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จุฬาลงกรณ์มหาวิทยาลัย

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CHEMICAL CONSTITUENTS AND BIOACTIVITIES OF *DENDROBIUM ELLIPSOPHYLLUM*

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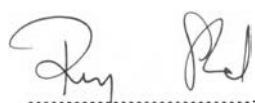
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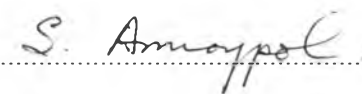


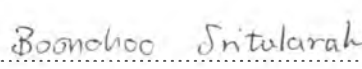
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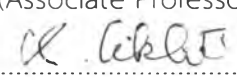
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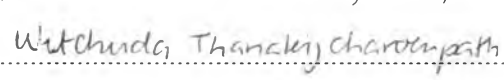

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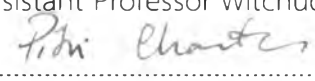
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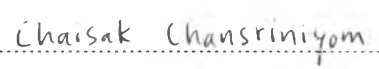

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(CHEMICAL CONSTITUENTS AND BIOACTIVITIES OF *DENDROBIUM ELLIPSOPHYLLUM*) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: รศ. ภก. ดร.บุญชู ศรีตุลารักษ์, อ.ที่ปรึกษาวิทยานิพนธ์ร่วม: ศ. ภก. ดร.กิตติศักดิ์ ลิขิตวิทยาวุฒิ, 176 หน้า.

วัตถุประสงค์การวิจัยครั้งนี้เพื่อศึกษาองค์ประกอบทางเคมีจากสิ่งสกัดในชั้นเมทานอล รวมถึงฤทธิ์ทางชีวภาพของเอื้องทองทั้งต้น ซึ่งยังไม่เคยมีผู้ทำการวิจัยมาก่อน สามารถแยกสารบริสุทธิ์ที่เคยมีรายงานมาก่อน 10 ชนิด ได้แก่ สารกลุ่มไบเบนซิล คือ moscatilin, 4,4'-dihydroxy-3,5-dimethoxybibenzyl และ 4,5,4'-trihydroxy-3,3'-dimethoxybibenzyl, กลุ่มฟลาโวนอยด์ ได้แก่ (2S)-homoeriodictyol, (2S)-eriodictyol, chrysoeriol และ luteolin, กลุ่มไดไฮโดรฟีแนนทริน คือ 4,5-dihydroxy-2,3-dimethoxy-9,10-dihydrophenanthrene, กลุ่มโครโมน คือ 5,7-dihydroxy-chromen-4-one และกลุ่มฟีนิลโพรพานอยด์ คือ phloretic acid ซึ่งสารทั้งหมดพิสูจน์โครงสร้างทางเคมีโดยเทคนิคสเปกโตรสโคปี (UV, IR, MS, NMR) ร่วมกับการเปรียบเทียบข้อมูลที่เคยมีรายงานมาแล้ว จากผลการทดสอบฤทธิ์ทางชีวภาพพบว่า 4,5,4'-trihydroxy-3,3'-dimethoxybibenzyl และ luteolin มีฤทธิ์ระดับปานกลางยับยั้งเซลล์มะเร็งช่องปาก KB (IC₅₀ 61.93 และ 56.22 μ M ตามลำดับ) ซึ่งมีชุดควบคุมผลบวก คือ ellipticine (IC₅₀ 4.99 μ M) และ doxorubicin (IC₅₀ 2.19 μ M) รวมทั้งในเซลล์มะเร็งเต้านม MCF-7 (IC₅₀ 135.48 และ 68.01 μ M ตามลำดับ) ซึ่งมีชุดควบคุมผลบวก คือ tamoxifen (IC₅₀ 20.46 μ M) และ doxorubicin (IC₅₀ 26.29 μ M) นอกจากนี้ 4,4'-dihydroxy-3,5-dimethoxybibenzyl, 4,5,4'-trihydroxy-3,3'-dimethoxybibenzyl, chrysoeriol และ luteolin ยังมีฤทธิ์ด้านการแพร่กระจายของเซลล์มะเร็งปอด H292 เกิดการตายของเซลล์มะเร็งแบบอะพอพโทซิส และกระตุ้นการเกิดอะนอยคิซิส โดย 4,5,4'-trihydroxy-3,3'-dimethoxybibenzyl (IC₅₀ 96.56 μ M) เกิดการตายแบบอะพอพโทซิสมากที่สุดอย่างมีนัยสำคัญเมื่อเปรียบเทียบกับกลุ่มควบคุม และกระตุ้นการเกิดอะนอยคิซิสออกฤทธิ์เร็วที่สุดที่ 6 ชั่วโมง ที่ความเข้มข้น 1 และ 5 μ M นอกจากนี้ 4,4'-dihydroxy-3,5-dimethoxybibenzyl ยังมีฤทธิ์ระดับอ่อนในการต้านไวรัสเริมชนิด HSV-1 และ HSV-2 (IC₅₀ 313.61 \pm 40.40 และ 334.56 \pm 52.66 μ M ตามลำดับ)

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สาขาวิชา เกษศาสตร์
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ลายมือชื่อนิสิต ...เกลสินี ธนากรเมธา
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BIOACTIVITIES

KASINEE TANAGORNMEATAR: CHEMICAL CONSTITUENTS AND
BIOACTIVITIES OF *DENDROBIUM ELLIPSOPHYLLUM*. ADVISOR: ASSOC.
PROF. BOONCHOO SRITULARAK, Ph.D., CO-ADVISOR: PROF. KITTISAK
LIKHITWITAYAWUID, Ph.D., 176 pp.

The objective of this study was to investigate the chemical constituents and biological activities of *Dendrobium ellipsophyllum*, a plant with no previous reports. The results led to the isolation of ten known compounds, consisting of three bibenzyls (moscatilin, 4,4'-dihydroxy-3,5-dimethoxybibenzyl, 4,5,4'-trihydroxy-3,3'-dimethoxybibenzyl), four flavonoids ((2S)-homoeriodictyol, (2S)-eriodictyol, chrysoeriol and luteolin), a dihydrophenanthrene, a chromone and a phenylpropanoids (4,5-dihydroxy-2,3-dimethoxy-9,10-dihydrophenanthrene, 5,7-dihydroxy-chromen-4-one and phloretic acid, respectively). Their structures were determined by spectroscopic analysis (NMR, MS) and comparison with the previously reported data. The results from bioassays revealed that 4,5,4'-trihydroxy-3,3'-dimethoxybibenzyl and luteolin had moderate cytotoxic activity against KB oral cavity cancer cells (IC_{50} 61.93 and 56.22 μ M, respectively), as compared with the positive controls ellipticine (IC_{50} 4.99 μ M) and doxorubicin (IC_{50} 1.53 μ M). The two compounds had cytotoxicity on MCF-7 breast cancer cells (IC_{50} 135.48 and 68.01 μ M, respectively), in comparison with tamoxifen (IC_{50} 20.46 μ M) and doxorubicin (IC_{50} 26.29 μ M). 4,4'-Dihydroxy-3,5-dimethoxybibenzyl, 4,5,4'-trihydroxy-3,3'-dimethoxybibenzyl, chrysoeriol and luteolin showed anti-metastatic activity on H292 lung cancer cells, displaying apoptosis induction and anoikis sensitizing activities. 4,5,4'-Trihydroxy-3,3'-dimethoxybibenzyl (IC_{50} 96.56 μ M) possessed highest cytotoxic activity and the fastest action in sensitizing the cells to anoikis at the concentrations of 1 and 5 μ M. Significant effects could be detected as early as 6 hours after exposure to the cells. Moreover, 4,4'-dihydroxy-3,5-dimethoxybibenzyl showed weak anti-herpes simplex virus activity against HSV-1 and HSV-2 with IC_{50} 313.61 \pm 40.40 and 334.56 \pm 52.66 μ M, respectively.

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LIST OF ABBREVIATIONS

Acetone- d_6	= Deuterated acetone
α	= Alpha
β	= Beta
br s	= Broad singlet (for NMR spectra)
$^{\circ}\text{C}$	= Degree Celsius
CC	= Column chromatography
CDCl_3	= Deuterated chloroform
CD_3OD	= Deuterated methanol
cm	= Centimeter
^{13}C NMR	= Carbon-13 Nuclear Magnetic Resonance
d	= Doublet (for NMR spectra)
dd	= Doublet of doublets (for NMR spectra)
δ	= Chemical shift
2D-NMR	= Two dimensional Nuclear Magnetic Resonance
$\text{DMSO-}d_6$	= Deuterated dimethylsulfoxide
ESIMS	= Electrospray Ionization Mass Spectrometry
EtOAc	= Ethyl acetate
FCC	= Flash Column Chromatography
g	= Gram
GF	= Gel Filtration Chromatography
Glc	= Glucose
Hr	= Hour
^1H -NMR	= Proton Nuclear Magnetic Resonance
HR-ESI-MS	= High Resolution Electrospray Ionization Mass Spectrometry
HSV-1	= Herpes Simplex Virus type 1
HSV-2	= Herpes Simplex Virus type 2
Hz	= Hertz
IC_{50}	= Concentration exhibiting 50% inhibition
IR	= Infrared spectrum

J	=	Coupling constant
Kg	=	Kilogram
λ_{max}	=	Wavelength at maximal absorption
ϵ	=	Molar absorptivity
$[M+H]^+$	=	Pseudomolecular ion
$[M+Na]^+$	=	Sodium-adduct molecular ion
m	=	Multiplet (for NMR spectra)
MeOH	=	Methanol
mg	=	Milligram
mL	=	Milliliter
μg	=	Microgram
$\mu\text{g/mL}$	=	Microgram per milliliter
μL	=	Microliter
μM	=	Micromolar
mm	=	Millimeter
MPLC	=	Medium Pressure Liquid Column Chromatography
MS	=	Mass spectrum
m/z	=	Mass to charge ratio
nm	=	Nanometer
NMR	=	Nuclear Magnetic Resonance
NOESY	=	Nuclear Overhauser Effect Spectroscopy
ppm	=	Part per million
Rha	=	Rhamnose
s	=	Singlet (for NMR spectra)
t	=	Triplet (for NMR spectra)
TLC	=	Thin Layer Chromatography
UV-VIS	=	Ultraviolet and Visible spectrophotometry
VLC	=	Vacuum Liquid Column Chromatography