



**UNIVERSITI PUTRA MALAYSIA**

***PHYTOCHEMISTRY AND BIOLOGICAL ACTIVITIES OF MESUA  
BECCARIANA (BAILL.) KOSTERM., MESUA FERREA L. AND MESUA  
CONGESTIFLORA***

**TEH SOEK SIN**

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**By**

**TEH SOEK SIN**

**Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in  
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**PHYTOCHEMISTRY AND BIOLOGICAL ACTIVITIES OF *MESUA BECCARIANA* (BAILL.) KOSTERM., *MESUA FERREA* L. AND *MESUA CONGESTIFLORA***

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**TEH SOEK SIN**

**July 2012**

**Chair : Professor Gwendoline Ee Cheng Lian, PhD**

**Faculty : Science**

Phytochemical studies carried out on *Mesua beccariana*, *Mesua ferrea* and *Mesua congestiflora* (Clusiaceae) resulted in the isolation of eight new compounds together with twelve known compounds. Different kinds of chromatographic techniques were utilized for the purification of these isolated compounds. The characterizations of these compounds were achieved through a variety of spectroscopic techniques such as 1D and 2D NMR, UV, IR and GC-MS.

The stem bark of *Mesua beccariana* furnished four new compounds which are two xanthenes, mesuarianone (**236**) and mesuasinone (**237**), a coumarin, beccamarin (**238**) and a cyclodione, mesuadione (**239**), along with several known compounds including two anthraquinones, 4-methoxy-1,3,5-trihydroxyanthraquinone (**240**) and 2,5-dihydroxy-1,3,4-

trimethoxy anthraquinone (**241**) as well as a xanthone 6-deoxyjacareubin (**116**). Meanwhile, seven xanthenes were isolated from the root bark of *Mesua ferrea* three of which are new: mesuaferrin A (**242**), mesuaferrin B (**245**) and mesuaferrin C (**243**). Four known compounds were identified as caloxanthone C (**244**), macluraxanthone (**87**), 1,5-dihydroxyxanthone (**70**) and tovopyrifolin C (**246**). Meanwhile, chemical investigations on *Mesua congestiflora* afforded a new benzophenone, congestiflorone (**247**) together with a known xanthone  $\alpha$ -mangostin (**106**). Several triterpenoids and sterols were obtained from the three *Mesua* species including friedelin (**183**), betulinic acid (**248**), stigmasterol (**187**) and  $\beta$ -sitosterol (**188**).

Structural modifications were carried out on several major compounds which were mesuarianone (**236**), beccamarin (**238**), caloxanthone C (**244**) and congestiflorone (**247**). The acetylation of mesuarianone (**236**) afforded both the mono and diacetate derivatives which were identified as mesuarianone acetate A (**249**) and mesuarianone dwiacetate B (**250**). However, the acetylation reactions of other major compounds only successfully yielded beccamarin acetate (**251**), caloxanthone C dwiacetate (**252**) and congestiflorone acetate (**253**), respectively.

Preliminary screenings were carried out on the crude extracts and pure compounds towards a panel of human cancer cell lines. The human cancer cell lines tested were Raji, SNU-1, K562, LS-174T, SK-MEL-28, IMR 32, HeLa, Hep G2 and NCI-H23. The cytotoxicity of mesuaferrin A (**242**), macluraxanthone (**87**) and  $\alpha$ -mangostin (**106**) were strong as they possess significant inhibitory effects against all the tested cell lines. Furthermore,

mesuaferrin B (**245**) and caloxanthone C (**244**) demonstrated strong cytotoxic activity against nearly all the tested cancer cell lines. Mesuaferrin B (**245**) exhibited mild activity towards IMR 32 and Raji cells while caloxanthone C (**244**) gave mild activity against LS-174T and SK-MEL-28 cells. The Raji, K562 and HeLa cell lines were discovered to be more vulnerable to the pure compounds. However, the SNU-1, LS-174T, SK-MEL-28, IMR 32, Hep G2 and NCI-H23 cell lines were less vulnerable to the rest of the pure compounds as their cell growth were only mildly inhibited. In addition, only the non-polar to semipolar extracts (hexane to ethyl acetate) of the three *Mesua* species contribute to the cytotoxic effects on the panel of human cancer cell lines. Preliminary insights towards the structure-activity relationships among a series of xanthone derivatives were studied. The substituent groups comprising diprenyls, dipyranos and prenyl pyrano of the xanthone derivatives promise the cytotoxicity towards almost all the tested cancer cell lines.

Antioxidant assay were evaluated using DPPH scavenging radical assay and Folin-Ciocalteu method. The methanol extracts of *Mesua beccariana* and *Mesua ferrea* showed high antioxidant activities with low EC<sub>50</sub> values of 12.70 and 9.77  $\mu\text{g}/\text{mL}$ , respectively which are comparable to that of ascorbic acid (EC<sub>50</sub> = 5.62  $\mu\text{g}/\text{mL}$ ). In contrast, only mesuaferrin A (**242**) and macluraxanthone (**87**) revealed mild scavenging potential against the DPPH radical with EC<sub>50</sub> values of 11.72 and 11.70  $\mu\text{g}/\text{mL}$ , respectively. The rest of the pure compounds possess no free radical scavenging activity. On the other hand, the methanol extracts of *Mesua beccariana* and *Mesua ferrea* exhibited high phenolic contents of 363.82 and 441.33  $\mu\text{g}$  in GAE while the ethyl acetate extract of *Mesua congestiflora* gave a higher phenolic content compared to its methanol extract with values of 369.26 and

273.87  $\mu\text{g}$  in GAE, respectively. The rest of the crude extracts contributed low to moderate phenolic content with GAE values less than 130  $\mu\text{g}$  of gallic acid per mg of extract.

Nitric oxide (NO) assay was another test which correlated with the antioxidant assay as the inflammation process was initiated by the invasions of free radicals. Anti-inflammatory assay screening using NO assay was only performed on the crude extracts of the three *Mesua* species. The hexane extract of all three *Mesua* species showed significant inhibitory activity of NO production with more than 70% inhibition. However, the dichloromethane and ethyl acetate extracts exhibited moderate to weak NO inhibitory effects while the methanol extracts were found to be inactive in suppressing NO production.

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

**FITOKIMIA DAN AKTIVITI BIOLOGI DARIPADA *MESUA BECCARIANA* (BAILL.) KOSTERM., *MESUA FERREA* L. DAN *MESUA CONGESTIFLORA***

Oleh

**TEH SOEK SIN**

**Julai 2012**

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Kajian fitokimia yang dilakukan ke atas *Mesua beccariana*, *Mesua ferrea* dan *Mesua congestiflora* (Clusiaceae) menghasilkan pengasingan lapan sebatian baru bersama-sama dengan dua belas sebatian yang diketahui. Pelbagai jenis teknik kromatografi telah digunakan untuk penulenan sebatian-sebatian. Pencirian sebatian-sebatian berikut telah dilakukan dengan menggunakan pelbagai teknik spektroskopi termasuk 1D dan 2D NMR, UV, IR dan GC-MS.

Kulit kayu batang *Mesua beccariana* memberikan empat sebatian yang baru iaitu dua xanton, mesuarianone (**236**) dan mesuasinone (**237**), coumarin, beccamarin (**238**) dan siklodione, mesuadione (**239**), bersama-sama dengan sebatian diketahui termasuklah dua antrakuinon, 4-metoksi-1,3,5-trihidroksi-antrakuinon (**240**) dan 2,5-dihidroksi-1,3,4-trimetoksi antrakuinon (**241**) serta satu xanton 6-deoksijacareubin ( **116**). Sementara itu,



tujuh xanton telah diasingkan daripada kulit akar *Mesua ferrea* di mana tiga yang baru: mesuaferrin A (242), mesuaferrin B (245) dan mesuaferrin C (243). Empat sebatian yang diketahui telah dikenalpasti sebagai caloxanton C (244), macluraxanton (87), 1,5-dihidroksixanton (70) dan tovopyrifolin C (246). Sementara itu, kajian kimia pada *Mesua congestiflora* telah memberi satu benzofenon yang baru, congestiflorone (247) bersama-sama dengan xanton yang diketahui iaitu  $\alpha$ -mangostin (106). Beberapa triterpenoid dan sterol juga diperolehi daripada tiga *Mesua* spesies iaitu friedelin (183), asid betulnik (248), stigmasterol (187) dan  $\beta$ -sitosterol (188).

Pengubahsuaian struktur yang telah dilakukan ke atas beberapa sebatian utama iaitu mesuarianone (236), beccamarin (238), caloxanthon C (244) dan congestiflorone (247). Asitilasi mesuarianone (236) memberikan kedua-dua mono dan diasetat yang dikenal pasti sebagai mesuarianone A asetat (249) dan mesuarianone dwiasetat B (250). Walau bagaimanapun, asitilasi sebatian-sebatian utama yang lain hanya berjaya menghasilkan beccamarin asetat (251), caloxanthon dwiasetat C (252) dan congestiflorone asetat (253).

Pemeriksaan awal telah dijalankan ke atas ekstrak mentah dan sebatian tulen terhadap panel garisan sel kanser manusia. Kanser sel manusia yang diuji ialah Raji, SNU-1, K562, LS-174T, SK-MEL-28, IMR 32, HeLa, Hep G2 dan NCI-H23. Sitotoksiti pada mesuaferrin A (242), macluraxantone (87) dan  $\alpha$ -mangostin (106) adalah baik kerana sebatian-sebatian ini mempunyai kesan perencatan yang ketara terhadap semua sel kanser yang diuji. Tambahan pula, mesuaferrin B (245) dan caloxanton C (244) menunjukkan aktiviti sitotoksik yang sangat positif terhadap hampir semua sel garisan kanser yang diuji.

Mesuaferin B (**245**) mempamerkan aktiviti sederhana terhadap IMR 32 dan Raji manakala caloxanton C (**244**) memberi aktiviti sederhana terhadap sel-sel LS-174T dan SK-MEL-28. Sel-sel Raji, K562 dan HeLa ditemui untuk menjadi lebih terdedah kepada sebatian tulen. Walau bagaimanapun, SNU-1, LS-174T, SK-MEL-28, IMR 32, Hep G2 dan NCI-H23 adalah kurang terdedah kepada seluruh sebatian tulen kerana pertumbuhan sel mereka kurang dihalangkan. Di samping itu, hanya ekstrak bukan polar dan semipolar (heksana sampai etil asetat) bagi tiga spesies *Mesua* yang menyumbang kepada kesan sitotoksik pada panel garisan sel kanser manusia. Kajian awal ke arah hubungan struktur-aktiviti di kalangan siri derivatif xanton telah dikaji. Kumpulan gantian terdiri daripada diprenyl, dipirano dan pirano prenyl derivatif xanton menjanjikan sitotoksiti terhadap hampir semua garisan sel kanser yang diuji.

Kajian antioksidan telah dinilai menggunakan radikal DPPH dan kaedah Folin-Ciocalteu. Ekstrak metanol untuk *Mesua beccariana* dan *Mesua ferrea* menunjukkan aktiviti antioksidan yang tinggi dengan nilai  $EC_{50}$  serendah 12.70 dan 9.77  $\mu\text{g} / \text{mL}$ , masing-masing setanding dengan asid askorbik ( $EC_{50} = 5.62 \mu\text{g}/\text{mL}$ ). Sebaliknya, hanya mesuaferin A (**242**) dan macluraxanthone (**87**) memberikan potensi sederhana terhadap radikal DPPH dengan nilai  $EC_{50}$  11.72 dan 11.70  $\mu\text{g}/\text{mL}$ , masing-masing. Sebatian tulen yang lain tidak mempunyai aktiviti merencatkan radikal bebas. Sebaliknya, ekstrak metanol *Mesua beccariana* dan *Mesua ferrea* mempamerkan kandungan fenolik yang tinggi 363.82 dan 441.33  $\mu\text{g}$  dalam GAE manakala ekstrak etil asetat *Mesua congestiflora* memberi kandungan fenolik yang lebih tinggi berbanding dengan ekstrak metanol dengan nilai 369.26 dan 273.87  $\mu\text{g}$  dalam GAE. Ekstrak mentah yang lain menyumbang kepada

kandungan fenolik dalam GAE yang rendah hingga sederhana iaitu kurang daripada 130  $\mu\text{g}$  asid Gallic/satu mg ekstrak.

Kajian Nitrik oksida (NO) adalah satu lagi ujian yang berhubung kait dengan kajian antioksidan kerana proses keradangan dimulakan oleh serangan radikal bebas. Saringan anti-radang menggunakan kajian NO hanya dijalankan ke atas ekstrak mentah tiga spesies *Mesua*. Ekstrak heksana bagi ketiga-tiga spesies *Mesua* menunjukkan aktiviti yang ketara dalam pengeluaran NO dengan lebih daripada 70% daripada perencatan. Walau bagaimanapun, ekstrak diklorometana dan etil asetat menunjukkan kesan yang sederhana dan lemah kepada kesan perencatan NO, manakala ekstrak metanol didapati tidak aktif dalam pengeluaran menekan NO.

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I certify that a Thesis Examination Committee has met on 11<sup>th</sup> July 2012 to conduct the final examination of Teh Soek Sin on his (or her) thesis entitled "Phytochemistry and Biological Activities of *Mesua beccariana* (Baill.) Kosterm., *Mesua ferrea* L. and *Mesua congestiflora*" 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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## DECLARATION

I declare that the thesis is my original work except for quotations 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 institution.

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**TEH SOEK SIN**

Date: 11 July 2012



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