PHYTOCHEMICAL CONSTITUENTS AND BIOLOGICAL ACTIVITIES OF Clausena excavata BURM. F., Micromelum minutum (G. FORST.) WIGHT & ARN. AND Melicope latifolia (DC.) T.G. HARTLEY (RUTACEAE)

LIM PEI CEE

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By

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

PHYTOCHEMICAL CONSTITUENTS AND BIOLOGICAL ACTIVITIES OF *Clausena excavata* BURM. F., *Micromelum minutum* (G. FORST.) WIGHT & ARN. AND *Melicope latifolia* (DC.) T.G. HARTLEY (Rutaceae)

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January 2020

Chairman : Nur Kartinee Binti Kassim, PhD
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The *Rutaceae* family has been used in traditional medicine practices to treat various ailments such as snake bites, fever, cough and diarrhoea. *Clausena excavata*, *Micromelum minutum* and *Melicope latifolia* are plants of the *Rutaceae* family grown locally in Malaysia. To date, there are limited studies on the activity of their extracts and compounds on antimicrobial activity against oral pathogenic bacteria, antioxidant capacity especially cellular antioxidant activity as well as cytotoxicity properties. Therefore, this study aimed to investigate the phytochemical constituents, antimicrobial, antioxidant and cytotoxicity properties of *C. excavata*, *M. minutum* and *M. latifolia*. A total of 24 compounds including one new conjugated sesquiterpene were isolated from *C. excavata*, *M. minutum* and *M. latifolia* using different chromatographic techniques. Structural elucidation was achieved by means of spectroscopic and spectrometric analysis.

Phytochemical investigation on stem bark of *C. excavata* yielded four coumarins (dentatin (**166**), nordentatin (**54**), clausenidin (**64**) and xanthoxyletin (**66**)), three alkaloids (heptazoline (**51**), clausine H (**167**) and heptaphylline (**67**)), together with clausenarin (**168**). Atranorin (**170**), a polyketide and lichexanthone (**171**), a xanthone were also first isolated from the *Clausena* species. Flavonoids namely araneosol (**173**), 5-hydroxyauranetin (**172**) and 5,7-dihydroxy-3,8,4'-trimethoxyflavone (**174**) together with stigmasterol (**169**) were isolated from the leaves of *M. minutum*. Meanwhile, *M. latifolia* leaves afforded one new conjugated sesquiterpene, trivially named as amelicarin (**176**) together with nine known compounds consist of sterol derivatives (β-sitosterol (**175**), β-sitostenone (**178**), stigmast-4-ene-6β-ol-3-one (**179**), stigmast-4-ene-3,6-dione (**177**)), four flavonoid glycosides (quercetin 3-*O*-

robinobioside (**181**), kaempferol 3-*O*-rutinoside (**182**), kaempferol 3-*O*-glucoside (**183**), kaempferol 3-*O*-arabinoside (**184**)) and one flavonoid (taxifolin (**180**)). These compounds are first reported from the species *M. latifolia*.

Disc diffusion antimicrobial assay against *S. mutans* and *E. faecalis* revealed the potency of hexane, ethyl acetate extracts and three compounds from *C, excavata* together with all extracts from *M. minutum* and *M. latifolia* against *S. mutans*. Further antimicrobial evaluation by determining the minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) indicated that *C. excavata* hexane extract showed the lowest MIC and MBC values 0.31 and 0.63 mg/mL respectively towards *S. mutans*. However, the selected compounds from *C. excavata* (clausine H, heptazoline and nordentatin) showed insignificant inhibition towards *S. mutans* suggested that the activity of the extracts could be due to synergistic effect of the compounds present in the hexane extract of *C. excavata*. None of the extracts and their isolated compounds showed significant activity towards *E. faecalis*. This is the first report in which the plant extracts and selected compounds were tested against *S. mutans* and *E. faecalis*.

Plant extracts were evaluated using chemical antioxidant assays as well as assessing their phenolic contents. All the methanol extracts showed high antioxidant capacities in all the assays where methanol extract from *C. excavata* exhibited potent activity based on DPPH, FRAP and CUPRAC assays while *M. minutum* and *M. latifolia* displayed relative higher activity with trolox equivalent values exceeded 1900 mg TE/g extract in TEAC and 2000 µmol TE/g extract in ORAC. Meanwhile, cellular antioxidant activity assay (CAA) of methanol extract of *M. latifolia* displayed highest activity (52.33 ± 1.53%) while taxifolin (**180**) showed 63.67 ± 1.53% decrease in cellular oxidative stress which was the highest among all the tested compounds.

WST cytotoxicity assay revealed the potency of hexane and ethyl acetate extract of *M.latifolia* towards KB cell line with half maximal inhibitory concentration (IC_{50}) of 23.67 ± 1.53 and 36.37 ± 5.19 µg/mL respectively without showing significant toxicity towards the noncancerous cell lines whereas the new compound, amelicarin (**176**) showed poor selectivity with low IC_{50} in all cell lines.

In conclusion, this study suggested the potential of *C. excavata*, *M. minutum* and *M. latifolia* as health promoting agents or as the sources of therapeutic alternatives.

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

SEBATIAN FITOKIMA DAN AKTIVIT BIOLOGI *Clausena excavata* BURM. F., *Micromelum minutum* (G. FORST.) WIGHT & ARN. DAN *Melicope latifolia* (DC.) T.G. HARTLEY (Rutaceae)

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Keluarga *Rutaceae* telah digunakan dalam amalan perubatan tradisional untuk merawat pelbagai penyakit seperti gigitan ular, demam, batuk dan cirit-birit. *Clausena excavata*, *Micromelum minutum* dan *Melicope latifolia* merupakan tumbuhan tempatan dalam keluarga *Rutaceae* yang terdapat di Malaysia. Kajian atas ekstrak dan sebatian spesies tersebut mengenai sifat antimikrob terhadap bakteria pathogen mulut, antioksidan kapasiti terutamanya antioksidan aktiviti dalam sel dan sifat sitotoksik masih terbatas. Justeru, kajian ini bertujuan untuk menyiasat sebatian fitokimia, sifat antimikrob, antioksidan dan sitotoksik *C. excavata*, *M. minutum* dan *M. latifolia.* Sejumlah 24 sebatian termasuk satu sesquiterpene berkonjugat baru telah diasingkan daripada *C. excavata*, *M. minutum* dan *M. latifolia* dengan menggunakan pelbagai teknik kromatografi. Struktur identifikasi telah dicapai melalui analisis spektroskopi dan spektrometrik.

Penyiasatan fitokimia batang *C. excavata* menghasilkan empat koumarin (dentatin (**166**), nordentatin (**54**), clausenidin (**64**) and xanthoxyletin (**66**)), tiga alkaloid (heptazolin (**51**), klausin H (**167**) and heptaphyllin (**67**)) sekali dengan klausenarin (**168**). Atranorin (**170**), poliketide and lichexanton (**171**), xanton turut diasing kali pertama daripada spesies *Clausena*. Flavonoid bernama araneosol (**173**), 5-hidroksiauranetin (**172**), 5,7-dwihidroksi-3,8,4'-trimetoksiflavon (**174**) dan stigmasterol (**169**) telah dihasilkan daripada daun *M. minutum*. Selain daripada itu, daun *M. latifolia* menghasilkan satu sesquiterpene berkonjugat dinamakan sebagai amelicarin (**176**) sekali dengan sembilan sebatian yang telah dikenali iaitu satu sterol derivatif (β-sitosterol (**175**), β-sitostenone (**178**), stigmast-4-ene-6β-ol-3-one (**179**), stigmast-4-ene-3,6-dione (**177**)), empat flavonoid glikosida (quercetin 3-*O*-robinobiosida (**181**), kaempferol 3-*O*-rutinosida (**182**), kaempferol 3-*O*-glukosida

(**183**), kaempferol 3-*O*-arabinosida (**184**)) dan satu flavonoid (taxifolin (**180**)). Ini adalah penemuan baharu disebabkan ini adalah kali pertama sebatian ini didapati dari spesies *M. latifolia.*

Antimikrob asai dengan kaedah penyebaran disk menunjukkan potensi ekstrak heksana, etil asetat dan empat sebatian *C, excavata* sekali dengan semua ekstrak *M. minutum* dan *M. latifolia* terhadap *S. mutans.* Penilaian antimikrob yang lebih lanjut dengan menentukan kepekatan perencatan minimal (MIC) dan kepekatan bakterisidal minimal (MBC) menunjukkan ekstrak heksana *C. excavata* memaparkan MIC dan MBC paling rendah dengan nilai 0.31 and 0.63 mg/mL terhadap *S. mutans*. Namun, sebatian pilihan *C. excavata* menujukkan perencatan yang tidak signifikan mencadangkan bahawa aktiviti ekstrak mungkin disebabkan kesan sinergi sebatian dalam ekstrak heksana *C. excavata.* Tiada ekstrak dan sebatian menunjukkan aktivit terhadap *E. faecalis.* Ini merupakan report pertama ujian ekstrak dan sebatian pilihan terhadap *S. mutans* and *E. faecalis.*

Ekstrak tumbuhan telah dinilai dengan asai kimia antioksidan sekali dengan penilai kandungan fenolik. Kesemua ekstrak metanol menunjukkan kapasiti antioksidan yang tinggi dalam semua asai dengan metanol ekstrak daripada *C. excavata* menujukkan aktiviti paling bagus berdasarkan kaedah DPPH, FRAP and CUPRAC manakala *M. minutum* dan *M. latifolia* memaparkan aktiviti relatif yang tinggi dengan nilai bersamaan trolox melebihi 1900 mg TE/g ekstrak dalam TEAC dan 2000 µmol TE/g extract dalam ORAC. Sementara itu, antioksidan aktiviti dalam sel (CAA) untuk ektrak metanol *M. latifolia* menunjukkan activity paling tinggi (52.33 ± 1.53%) manakala taxifolin (**180**) menurun oksidatif stres dalam sel sebanyak 63.67 ± 1.53% yang paling tinggi berbanding dengan sebatian lain yang dinilai.

Asai sitotoksik WST menunjukkan potensi ekstrak heksana dan etil asetat *M.latifolia* terhadap sel KB dengan nilai kepekatan perencatan separuh maksima (IC_{50}) 23.67 ± 1.53 dan 36.37 ± 5.19 µg/mL tanpa menunjukkan kesan toksik terhadap sel bukan kanser manakala sebatian baru, amelicarin (**176**) menunjukkan aktiviti kurang selektif dengan IC_{50} yang rendah dalam semua sel.

Kesimpulannya, kajian ini mencadangkan potensi *C. excavata*, *M. minutum* and *M. latifolia* sebagai agen penjagaan kesihatan atau sebagai sumber alternatif terapeutik.

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

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LIST OF SYMBOLS AND ABBREVIATIONS

A	Absorbance
Ace	Acetone
α	Alpha
ATCC	American Type Culture Collection
NH_4Ac	Ammonium Acetate
AA	Antioxidant Activity
AUC	Area Under Curve
AAPH/ABAP	2,2'-Azobis(2-amidinopropane) Dihydrochloride
ABTS	2,2'-Azinobis(3-ethylbenzothiazoline-6-sulfonic Acid
β	Beta
BHI	Brain Heart Infusion
br	Broad
C	Carbon
^{13}C	Carbon-13
CAA	Cellular Antioxidant Activity Assay
δ	Chemical Shift
CHX	Chlorhexidine
$CHCl_3$	Chloroform
FCR-3	Chloroquine-resistant
D-10	Chloroquine-sensitive
CLSI	Clinical and Laboratory Standards Institute
R^2	Coefficient of Determination
CoA	Coenzyme A

CFU	Colony-Forming Unit
CC	Column Chromatography
c	Concentration
COSY	Correlated Spectroscopy
J	Coupling Constant
$CuCl_2$	Cupric Chloride
Cu^{2+}	Cupric Ion
CUPRAC	Cupric Ion Reducing Antioxidant Capacity
Cu+	Cuprous
°C	Degree in Celcius
DNA	Deoxyribonucleic Acid
$CDCl_3$	Deuterated Chloroform
CD_3OD	Deuterated Methanol
D	Dextrorotatory
DCFH-DA	2',7'-Dichlorofluorescin Diacetate
DMSO	Dimethyl Sulfoxide
DPPH	2,2-Diphenyl-1-picryl Dihydrazyl
d	Doublet
dd	Doublet of Doublets
DEPT	Distortionless Enhancement by Polarization Transfer
ET	Electron Transfer
EtOH	Ethanol
EI-MS	Electron Impact-Mass Spectrometry
EtOAc	Ethyl Acetate
$FeCl_3.6H_2O$	Ferric Chloride Hexahydrate

Fe^{3+}	Ferric Ion
FRAP	Ferric Reducing Antioxidant Power
Fe^{2+}	Ferrous Ion
GAE	Gallic Acid Equivalent
GCMS	Gas Chromatography Mass Spectrometry
$^{2}J_{CH}$	Geminal Carbon-Proton Coupling Constant
^{2}J	Geminal Coupling
$^{2}J_{HH}$	Geminal Proton-Proton Coupling Constant
g	Gram
IC_{50}	Half Maximal Inhibitory Concentration
Hz	Hertz
HMBC	Heteronuclear Multiple Bond Correlation
HMQC	Heteronuclear Multiple Quantum Correlation
HSQC	Heteronuclear Single Quantum Coherence Spectroscopy
Hex	Hexane
HR-ESI-MS	High Resolution-Electronspray Ionization-Mass Spectrometry
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
h	Hour
MCF-7	Human Breast Carcinoma Cell Line
KKU-100	Human Cholangiocarcinoma Cell Line
BT-549	Human Ductal Carcinoma Cell Line
HT-1080	Human Fibrosarcoma Cell Line
SMMC-7721	Human Hepatocarcinoma Cell Line

HepG2	Human Hepatocellular Carcinoma Cell Line
HIV	Human Immunodeficiency Virus
NCI-H187	Human Lung Carcinoma Cell Line
H1299	Human Non-Small Lung Carcinoma Cell Line
SK-OV-3	Human Ovary Adenocarcinoma Cell Line
KB	Human Papilloma Cell Line
HL60	Human Promyeolocytic Leukemia Cell Line
SK-MEL	Human Skin Melanoma Cell Line
CEM-SS	Human T-lymphoblastic Leukemia Cell Line
HCl	Hydrochloric Acid
HAT	Hydrogen Atom Transfer
Trolox	6-hydroxy-2,5,7,8-tetra-methylchroman-2-carboxylic acid
IR	Infrared
kg	Kilogram
LOX	Lipoxygenase
L	Litre
Lit.	Literature
m/z	Mass over Charge Ratio
MS	Mass Spectrometry
λ_{max}	Maximum wavelength
ν_{max}	Maximum wavenumber
LC_{50}	Median Lethal Dose
MHz	Mega Hertz
m.p.	Melting Point
MeOH	Methanol

µg	Microgram
µL	Microlitre
µM	Micromolar
mg	Milligram
mL	Millilitre
mm	Millimetre
mM	Millimolar
MBC	Minimal Bactericidal Concentration
MIC	Minimal Inhibitory Concentration
min	Minute
ε	Molar Absorptivity
M	Molar Mass
M^+	Molecular Ion
VERO	Monkey Kidney Epithelial Cell Line
3T3	Mouse Fibroblast Cell Line
m	Multiplet
nm	Nanometre
NCNPR	National Center for Natural Products Research
Nc	Neocuproine
N	Nitrogen
NOESY	Nuclear Overhauser Effect Spectroscopy
NMR	Nuclear Magnetic Resonance
O	Oxygen
ORAC	Oxygen Radical Absorbance Capacity
ppm	Parts Per Million

%	Percent
PBS	Phosphate Buffered Saline
KBr	Potassium Bromide
$K_2S_2O_8$	Potassium Persulfate
pH	Potential of Hydrogen
H	Proton
^1H	Proton-1
q	Quartet
INS-1	Rat Insulinoma Cell Line
tsFT210	Rat Mutant Mammalian Cell
RNS	Reactive Nitrogen Species
ROS	Reactive Oxygen Species
Rel. Int.	Relative Intensity
RP	Reversed Phase
s	Singlet
Na	Sodium
NaCl	Sodium Chloride
SPE	Solid Phase Extraction
$[\propto]_D^{20}$	Specific rotation in the Sodium D Line Region at 20 °C
SD	Standard Deviation
H_2SO_4	Sulfuric acid
LLC-PK_1	*Sus scrofa* Kidney Epithelial Cell Line
TMS	Tetramethylsilane
TLC	Thin Layer Chromatography
TPC	Total Phenolic Content

t	Triplet
TPTZ	2,4,6-tri(2-pyridyl)-striazine
TE	Trolox Equivalent
TEAC	Trolox Equivalent Antioxidant Capacity
2D	Two-Dimentional
UATR	Universal Attenuated Total Reflection
UV	Ultraviolet
UV-Vis	Ultraviolet-visible
FDA	US Food and Drug Administration
$^3J_{CH}$	Vicinal Carbon-Proton Coupling Constant
^3J	Vicinal Coupling
$^3J_{HH}$	Vicinal Proton-Proton Coupling Constant
WST-8	Water-Soluble Tetrazolium Salt
λ	Wavelength
cm^{-1}	Wavenumber
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

Rutaceae, commonly known as the rue or citrus family, placed in the order Sapindales, containing about 1730 species among 158 genera (Shivakumar, Appelhans, Johnson, Carlsen, & Zimmer, 2017). The Rutaceae is well known for the important species in the family which is *Citrus*, including the orange (*Citrus sinensis*), lemon (*Citrus limon*), grapefruit (*Citrus paradise*) and lime (*Citrus aurantifolia*). Other profound genera include *Clausena*, *Micromelum* and *Melicope*. Numerous secondary metabolites have been isolated from *Rutaceae* family, in particular coumarins, lignans and alkaloids, and some of which have high potential to be developed into medicine as they exhibit pharmacologic activities such as anti-toxicity (Tan *et al*., 2009), anti-plasmodial (Susidarti *et al*., 2014) as well as anti-hyperglycaemic, anti-hyperlipidaemia and anti-apoptic activities (Koriem *et al*., 2014).

Clausena excavata Burm. f. is an evergreen wild shrub or a small slender tree (Ismail *et al.*, 2011). The plant is traditionally used in treatment of colds, stomach disorders (Waziri *et al*., 2016), snakebites and as a detoxifying agent (Wu & Furukawa, 1982). In the past few decades, the plant has been reported to show anti-inflammatory, antimicrobial, antioxidant, and analgesic activities (Albaayit, Abba, Rasedee, & Abdullah, 2015a; Cheng *et al*., 2009). It is noteworthy that the plant possesses cytotoxic properties due to the presence of coumarins derivatives which has drawn the interest of researchers to investigate further.

Micromelum minutum (G. Forst.) Wight and Arn., commonly known as lime berry, is a small to medium-sized shrub This species has been widely used for medicinal purposes especially to cure fever and giddiness whereas the boiled roots are made into a poultice to treat ague (Burkill, 1935). This plant were scientifically reported to exhibit anti-hyperglycemic, anti-hyperlidemic and cytotoxic activities which is associated to the high coumarin content (Koriem *et al*., 2013).

Melicope latifolia (DC.) T. G. Hartley is a wild evergreen tree, commonly known as "pepau" in Malaysia and "kisampang" in Indonesia, where the leaves are used to treat fever and cramps. The plant was reported to have antiviral activities against hepatitis C virus (Wahyuni *et al*., 2013).

According to the above-mentioned information, as part of the ongoing effort to discover potential lead compounds from plants, plants of the family Rutaceae were

selected for investigation based on their rich chemistry and history of providing active compounds inspired from ethno-medicinal uses. In fact, there are still many species under the Rutaceae family remain scientifically uninvestigated. Thus, *C. excavata* and *M. minutum* were opted for this work as the literature study shown that they possess a great deal of potential phytochemical constituents that are worthwhile to be further studied whereas *M. latifolia* was chosen for the lack of report on the scientific studies. The aim of this work was to obtain potential biological active compounds from the plant species since there are limited studies on the activity of their extracts and compounds on antimicrobial activity against oral pathogenic bacteria (*Streptococcus mutans* and *Enterococcus faecalis*), antioxidant capacity especially cellular antioxidant activity as well as cytotoxicity properties against cancerous cell lines (skin melanoma (SK-MEL), oral cancer (KB), breast cancer (BT-549) and ovarian cancer (SK-OV-3)) and two non-cancerous kidney cell lines (LLC-PK1 and VERO).

In our attempt to isolate chemical constituents from plant extracts, various column chromatographic techniques were employed throughout the isolation process. Structure of the chemical constituents were elucidated with the aid of spectroscopic analyses namely NMR and MS and further supported by comparison with previously reported literature values. Antimicrobial assays of the extracts and compounds were assessed using disc diffusion and broth microdilution methods. Antioxidant properties of the extracts were evaluated using various chemical antioxidant assays (DPPH, ABTS, FRAP, CUPRAC, TPC, ORAC) and cellular antioxidant activity assay (CAA). Cytotoxicity of the extracts and compounds were evaluated using WST cytotoxicity assay.

The objectives of the study were to:

i. isolate and purify pure compounds from *C. excavata*, *M. minutum* and *M. latifolia*.

ii. elucidate the chemical structures of pure compounds

iii. investigate biological activites (antimicrobial, antioxidant, cytotoxicity) of the extracts and selected compounds from *C. excavata*, *M. minutum* and *M. latifolia*

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