**, artonin E **(80)**, elastichalcone B **(109)**, cycloartocarpesin **(111)** dan elastixanthone **(113)** exhibited good potential for further development as antioxidant agent with IC_{50} values of 40.02, 11.50, 11.30, 11.89 and 21.60 µg/ml, respectively. Cytotoxic assay carried out on the isolated compound revealed that artonin E **(80)** possesses potent cytotoxic activity against human estrogen receptor (ER+) positive breast cancer (MCF-7) and human estrogen receptor (ER-) negative (MDA-MB 231) with IC_{50} value of 2.5 and 15 µg/ml, respectively. Similarly, artonin E **(80)** and elastichalcone B **(109)** displayed broad spectrum of antimicrobial activities on the growth of *Bacillus ATCC, B. cereus, B. subtilis, S. aureus ATCC, S. aureus IMR, S. pyogenes, E. coli* and *S. epidermidis*.

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Abstrak tesis yang dikemukakan kepada senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Master Sains.

KANDUANGAN KIMIA DAN AKTIVITI BIOLOGI DARIPADA *ARTOCARPUS ELASTICUS* REINW. EX BLUME

Oleh

FAIQAH BINTI RAMLI

Mei 2013

Pengerusi: Profesor Mawardi Rahmani, PhD

Fakulti : Sains

Kajian fitokimia dan aktiviti biologi ke atas kulit batang dan daun *Artocarpus elasticus* telah dijalankan. Pelbagai teknik kromatografi seperti turus graviti, kromatografi turus vakum, kromatografi radial dan kromatografi lapisan nipis telah digunakan untuk penulenan beberapa sebatian daripada kelas yang berbeza seperti triterpena, calkon, flavon, dan xanton. NMR, MS, IR, UV dan juga pembandingan dengan data literatur telah digunakan untuk pengenalpastian struktur sebatian yang telah dipencilkan. Ekstrak mentah dan sebahagian sebatian yang telah dipencilkan telah diuji aktiviti antioksidan, sitotoksik dan antimikrob dengan masing-masing menggunakan kaedah 2,2-difenil-1-pikrilhidrazil (DPPH), mikrokultur tetrazolium garam dan peresapan cakera. Sel yang digunakan untuk ujikaji sitotoksik adalah kanser payudara (MCF-7), penerima estrogen negative manusia (MDA-MB 231), hepatokarsinoma manusia (HepG2), dan sel manusia normal (WLR-68). Aktiviti mikrob telah diuji ke atas *Bacillus ATCC, Bacillus cereus, Bacillus subtilis, Staphylococcus aureus ATCC, Staphylococcus aureus IMR, Staphylococcus*

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pyogenes, Staphylococcus epidermidis, S1211 IMR, Pseudomonas aeruginosa, Klebsiella sp., Pseudomonas multocida, Enterobacter cloacae dan *Escherichia coli.*

Kerja pemencilan ke atas daun *Artocarpus elasticus* yang diperoleh dari Gunung Nuang, Selangor, Malaysia telah membawa kepada pemencilan tiga dihidrocalkon, elasticalkon A **(105)**, elasticalkon B **(107)**, elasticalkon C **(109)** dan asid *p*-hidroksibenzoik **(112)**, sikloartokarpesin **(111)**, dan stigmasterol **(96**). Kajian yang sama ke atas kulit batang *Artocarpus elasticus* yang diperoleh dari Sarawak, Malaysia telah membawa kepada pemencilan satu flavon baru elastixanton **(113)**, bersama dengan tiga flavon lain yang dikenali sebagai, cycloartobiloxanthone **(15)** dan artobiloxanthone **(79)** dan artonin E **(80).**

Ujian aktiviti biologi telah dijalankan ke atas semua sebatian yang telah dipencilkan. Walau bagaimanapun, lima flavon, sikloartobiloxanton **(15)**, artonin E **(80),** elasticalkon C **(107)**, sikloartokarpesin **(111)**, dan elastixanton **(113)** menunjukkan potensi yang baik sebagai ajen antioksidan dengan IC_{50} 40.02, 11.53, 11.30, 11.89 dan 21.60 µg/ml. Kaedah sitotoksik ke atas kesemua sebatian menunjukkan artonin E **(80)** mempunyai aktiviti sitotoksik ke atas sel kanser payudara (MCF-7) dan penerima estrogen negatif (MDA-MB 231) dengan nilai IC_{50} 2.5 dan 15 µg/ml. Namun begitu, hanya artonin E **(80)** dan elasticalkon B **(109)** sahaja menunjukkan perencatan yang kuat ke atas pertumbuhan *Bacillus ATCC, B. cereus, B. subtilis, S. aureus ATCC, S. aureus IMR, S. pyogenes, E. coli* dan *S. epidermidis.*

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I certify that an Examination Committee has met on date of viva to conduct the final examination of name of student on his degree thesis entitled "Chemical Constituents And Biological Activities Of *Artocarpus elasticus* Reinw ex Blume" inaccordance with Universiti Pertanian Malaysia (Higher Degree) Act 1980 and Universiti Putra Malaysia (Higher Degree) Regulations 1981. The Committee recommends that the candidate be awarded the relevant degree.

Members of the Examination Committee are as follows:

Mohamed Ibrahim bin Mohamed Tahir, PhD
Senior Lecturer
Faculty of Science
Universiti Putra Malaysia
(Chairman)

Intan Safinar binti Ismail, PhD
Senior Lecturer
Faculty of Science
Universiti Putra Malaysia
(Internal Examiner)

Gwendoline Ee Cheng Lian, PhD
Professor
Faculty of Science
Universiti Putra Malaysia
(Internal Examiner)

Farediah binti Ahmad, PhD
Associate Professor
Faculty of Science
Universiti Teknologi Malaysia
(External Examiner)

_____
BUJANG BIN KIM HUAT, PhD
Professor/Deputy Dean
School of Graduate Studies
Universiti Putra Malaysia

Date:

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This thesis submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

Mawardi Rahmani, PhD
Professor
Faculty of Science
Universiti Putra Malaysia
(Chairman)

Aspollah Mohd Sukari
Professor
Faculty of Science
Universiti Putra Malaysia
(Member)

Abdah Md Akim
Senior Lecturer
Faculty of Medicine and Health Science
Universiti Putra Malaysia
(Member)

BUJANG BIN KIM HUAT, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia
Date:

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DECLARATION

I declare that this thesis is my original work except for quotation and citations, which have been duly acknowledged. I also declared that it has not been previously, and is not concurrently, submitted for any other degree at Universiti Putra Malaysia or at any other Institutions.

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FAIQAH BINTI RAMLI

Date: 22 May 2013

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LIST OF ABBREVIATIONS

δ	Chemical shift in ppm
λ_{max}	Maximum wavelength in mm
^{13}C	Carbon-13
COSY	Correlated spectroscopy
DEPT	Distortionless Enhancement By Polarization Transfer
EIMS	Electrom Impact Mass Spectroscopy
GC-MS	Gas Chromatography-Mass Spectroscopy
^{1}H	proton
HMBC	Heteronucluear Multiple Bond Connectivity
HMQC	Heteronucluear Multiple Quantum Coherence
IC_{50}	Inhibition concentration at 50 percent
M.S	Mass spectrometry
m/z	Mass per charge
IR	Infrared
UV	ultraviolet
APT	Attached proton test

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CHAPTER 1

INTRODUCTION

1.1 Introduction

It is a well known fact that plants play an important role in daily human life by providing oxygen, food, wood, furniture, rubber and are even used in traditional medicines which contribute to the economic development in certain countries (Raskin *et al*., 2002). Studies have exhibited that chronic diseases such as stroke, myocardial infarction, certain type of cancers, diabetes mellitus, Alzheimer's disease, allergy, septic shock, osteoporosis, neurodegeneration and some other diseases associated with aging are easier to prevent than to cure, and that consumption of phytochemical-rich fruits and vegetables, along with culinary herbs and spices, can reduce the risk of developing such condition (Vickery *et al.*, 1981).

Over the centuries, drugs were entirely of natural origin and composed of herbs, animal products, and inorganic materials. Early remedies may have combined these ingredients, but it is certain that those treatments were effective, leading to early herbals. As chemical techniques improve, the active constituents were isolated from plants, structurally characterized, and further synthesized in the laboratory. Sometimes, more effectively, better drugs were produced by structural modifications, or by total synthesis of analogues of the active principles. Even so, herbal remedies are also enjoying revival as modern drugs (Dewick, 2001).

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In Malaysia, 55.4% are still covered by tropical forest all over the country. Studies on local Malaysian plants such as turmeric *(Curcuma domestica)*, betel leaf (*Piper betel*), pandan leaf (*Panadanus odorus*), asam gelugur (*Garnicia atroviridis*), mengkudu (*Morinda citrifolia*), pegaga (*Centella asiatica*), ginger (*Zingiber officinale*), and cassava shoot (*Manihot asculenta*) have been shown to exhibit various good biological activity (Sies, 1996).

The world has witnessed intense research on *Artocarpus* genus which is distributed in South East Asia including Malaysia. *Artocarpus* species are large evergreen trees that have edible fruits. They are use for furniture and building materials due to their strong and durable dark-colored wood (Jayasinghe *et al*., 2006; Hakim *et al*., 2005). The fruits, roots, buds and leaves are also widely used as traditional medicine against various diseases such as malaria fever, liver cirrhosis, hypertension, and diabetes. Regarding the chemical constituent, many chalcones, flavanoids, xanthones and triterpenes have been reported from various *Artocarpus* species. Recent investigations show that the flavanoids that present in both lower and higher plants posses antioxidant, anticancer, antiplatelet, anti-inflammatory effects and protects the body from mutagens such as smoke and other pollutants (Radwan *et al*., 2009).

Plants are potential sources of natural antioxidant. They produce various antioxidative compounds to counteract reactive oxygen species (ROS) in order to survive. ROS include free radicals such as hydroxyl radicals (OH·) and superoxide anion radicals (O^{2-}), and non free-radicals such as H_2O_2 and single hydrogen are various forms of activated oxygen. Studies have shown that ROS can cause aging, cancer and many other diseases as they can induce some oxidative damage to

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biomolecules such as lipids, nucleic acids, proteins and carbohydrates (Choi *et al*., 2006; Fareidoon *et al*., 2007). Several studies had been conducted to estimate the relationship between phenolic compounds and antioxidant activity. The phenolic compound effect as antioxidant has been demonstrated in many systems through *in vitro* studies as in human low density lipoprotein and liposomes (Katalinic *et al*., 2004).

Antimicrobial resistance is a global concern since it is now recognized that resistant microorganisms are prevalent in both the inpatient and outpatient population. The world currently face antibiotic-resistant microbes such as *Mycibacterium tuberculosis, Staphyloccus aureus,* and *Streptococcus pneumonia* that quickly evolve pathways around singular antimicrobial agents. Plants already demonstrated the sensible strategy of using multiple biologically active chemicals to outsmart the adaptable microbial pests (Blondeau *et al.,* 1999). It is shown that green tea *(Camellia sinesis)* extract is effective in the prevention of dental cavity because of the antibacterial activity of the flavour compounds and the antiplaque activity of the polyphenols extracted from the plant (Cseke *et al.,* 2006).

Although several new antimicrobial drugs have recently been introduced and additional ones are forthcoming, experience suggests that, as new drugs become widely deployed, resistance to these agents will emerge and spread as well. Successful control of antibiotic resistance will require both the continued development of new drugs and the judicious use of our current arsenal of antibiotics (Blondeau *et al.,* 2000).

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Taxol is a unique taxane diterpene amide that possesses antitumor and antiluekemic properties. Until recently, taxol could not be synthesized, and the most economical taxol was from Pacific yew (*Taxus brevifolia).* Thus, to obtain this anticancer drug, large areas of Pacific yew forests in United States were destroyed.

Flavonoids extracted from several plants display antimutagenic and anticancer activity through modulation of cell-signalling pathways related to cell growth and proliferation. Thus, recent years the world has witness rapid bioactivity research on flavonoid for new and alternative compound that can be used as cure (Cseke *et al.,* 2006).

1.2 Problem Statement

Several constituents including chalcones, flavanoids, xanthones and triterpenes isolated from Moraceae plants were reported to have biological activities such as antifungal, antibacterial, antimalarial and cytotoxic activities. Some of the compounds isolated are particularly important and relevant for many applications such as prevention of cancer or stroke (Hakim, 2010). Demand for natural ingredients which are reported to be safe and health-promoting property is increasing due to the awareness of consumers on health diet (Raskin *et al*., 2002). Hence, the past few decades have witnessed intense research devoted to the antioxidant, cytotoxic, antimicrobial and anti-inflammatory properties of phenolic compounds found in *Artocarpus* species (Jagtap *et al.,* 2010). Thus, bioassay activities of *Artocarpus elasticus* are of interest.

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1.3 Objectives and Scope of Study

The objective of this study is to extract and isolate the compounds from two different parts of *Artocarpus elasticus*, which were collected from Gunung Nuang, Selangor and Sarawak, respectively. Further, biological activity of crude extracts and the compounds will be tested using DPPH, MTT and disc diffusion assays. The scope of the study is the extraction of the plants was done by cold percolation method using solvent of increasing polarity (hexane, chloroform/ethyl acetate, and methanol) for three days and three times each. The pure compounds were isolated using various chromatography techniques such as thin layer chromatography (TLC), gravity column chromatographic, vacuum liquid chromatography (VLC) and chromatotron. The structures of the isolated compounds will be determined spectroscopically by interpreting various spectral data including NMR, MS, IR, and UV and through comparison with data of related compounds in the literature. The biological activity of the crude extracts and pure compounds were tested using the DPPH, MTT and disc diffusion method.

1.4 Significance of Study

To best of our knowledge, phytochemical studies on leaves of the plant have not been done before. However, previous studies reported the isolation of flavonoid derivatives and their interesting biological activities from bark of *A. elasticus*. The chemical deviation and biological activities of the isolated compounds were determined.

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