The 34th Symposium of Natural Products

October 17 (Thu) – 19 (Sat), 2019
Chang Gung University of Science and Technology, Taoyuan, Taiwan

Organizer：The Society of Chinese Natural Medicine
Chang Gung University of Science and Technology
Chang Gung University

Co-Organizer：Ministry of Science and Technology
Department of Chinese Medicine and Pharmacy, Ministry of Health and Welfare
National Research Institute of Chinese Medicine, Ministry of Health and Welfare
Fu Jen Catholic University
Industrial Technology Research Institute
Ching Kang Foundation for Pharmacy Promotion

第三十四屆天然藥物研討會

主辦單位：中華天然藥物學會
長庚科技大學
長庚大學

協辦單位：科技部
衛生福利部中醫藥司
衛生福利部中醫藥研究所
輔仁大學
財團法人工業技術研究院
財團法人中華景康藥學基金會

時間：中華民國 108 年 10 月 17 日（星期四）至 10 月 19 日（星期六）
地點：長庚科技大學 第二教學大樓 B1F 國際會議廳(一)、(二)
地址：333 桃園市龜山區文化一路 261 號

Contents

Organizing Committees

1.1. Local Organizing Committee

President: Tsong-Long Hwang (Chang Gung University of Science and Technology)
Vice President: Ping-Jyun Sung (National Dong Hwa University)
Secretary Generals: Yu-Chia Chang (Chang Gung University of Science and Technology)
Kuei-Hung Lai (Chang Gung University of Science and Technology)
Secretariat: Yi-Hsuan Wu (Chang Gung University of Science and Technology)
Po-Jen Chen (Providence University)
Shih-Hsin Chang (Chang Gung University of Science and Technology)
Yi-Hsiu Wu (Chang Gung University of Science and Technology)
Hsiao-Jou Wu (Chang Gung University of Science and Technology)

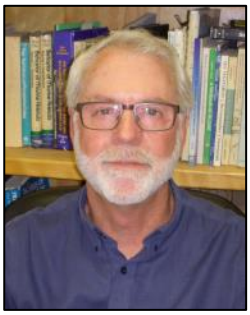
1.2. Regional Scientific Committee *(listed in alphabetical order)*

Ching-Chiung Wang (Taipei Medical University)
Chin-Chung Wu (Kaohsiung Medical University)
Chieh-Fu Chen (National Yang-Ming University)
Ching-Kuo Lee (Taipei Medical University)
Chuang-Ye Hong (Taipei Medical University)
Fang-Rong Chang (National Research Institute of Chinese Medicine)
Hsiao-Chang Chuang (Chuang Song Zong Pharmaceutial co., Ltd.)
Hsi-Lung Hsieh (Chang Gung University of Science and Technology)
Ih-Sheng Chen (Kaohsiung Medical University)
Ji-Hua Gu (National Taiwan University)
Jia-You Fang (Chang Gung University)
Kuang-Hsiung Chang (Min Tong Pharmaceutical Co., Ltd.)
Mei-Hsien Lee (Taipei Medical University)
Ming-Tsuen Hiseh (China Medical University)
Po-Chow Hsieh (China Medical University)
Sung-I Tsai (Kaiser Pharmaceutical Co., Ltd.)
Sheng-Yang Wang (National Chung Hsing University)
Tian-Shung Wu (National Cheng Kung University)
Wu-Chang Chuang (Brion Research Institute of Taiwan)
Wei-Chu Li (Sheng Chang Pharmaceutical Co., Ltd.)
Wen-Tien Huang (Joben Bio-Medical Co., Ltd.)
Yang-Chang Wu (China Medical University)
Yao-Haur Kuo (National Research Institute of Chinese Medicine)
Yuan-Shiun Chang (China Medical University)

1.3. Invited Speakers

Keynote Speakers

Kuo-Hsiung Lee
University of North Carolina at Chapel Hill



William H. Gerwick
University of California San Diego

Jean-Luc Wolfender
University of Geneva

Nicholas H. Oberlies
The University of North Carolina at Greensboro

Plenary Lecturers

Fang-Rong Chang
National Research Institute of Chinese Medicine

Hung-Rong Yen
China Medical University

Jia-You Fang
Chang Gung University

Yu-Liang Yang
Academia Sinica

Jim-Tong Horng
Chang Gung University

Hsin-Chih Lai
Chang Gung University

Tzong-Huei Lee
National Taiwan University

Jih-Jung Chen
National Yang-Ming University

Ping-Chung Kuo
National Cheng Kung University

Mei-Hsien Lee
Taipei Medical University

Tsong-Long Hwang
Chang Gung University of Science and Technology

General Information

2.1. Conference Date

Thursday to Saturday, October 17–19, 2019

2.2. Conference Venue

Venue: The International Conference Hall (1&2), B1F of the Second Education Building, Chang Gung University of Science and Technology, Taoyuan, Taiwan

Address: No.261, Wenhua 1st Rd., Guishan Dist., Taoyuan City 33303, Taiwan

Tel.: (03)211-8800 ext. 5523

Official Website: http://34th.twsymposium.com/

2.3. Location of Conference Venue

2.4. Public Shuttle Information

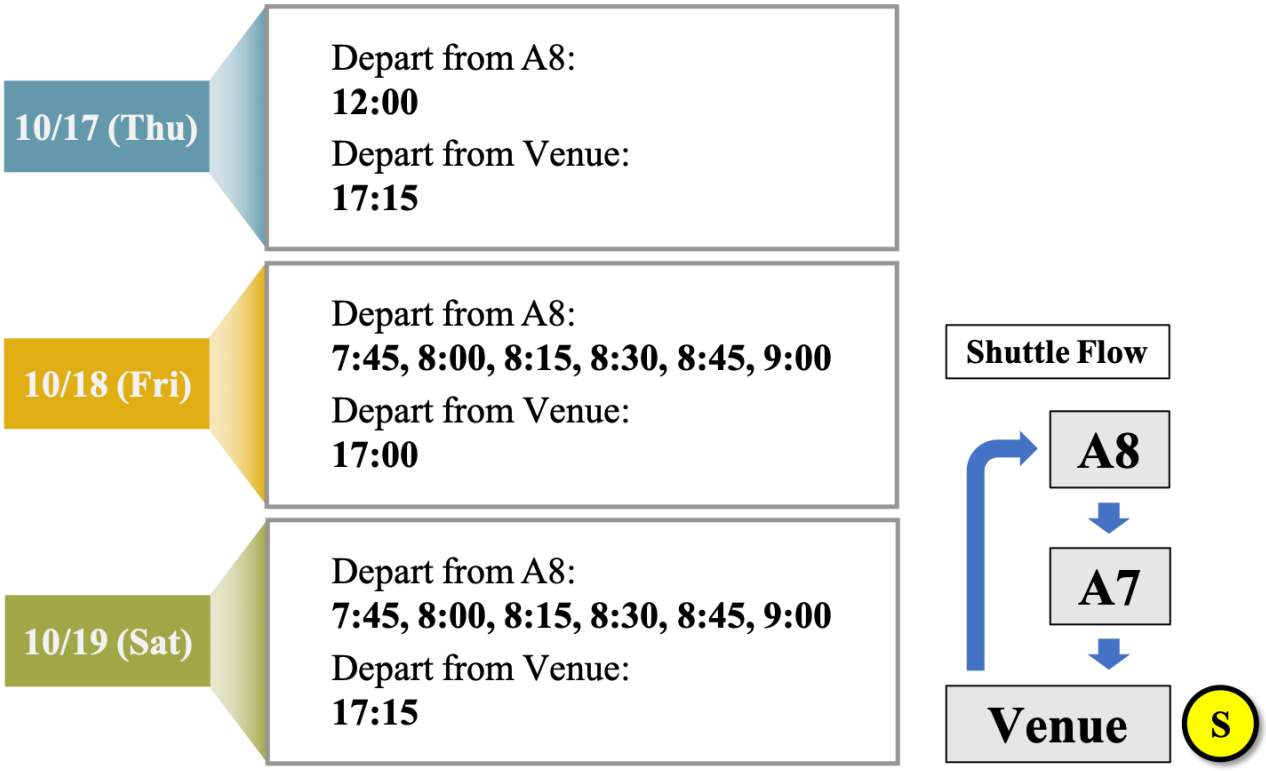
(1) Chang Gung University ←→ Linkou Chang Gung Hospital (A8 Station)

次	星期一至星期五(Mon.~Fri.)		星期六(Sat.)	
	總院	校區	總院	校區
	Hospital	Chang Gung University	Hospital	Chang Gung University
1	06:20	06:30	06:20	06:30
2	06:30	06:40	*06:50	*07:15
3	06:40	06:50	*07:35	*07:55
4	*06:50	*07:10	08:15	08:25
5	⊕07:15	⊕07:25	08:45	08:55
6	*07:35	*07:55	09:20	09:30
7	⊕07:40	⊕07:50	*09:25	*09:45
8	⊕08:10	⊕08:20	09:50	10:00
9	08:15	08:25	10:20	10:30
10	08:45	08:55	10:50	11:00
11	09:20	09:30	*11:00	*11:20
12	09:50	10:00	11:20	11:30
13	10:20	10:30	*11:40	*12:00
14	10:50	11:00	⊕*12:05	⊕*12:25
15	⊕11:20	⊕11:30	*12:20	*12:40
16	*11:50	*12:10	⊕*12:40	⊕*13:00
17	12:30	12:40	*12:50	*13:10
18	⊕*12:40	⊕*13:00	*13:00	*13:20
19	13:20	13:30	⊕*13:15	⊕*13:35
20	13:50	14:00	13:40	13:50
21	14:20	14:30	14:10	14:20
22	14:50	15:00	14:40	14:50
23	⊕15:00	⊕15:10	*15:10	*15:30
24	⊕15:10	⊕15:20	*15:40	*16:00
25	*15:20	*15:40	*16:10	*16:30
26	⊕15:55	⊕16:05	16:30	16:40
27	⊕16:05	⊕16:15	17:00	17:10
28	*16:10	*16:30	17:30	17:40
29	16:20	16:30	⊕18:00	⊕18:10
30	⊕16:35	⊕16:45	18:30	18:40
31	16:50	17:00	*18:40	*19:00
32	17:10	17:20	19:00	19:10
33	17:20	17:30	19:30	19:40
34	⊕17:35	⊕17:45	20:00	20:10
35	17:50	18:00	*20:20	*20:40
36	18:20	18:30	21:00	21:10
37	18:50	19:00	21:40	21:50
38	19:20	19:30	*21:50	*22:10

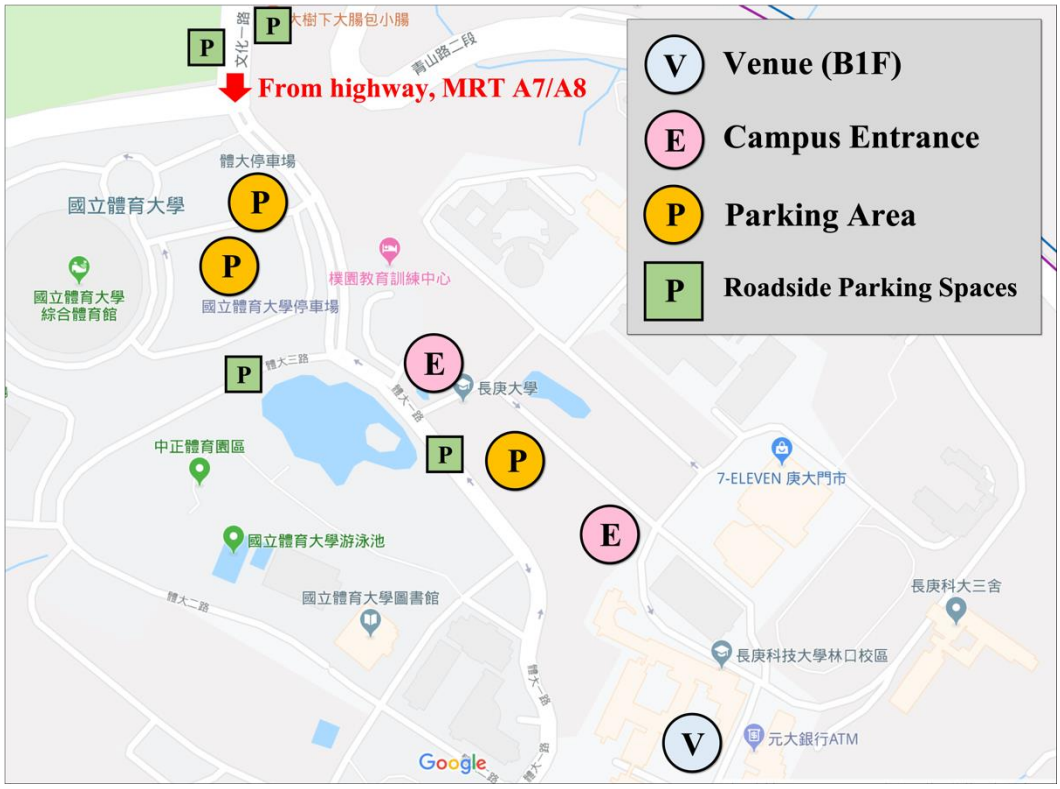
39	19:45	19:55	22:10	22:20
40	20:15	20:25	22:40	22:50
41	*20:50	*21:10	23:10	23:20
42	21:00	21:10	23:40	23:50
43	21:30	21:40	00:10	00:20
44	*21:55	*22:15	*00:25	*00:45
45	21:55	22:05		
46	22:20	22:30		
47	22:45	22:55	＊：總院→社區→校區→總院	
48	23:10	23:20	⊕：支援車輛，非社校區本線班車	
49	●23:40	●23:50	●：總院→校區→社區	
50	00:10	00:20		
51	*00:25	*00:45		

(2) From Taipei Station (2001), Taipei Chang Gung (2000), Taoyuan Station (2003), Zhongli Station (2004), Keelung Chang Gung (2002), please refer to Formosa Fairway Corporation website for the driving route and time.

2.5. Schedule of Conference Shuttle



2.6. Parking Guide



2.7. Campus Map

2.8. Instruction for Lecturer

Lecturer Preview Room

A preview room for the invited lecturers is arranged in the left front of the conference hall (1). The Wi-Fi network and refreshments will be served in the preview room. Please contact the on-site staff for assistance.

Language

The official language of the Main Conference Day 1 (October 18th) is English, which will be used in all presentations and printed materials.

2.9. Instruction for Poster and Poster Flash Presenter

"Poster" Presentation Notice

(1) The poster size must be 90 cm x 120 cm (portrait).
(2) The poster session area is located beside the Conference Hall (1).
(3) Poster numbers are listed in the program book (part 4.3). Please refer to your poster number, setup/tear down your poster before/after poster session (11:30–13:00 of Oct. 19th).

"Poster Flash" Presentation Notice

(1) The poster flash presentation will be held at 14:30–16:00 of Oct. 19th in the Conference Hall (1).
(2) The time limitation is "100 sec" for individual presenter excluding the time of transition setting.
(3) Presentations should be prepared with compatible format in a Windows system; there will not be any MAC equipment available.
(4) Prepare your slide (only ONE slide allowed!) to communicate key findings, not details. "No" discussion time will be provided. Do "not" spend time to acknowledge co-workers, institutes etc.
(5) Please make sure that you clearly announce the number of the poster board where your poster is displayed.
(6) Excessive use of organization logos advertisements is not allowed.
(7) Review your presentation slide on a different machine from which it was originally prepared to ensure everything works properly.
(8) Reserve your presentation on a USB flash drive to the meeting.
(9) The outstanding poster flash presenters will be eligible for awards as follows.

Groups/Awards	**The First Prize (NT 5,000)**	**The Second Prize (NT 3,000)**	**The Third Prize (NT 2,000)**	**Honorable Mention (NT 1,000)**
Natural Products Chemistry	1 Awardee	1 Awardee	1 Awardee	2 Awardees
Natural Products Pharmacology	1 Awardee	1 Awardee	1 Awardee	2 Awardees
Traditional Chinese Medicine	1 Awardee	1 Awardee	1 Awardee	2 Awardees
The 34th Symposium of Natural Products Distinguished Award (NT 10,000)				
1 Awardee				

Scientific Program

3.1. Scientific Program

Venue: Chang Gung University of Science and Technology, Taoyuan, Taiwan
Date: October 17th (Thu) -19th (Sat), 2019

October 17th (Thu): Pre-Symposium/Student Workshop

Date/Time	Lecturer	Topics
10 : 00 – 12 : 00	Registration/Networking	
12 : 00 – 13 : 30	Lunch	
Chair：Dr. Po-Jen Chen		
14 : 00 – 14 : 30	Austin Changou (Taipei Medical University, Taiwan)	From Potato to Potahto - the power of isolation
14 : 30 – 15 : 00	Hideto Imai (Japan Analytical Industry Co., Ltd.)	Unique separation technique for organic synthesis and bio active substances in natural products chemistry
15 : 00 – 15 : 30	Coffee Break	
15 : 30 – 16 : 00	Kurt Chen (Mass Solutions Technology Co., Ltd.)	Sepbox - Automatic two dimension nature product separation system introduction
16 : 00 – 16 : 30	Alex Lai (Agilent Technologies, lnc.)	Breakthrough of two-dimensional chromatography technology in traditional Chinese medicine analysis
16 :30 – 17 : 00	Amber Liu (Shimadzu Scientific Instruments (Taiwan) Co., Ltd.)	Feature of Shimadzu LC-Q-TOF and its application in natural product study
17 : 30 –	Welcome party	

October 18th (Fri): Main Symposium/Day 1

Date/Time	Lecturer	Topics
08 : 30 – 09 : 00	Registration/Networking	
09 : 00 – 09 : 30	Opening Ceremony	
Chair: Prof. Ying-Tung Lau		
09 : 30 – 10 : 10	Prof. Kuo-Hsiung Lee (University of North Carolina at Chap Hill, USA)	Recent Advancements in the Discovery & Development of Anticancer & Anti-AIDS Clinical Trial Candidates from Chinese Herbal Medicine
10 : 10 – 10 : 30	Coffee Break	
Chairs：Prof. Yang-Chang Wu (China Medical University) Prof. Jyh-Horng Sheu (National Sun Yat-sen University)		
10 : 30 – 11 : 10	Prof. William H. Gerwick (University of California San Diego, USA)	Developing New Drug Leads from Marine Cyanobacterial Natural Products
11 : 10 – 11 : 50	Prof. Jean-Luc Wolfender (University of Geneva, Switzerland)	Innovative omics-based approaches for prioritization and efficient targeted isolation of valuable natural products – A change of paradigm in pharmacognosy
11 : 50 – 13 : 30	Lunch (SCNM Members Meeting)	
Chairs：Prof. Ping-Jyun Sung (National Dong Hwa University) Prof. Chih-Chuang Liaw (National Sun Yat-sen University)		
13 : 30 – 14 : 10	Prof. Nicholas Oberlies (University of North Carolina at Greensboro, USA)	Interspecific Interactions: Chemical Diversity via Mapping the Fungal Battlefield
14 : 10 – 14 : 40	Prof. Fang-Rong Chang (National Research Institute of Chinese Medicine, Ministry of Health and welfare, Taiwan)	Miniature of Traditional Medicine Research - An Overview of National Research Institute of Chinese Medicine (NRICM)
14 : 40 – 15 : 10	Prof. Hung-Rong Yen (China Medical University, Taiwan)	Traditional Chinese Medicine for Cancer Patients in Taiwan
15 : 10 – 15 : 30	Coffee Break	
Chairs：Prof. Ching-Chiung Wang (Taipei Medical University) Prof. Chin-Chung Wu (Kaohsiung Medical University)		
15 : 30 – 16 : 00	Prof. Jia-You Fang (Chang Gung University, Taiwan)	The Application of Natural Products on the Management of Skin-Related Disorders
16 : 00 – 16 : 30	Dr. Yu-Liang Yang (Academia Sinica, Taiwan)	Disarm the Function of Siderophore in the Combat between Fungi and Bacteria
18 : 00 – 20 : 00	Gala Dinner	

October 19th (Sat): Main Symposium/Day 2

Date/Time	Lecturer	Topics
Chairs：Prof. Hsi-Lung Hsieh (Chang Gung University of Science and Technology) Prof. Pei-Wen Hsieh (Chang Gung University)		
09 : 00 – 09 : 30	Prof. Jim-Tong Horng (Chang Gung University, Taiwan)	Identification of Natural Inhibitors Targeting Enterovirus A71 VP1-receptor Interaction
09 : 30 – 10 : 00	Prof. Hsin-Chih Lai (Chang Gung University, Taiwan)	Development of Prebiotics, Probiotics and Postbiotics
10 : 00 – 10 : 30	Coffee Break	
Chairs：Prof. Jih-Hwa Guh (National Taiwan University) Prof. Ching-Kuo Lee (Taipei Medical University)		
10 : 30 – 11 : 00	Prof. Tzong-Huei Lee (National Taiwan University, Taiwan)	Development of antifungal and anticancer drugs from fungal strains by a strategic approach
11 : 00 – 11 : 30	Prof. Jih-Jung Chen (National Yang Ming University, Taiwan)	Bioactive Natural Products with Anti-inflammatory and Anti-angiogenic Effects from Formosan Plants
11 : 30 – 12 : 00	Poster session	
12 : 00 – 13 : 00	Lunch	
Chairs：Prof. Yao-Haur Kuo (National Research Institute of Chinese Medicine) Prof. Yuan-Bin Cheng (Kaohsiung Medical University)		
13 : 00 – 13 : 30	Prof. Ping-Chung Kuo (National Cheng Kung University, Taiwan)	Anti-Inflammatory Principles from *Vigna luteola*
13 : 30 – 14 : 00	Prof. Mei-Hsien Lee (Taipei Medical University, Taiwan)	Exploration of Osteogenic Potential of Taiwanese Plants and Designing Novel Models for Screening
14 : 00 – 14 : 30	Prof. Tsong-Long Hwang (Chang Gung University of Science and Technology, Taiwan)	The Opportunity of Discovering Drug Leads for Treating Neutrophilic Inflammatory Diseases
14 : 30 – 16 : 00	Poster Flash/ Chair：Dr. Po-Jen Chen	
16 : 00 – 16 : 30	Coffee Break	
16 : 30 – 17 : 00	Poster Award/Closing Ceremony	

3.2. 中文議程

地點: 長庚科技大學
研討會日期：民國一〇八年 十月十七日（週四）至十九日（週六）

十月十七日（四）：會前會/天然物層析與質譜技術工作坊

日期/時間	演講人	主題
10 : 00 – 12 : 00	邀請講員報到/註冊/報到/聯誼	
12 : 00 – 13 : 30	午餐	
主持人：陳柏任博士		
14 : 00 – 14 : 30	Austin Changou (Taipei Medical University, Taiwan)	From Potato to Potahto - the power of isolation
14 : 30 – 15 : 00	Hideto Imai (Japan Analytical Industry Co., Ltd.)	Unique separation technique for organic synthesis and bio active substances in natural products chemistry
15 : 00 – 15 : 30	Coffee break	
15 : 30 – 16 : 00	Kurt Chen (Mass Solutions Technology Co., Ltd.)	Sepbox - Automatic two dimension nature product separation system introduction
16 : 00 – 16 : 30	Alex Lai (Agilent Technologies, lnc.)	Breakthrough of two-dimensional chromatography technology in traditional Chinese medicine analysis
16 :30 – 17 : 00	Amber Liu (Shimadzu Scientific Instruments, Co., Ltd.)	Feature of Shimadzu LC-Q-TOF and its application in natural product study
17 : 30 –	歡迎會	

十月十八日（五）：主會/第一天

日期/時間	演講人	主題
08 : 30 – 09 : 00	註冊/報到	
09 : 00 – 09 : 30	開幕典禮，貴賓致辭	
主持人：樓迎統教授		
09 : 30 – 10 : 10	Prof. Kuo-Hsiung Lee (University of North Carolina at Chapel Hill, USA)	Recent Advancements in the Discovery & Development of Anticancer & Anti-AIDS Clinical Trial Candidates from Chinese Herbal Medicine
10 : 10 – 10 : 30	Coffee break	
主持人：吳永昌教授、許志宏教授		
10 : 30 – 11 : 10	Prof. William H. Gerwick (University of California San Diego, USA)	Developing New Drug Leads from Marine Cyanobacterial Natural Products
11 : 10 – 11 : 50	Prof. Jean-Luc Wolfender (University of Geneva, Switzerland)	Innovative omics-based approaches for prioritization and efficient targeted isolation of valuable natural products – A change of paradigm in pharmacognosy
11 : 50 – 13 : 30	午餐/中華天然藥物學會會員大會(國際會議廳二)	
主持人：宋秉鈞教授、廖志中教授		
13 : 30 – 14 : 10	Prof. Nicholas Oberlies (University of North Carolina at Greensboro, USA)	Interspecific Interactions: Chemical Diversity via Mapping the Fungal Battlefield
14 : 10 – 14 : 40	張芳榮教授 (衛福部國家中醫藥研究所)	Miniature of Traditional Medicine Research - An Overview of National Research Institute of Chinese Medicine (NRICM)
14 : 40 – 15 : 10	顏宏融教授 (中國醫藥大學中醫學系)	Traditional Chinese Medicine for Cancer Patients in Taiwan
15 : 10 – 15 : 30	Coffee break	
主持人：王靜瓊教授、吳志中教授		
15 : 30 – 16 : 00	方嘉佑教授 (長庚大學中醫學系)	The Application of Natural Products on the Management of Skin-Related Disorders
16 : 00 – 16 : 30	楊玉良博士 (中央研究院農業生物科技研究中心)	Disarm the Function of Siderophore in the Combat between Fungi and Bacteria
18 : 00 – 20 : 00	晚宴	

十月十九日（六）：主會/第二天

日期/時間	演講人	主題
主持人：謝喜龍教授、謝珮文教授		
09 : 00 – 09 : 30	洪錦堂教授 (長庚大學生物醫學研究所)	Identification of Natural Inhibitors Targeting Enterovirus A71 VP1-receptor Interaction
09 : 30 – 10 : 00	賴信志教授 (長庚大學醫學生物技術暨檢驗學系)	Development of Prebiotics, Probiotics and Postbiotics
10 : 00 – 10 : 30	Coffee Break	
主持人：顧記華教授、李慶國教授		
10 : 30 – 11 : 00	李宗徽教授 (國立台灣大學漁業科學研究所)	Development of antifungal and anticancer drugs from fungal strains by a strategic approach
11 : 00 – 11 : 30	陳日榮教授 (國立陽明大學藥學系)	Bioactive Natural Products with Anti-inflammatory and Anti-angiogenic Effects from Formosan Plants
11 : 30 – 12 : 00	Poster session	
12 : 00 – 13 : 00	午餐	
主持人：郭曜豪教授、鄭源斌教授		
13 : 00 – 13 : 30	郭賓崇教授 (國立成功大學藥學系)	Anti-Inflammatory Principles from *Vigna luteola*
13 : 30 – 14 : 00	李美賢教授 (台北醫學大學生藥學研究所)	Exploration of Osteogenic Potential of Taiwanese Plants and Designing Novel Models for Screening
14 : 00 – 14 : 30	黃聰龍教授 (長庚科技大學民生學院)	The Opportunity of Discovering Drug Leads for Treating Neutrophilic Inflammatory Diseases
14 : 30 – 16 : 00	Poster Flash/主持人：陳柏任博士	
16 : 00 – 16 : 30	Coffee Break	
16 : 30 – 17 : 00	Poster Award 頒獎與閉幕典禮	

Contents of Abstract

4.1. Keynote Speech (KS)

4.2. Plenary Lecture (PL)

4.3. Poster (NPC, NPP, and TCM)

Natural Products Chemistry (NPC)

Natural Products Pharmacology (NPP)

Traditional Chinese Medicine (TCM)

Exhibiting and Advertising Sponsorship

4.1. Special Sponsorship

正茂生物科技有限公司	Genmall Biotechnology Co., Ltd.
台塑生醫科技股份有限公司	Formosa Biomedical Technology Corporation
明通化學製藥股份有限公司	Min Tong Pharmaceutical Co., Ltd.
勝昌製藥廠股份有限公司	Sheng Chang Pharmaceutical Co., Ltd.

(依名稱首字筆畫排列)

4.2. Exhibiting Sponsorship

力方科技有限公司	KM3 Scientific Corporation
友德國際股份有限公司	Utek International Corporation
台灣安捷倫科技股份有限公司	Agilent Technologies (Taiwan)
伯森生物科技股份有限公司	Blossom Biotechnologies, Inc.
俊懋企業股份有限公司	Inpac International Corporation
美商沃特斯國際公司台灣分公司	Waters Corporation (Taiwan)
創源生物科技公司	GGA Corporation
萊富生命科技股份有限公司	Life Technologies
德怡科技有限公司	Taqkey Science Corporation Co., Ltd.

(依名稱首字筆畫排列)

4.3. Advertising Sponsorship

三典科技股份有限公司	Sunpoint Scientific Instrument Co., Ltd.
友和貿易股份有限公司	Uni-Onward Corporation
台超萃取洗淨精機股份有限公司	Taiwan Supercritical Technology Co., Ltd.
尚博生物科技有限公司	Cell-Bio Biotechnology Co., Ltd.
勁因科技有限公司	GeneLabs Life Science Corporation
風澤中醫診所	Fengzemed TCM Clinics
康寧生物科技股份有限公司	Corning Life Sciences
順天堂藥廠股份有限公司	Sun Ten Pharmaceutical Co., Ltd.
新丹企業有限公司	Scientific Hightek Co. Ltd.
群研科技有限公司	Group Research Tech. Inc.
圖爾斯生物科技股份有限公司	Biotools Co. Ltd.
諾貝爾生物有限公司	Taigen Bioscience Corporation
鴻鎰科儀有限公司	Green Tree Scientific & Instrument Co.

(依名稱首字筆畫排列)

INVITED LECTURES

Kuo-Hsiung Lee, Ph.D.

-Personal Information-

Name/Title Kuo-Hsiung Lee/Kenan Distinguished Professor/Academician

-Education and Training Background-

Institution	Degree	Year Conferred	Field of Study
Kaohsiung Medical University	B.S.	1961	Pharmacy
Kyoto University	M.S.	1965	Pharmaceutical Chemistry
University of Minnesota	Ph.D.	1968	Medicinal Chemistry
University of California	Postdoc.	1968-70	Organic Chemistry

-Employment History-

Position/Institution	Year Conferred
Kenan Distinguished Professor of Medicinal Chemistry, University of North Carolina at Chapel Hill (UNC)	1992-present
Director of Natural Products Research Laboratories, UNC	1983-present
Chair, Division of Medicinal Chemistry and Natural Products, UNC	1998-99
Professor of Medicinal Chemistry, UNC	1977-91
Associate Professor of Medicinal Chemistry, UNC	1974-77
Assistant Professor of Medicinal Chemistry, UNC	1970-74

-Current Research Program-

Medicinal Chemistry, Bioactive Natural Products, New Drug Discovery and Development, and Chinese Medicine

-Selected Publications-

1. Liu Q, Cheng YY, Li W, Huang L, Asada Y, Hsieh MT, Morris-Natschke SL, Chen CH, Koike K, **Lee KH***. Synthesis and structure-activity relationship correlations of gnidimacrin derivatives as potent HIV-1 inhibitors and HIV latency reversing agents. *J. Med. Chem.* **2019**, *62*, 6958-71.
2. Huang YS, Lu Y, Chen CH, **Lee KH***, Chen DF*. Potent anti-HIV ingenane diterpenoids from *Euphorbia ebracteolata*. *J. Nat. Prod.* **2019**, *82*, 1587-92.
3. Li J, Chang LC, Hsieh KY, Hsu PL, Capuzzi SJ, Zhang YC, Li KP, Morris-Natschke SL, Goto M, **Lee KH***. Design, synthesis and evaluation of anti-proliferative activity of fluorinated betulinic acid. *Bioorg. Med. Chem.* **2019**, *27*, 2871-82.
4. Wu H, Ma G, Yang Q, Zhu Y, Huang L, Tian Y, Yang X, Zhang M, Chen CH, Morris-Natschke SL, Yang M, Xu X, **Lee KH***. Discovery and synthesis of novel beesioside I derivatives with potent anti-HIV activity. *Eur. J. Med. Chem.* **2019**, *166*, 159-66.

Recent Advancements in the Discovery & Development of Anticancer & Anti-AIDS Clinical Trial Candidates from Chinese Herbal Medicine

Kuo-Hsiung Lee

Kenan Distinguished Professor of Medicinal Chemistry and Director of Natural Products Research Laboratories, University of North Carolina at Chapel Hill
Academician of Academia Sinica
Chair Professor and Honorary Director of Chinese Medicine Research and Development Center, China Medical University and Hospital
Chair Professor, Kaohsiung Medical University

Bioactive natural products, especially those originating from Chinese Herbal Medicine, are still the best sources for producing modern drugs. Novel bioactive natural products can be developed as drugs, used as templates for drug design, and serve as tools to elucidate the biochemical mechanism of action (MOA) in various diseases. Studies on plant-derived natural products yield novel structure types, which are unlikely to be discovered through a single-target or MOA-based method using high throughput screening of general chemical libraries.

In the author's Natural Products Research Laboratories (NPRL), modern medicinal chemistry is combined with cutting-edge life science technologies to investigate Chinese herbal medicines. The NPRL has discovered several thousand bioactive natural products and their synthetic derivatives/analogs, providing leads for a new generation of drug design against cancer, AIDS, and other diseases.

Examples will be presented of many natural products-based drugs now in clinical use, as well as numerous novel natural product-related compounds from various structural classes currently in clinical use, clinical trial or preclinical study that have been discovered by the author's NPRL in anticancer and anti-AIDS research programs. Examples from the anticancer research program include **Flolinnib**, **JC-9**, **ENT**, **PBT-1**, **DETD-35**, **pulsatilla saponin D** and **20-sulfonylamidine camptothecin analogs/derivatives** for treating various cancers. The NPRL has also made notable advances in anti-AIDS research first with the discovery of **bevirimat**, the first-in-class anti-HIV maturation inhibitor, which was in Phase II clinical trials. Big pharma (GSK, BMS) has also continued to develop **bevirimat** analogs in clinical trials. In addition, **gnidimacrin** was first discovered by the NPRL as the most potent HIV latency reversing agent and the only single agent than can consistently reduce the frequency of latent HIV-1 infected cells at picomolar level.

William H. Gerwick, Ph.D.

-Personal Information-

Name/Title William H. Gerwick/Distinguished Professor

-Education and Training Background-

Institution	Degree	Year Conferred	Field of Study
University of California, Davis	B.S.	1976	Biochemistry
University of California, San Diego	Ph.D.	1981	Oceanography
University of Connecticut	Postdoc.	1982	Pharmacy

-Employment History-

Position/Institution	Year Conferred
Director of Center for Marine Biotechnology and Biomedicine, Scripps Institution of Oceanography	2015-present
Invited member of Oceans and Human Health Initiative National Advisory Panel	2011-present
Distinguished Professor of Scripps Institution of Oceanography and Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego	2011-present
Adjunct Professor of Chemistry, University of Aberdeen, Scotland, UK	2010-present

-Current Research Program-

Development of a Gallinamide A Inspired Anti-Chagas Therapeutic, 2017-2019

-Selected Publications-

1. Liu Q, Yu HB, Glukhov E, Li Y, Iwasaki A, Gerwick L, Dorrestein PC, Jiao BH, **Gerwick WH***. Cytotoxic microcolin lipopeptides from the marine cyanobacterium *Moorea producens*. *J. Nat. Prod.* **2019**, *82*, 2608-19.
2. Hou XM, Wang CY, **Gerwick WH***, Shao CL*. Marine natural products as potential anti-tubercular agents. *Eur. J. Med. Chem.* **2019**, *165*, 273-92.
3. Moss NA, Leão T, Rankin MR, McCullough TM, Qu P, Korobeynikov A, Smith JL, Gerwick L, **Gerwick WH***. Ketoreductase domain dysfunction expands chemodiversity: malyngamide biosynthesis in the cyanobacterium *Okeania hirsuta*. *ACS Chem. Biol.* **2018**, *13*, 3385-95.
4. Tao Y, Li P, Zhang D, Glukhov E, Gerwick L, Zhang C, Murray TF, **Gerwick WH***. Samholides, swinholide-related metabolites from a marine cyanobacterium cf. *Phormidium* sp. *J. Org. Chem.* **2018**, *83*, 3034-46.
5. Shao CL, Mou XF, Cao F, Spadafora C, Glukhov E, Gerwick L, Wang CY, **Gerwick WH***. Bastimolide B, an antimalarial 24-membered marine macrolide possessing a tert-butyl group. *J. Nat. Prod.* **2018**, *81*, 211-5.

Developing New Drug Leads from Marine Cyanobacterial Natural Products

William H. Gerwick

Center for Marine Biotechnology and Biomedicine, Scripps Institution of Oceanography and Skaggs School of Pharmacy and Pharmaceutical Science, University of California San Diego, La Jolla, California 92093 USA

Marine life forms have been explored for their unique natural products over the past 50 years, and many thousands of new compounds have been discovered and described. From these efforts, some 13 drugs have been developed that are in clinical use today to treat human disease, mainly in the area of oncology. Our work has focused on the rich natural products of marine algae and cyanobacteria, and has focused on discovery of metabolites with anticancer, neuroactive and antiparasitic disease activities. One such project began with a small collection of a filamentous marine cyanobacterium from Curaçao, and resulted in our discovery of the first epoxy ketone metabolites to be described from the marine environment. These new metabolites, carmaphycins A and B, are highly toxic to cancer cells and several classes of parasites; resultantly, we synthesized over 100 analog structures and discovered that different modifications yield derivatives with selective activity to different classes of parasites and human cells. The molecular target of the carmaphycins and their derivatives has been identified as the 20S proteasome, the molecular machine within cells that is responsible for protein degradation. We are now in the process of advancing different lead compounds towards advanced pre-clinical evaluation for treatment of *Plasmodium falciparum* (malaria), *Trichomonas* sp., the human constitutive proteasome (cancer), and the human immunoproteasome (immune disorders).

Jean-Luc Wolfender, Ph.D.

-Personal Information-

Name/Title Jean-Luc Wolfender/Professor

-Education and Training Background-

Institution	Degree	Year Conferred	Field of Study
University of Lausanne	Ph.D.	1993	Pharmacognosy
University of California San Francisco	Postdoc.		

-Employment History-

Position/Institution

Professor of Phytochemistry and Bioactive Natural Product research unit of Pharmaceutical Sciences of the University of Geneva

Vice dean of the Faculty of Sciences, University of Geneva

-Current Research Program-

The research of novel inducible bioactive natural products in response to various biotic and abiotic stimuli as well for the study of the mode of action of phytopharmaceuticals from a systems biology perspective.

-Selected Publications-

1. Diop EHA, Queiroz EF, Marcourt L, Kicka S, Rudaz S, Diop T, Soldati T, **Wolfender JL***. Antimycobacterial activity in a single-cell infection assay of ellagitannins from Combretum aculeatum and their bioavailable metabolites. *J. Ethnopharmacol.* **2019**, *238*, 111832.
2. Azzollini A, Boggia L, Boccard J, Sgorbini B, Lecoultre N, Allard PM, Rubiolo P, Rudaz S, Gindro K, Bicchi C, **Wolfender JL***. Dynamics of metabolite induction in fungal co-cultures by metabolomics at both volatile and non-volatile levels. *Front. Microbiol.* **2018**, *9,* 72
3. Diop EA, Queiroz EF, Kicka S, Rudaz S, Diop T, Soldati T, **Wolfender JL***. Survey on medicinal plants traditionally used in Senegal for the treatment of tuberculosis (TB) and assessment of their antimycobacterial activity. *J. Ethnopharmacol.* **2018**, *216*, 71-78.
4. **Wolfender JL***, Marti G, Thomas A, Bertrand S. Current approaches and challenges for the metabolite profiling of complex natural extracts. *J. Chromatogr. A.* **2015**, *1382*, 136-64.
5. Bertrand S, Bohni N, Schnee S, Schumpp O, Gindro K, **Wolfender JL***. Metabolite induction via microorganism co-culture: a potential way to enhance chemical diversity for drug discovery. *Biotechnol. Adv.* **2014**, *32*, 1180-204.

Innovative Omics-based Approaches for Prioritization and Efficient Targeted Isolation of Valuable Natural Products – A Change of Paradigm in Pharmacognosy

Jean-Luc Wolfender, Emerson Ferreira Queiroz, Pierre-Marie Allard

School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, CMU – Rue Michel Servet 1, 1211 Geneva 11, Switzerland

The recent rapid innovations made in metabolite profiling and bioassays may lead to a change of paradigm in natural products (NP) research. Indeed having at hand full or partial of structure of possibly all metabolites in given natural extract at different quantitative levels open the possibility to perform pharmacognosy studies from a more holistic perspective.
The increasingly amount of accurate metabolome data that can be acquired on massive sample sets, notably through high resolution mass spectrometry data dependent MS/MS analyses (HRMS/MS), allows mapping of natural extracts at an unprecedented precision level [1]. While the acquisition of larger volumes of data is ongoing, contextualizing it is a lagging process. For this the establishment of integrated and open databases ecosystem could be extremely valuable to nurture pharmacognosy in the years to come and have finally general positive societal outcomes [2]. Fast progresses are foreseen bringing together recent computational / analytical approaches linking invaluable published knowledge brought by pharmacognosy mainly based on bioactivity guided isolation studies.
In this context we push forward our applications and further development of UHPLC-HRMS/MS Molecular network (MN) approaches [3,4] to provide enhanced annotation confidence level though multiple scores integrating notably taxonomy information and MN structural consistency as well as other orthogonal analytical data (chromatographic retention, Collisional Cross Section in IMS…). Benchmarking of such approaches is currently assessed by profiling mixtures of herbs with well-studied composition.
Different recent applications of our metabolomics and phytochemical investigations will illustrated these aspects, especially in the context of bioactive NPs prioritisation [5]. An ideal workflow will be presented and discussion on what is readily implemented and is still required will be made, notably in term of contextualisation of the data.

References

[1] Wolfender, J.L.; Nuzillard, J.M.; van der Hooft, J.J.J.; Renault, J.H.; Bertrand, S. *Anal Chem*, 2019, *91*, 704-742.
[2] Allard, P.-M.; Bisson, J.; Azzollini, A.; Pauli, G.F.; Cordell, G.A.; Wolfender; J.-L. *Curr Opin Biotech* 2018, *54*, 57-64.
[3] Allard, P.M.; Peresse, T.; Bisson, J.; Gindro, K.; Marcourt, L.; Pham, V.C.; Roussi, F.; Litaudon, M.; Wolfender, J.L. *Anal Chem* 2016, *88*, 3317-3323
[4] Allard, P.-M.; Genta-Jouve, G.; Wolfender J.-L. *Curr. Opin. Chem. Biol*., 2017, *36*, 40-49.
[5] Wolfender, J.-L., Litaudon, M. Touboul, D. and Queiroz, E.F. *Nat. Prod. Rep*. 2019, *36*, 855 – 868.

Nicholas H. Oberlies, Ph.D.

-Personal Information-

Name/Title Nicholas H. Oberlies/Patricia A. Sullivan Distinguished Professor

-Education and Training Background-

Institution	Degree	Year Conferred	Field of Study
Miami University	B.S.	1992	Chemistry
Purdue University	Ph.D.	1997	Medicinal Chemistry and Pharmacognosy
American Cyanamid	Postdoc.	1998	Chemistry

-Employment History-

Position/Institution	Year Conferred
Patricia A. Sullivan Distinguished Professor of Chemistry, University of North Carolina at Greensboro	2016-present
Associate Professor, Department of Chemistry & Biochemistry, University of North Carolina at Greensboro	2009-16

-Current Research Program-

Chemical diversity of fungal metabolites via epigenetic modification and precursor directed biosynthesis

-Selected Publications-

1. **Oberlies NH***, Knowles SL, Amrine CSM, Kao D, Kertesz V, Raja HA. Droplet probe: coupling chromatography to the in situ evaluation of the chemistry of nature. *Nat. Prod. Rep.* **2019**, *36*, 944-59.
2. Paguigan ND, Rivera-Chávez J, Stempin JJ, Augustinović M, Noras AI, Raja HA, Todd DA, Triplett KD, Day C, Figueroa M, Hall PR, Cech NB, **Oberlies NH***. Prenylated diresorcinols inhibit bacterial quorum sensing. *J. Nat. Prod.* **2019**, *82*, 550-8.
3. Knowles SL, Raja HA, Wright AJ, Lee AML, Caesar LK, Cech NB, Mead ME, Steenwyk JL, Ries LNA, Goldman GH, Rokas A, **Oberlies NH***. Mapping the fungal battlefield: using in situ chemistry and deletion mutants to monitor interspecific chemical interactions between fungi. *Front. Microbiol.* **2019**, *10*, 285.
4. El-Elimat T, Raja HA, Ayers S, Kurina SJ, Burdette JE, Mattes Z, Sabatelle R, Bacon JW, Colby AH, Grinstaff MW, Pearce CJ, **Oberlies NH***. Meroterpenoids from *Neosetophoma* sp.: a dioxa[4.3.3]propellane ring system, potent cytotoxicity, and prolific expression. *Org. Lett.* **2019**, *21*, 529-34.
5. Rivera-Chávez J, Raja HA, Graf TN, Burdette JE, Pearce CJ, **Oberlies NH***. Biosynthesis of fluorinated peptaibols using a site-directed building block incorporation approach. *J. Nat. Prod*. **2017**, *80*, 1883-92.

Interspecific Interactions: Chemical Diversity via Mapping the Fungal Battlefield

Nicholas Oberlies, Ph.D.

Patricia A. Sullivan Distinguished Professor of Chemistry
Department of Chemistry & Biochemistry
University of North Carolina at Greensboro

A common question in the field of natural products research is: *why did that organism choose to biosynthesize those compounds*? Of course, the simple answer is that we, as humans, don't really know. However, the common postulate is that the secondary metabolites give the organism some sort of advantage, particularly with respect to chemical defense. If true, can we then set up experiments where organisms must 'fight' for their turf, essentially using co-culturing as a way to force the production of secondary metabolites, perhaps causing the amplification of production and/or the stimulation of otherwise silent biosynthetic gene clusters. Using a series of tools that profile the chemistry of fungal cultures *in situ*, our team has been pursuing these questions, both to probe some of the basics of fungal ecology and biology, as well as, to potentially generate new chemical diversity. This talk will explain some of the underlying tools used to assess the chemistry of fungal (and other microbial) cultures via mass spectrometry, and then apply those skills and databases to understanding fungal chemistry *in situ*.

Fang-Rong Chang, Ph.D.

-Personal Information-

Name/Title Fang-Rong Chang/Professor/Director/Doctor Honoris Causa

-Education and Training Background-

Institution	Degree	Year Conferred	Field of Study
Chung-Shan Medical University	B.S.	1988	Nutrition
Kaohsiung Medical University	M.S.	1991	Pharmacognosy
Kaohsiung Medical University	Ph.D.	1995	Pharmacognosy
University of North Carolina at Chapel Hill, USA	Postdoc.	2001	Natural Products & Medicinal Chemistry
Okayama University of Science, Japan	Postdoc.	2004	Transgenic Plant Assay Related to Estrogenic Receptors

-Employment History-

Position/Institution	Year Conferred
Director of National Research Institute of Chinese Medicine (NRICM), Ministry of Health and Welfare	2018-present
Professor of Pharmacognosy and Graduate Institute of Natural Products, KMU	2005-present
Vice Dean of Office of Global Affairs, KMU	2013-2018

-Current Research Program-

Natural Products Chemistry, Medicinal Chemistry, Cross kindom Assay, Genetic and Epigenetic Modulation for Fungal Secondary Metabolites, Functional Food, Traditional Chinese (Herbal) Medicine, and New Drug Development.

-Selected Publications-

1. Yen CH, Lai CC, Shia TH, Chen M, Yu HC, Liu YP, **Chang FR***. *Gynura divaricata* attenuates tumor growth and tumor relapse after cisplatin therapy in HCC xenograft model through suppression of cancer stem cell growth and Wnt/β-catenin signaling. *J. Ethnopharmacol.* **2018**, *213*, 366-75.
2. Korinek M, Tsai YH, El-Shazly M, Lai KH, Backlund A, Wu SF, Lai WC, Wu TY, Chen SL, Wu YC, Cheng YB, Hwang TL*, Chen BH*, **Chang FR***. Anti-allergic hydroxy fatty acids from *Typhonium blumei* explored through ChemGPS-NP. *Front. Pharmacol.* **2017**, *8*, 356.
3. Yu SY, Wang SW, Hwang TL, Wei BL, Su CJ, **Chang FR***, Cheng YB*. Components from the leaves and twigs of mangrove *Lumnitzera racemosa* with anti-angiogenic and anti-inflammatory effects. *Mar. Drugs* **2018**, *16*, 404

Miniature of Traditional Medicine Research - An Overview of National Research Institute of Chinese Medicine (NRICM)

Prof. Dr. Dr. h.c. mult. Fang-Rong Chang

Director, National Research Institute of Chinese Medicine, Ministry of Health and Welfare, Taiwan
Professor, Graduate Institute of Natural Products, College of Pharmacy, Kaohsiung Medical University, Taiwan
Honorary Doctor, Uppsala University, Sweden
Doctor Honoris Causa, University of Szeged, Hungary

Nowadays, a combination therapy and research with integration of western and traditional medicine for vital diseases is going far advance faster and faster. In Taiwan, the treatment outcomes had been greatly improved under combining modern medicine and/or surgery together with traditional acupuncture and traditional medication. WHO also setup traditional medicine as one of important sectors in health care in the world.
National Research Institute of Chinese Medicine (NRICM), Ministry of Health and Welfare, is the apex and only national research institute in traditional medicine in Taiwan. The studies at NRICM is divided into five parts: 1. Literature and Informatics 2. Materia Medica Development 3. Medicinal Chemistry 4. Basic Medicine, 5. Clinical Medicine. The institute integrates not only modern theories and technology but also big data systems under systematic and statistic ways in research and development for traditional medicine. Evidence-based solutions for traditional medicine are a key for future in production of high standard drugs and biotech products, treatment of diseases, improvement quality of life, and benefit to the mankind.

Keywords**:** National Research Institute of Chinese Medicine (NRICM), traditional medicine, Chinese medicine

Hung-Rong Yen, Ph.D.

-Personal Information-

Name/Title Hung-Rong Yen/Vice Dean/Director

-Education and Training Background-

Institution	Degree	Year Conferred	Field of Study
China Medical University	M.D.	1997	Chinese Medicine
Chang Gung University	Ph.D.	2010	Clinical Medical Sciences
Johns Hopkins University	Research Fellow	2010	Medicine

-Employment History-

Position/Institution	Year Conferred
Vice Dean of Chinese Medicine, China Medical University	2018-present
Associate Editor of Complementary Therapies in Medicine (Elsevier)	2018-present
Chief Executive Officer of Secretariat of the Global University Network of Traditional Medicine (GUNTM)	2018-present
Director of Research Center for Chinese Herbal Medicine, China Medical University	2017-present
Director of Research Center for Traditional Chinese Medicine, The Aim for the Top University Plan, China Medical University	2017-17
Deputy Director of Research Center for Chinese Herbal Medicine, China Medical University	2016-17

-Current Research Program-

Immunology, Traditional Chinese Medicine, Pediatrics, Integrative Medicine

-Selected Publications-

1. Song YC, Hung KF, Liang KL, Chiang JH, Huang HC, Lee HJ, Wu MY, Yu SJ, Lo HY, Ho TY, **Yen HR***. Adjunctive Chinese herbal medicine therapy for nasopharyngeal carcinoma: Clinical evidence and experimental validation. *Head Neck* **2019**, *41*, 2860-72.
2. Kuo YT, Chang TT, Muo CH, Wu MY, Sun MF, Yeh CC, **Yen HR***. Use of Complementary Traditional Chinese Medicines by adult cancer patients in Taiwan: a nationwide population-based study. *Integr. Cancer. Ther.* **2018**, *17*, 531-41.
3. Huang TP1, Liu PH, Lien AS, Yang SL, Chang HH, **Yen HR***. Characteristics of traditional Chinese medicine use in children with asthma: a nationwide population-based study. *Allergy* **2013**, *68*, 1610-3.

Traditional Chinese Medicine for Cancer Patients in Taiwan

Hung-Rong Yen, M.D., Ph.D.

School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan
Research Center for Traditional Chinese Medicine, China Medical University Hospital, Taichung, Taiwan

Many cancer patients seek complementary therapies. We investigated the use of traditional Chinese medicine (TCM) by Taiwanese cancer patients and conducted basic and clinical studies to delineate its potential benefits. We analyzed the registry database and included all cancer patients in Taiwan. Patients were categorized as TCM users or non-TCM users, followed by matching with age, sex, comorbidity, conventional treatment, and index year to compare the risk of mortality and survival rate. The prescribed Chinese herbal medicine (CHM) was further investigated in the laboratory or clinical trial. Compared to non-TCM users, TCM users were younger and more likely to be female, white-collar workers, and reside in highly urbanized areas. The average interval between cancer diagnosis and TCM consultation was 15.3 months. The most common cancer type was breast cancer in TCM users (19.4%), and intrahepatic bile duct cancer in non-TCM users (13.6%). A total of 33.1% of TCM users visited TCM clinics more than 9 times per year. Overall, TCM users had a lower adjusted hazard ratio for mortality (aHR = 0.69, 95% CI: 0.68-0.70). For leukemia, we conducted a laboratory investigation and clinical trial on Sheng-Yu-Tang to prove its efficacy. For nasopharyngeal carcinoma, we have also shown the prescribed CHM, Gan-Lu-Yin, is effective against tumor in vitro and in a tumor-bearing murine model. This study provides an overview of TCM usage among cancer patients in Taiwan. Our big data-bench-bedside approach could be developed as a powerful tool for new drug development or for future clinical trials.

Jia-You Fang, Ph.D.

-Personal Information-

Name/Title Jia-You Fang/Professor

-Education and Training Background-

Institution	Degree	Year Conferred	Field of Study
Kaohsiung Medical University	Ph.D.	1996	Pharmaceutical Sciences

-Employment History-

Position/Institution	Year Conferred
Professor of Graduate Institute of Natural Products, Chang Gung University	2004-present
Visiting Professor of College of Pharmacy, King Saud University	2009-present
Dean and Professor of College of Human Ecology, Chang Gung University of Science and Technology	2010-15
Associate Professor of Graduate Institute of Natural Products, Chang Gung University	2001-04
Associate Professor of School of Pharmacy, Taipei Medical University	1998-01
Associate Professor of School of Pharmacy, Chia Nan University of Pharmacy and Science	1996-98

-Current Research Program-

Pharmaceutics, Drug targeting, Cosmetic science, and Nanomedicine

-Selected Publications-

1. Weng JR, Huang TH, Lin ZC, Alalaiwe A, **Fang JY***. Cutaneous delivery of [1-(4-chloro-3-nitrobenzenesulfonyl)-1*H*-indol-3-yl]-methanol, an indole-3-carbinol derivative, mitigates psoriasiform lesion by blocking MAPK/NF-κB/AP-1 activation. *Biomed. Pharmacother.* **2019**, *119*, 109398.
2. Lin MH, Hung CF, Hsu CY, Lin ZC, **Fang JY***. Prodrugs in combination with nanocarriers as a strategy for promoting antitumoral efficiency. *Future Med. Chem.* **2019**, *11*, 2131-50.
3. Yang SC, Huang TH, Chiu CH, Chou WL, Alalaiwe A, Yeh YC, Su KW, **Fang JY***. The atopic dermatitis-like lesion and the associated MRSA infection and barrier dysfunction can be alleviated by 2,4-dimethoxy-6-methylbenzene-1,3-diol from *Antrodia camphorate*. *J. Dermatol. Sci.* **2018**, *92*, 188-96.
4. Lin YC, Lin CF, Alalaiwe A, Wang PW, Fang YP*, **Fang JY***. UV filter entrapment in mesoporous silica hydrogel for skin protection against UVA with minimization of percutaneous absorption. *Eur. J. Pharm. Sci.* **2018**, *122*, 185-94.

The Application of Natural Products on the Management of Skin-related Disorders

Jia-You Fang

Pharmaceutics Laboratory, Graduate Institute of Natural Products, Chang Gung University, Kweishan, Taoyuan, Taiwan

In recent years, the concept of using natural products or herbal drugs as the actives for treating skin diseases has attracted increasing attention. It has been demonstrated that natural products used for skin disease therapy provide some advantages over conventional drugs, including increased bioactivity, improved permeability and bioavailability, prolonged half-life, tissue targeting, as well as minimal side effects. This presentation highlights recent developments using herbal approaches for the management of skin diseases such as psoriasis, atopic dermatitis, and cutaneous infection with drug-resistant bacteria. I systematically introduce the concepts and amelioration mechanisms of the natural medicine for the therapy of the inflammatory diseases. Topical application provides a direct and efficient method for skin targeting. Unfortunately, drug uptake by the skin is always limited due to the barrier function of the stratum corneum and the epidermal tight junction. The modification of the chemical structures of the natural compounds is advantageous to enhance the delivery into/across skin. As a continuing effort to elucidate the impact of structure modification upon cutaneous absorption behavior, my lab attempts to assess the skin permeation of a series of natural product by methylation and acetylation. The natural compounds would become the prodrugs for promoting the skin permeation thus the subsequent bioactivity. In this presentation, I also introduce the idea of structure modification as a strategy to elevate natural product absorption via skin.

Keywords: natural product; herb; skin diseases; skin delivery; inflammation

Yu-Liang Yang, Ph.D.

-Personal Information-

Name/Title Yu-Liang Yang/Assistant Research Fellow

-Education and Training Background-

Institution	Degree	Year Conferred	Field of Study
Kaohsiung Medical University	B.S.	1999	Pharmacy
Kaohsiung Medical University	Ph.D.	2004	Pharmacy, Natural Products Chemistry
Academia Sinica	Postdoc.	2004-08	Biochemistry
University of California, San Diego	Postdoc.	2009-11	Mass Spectrometry

-Employment History-

Position/Institution	Year Conferred
Assistant Research Fellow, Agricultural Biotechnology Research Center, Academia Sinica	2011-present

-Current Research Program-

Microbial Interaction, Imaging Mass Spectrometry, Natural Products Chemistry, Plant and Insect Microbiome

-Selected Publications-

1. Chen PY, Hsieh CH, Shih CJ, Lin YJ, Tsao CW, **Yang YL***. Exploration of fungal metabolic interactions using imaging mass spectrometry on nanostructured silicon. *J. Nat. Prod.* **2018**, *81*, 1527-33.
2. Ho YN, Lee HJ, Hsieh CT, Peng CC, **Yang YL***, Chemistry and biology of salicyl-capped siderophores. *Stud. Nat. Prod. Chem.* **2018**, *59*, 431-90.
3. Shu LJ, **Yang YL***. *Bacillus* classification based on matrix-sssisted laser desorption ionization time-of-flight mass spectrometry-effects of culture conditions. *Sci. Rep.* **2017**, *7*, 15546.
4. Ho YN, Shu LJ, **Yang YL***. Imaging mass spectrometry for metabolites: technical progress, multimodal imaging and biological interactions. *Wiley Interdiscip. Rev. Syst. Biol. Med.* **2017**, *9*, e1387.
5. Chen WJ, Kuo TY, Hsieh FC, Chen PY, Wang CS, Shih YL, Lai YM, Liu JR, **Yang YL***, Shih MC*. Involvement of type VI secretion system in secretion of iron chelator pyoverdine in *Pseudomonas taiwanensis*. *Sci. Rep.* **2016**, *6*, 32950.

Disarm the Function of Siderophore in the Combat between Fungi and Bacteria

Yu-Liang Yang

Agricultural Biotechnology Research Center, Academia Sinica, Taipei 11529, Taiwan

Microbes occupying a niche compete with or, at times, act symbiotically with others to induce factors essential for reproduction and survival. Within such a niche, microbes employ a diverse array of bioactive metabolites to mediate interactions with their neighbors, competitors, and predators. Iron is an important element for living organisms. It is involved in many cellular processes such as acting as a cofactor for crucial enzymatic reactions and being involved in the electron transport chain and syntheses of DNA and RNA. Under iron-limiting conditions, microbes produce low molecular weight iron chelators, known as siderophores, to facilitate the acquisition of iron from the environment. Therefore, siderophores also play an important role in the combat of microbes. Pyochelin is a well-known siderophore of *Burkholderia* and *Pseudomonas* species, and many of them show the high potential of biological control abilities against soil-borne plant pathogens. We have discovered one *Burkholderia cenocepacia* strain, 869T2, showing strong antagonistic effect against *Phellinus noxius*, the pathogen of brown root rot disease. Here we report the identification of an enzymatic transformation of pyochelin by *P. noxius* strain 2252 in the competitive interaction with *B. cenocepacia* 869T2. I will introduce how we employ integrated omics approach to explore this metabolic interaction between fungi and bacteria. Enzymatic degradation or transformation of secondary metabolites provides protection by inactivating the antagonistic and competitive functions. However, beyond antibiotic resistance, relatively rare is known about enzymatic transformations of secreted siderophores that occur during microbial interactions. The results we learned from nature may lead to a better understanding of the ecological niche occupied by those microbes, and improve production and formulation of microbes and their metabolites to enhance the efficacy in agriculture.

Keywords: *Phellinus noxius*, iron, pyochelin, *Burkholderia cenocepacia*

Jim-Tong Horng, Ph.D.

-Personal Information-

Name/Title Jim-Tong Horng/Professor/Head

-Education and Training Background-

Institution	Degree	Year Conferred	Field of Study
National Taiwan University	B.S.	1988	Medical Technology
National Taiwan University	M.S.	1991	Biochemistry
University of Cambridge	Ph.D.	1994	Biochemistry
University of California, San Francisco	Postdoc.	1999	Biochemistry and Biophysics

-Employment History-

Position/Institution	Year Conferred
Professor, Department of Biochemistry and Molecular Biology, Chang Gung University	2012-present
Associate Professor, Department of Biochemistry and Molecular Biology, Chang Gung University	2007-12
Assistant Professor, Department of Biochemistry and Molecular Biology, Chang Gung University	1999-07

-Current Research Program-

I have been researching enterovirus (EV)A71 and influenza virus for many years, especially focusing on virus-host interaction and antiviral developments. My team has achieved important milestones such as the development of small molecules and natural products that successfully inhibit EV-A71 and influenza virus, and other several RNA viruses.

-Selected Publications-

1. Sethy B, Hsieh CF, Lin TJ, Hu PY, Chen YL, Lin CY, Tseng SN, **Horng JT***, Hsieh PW*. Design, synthesis, and biological evaluation of itaconic acid derivatives as potential anti-influenza agents. *J. Med. Chem*. **2019**, *62*, 2390-403.
2. Tang WF, Huang RT, Chien KY, Tang P, **Horng JT***. Large-scale proteomic identification of targets of cellular miR-197 downregulated by enterovirus A71. *J. Proteome Res.* **2018**, *18*, 449-60.
3. Jheng JR, Lau KS, Lan YW, **Horng JT***. A novel role of ER stress signal transducer ATF6 in regulating enterovirus A71 viral protein stability. *J Biomed. Sci*. **2018**, *25*, 9.
4. Chang YH, Lau KS, Kuo RL, **Horng JT***. dsRNA binding domain of PKR is proteolytically released by enterovirus A71 to facilitate viral replication. *Front. Cell Infect. Microbiol.* **2017**, *7*, 284.

Identification of Natural Inhibitors Targeting Enterovirus A71 VP1-receptor Interaction

Jim-Tong Horng, Chung-Fan Hsieh, and Jia-Rong Jheng

Department of Biochemistry and Molecular Biology, and Research Center for Emerging Viral Infections, College of Medicine, Chang Gung University, Kweishan, Taoyuan, Taiwan, R.O.C.

We employed a chemical genetics approach to identify novel natural inhibitors of enterovirus A71 (EV-A71) and to explore the functions of a particular viral protein during EV-A71 infection. In this talk, I will be presenting the results of our recent investigation on the anti-EV-A71 mechanism of two natural products with similar chemical structures, but obtained from two different herbal medicines. These two natural products exhibited similar inhibitory mechanisms, with only subtle differences. Results of the time-of-addition assay suggested that these natural inhibitors affected an early stage of virus infection. Further experiments revealed that they target viral particles directly, thereby interfering with virus-receptor interactions. Sequencing of the plaque-purified resistant viruses showed different mutations for these two natural inhibitors, but all located near the five-fold axis of viral capsid protein, VP1. The recombinant viruses carrying these mutations could bind to the heparan sulfate receptor but not to PSGL1 or hSCARB2, because they were refractory to inhibition by these natural products. Thus, the chemical genomics strategy helped us gain insights into the virus-receptor interactions.

Hsin-Chih Lai, Ph.D.

-Personal Information-

Name/Title Hsin-Chih Lai/Professor

-Education and Training Background-

Institution	Degree	Year Conferred	Field of Study
National Taiwan University	B.S.	1986	Medical Technology
National Yang-Ming Medical University	M.S.	1988	Microbiology and Immunology
Cambridge University	Ph.D.	1994	Pathology

-Employment History-

Position/Institution	Year Conferred
Professor, Chang Gung University (CGU)	2007-present
Director, Microbiota Research Center, CGU	2017-present
Director, Division of Medical Biotechnology, Institute of Biomedicine Research, CGU	2008-18
Director, Department of Medical Biotechnology and Laboratory Science, College of Medicine, CGU	2008-18
Professor, National Taiwan University	2006-07

-Current Research Program-

Gut microbiota, Inflammation

-Selected Publications-

1. Wu TR, Lin CS, Chang CJ, Lin TL, Martel J, Ko YF, Ojcius DM, Lu CC, Young JD*, **Lai HC***. The gut commensal *Parabacteroides goldsteinii* plays a predominant role in the anti-obesity effects of polysaccharides isolated from *Hirsutella sinensis* mycelium. *Gut* **2019**, *68*, 248-62.
2. Chang CJ, Lu CC, Lin CS, Martel J, Ko YF, Ojcius DM, Wu TR, Tsai YH, Lu JJ, Yeh TS, **Lai HC***, Young JD*. *Antrodia cinnamomea* reduces obesity and modulates the gut microbiota in high-fat diet-fed mice. *Int. J. Obes*. **2018**, *42*, 231-43.
3. Martel J, Ojcius DM, Chang CJ, Lin CS, Lu CC, Ko YF, Tseng SF, **Lai HC***, Young JD*. Anti-obesogenic and antidiabetic effects of plants and mushrooms. *Nat. Rev. Endocrinol.* **2017**, *13*, 149-60.
4. Chang CJ, Lin CS, Lu CC, Martel J, Ko YF, Ojcius DM, Tseng SF, Wu TR, Chen YYM, Young JD*, **Lai HC***. *Ganoderma lucidum* reduces obesitly in mice by modulating the composition of the gut microbiota. *Nat. Commun*. **2015**, *6*, 7489.

Development of Prebiotics, Probiotics and Postbiotics

Hsin-Chih Lai

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Research Center of Bacterial Pathogenesis, Chang Gung University, Taoyuan 33302, Taiwan

Traditional Chinese Medicines (TCM) that is the wisdom of our ancestors have been used to treat diseases of the folks for thousands of years, Specifically, TCM shows most efficient effects on treatment of chronic inflammation related diseases. Even though TCM has been used for such a long time, the underlying mechanisms of amelioration remain mostly not characterized. The gut microbiome has been shown to be essential for maintenance of host physiology homeostasis, and is closely related to development of chronic inflammation related diseases under dysbiosis. To continue to address the molecular mechanisms of TCM act, microbiome related multi-omics platforms together with strict validation are used. Subsequent development of prebiotics, probiotics and postbiotics is expected for better and consistent prevention or treatment of the many chronic inflammation related diseases.

Tzong-Huei Lee, Ph.D.

-Personal Information-

Name/Title Tzong-Huei Lee/Professor

-Education and Training Background-

Institution	Degree	Year Conferred	Field of Study
National Taiwan University	B.S.	1987	Zoology
National Taiwan University	M.S.	1991	Fisheries Science
National Taiwan University	Ph.D.	1993	Zoology
Academia Sinica	Postdoc.	1998-02	Plant and Microbial Biology

-Employment History-

Position/Institution	Year Conferred
Professor, Institute of Fisheries Science, National Taiwan University	2014-present
Professor, Graduate Institute of Pharmacognosy, Taipei Medical University (TMU)	2012-14
Associate Professor, Graduate Institute of Pharmacognosy, TMU	2007-12
Assistant Professor, Graduate Institute of Pharmacognosy, TMU	2003-07
Investigator, Golden Biotech. Co.	2002-03

-Current Research Program-

1. Development and application of the bioactive agents from marine bioresources
2. Microbial fermentation and application
3. Biosynthetic pathway of the active principles

-Selected Publications-

6. Lee MS, Yang YL, Wu CY, Chen YL, Lee CK, Tzean SS, **Lee TH***. Efficient identification of fungal antimicrobial principles by tandem MS and NMR database. *J. Med. Chem.* **2019**, in press.
7. Jan JS, Yang CH, Wang MH, Lin FL, Yen JL, Hsieh I, Khotimchenko M, **Lee TH***, Hsiao G*. Hirsutanol A attenuates lipopolysaccharide-mediated matrix metalloproteinase 9 expression and cytokines production and improves endotoxemia-induced acute sickness behavior and acute lung injury. *Mar. Drugs*. **2019**, *17*, 360.
8. Lin FL, Cheng YW, Yu M, Ho JD, Kuo YC, Chiou GCY, Chang HM, **Lee TH***, Hsiao G*. The fungus-derived retinoprotectant theissenolactone C improves glaucomalike injury mediated by MMP-9 inhibition. *Phytomedicine.* **2019**, *56*, 207–14.
9. Chen MC, Wang GJ, Kuo YH, Chiang YH, Cho TY, Ju YM, **Lee TH***. Isoprenyl phenolic ethers from the termite nest-derived medicinal fungus *Xylaria fimbriata*. *J. Food Drug Anal.* **2019**, *27*, 111-7.

Development of Antifungal and Anticancer Drugs from Fungal Strains by a Strategic Approach

Tzong-Huei Lee

Institute of Fisheries Science, National Taiwan University, Taipei, Taiwan 10617

The continuous re-isolation of the known and non-applicable compounds that is time-consuming and wasting resources is still a critical problem in the discovery of bioactive entities from natural resources. To efficiently address the problem, high performance liquid chromatography-diode array detector-microfractionation (HPLC-DAD-microfractionation) guided by disk agar diffusion assay was developed, and the active compounds were further identified using the tandem mass spectrometry (MS/MS)-based molecular networking and further supported by ^{13}C NMR database. Of 150 fungal strains screened, the methanolic extracts of *Phoma herbarum* PPM7487, *Cryptosporiopsis ericae* PPM7405, and *Albifimbria verrucaria* PPM945 exhibited potent antimicrobial activities against *Candida albicans* SC5314 and *Cryptococcus neoformans* H99 in the preliminary agar diffusion assay. One new trichothecene-type sesquiterpene derivative **1**, namely trichoverrin D, together with nineteen known entities **2**–**20** were isolated and identified from the three fungal strains through above protocol, and the antifungal activities of compounds **1**–**20** were also evaluated against *C. albican* SC5314, *C. albican* 12-99, *C. albican* 89, and *C. neoformans* H99. By employing the same method, six new polyketides **21**–**26**, namely phomaketides A – E and pseurotin A_3, in addition to eight known compounds **27**–**34** were purified from the fermented broth and mycelium of a fungal strain *Phoma* sp. NTOU4195 isolated from a marine edible red algae *Pterocladiella capillacea*. The chemical structures were established by interpretations of the spectral data. The anti-angiogenic and anti-lymphangiogenic effects of compounds **21**–**34** were evaluated in human endothelial progenitor cells (EPCs) and lymphatic endothelial cells (LECs), respectively. Of these, compound **21** exhibited potent anti-angiogenic and anti-lymphangiogenic activity by suppressing tube formation of EPCs and by inhibiting growth of LECs with IC_{50} values of 8.1 ± 0.5 and 3.7 ± 0.6 μM, respectively. Animal tests were also conducted in this study.

Jih-Jung Chen, Ph.D.

-Personal Information-

Name/Title Jih-Jung Chen/Professor

-Education and Training Background-

Institution	Degree	Year Conferred	Field of Study
China Medical University	B.S.	1989	Medical Biotechnology
Kaohsiung Medical University	M.S.	1994	Natural Product Chemistry
Kaohsiung Medical University	Ph.D.	1997	Pharmacy

-Employment History-

Position/Institution	Year Conferred
Professor, Faculty of Pharmacy, National Yang-Ming University (NYMU)	2017-present
Jointly Appointed Professor, Institute of Biopharmaceutical Sciences, NYMU	2017-present
Jointly Appointed Professor, Institute of Traditional Medicine, NYMU	2018-present
Professor, Department of Pharmacy, Tajen University (TAJEN)	2008-16
Director, Chinese Herbal Medicine Research Center, TAJEN	2008-09
Director, Precision Instruments Center, TAJEN	2010-11
Assistant/Associate Professor, Department of Pharmacy, TAJEN	1997-07

Current Research Program-

New drug development, Translational medicine research, Bioactive natural product research, Functional food R&D, Traditional Chinese Medicine (TCM) research, Pharmacognosy & medicinal botany

-Selected Publications-

1. Yang CY, Chen Y, Lin CY, Chen YH, Lin CY, Chi CW, Chen YJ, Liu SC, Chang TK, Tang CH, Lai YW, Tsai HJ, **Chen JJ***, Wang SW*. Garcimultiflorone K inhibits angiogenesis through Akt/eNOS- and mTOR-dependent pathways in human endothelial progenitor cells. *Phytomedicine* **2019**, in press.
2. Tsai YC, Wang SL, Wu MY, Liao CH, Lin CH, **Chen JJ***, Fu SL*. Pilloin, a flavonoid isolated from *Aquilaria sinensis*, exhibits anti-inflammatory activity in vitro and in vivo. *Molecules* **2018**, *23*, 3177.
3. Cheng LY, Tsai TC, Fu SL, Cheng MJ, Sung PJ, Chung MI*, **Chen JJ***. Acylphloroglucinol derivatives from *Garcinia multiflora* with anti-inflammatory effect in LPS-induced RAW264.7 macrophages. *Molecules* **2018**, *23*, 2587.

Bioactive Natural Products with Anti-inflammatory and Anti-angiogenic Effects from Formosan Plants

Jih-Jung Chen[a,*], Shih-Wei Wang[b], Cheng-Shin Yang[a]

[a]Faculty of Pharmacy, School of Pharmaceutical Sciences, National Yang-Ming University,112, Taipei, Taiwan, E-mail: chenjj@ym.edu.tw
[b]Department of Medicine, Mackay Medical College, No. 46, Sec. 3, Zhongzheng Rd., Sanzhi Dist., New Taipei City, Taiwan.

Garcinia mangostana L. (Guttiferae) is an evergreen tree, distributed in tropical Southeast Asia and contained abundant xanthones. Investigation of EtOAc-soluble fraction of pericarp of *G. mangostana* has led to the isolation of three new xanthones, garcimangone A (**1**), garcimangone B (**2**), and garcimangone C (**3**), together with 18 known compounds (**4**–**21**). Among the isolates, garcinone D (**6**), β-mangostin (**8**), ananixanthone (**14**), morusignin J (**15**), fuscaxanthone C (**16**) and pruniflorone R (**17**) significantly decreased NO production at 25 μM in lipopolysaccharide (LPS)-stimulated RAW264.7 macrophages. Compounds **15** and **16** could also reduce the production of pro-inflammatory cytokines (TNF-α and IL-6) in LPS-stimulated macrophages. Furthermore, compound **15** inhibited the expression of iNOS through reduction of NF-κB activation as well as phosphorylation of ERK and JNK in LPS-stimulated macrophages. On the other hand, compound **15** could also polarize the M1 phenotype macrophages induced by LPS to become M2 phenotype through increasing the expression of M2 markers (KLF4 and arginase 1) and showed its anti-inflammatory potential.
Garcimultiflorone K is a novel polyprenylated polycyclic acylphloroglucinol isolated from the stems of *Garcinia multiflora* that exhibits promising anti-angiogenic activity in human endothelial progenitor cells (EPCs). Our investigations revealed that garcimultiflorone K suppressed EPCs angiogenesis through Akt, mTOR, p70S6K, and eNOS signaling cascades. Notably, garcimultiflorone K dose-dependently impeded angiogenesis in zebrafish embryos. Garcimultiflorone K appears to have potential in the treatment of angiogenesis-related diseases.

Keywords: *Garcinia mangostana*, morusignin J, anti-inflammatory effect, *Garcinia multiflora*, garcimultiflorone K, anti-angiogenic activity

Ping-Chung Kuo, Ph.D.

-Personal Information-

Name/Title Ping-Chung Kuo/Associate Professor

-Education and Training Background-

Institution	Degree	Year Conferred	Field of Study
National Cheng Kung University	Ph.D.	2004	Organic Chemistry

-Employment History-

Position/Institution	Year Conferred
Assistant Professor, School of Pharmacy, National Cheng Kung University	2016-17
Associate Professor, Dept. of Biotechnology, National Formosa University	2008-16

Current Research Program-

1. Isolation and characterization of natural constituents from plant origin
2. Study of bioactive molecules in depth using modern analytical techniques
3. Synthesis and structure-activity relationship studies of bioactive molecules
4. Development of the new synthetic methodologies
5. Assessment of bioactivities for natural products

-Selected Publications-

1. Shiao HT, Lee YC, Liu YC, **Kuo PC***, Wu SN*. Differential suppression of delayed-rectifier and inwardly rectifier K^+ currents by a group of *ent*-kaurane-type diterpenoids from *Croton tonkinensis*, in microglial cells. *Eur. J. Pharmacol.* **2019**, in press.
2. Li YC, Wu CJ, Lin YC, Wu RH, Chen EY, **Kuo PC***, Tzen JCT*. Identification of two teaghrelins in Shy-jih-chuen oolong tea. *J. Food Biochem.* **2019**, *43*, e12810.
3. Lam SH, Li YC, **Kuo PC***, Hwang TL, Yang ML, Wang CC, Tzen JTC*. Chemical constituents of *Vigna luteola* and their anti-inflammatory bioactivity. *Molecules* **2019**, *24*, 1371.
4. Li YC, **Kuo PC***, Yang ML, Chen TY, Hwang TL, Chiang CC, Thang TD, Tuan NN, Tzen JTC*. Chemical constituents of the leaves of *Peltophorum pterocarpum* and their bioactivity. *Molecules* **2019**, *24*, 240.
5. Lam SH, Chen PH, Hung HY, Hwang TL, Chiang CC, Thang TD, **Kuo PC***, Wu TS*. Chemical constituents from the stems of *Tinospora sinensis* and their bioactivity. *Molecules* **2018**, *23*, 2541.
6. Chen GH, Li YC, Lin NH, **Kuo PC***, Tzen JTC*. Characterization of vasorelaxant principles from the needles of *Pinus morrisonicola* Hayata. *Molecules* **2018**, *23*, 86.
7. **Kuo PC**, Yang CJ, Lee YC, Chen PC, Liu YC*, Wu SN*. The comprehensive electrophysiological study of curcuminoids on delayed-rectifier K^+ currents in insulin-secreting cells. *Eur. J. Pharmacol.* **2018**, *819*, 233-47.

Anti-inflammatory Principles from *Vigna luteola*

Ping-Chung Kuo[a,*], Sio-Hong Lam[a,†], Yue-Chiun Li[b,†], Tsong-Long Hwang[c], Jason T.C. Tzen[b,*]

[a]School of Pharmacy, College of Medicine, National Cheng Kung University, Tainan 701, Taiwan
[b]Graduate Institute of Biotechnology, National Chung-Hsing University, Taichung 402, Taiwan
[c]Graduate Institute of Natural Products, College of Medicine, Chang Gung University, Taoyuan 333, Taiwan

Plenty of phytochemicals isolated from dietary and medicinal plants, such as curcumin, epigallocatechin gallate, and soy isoflavones have been considered as promising sources of potential anticancer agents, and are one of the important sources for cancer treatment. In our previous research, the constituents and anti-inflammatory bioactivity of *V. vexillata* were investigated and the results exhibited potent inhibition activity of superoxide generation and elastase release. Preliminary bioassay data indicated that the methanol extract and fractions of *V. luteola* also displayed the significant inhibition of superoxide generation and elastase release by human neutrophils in response to fMLP/CB. Therefore, in the present study it was aimed to characterize the chemical constituents and anti-inflammatory bioactivity of *V. luteola*. Seventy-three compounds were identified from the methanol extract of *V. luteola*, and among these three new compounds (**1-3**) were characterized by spectroscopic and mass spectrometric analyses. The isolated constituents were assessed for anti-inflammatory potential evaluation, and several purified principles exhibited significant superoxide anion and elastase inhibition. According to the anti-inflammatory activity experimental data in this study, the crude extract and purified constituents of *V. luteola* are potential to be developed as new lead compounds or health food ingredients in the future.

Mei-Hsien Lee, Ph.D.

-Personal Information-

Name/Title Mei-Hsien Lee/Professor

-Education and Training Background-

Institution	Degree	Year Conferred	Field of Study
Taipei Medical College	B.S.	1991	Pharmacy
Taipei Medical College	M.S.	1993	Pharmacy
Taipei Medical College	Ph.D.	1996	Pharmacy

-Employment History-

Position/Institution

Lecturer, Graduate Institute of Pharmacognosy, College of Pharmacy, Taipei Medical University (TMU)

Associated Professor, Graduate Institute of Pharmacognosy, College of Pharmacy, TMU

Professor, Graduate Institute of Pharmacognosy, College of Pharmacy, TMU

Visiting scholar, Institute of Molecular Biology, Academia Sinica

Chairman, Graduate Institute of Pharmacognosy, TMU

Chairman, Program for the Clinical Drug Discovery from Botanical Herbs, TMU

-Current Research Program-

1. The analysis and extraction/purification/identification of Chinese herbal medicines and prescriptions or native plants of Taiwan
2. To establish several platforms of aging-related diseases, including osteoporosis, neuro-degenerative diseases, skin aging, and photoaging, for phytohemicals/nutraceuticals/drugs screening
3. Preventive medicines
4. The development of external herbal preparations

-Selected Publications-

10. Imtiyaz Z, Wang YF, Lin YT, Liu HK, **Lee MH***. Isolated compounds from *Turpinia formosana* Nakai induce ossification. *Int. J. Mol. Sci.* **2019**, *20*, 3119.
11. Huang CY, Lin YT, Kuo HC, Chiou WF, **Lee MH***. Compounds isolated from *Eriobotrya deflexa* leaves protect against ultraviolet radiation B-induced photoaging in human fibroblasts. *J. Photochem. Photobiol. B* **2017**, *175*, 244-53.
12. Lin RD, Chen MC, Liu YL, Lin YT, Lu MK, Hsu FL, **Lee MH***. New whitening constituents from Taiwan-native *Pyracantha koidzumii*: structures and tyrosinase inhibitory analysis in human epidermal melanocytes. *Int. J. Mol. Sci.* **2015**, *16*, 28598-613.

Exploration of Osteogenic Potential of Taiwanese Plants and Designing Novel Models for Screening.

Mei-Hsien Lee[a,b,*], Yi-Tzu Lin[b], Zuha Imtiyaz[b]

[a]Graduate Institute of Pharmacognosy, College of Pharmacy, Taipei Medical University, Taipei 110, Taiwan
[b]PhD in Clinical Drug Development of Herbal Medicine, Graduate Institute of Pharmacognosy, Taipei Medical University, Taipei 110, Taiwan

Skeleton is a dynamic organ undergoing continuous metabolism. This metabolism comprises of bone resorption and bone formation controlled by predominantly two types of cells osteoclasts and osteoblasts respectively. These cells are formed from the same progenitor cells however the differentiation and control mechanism are diverse. Imbalance in this metabolic process leads to the onset of medical conditions such as osteopenia, osteoporosis and frequent fractures. With all the advancement in the research and development, conditions such as osteoporosis still have some unmet needs which limits the prevention and absolute treatment. While several classes of drugs against osteoporosis are currently available in the market, they are associated with certain side effects which renders them unsafe for long term use. Plants possess numerous metabolites, some of which possess the medicinal value making plants of therapeutic value. In our studies we explore the bone formation properties of the medicinal plants that have been reported to be beneficial in folk medicine using human osteoblast (Hob). We study the activities and the mechanism of action of the potent compounds that can enhance the bone formation without hampering the actual balance between the two processes of the metabolism. We also study the effect of these potent entities *in vivo* by artificially mimicking the human post-menopausal condition in mice by ovariectomy. We monitor the effect of plants and active compounds on the levels of bone mass density and fragility of the bones. Our research also includes designing of new screening models based on the novel genetic biomarkers related to the osteoporosis, this can help us find new target pathways or transcription factor which can be used to screen the potential drugs, compounds or traditional medicine formulae against osteoporosis.

Tsong-Long Hwang, Ph.D.

-Personal Information-

Name/Title Tsong-Long Hwang/Distinguished Professor/Dean

-Education and Training Background-

Institution	Degree	Year Conferred	Field of Study
Kaohsiung Medical University	B.S.	1991	Pharmacy
Kaohsiung Medical University	M.S.	1993	Pharmacology
National Taiwan University	Ph.D.	2000	Pharmacology

-Employment History-

Position/Institution	Year Conferred
Dean, College of Human Ecology, Chang Gung University of Science and Technology (CGUST)	2015-present
Distinguished Professor, Graduate Institute of Health Industry Technology, CGUST	2017-present
Professor, Graduate Institute of Health Industry Technology, CGUST	2015-present
Professor, Graduate Institute of Natural Products Chang Gung University (CGU)	2009-present
Deputy Director, School of Traditional Chinese Medicine, CGU	2010-15
Associate Professor, Graduate Institute of Natural Products, CGU	2005-09
Assistant Professor, Graduate Institute of Natural Products, CGU	2000-05

-Current Research Program-

Inflammatory and immune pharmacology, Molecular signaling, and Drug development

-Selected Publications-

1. Tsai YF, Chen CY, Chang WY, Syu YT, **Hwang TL***. Resveratrol suppresses neutrophil activation via inhibition of Src family kinases to attenuate lung injury. *Free Radic. Biol. Med.* **2019**, *145*, 67-77.
2. Chen PJ, Ko IL, Lee CL, Hu HC, Chang FR, Wu YC, Leu YL, Wu CC, Lin CY, Pan CY, Tsai YF, **Hwang TL***. Targeting allosteric site of AKT by 5,7-dimethoxy-1,4-phenanthrenequinone suppresses neutrophilic inflammation. *EBioMedicine* **2019**, *40*, 528.
3. Liu FC, Yu HP, Chen PJ, Yang HW, Chang SH, Tzeng CC, Cheng WJ, Chen YR, Chen YL*, **Hwang TL***. A novel NOX2 inhibitor attenuates human neutrophil oxidative stress and ameliorates inflammatory arthritis in mice. *Redox Biol.* **2019**, *26*, 101273.
4. Lin CY, Hsu CY, Elzoghby AO, Alalaiwe A, **Hwang TL***, Fang JY*. Oleic acid as the active agent and lipid matrix in cilomilast-loaded nanocarriers to assist PDE4 inhibition of activated neutrophils for mitigating psoriasis-like lesions. *Acta Biomater*. **2019**, *90*, 350-61.

The Opportunity of Discovering Drug Leads for Treating Neutrophilic Inflammatory Diseases

Tsong-Long Hwang

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Neutrophils play a noteworthy role in acute and chronic inflammatory diseases as well as autoimmune disorders. During the inflammatory process, neutrophils are recruited into inflammatory areas to eliminate invasive pathogens. However, excessive recruitment and activation of neutrophils are harmful to healthy tissues. The reactive oxygen species, proteases, and neutrophil extracellular traps released by activated neutrophils can damage healthy surrounding cells and cause inflammatory diseases. An increasing body of evidence shows that neutrophils involve not only in infective diseases but also in sterile inflammatory disorders. Therefore, understanding the regulation of neutrophil activation has become increasingly important. In this presentation, I will discuss how neutrophils can be controlled by chemical compounds to ameliorate neutrophilic inflammatory diseases.

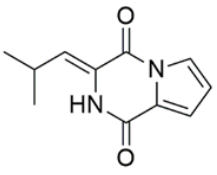
POSTER PAPERS

The Analysis of Secondary Metabolite of Symbiotic Bacterium, *Vibrio tubiashii*, from the Sponge, *Agelas nemoechinata*

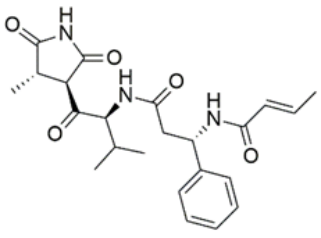
洪茂軒Mao-Xuan Hung[a,#], 廖志中Chih-Chuang Liaw[a,b,*]

[a]Department of Marine Biotechnology and Resources; [b]Doctor Degree Program in Marine Biotechnology, National Sun Yat-sen University, Kaohsiung, Taiwan

Literature survey indicated that many sponge-derived chemicals with remarkable activities are used as clinical therapeutics. More evidences indicated that sponges are regarded as chemical factory because microbial density in some marine sponges may account up to 60% of the biomass of sponges. In the previous study, the EA extract of the sponge, *Agelas nemoechinata*, showed inhibitory activity against *Staphylococcus aureus* and *S. epidermids.* We are interested if the symbiotic microbes are partially charge of the bioactivities of the sponge. We try to isolate bioactive bacteria from the sponge, *A. nemoechinata.* Among them, the strain DJW05-1, identified as *Vibrio tubiashii* by 16S rRNA sequencing analysis, showed clear inhibitory activity against several bacterial indicators, such as *Escherichia coli*, *S. aureus*, *Salmonella typhimurium*, *Acinetobacter baumannii*. Besides, *V. tubiashii* was reported as a facultative anaerobic bacterium. Thus, we culture the strain DJW05-1 on marine agar under aerobic and anaerobic conditions, respectively, for three days and compare with their metabolites each other. Apparently, the strain DJW05-1 in anaerobic condition lost its antimicrobial activity. We further isolated eight compounds, including two new compounds, DJWF5-3 and DJWF3-6-2, as well as six known compounds, andrimid, moiramide B, cyclo(L-Pro-L-Leu), cyclo(L-Pro-L-Phe), cyclo(D-Pro-L-Phe), and indole-3-aldehyde from the bioactive fractions of the EA extract of the strain DJW05-1 in aerobic condition by bioassay-guided-fractionation isolation. Among them, andrimid was one of the active compounds, of which the biosynthesis genomes have been identified by Joy Clardy's group in 2006. Based on Mass spectral molecular network analysis, we isolated a series of andrimid-like compounds which showed similar mass fragmentation patterns as that of andrimid. We elucidate the structures of those compounds based on 1D and 2D NMR and mass spectral analysis. Moreover, the antimicrobial activity of all isolates is under investigation.



DJWF3-6-2



DJWF5-3

Keywords: sponge, anaerobic, *Vibrio tubiashii*, *Agelas nemoechinata*, andrimid

The Study on Chemical Components of Seahorse, *Hippocampus kuda*

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Seahorses have been widely used as a traditional Chinese medicine with long history for promoting blood circulation, treating oligospermatism and arthritis. Previous pharmacological studies suggested that seahorse in Chinese medicine not only had hormone-like activities, boosting hematopoiesis function, but also showed activities of anti-tumor, anti-aging, anti-fatigue and Ca^{2+} channel blocking. Literature survey indicated only few papers mentioned the chemical constituents of the genus *Hippocampus*, such as steroids, peptides, essential amino acids, fatty acids and trace elements, no more detailed researches about the bioactive components of the genus *Hippocampus*. Herein, we would like to explore the secondary metabolites of *H. kuda* by Mass-based molecular network analysis. *Hippocampus kuda*, one species of the genus *Hippocampus* as a medical material in Chinese medicine, was cultured and provided by a Taiwan biotech company. Following the repeated chromatographic analysis, we isolated some steroid-type compounds and also found that some Mass spectral signals with more than one thousand Daltons in the methanol layer of *H. kuda* extract. In the poster, we will exhibit our research results on chemical components of *H. kuda*.

keywords: seahorse, *Hippocampus kuda,* Mass-based molecular network analysis

Flavonoids from the *Helminthostachys zeylanica*

方舜億 Shuin-Yi Fang[a,b,#], 謝慶良 Ching-Liang Hsieh[c], 廖志中 Chih-Chuang Liaw[a,*]

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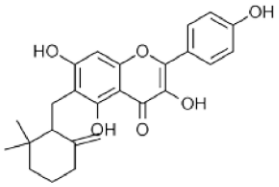
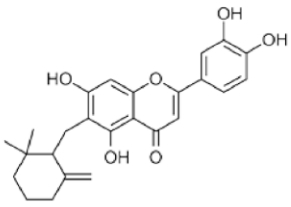
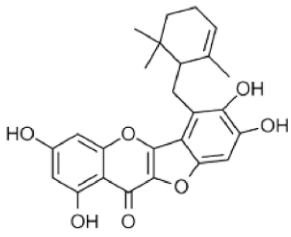
Helminthostachys zeylanica (Ophioglossaceae) is an indigenous fern discovered at southeastern Asia, and few reports about the distribution of the fern have been documented in mountain areas of Taiwan. The bioactive components from the fern are unique flavonoids that one or two isoprene units are cyclized on different position, which have been reported many bioactivities, such as anti-inflammation, cytotoxicity etc. To accelerate the isolation of new bioactive compounds efficaciously, we tried to target the active components of the ethyl-acetate layer of *H. zeylanica* by Mass-based molecular network analysis. Following repeated chromatographic isolation, we obtained seven compounds, including one new compound (HZE 11-δ), as well as six known compounds, ugonins J, M, N, P and U, and 7-(3,4-dihydroxyphenyl)-4,6-dihydroxy-2,3,3-trimethyl-2*H*-furo[3,2-*g*]chromen-5-one). The structures of all isolated compounds were identified by using 1D and 2D-NMR and MS spectral data, respectively, and the bioactivity of all the isolates are under investigation.



HZE 11-δ*



Ugonins J



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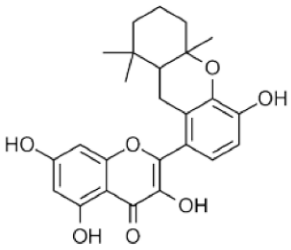

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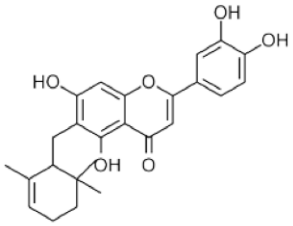
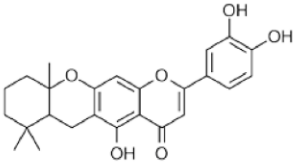
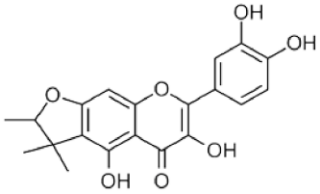


Ugonin P



Ugonin U



7-(3,4-dihydroxyphenyl)-4,6-dihydroxy-2,3,3-trimethyl-2H-furo[3,2-g]chromen-5-one

Keywords: *Helminthostachys zeylanica;* Flavonoids; Ugonin

Azaphilones and Monacolins from *Monascus pilosus* BCRC 38144

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Fungi of the genus *Monascus* (Monascaceae) have been used to ferment rice in Asia for over 1000 years. It has been widely utilized as food additives, natural food coloring agent, antiseptic, and healthy food. The production of red yeast rice was also used as Chinese folk medicine and recorded in old Chinese literature for easing digestion and soothing pain. *Monascus*-fermented rice has been reported various biological functions and plenty of secondary metabolites. However, their pharmacological and toxicological effects still unknown or unclear, which is valuable for further research.

Red yeast rice was a great invention in ancient China and was used as Chinese medicine to strengthen the spleen, promote digestion, eliminate dampness and phlegm, promote blood circulation, and remove blood stasis.

In Taiwan, there are forty *Monascus* derivatives healthy food approved by Taiwan Food and Drug Administration (TFDA) as regulating blood cholesterol function. To be the safety healthy food, the proportion of hepato-nephrotoxic ingredients–citrinin contained in *Monascus* healthy food is strictly examined. During our search in *Monascus* spp. sources, *M. pilosus* BCRC 38144 stand out resulting in its plentiful metabolites in our preliminary HPLC profile analyses. It is also worth pointing out that *M. pilosus* BCRC 38144 is a citrinin-free strain. In this report, the dried red yeast rice of *M. pilosus* BCRC 38144 was extracted three times with 95% EtOH, and partitioned with EtOA/water (1:1) to afford an EtOAc layer and water layer. Investigation of the EtOAc-soluble layer has led to the isolation of two new azaphilones: monapilosones A & B (**1** & **2**), three new monacolins: monacolins T–V (**3**–**5**), together with four known ones: monacolin K (**6**), hydromonacolin S (**7**), monascodilone (**8**), and monasfluore B (**9**). Those structures were elucidated by 1D and 2D-NMR spectroscopy together with HRESIMS analysis and compared with the literature data for structurally related compounds. Some of them have been evaluated their anti-lipid droplet (LD) accumulation activity. Among them, monacolin K (**6**) and monasfluore B (**9**) reduced the LD accumulation activity with 39.9±26.1 and 24.5±12.5 % in 20 μM, respectively. The results may helpful for anti-NAFLD (non-alcoholic fatty liver disease drug) development.

Keywords: *Monascus* spp., mycelia, azaphilone, monacolin, anti-NAFLD

Chemical Constituents and Anti-inflammatory Activity from the Root of *Machilus zuihoensis* var. *mushaensis*

Shuen-Shin Yang 楊舜心 [a,#], Tsong-Long Hwang 黃聰龍 [b], Ming-Jen Cheng 鄭銘仁 [c], Ih-Sheng Chen 陳益昇 [a], Hsun-Shuo Chang 張訓碩 [a,*]

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Inflammation is the normal response to infection or injury of the body. It involves the activation of the immune system, including the recruitment of immune cells and antibodies, to eliminate invasive pathogens, repair damaged tissue, and accelerate wound healing. However, prolonged inflammation might lead to tissue destruction, organ dysfunction, or even death. Although there are some anti-inflammatory drugs in clinical, many of them exhibited several side effects in the gastrointestinal tract, liver, etc. Development of the novel anti-inflammatory drug is an urgent issue.

Approximately 60 species of Formosan Lauraceous plants have been screened for the anti-inflammatory activity by using the fMLP / CB-induced superoxide production platform. Among them, the root of *Machilus zuihoensis* var. *mushaensis* (F.Y. Lu) Y. C. Liu is outstanding than other samples due to its high anti-inflammatory activity, which can both inhibit superoxide anion and elastase release at 1 μg/ml. *M. zuihoensis* var. *mushaensis* is an endemic, large ever-green tree distributed at medium altitudes throughout Taiwan.

Up to the time, there are only two reports mentioned about the chemical constituents from the leaves and stem of *M. zuihoensis* var. *mushaensis*, the ingredients and bioactivity of the roots of this species have not been studied yet. The methanolic extracts of the root of this species were partitioned into water-soluble and ethyl acetate layers. The ethyl acetate layer showed a potent activity toward fMLP / CB-induced superoxide production inhibitory activity.

Bioassay-guided fractionation of the active ethyl acetate layer from the root of this plant led to the isolation of one new benzenoid, machimushal (**1**), one new sesquiterpene, mushadiol (**2**), along with 26 known compounds, including one benzenoid, five butanolides, ten lignans, and ten sesquiterpenes. The structures of these compounds were elucidated by NMR spectra, UV, IR, and MS analyses. The isolation of chemical constituents and the anti-inflammatory activity of the isolates are still in progress.

Keywords: Lauraceae, *Machilus zuihoensis* var. *mushaensis*, anti-inflammatory activity, butanolide, sesquiterpene

Exploration of Antimicrobial Cyclic Peptides from *Massilia* sp. YMA4 using an Integrated Omics Strategy

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The aim of this study was to explore the antimicrobial compounds from a marine-derived bacterium *Massilia* sp. YMA4. The antagonist test revealed that *Massili* sp. YMA4 effectively inhibited *Staphylococcus aureus* in various culture conditions. Therefore, we employed *in-situ* metabolomic analysis including imaging mass spectrometry (IMS) to detect the potential antimicrobial compounds of Massilia sp. YMA4. In the IMS analysis, several unique signals, including *m/z* 1098, 1126, 1148, 1170, 1172, and 1188, only appeared in the inhibition zone between *Massilia* sp. YMA4 and *S. aureus*, suggesting that these signals are potential antibiotics. Structures of those signals were further elucidated by combining biosynthetic gene clusters (BGCs) analysis and comparative metabolomic analysis of *Massilia* sp. YMA4. They were identified as nonribosomal peptides, empedopeptins, which comprised of a fatty acid tail and eight amino acid residues. Furthermore, we constructed the mutant strains of empedopeptins biosynthetic genes. The antagonist test revealed that those mutant strains were unable to inhibit the growth of *S. aureus* growth, demonstrating that empedopeptins are the major antimicrobial substances of *Massilia* sp. YMA4. By using this integrated omics strategy, we identified 45 empedopeptin analogs (17 cyclic peptides and 28 linear peptides) from *Massilia* sp. YMA4 and its mutant strains.

Keywords: *Massilia, antimicrobial,* imaging mass spectrometry, metabolomics, biosynthetic gene cluster

New Scalarane-type Sesterterpenoids from Marine Sponge *Ircinia felix*

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[d]Department of Marine Biotechnology and Resources, National Sun Yat-Sen University, Lien-Hai Road, Kaohsiung 804, Taiwan
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Marine sponge-derived natural products possess many classes of secondary metabolites. For instance, there were 18 identified chemical classes of the isolated new compounds during the last decade, including acid, alkaloid, ester, fatty acid, glycoside, ketone, lipid, macrolide, alcohol, peptide, peroxide, polyketide, quinone, steroid, sterol, terpene, terpenoid and unclassified. Among them, scalarane-type sesterterpenoids emerged as an interesting group of terpenoids isolated from marine sponges and shell-less mollusks. Scalarane sesterterpenoids demonstrated a wide spectrum of interesting biological properties, such as anti-inflammation, cytotoxicity, anti-feedant, anti-microbial, anti-fungal, ichthyotoxicity, anti-tubercular, anti-HIV, anti-fouling, inhibition of platelet-aggregation, inhibition of transactivation for the nuclear hormone receptor (FXR, farnesoid X-activated receptor), and stimulation of nerve growth factor synthesis. In the further study of metabolites from marine sponge *Ircinia felix*, four new 24-homoscalarane analogues, felixins H–K (**1**–**4**) and eight known scalarane-type sesterterpenoids were isolated. The structures of scalaranes **1**–**12** were elucidated on the basis of spectroscopic analysis. Cytotoxicity of scalaranes **1**–**12** against the proliferation of a limited panel of tumor cell lines was evaluated.

Keywords: marine natural products, marine sponge, scalarane, cytotoxicity

Forward and Reverse *In Silico* Analysis with Metabolomics for Prediction and Identification of an Unknown Polyketide of *Beauveria bassiana*

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[a]Agricultural Biotechnology Research Center, Academia Sinica, 11529 Taipei, Taiwan.
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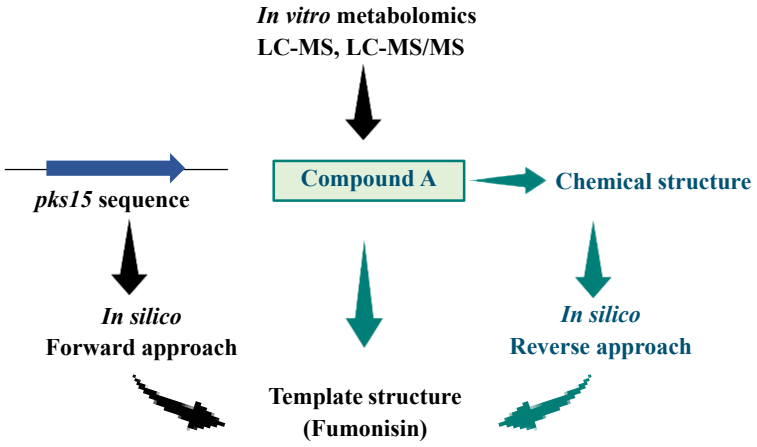
Beauveria bassiana BCC2660 is an entomopathogenic fungus producing polyketides which are secondary metabolites synthesized by polyketide synthases (PKSs). Polyketides are important for pharmaceutical and biological activities. PKS15, an iterative polyketide synthase of *B. bassiana*, has crucial roles in fungal sporulation and virulence against insects. However, to identify the metabolite of PKS15 is very challenged. *In silico* analysis of forward and reverse approaches have been considered together with metabolomics to predict the candidate metabolite of PKS15. *In silico* forward approach of the *pks15* sequence demonstrated that the highly reducing and iterative PKS15 contains a single set of catalytic domains, KS-AT-DH-ER-KR. These catalytic domains are highly similar to those of fumonisin synthase except lacking a *C*-methyltransferase domain in PKS15. Moreover, PKS15 has an aspartate aminotransferase (AAT) domain for transferring an aspartate to the polyketide backbone. *In vitro* comparative metabolomics analysis of *B. bassiana* wild type and Δ*pks15* mutant using LC-MS and LC-MS/MS supported the *in silico* forward analysis. Candidate metabolite structure of PKS15 was proposed as a linear structure lacked methyl group, which is similar to that of fumonisin and composed an aspartate. Likewise, *in silico* reverse approach based on candidate metabolite structure was also supported similarity to fumonisin as *in silico* forward analysis. These data demonstrated that the combination method of *in silico* and mass spectrometry analyses has a great potential to predict and identify a candidate metabolite of an iterative polyketide synthase. This would facilitate the selection of candidates and discover novel compounds.



Keywords: iterative polyketide synthase, LC-MS, aminotransferase

New 1,4-Dienonesteroids from an Octocoral *Dendronephthya* sp. and their Anti-Inflammatory Activity

黃清豪 Thanh-Hao Huynh[a,b,#], 溫志宏 Zhi-Hong Wen[c], 宋秉鈞 Ping-Juyn Sung[a,b,c,*]

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Two new steroids, dendronesterones D (**1**) and E (**2**), featuring with 1,4-dienone moiety, along with three known steroids, methyl 3-oxochola-4,22-diene-24-oate (**3**), 5α,8β-epidioxy-24(*S*)-methyl-cholesta-6,22-dien-3β-ol (**4**), and 5α,8β-epidioxy-24(*S*)-methyl-cholesta-6,9(11),22-trien-3β-ol (**5**), were isolated from an octocoral *Dendronephthya* sp. The structures of these steroids were elucidated by using spectroscopic methods and steroids **1** and **2** were found to exhibit significant in vitro anti-inflammatory activity in LSB-induced RAW264.7 macrophage cells by inhibiting the expression of iNOS protein.

Keywords: Dendronesterone; *Dendronephthya;* anti-inflammatory; iNOS

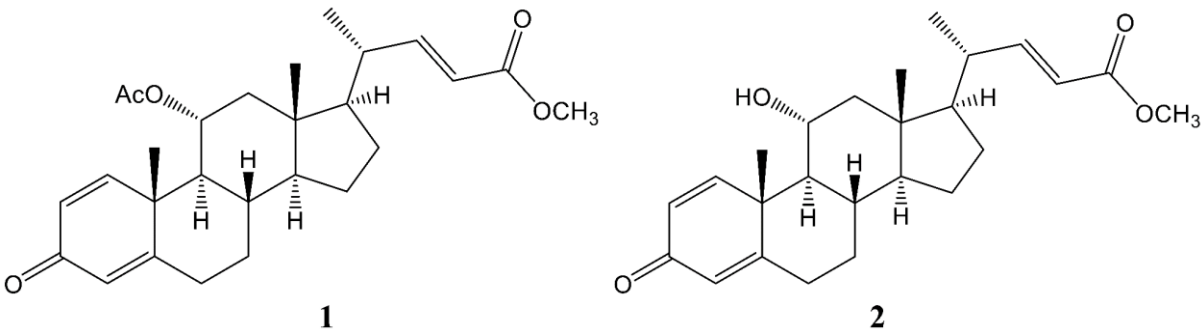

Figure 1. Structures of dendronesterones D (**1**) and E (**2**)

New Briarane-type Diterpenoids from the Octocoral *Briareum* sp.

胡瓊止 Chiung-Chih Hu[a,#], 彭柏融 Bo-Rong Pong[a,b], 陳又瀅 You-Ying Chen[a,c], 宋秉鈞 Ping-Jyun Sung[a,c,*]

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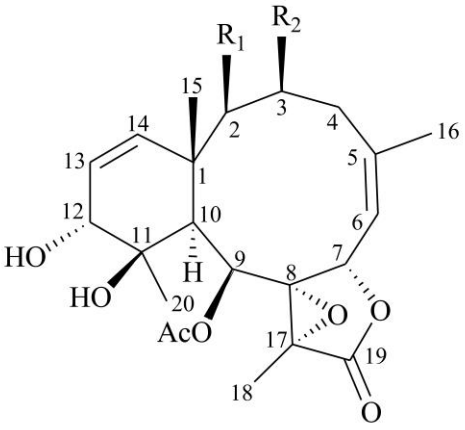
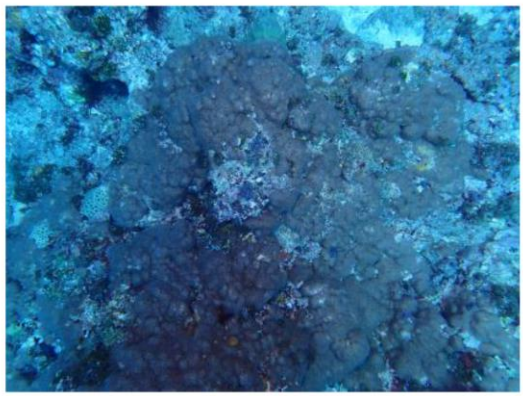
Chemical investigation of the extract from the supercritical carbon dioxide extraction of an octocoral identified as *Briareum* sp. (family Briareidae), afforded a pair of new acetyl isomers, briaviolides Y (**1**) and Z (**2**), belonging to briarane diterpenoids (3,8-cyclized cembranoid). The strictures of briaranes **1** and **2**, including their relative configurations, were elucidated on the basis of NMR spectroscopic analysis. Bioactivity for these two compounds will be evaluated.



1: R_1 = OAc, R_2 = OH
2: R_1 = OH. R_2 = OAc



Briareum sp.

Keywords: *Briareum*, briarane, briaviolide, octocoral

Alkaloids from the Zoanthid *Zoanthus vietnamensis* with Anti-Lymphangiogenic Activity

陳姝蓉 Shu-Rong Chen[a,#], 王士維 Shih-Wei Wang[a,b], 張芳榮 Fang-Rong Chang[a,c,d,*], 鄭源斌 Yuan-Bin Cheng[a,d,*]

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Eleven new secondary metabolites, [kuroshines H–J (**1**–**3**), 27-methyl glycinate zoanthenamine (**4**), 27-hydroxyzoanthenamine (**5**), 27-methyl glycinate kuroshine A (**6**), 27-hydroxykuroshine A (**7**), 3*β*-hydroxy-28-deoxyzoanthenamine (**8**), 14*α*-hydroxy-28-deoxyzoanthenamine (**9**), 27-hydroxy-28-deoxyzoanthenamine (**10**), and kuroshine K (**11**)], along with seven known compounds (**12**–**18**) were isolated from the zoanthid, *Zoanthus vietnamensis*. The structures of all isolated components were elucidated by spectroscopic data (IR, MS, NMR, and UV), especially 2D NMR analyses. The absolute configurations of **1** and **2** were determined by using X-ray single crystallography. Compounds **1**–**3** have an unprecedented ether linkage between C-15 and C-28. The unusual substituent, methyl glycinate, attaching at C-27 in compounds **4** and **6** was first found in zoanthamine-type alkaloid. The anti-lymphangiogenic activities of seventeen isolated compounds were evaluated. Compounds **4**, **5**, and **10** exerted the promising anti-lymphangiogenic functions by reducing cell growth and tube formation of human lymphatic endothelial cells (LECs) with IC_{50} values of 40.3 ± 1.9, 52.0 ± 5.0, and 50.1 ± 3.7 μg/mL, respectively. In addition, the structure-activity relationships of isolated alkaloids against lymphangiogenesis of LECs were discussed.

Keywords: alkaloids, *Zoanthus vietnamensis*, anti-lymphangiogenic activity

Synthesis of Natural Products Inspired, Neutrophil Targeted, Anti-inflammatory Drugs

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Natural products play very crucial role in the development of drugs. A successful novel approach for the synthesis of hybrid molecules with β-carboline and/or combretastatin basic moieties has been developed. Pictet- Spengler reaction is the key to combine these two moieties. As a result 25 compounds have been synthesized and characterized by using NMR (^{1}H, ^{13}C, COSY) and mass spectroscopic techniques. Neutrophils are involved in various inflammatory diseases thus all synthetics were evaluated against human neutrophils and structure activity relationships have been developed in order to achieve potential drug candidate. The results indicated that many compounds have moderate activity and compound HK-26 significantly inhibited fMLF-induced superoxide anion generation and elastase release with IC_{50} values of 1.44 and 5.44 μM, respectively. This strategy could be very useful in the development of potential neutrophil targeted anti-inflammatory drug candidate in the future endeavors.

Keywords: Chemical synthesis, β-carboline, combretastatin, neutrophils, anti-inflammatory drugs

Discovery of Flavonoids as Potent Fms-like Tyrosine Kinase 3 (FLT3) Inhibitors Against Acute Myeloid Leukaemia (AML)

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[a]Graduate Institute of Cancer Molecular Biology and Drug Discovery, College of Medical Science and Technology, Taipei Medical University, Taipei 110, Taiwan
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[c]Biomedical Commercialization Center, Taipei Medical University, Taipei 110, Taiwan
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[e]Graduate Institute of Pharmacognosy, College of Pharmacy, Taipei Medical University, Taipei 110, Taiwan
[f]Ph.D. Program for the Clinical Drug Discovery from Botanical Herbs, College of Pharmacy, Taipei Medical University, Taipei 110, Taiwan
[g]School of Pharmacy, National Defense Medical Center, Taipei 114, Taiwan

Acute myeloid leukemia (AML) is an aggressive disease with a high degree of relapse and poor prognosis disease. In up to 70% of AML patients, FMS-like tyrosine kinase 3 (FLT3) is expressed at a high level and associated with poor prognosis. Overexpression of wild-type FLT3 induces proliferation and inhibits apoptosis in AML cells. FLT3 mutations constitutively activate FLT3 kinase activity, resulting in uncontrolled proliferation. Therefore, inhibiting FLT3 activity has been recognized as a novel therapy for AML patients. Flavonoids are a group of phytochemicals with anti-cancer therapeutic potential. In this study, we identified several potential flavonoids with FLT3 inhibition activity. Among these compounds, compound **40** not only exhibited the most potent FLT3 inhibition activity (IC_{50} = 440.6 nM), but also against FLT3-D835Y and FLT3-ITD mutants (IC_{50} = 228.8 and 389.0 nM). The key interactions in the FLT3 binding site were identified by analyzing the inhibition results and performing a structure-activity relationship (SAR) analysis of flavonoids. Furthermore, the cellular assays revealed that compounds **28**, **31**, **32** and **40** exhibited significant cytotoxicity against two human AML cell lines (MOLM-13 and MV-4-11). Together, our compounds have the potential to be further optimized as more potent FLT3 inhibitors and also provide valuable chemical information for the development of new AML drugs.

Keywords: Acute myeloid leukemia, FLT3, Flavonoids

A Bio-Inspired Common Intermediate for the Total Syntheses of Palhinine Alkaloids

陳致銘 Chih-Ming Chen[a,b,#], 蕭暉議 Hui-Yi Shiao[a], 薩德雷 Julakanti Satyanarayana Reddy [a], 張一寧 Yi-Ning Teoh[a,b], 林聖國 Sheng-Kuo Lin[a,b], 汪炳鈞 Biing-Jiun Uang[b], 謝興邦 Hsing-Pang Hsieh[a,b,*]

[a]Institute of Biotechnology and Pharmaceutical Research, National Health Research Institutes,Miaoli County 35053, Taiwan
[b]Department of Chemistry, National Tsing Hua University, Hsinchu 30013, Taiwan

Palhinine alkaloids, a novel *Lycopodium* alkaloid family, contain a highly ring strain cage like skeleton, a nine-membered azonane ring fused with an isotwistane framework through two vicinal quaternary centers. Due to the isotwistane skeleton would increase ring strain of nine-membered ring hindering cyclization reaction, hence we installed the nine-membered azonane ring at early stage through S_N2 cyclization; the isotwistane skeleton was constructed by a Diels-Alder reaction of masked *ortho*-benzoquinone, a homologation reaction, and a thiol-mediated acyl radical cyclization to accomplish the bio-inspired 5/6/6/9 tetracyclic intermediate; finally, the biomimetic intermediate was utilized to synthesis isopalhinine A, palhinine A, and palhinine D through a bio-inspired synthetic strategy.

Keywords: acyl radical cyclization, biomimetic synthesis, Diels-Alder reaction, isotwistane, palhinine alkaloid

Bioactivity-guided Isolation of Anti-inflammatory 9,11-Secosteroids from the Soft Coral *Sinularia leptoclados*

張祐嘉 Yu-Chia Chang[a,#], 謝喜龍 Hsi-Lung Hsieh[a], 賴慶隆 Ching-Long Lai[a,*], 黃聰龍 Tsong-Long Hwang[a,b,*]

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Marine organisms have provided a large number of bioactive natural products, several of them with unusual structures and interesting biological activities. In Alcyonacean soft corals, genus *Sinularia* is one of the most widely distributed soft coral. It constitutes a dominant portion of the biomass in the tropical reef environment. Using bioassay-guided fractionation based on anti-inflammatory effects, two new 9,11-secosteroids, sinleptosterols A (**1**) and B (**2**) were isolated from soft coral *Sinularia leptoclados*, along with five known analogues 8*α*H-3*β*,11-dihydroxy-24-methylene-9,11-secocholest-5-en-9-one (**3**), 8*β*H-3*β*,11-dihydroxy-24-methylene-9,11-secocholest-5-en-9-one (**4**), leptosterol A (**5**), (24*S*)-3*β*,11-dihydroxy-24-methyl-9,11-secocholest-5-en-9-one (**6**) and 3*β*,11-dihydroxy-9,11-secogorgost-5-en-9-one (**7**). The structures of the new metabolites were elucidated on the basis of extensive spectroscopic analysis and by comparison of their NMR data with those of known compounds. Compound **4** showed significant inhibition against elastase release and superoxide anion generation, with the IC_{50} values of 2.96 and 1.63 μM, respectively. Our data indicated that the isolated series of 9,11-secosteroids demonstrated structural features and anti-inflammatory activity which could be further developed into therapeutic entities.

Keywords: *Sinularia leptoclados*, bioassay-guided fractionation, 9,11-secosteroids, superoxide, elastase

Study on the Biosynthesis of Vitroprocines through Key Enzymes by Recombinant DNA Technology

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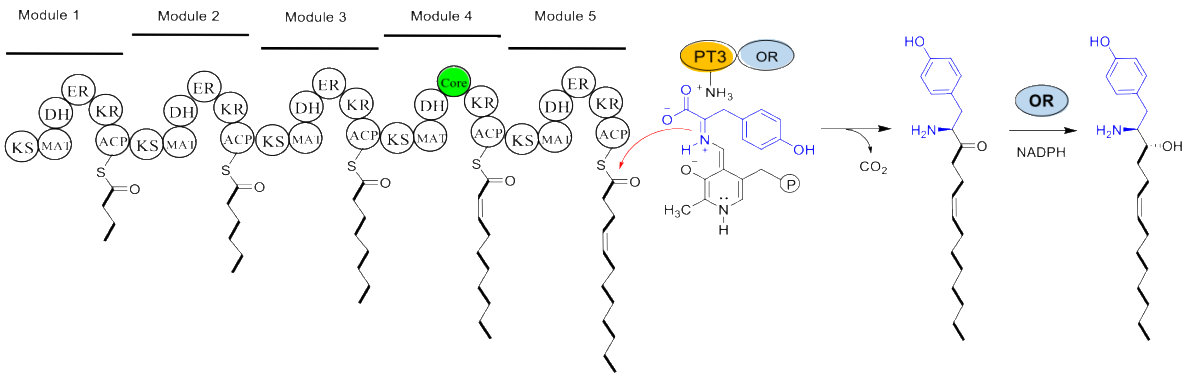
Antibiotic abuse results in the exponential increasing of the antibiotic-resistant pathogens, which increases mortality and also leads to higher medical cost. It becomes imperative to find new antibiotics against such antibiotic-resistant pathogen-associated hospital-acquired infections (HAIs). In our previous study, we isolated the new antibiotics, vitroprocines, a type of amino-polyketide derivatives, from marine *Vibrio* sp. QWI-06 against several indicator bacteria, such as *Staphylococcus aureus*, *Klebsiella pneumonia*, and *Acinetobacter baumannii*. The biosynthesis of vitroprocines is related to the condensation of tyrosine and a fatty acid chain catalyzed by a pyridoxal 5'-phosphate (PLP)-dependent enzyme, which is like those biosyntheses of fumonisins by alanine, and sphingosine by serine. By genome mining the whole genome sequences of *Vibrio* sp. QWI-06, four sets of putative PLP-dependent enzyme genes, *PTs-1~4*, of the *Vibrio* were found. Through recombinant DNA technology, we successfully overexpressed three of them (*PTs-2~4*) by using *Escherichia coli* system. Furthermore, in the examination of biological function of those PTs 2-4 enzymes, incubated with various amino acids and lauroyl CoA, we found that only PT-3 works as the PLP-dependent acyl-CoA transferases and synthesizes vitroprocine analogues. Moreover, an unique reductase whose genome just located downstream of *PT-3* was also characterized, and suggested to reduce the ketone group into hydroxyl in the biosynthesis of vitroprocines.



Key words：vitroprocines ; *Vibrio* sp. QWI-06 ; PLP-dependent enzyme, reductase

Isomalabaricane Triterpenes from the Marine Sponge *Rhabdastrella* sp.

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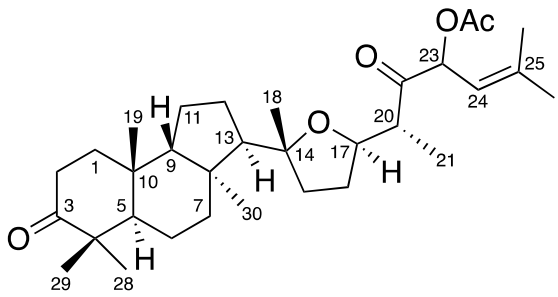
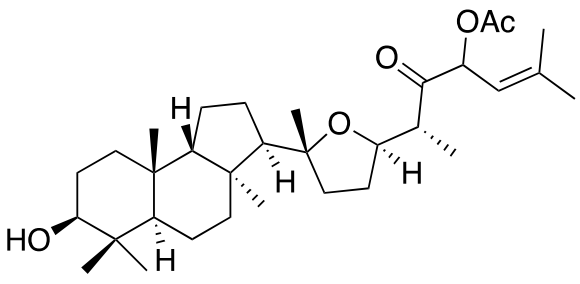
The isomalabaricane triterpenes are some of the most frequently encountered natural products in sponges of the genus *Rhabdastrella*, *Stelletta*, *Jaspis* and *Geodia*, all of which belong to the order Astrophorida. In the current study, two new isomalabaricane-type triterpenes rhabdastin H (**1**) and rhabdastin I (**2**) were isolated from the marine sponge *Rhabdastrella* sp.. The structures were elucidated based on extensive spectroscopic analyses. Among these metabolites, **1** and **2** were found to possess the only reported tetrahydrofuran moiety of all marine-derived isomalabaricanes. All isolates were evaluated for their anti-proliferative properties, while only **1** and **2** showed moderate anti-leukemic activities against Molt 4 and K562 cell lines.



1



2

Keywords: isomalabaricane, *Rhabdastrella*, tetrahydrofuran moiety, anti-leukemia

Constituents from the Seashore Plant *Tribulus terrestris*

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Tribulus terrestris has been used in the traditional medicine in China for treating cardiac diseases, oedema, and aphrodisiac for a long time. It contains diversity of compounds including flavonoids, alkaloids, saponins, and glycosides. Multiple reference showed that those compounds from *T. terrestris* exhibited antioxidant and antihypertensive activity which led us to investigate the potential bioactive compounds. Two alkaloids, (*R*)-*N*-trans-feruloyloctopamine (**1**) and tribulusamide C (**2**) were isolated from the fruits of *T. terrestris*. The structures of compounds **1** and **2** were elucidated using 1D and 2D NMR spectroscopic analysis.

Keywords: *Tribulus terrestris*, alkaloids, fruit

Identification and Biosynthetic Gene Cluster Analysis of Siderophores from *Vibrio harveyi* H100-10

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Vibrio spp., gram-negative pathogens, inhabit in marine and estuarine and cause a huge economic loss in aquaculture. The threat of *Vibrio*-related diseases (Vibriosis) has become a major issue in global aquaculture. However, the relationship between the metabolites and the pathogenesis of *Vibrio* spp. remains unknown. In the present study, we isolated five *Vibrio* strains from the seawater in Qi-jin coastal area (Kaohsiung, Taiwan). By using chelating ability Chrome Azurol S assay, we found the strain H100-10 showed the strongest iron-chelating ability. The average nucleotide identity and digital DNA-DNA hybridization analysis deduced from the whole genome sequence suggests the strain H100-10 is closed to *Vibrio harveyi* NBRC 15634. Interestingly, the biosynthetic gene clusters analysis using antiSMASH indicated the strain H100-10 and NBRC 15634 produces different siderophores. The isolation and structure elucidation of siderophores from the strain H100-10 is ongoing.

Keywords: *Vibrio*, siderophore, CAS assay, biosynthesis

Secondary Metabolites from the Bulb of *Tulipa edulis*

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Tulipa edulis (Liliaceae) is a perennial herb and the bulb of this species is used as the traditional Chinese medicine (TCM) for treatment of a variety of tumors, sore throat, and scrofula etc. However, anti-melanogenesis and antioxidant properties of this TCM have not been reported. In our preliminary study, the ethyl acetate-soluble fraction (TEE) showed significant anti-melanogenesis and anti-ROS activities, this study was conducted to investigate the secondary metabolites isolated from *T. edulis*. Currently, the chemical isolation and bioassay of *T. edulis* are still undergoing.

Keywords: *Tulipa edulis*, Liliaceae, Anti-melanogenesis, Antioxidant

Secondary Metabolites from the Seashore Plant *Ficus septica*

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Dengue virus is a deadly virus prevalent in the tropics. Previous study showed that the leaves of *Ficus septica* demonstrated that the activity of anti-dengue virus. In order to find the potential bioactive compounds, the methanolic extract of *F. septica* was investigated. In this present study, there are one diterpene, phytol (**1**), two sterols, *β*-sitosterol (**2**) and 7*α*-hydroxysitosterol (**3**), and three triterpenoids, uvaol (**4**), α-amyrin (**5**) and *β*-amyrin (**6**) were isolated from the leaves of *F. septica*.

Keywords: *Ficus septica;* sterol; triterpenoid; leaves

Mannoglucan from *Poria cocos* and Its Anti-cancer Related Activities

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Poria cocos (Polyporaceae), is a fungus used in traditional Chinese medicine. A study of the valuable sulfated polysaccharides (SPS) with the structure and pharmaceutical benefits from the mycelial culture conditions of *P. cocos* was attempted. The SPSs were fractionated by gel filtration chromatography, and a fucose-containing mannoglucan (denoted as PC-SPS-Fr.II) was isolated and identified. PC-SPS-Fr.II was identified by NMR techniques, and one possible repeat unit was proposed. The main skeleton was a 1,3-β-mannoglucan, 28 mers per repeat unit, with two interlaced 6-*O*-α-L-fucosyl 1,4-α-Glc and the two 1,4-α-Gal branches. The biological functional assay showed that PC-SPS-Fr.II slightly suppressed the cell viability but dramatically inhibited cell migration in the highly metastatic human lung cancer cell line CL1-5 cells. Mechanistically, PC-SPS-Fr.II dramatically downregulated the expression of TGFβRI and concomitantly inhibited phosphorylation of FAK and AKT. This is the first paper reporting a highly branched 1,3-β-mannoglucan from *P. cocos* and its anti-lung cancer CL1-5 cells migration activities.

Keywords: polysaccharides, *Poria cocos*, NMR, lung cancer, cell migration

The Effects of Light Quality on Tissue Culture Growth and Secondary Metabolites of *Glechoma hederacea* L. var. *grandis* (A. Gray) Kudo

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In pursuit of better health, pharmaceutical compounds from nature have regained attention. “Returning to nature” and “green consumption behavior” have become a way of vogue. Therefore, natural products become a better choice to promote health. Chinese herbal medicine has a long history in treating different illness. The quality of herbs is one of the important factors to ensure clinical effectiveness. *Glechoma hederacea* L. var. *grandis* (A. Gray) Kudo is an aromatic, perennial, evergreen creeper of the mint family Lamiaceae. The whole herb or stems and leaves of *G. hederacea* var. *grandis* have been used as medicine. Due to its effects of detoxification and swelling dilation, *G. hederacea* var. *grandis* is used to treat several diseases, such as rheumatoid arthritis (RA), common cold and cough, toothache, snake bite, and scabies. Therefore, *G. hederacea* var. *grandis* is one of important Chinese herbal medicine with potentials for further development.
G. hederacea var. *grandis* grows in low altitude region and is consumed as both food and medicine. Unfortunately, the environment to grow *G. hederacea* var. *grandis* is gradually shrinking. Varying levels of active ingredients in *G. hederacea* var. *grandis* is another major concern. Therefore, this study aims to investigate the effect of light quality on the level of phenylpropanoid in the tissue culture seedling of *G. hederacea* var. *grandis* .The results showed that the stem segment cultivate of *G. hederacea* var. *grandis* planted in the Murashige and Skoog medium (MS) which contained 2 mg/l of 6-benzylaminopurine (BA) and 0.2 mg/l of α-naphthaleneacetic acid (NAA), and under the white light plant growth lamp had induced 13±0.5 of the growth of adventitious buds. The growth of adventitious buds had increased to 29±1.2 when the tissue culture seedlings were under the yellow light (2700K), which effectively increased the bud proliferation rate. For phenylpropanoid, higher levels of caffeic acid (0.32±0.01mg/g) and chlorogenic acid (0.26±0.01mg/g) and ferulic acid (0.28±0.03mg/g) were detected when the tissue culture seedlings were grown under blue light (6B3IR) as compared to white light. The results presented here showed that blue light (6B3IR) stimulated the highest level of phenylpropanoid in tissue culture seedlings of *G. hederacea* var. *grandis*. This research, therefore, can enhance the effective usage of *G. hederacea* var. *grandis*.

Key Words：*Glechoma hederacea* L. var. *grandis* (A. Gray) Kudo、Light Quality、caffeic acid、ferulic acid、chlorogenic acid

MALDI Biotyper System Establishment and Application of Indigenous *Thraustochytrids* of Taiwan

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Thraustochytrids are a group of marine osmoheterotrophic, straminipilan protists that grow in the neritic and oceanic water, especially in mangrove region, and probably play an important role as saprobes. The high content of ω-3 polyunsaturated fatty acids (PUFA) makes *Thraustochytrids* as a candidate source for commercial docosahexaenoic acids (DHA) and eicosapentaenoic acid (EPA). To search indigenous *Thraustochytrids* with commercial value, we tried to collect the indigenous species of *Thraustochytrids* from mangrove regions of Taiwan and analyze their levels of PUFA (such as DHA and EPA) and carotenoids (such as astaxanthin). On the other hand, although some taxonomic characterizations, even morphology and molecular identification, of the *Thraustochytrids* have been established, the procedure of the species identification is still time- and cost-consumed. Based on the rapidity and efficacy of MALDI biotyper systems on the species identification of the pathogens in hospitals, we would try to establish the MALDI biotyper database of the *Thraustochytrid* strains by the modified MALDI method to facilitate the species identification of indigenous *Thraustochytrids* from mangrove regions of Taiwan. Besides, we also try to evaluate the effects of various *Thraustochytrids* with PUFA and/or carotenoids as the food supplementary for the shrimp aquaculture.

Keywords: *Thraustochytrids*, PUFA, carotenoids, MALDI biotyper, food supplementary for the shrimp

Morphological and Microscopic Identification of Three Turmeric Cultivars (TN1-3) in Nantou and Phytochemical Investigation of Their Constituents Using RP-HPLC-UV

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Turmeric (*Curcuma* species) is a member of the Zingiberaceae family that gained considerable attention in the medical field in the last few decades due to its profound medicinal values. In Ayurvedic practices in India, *C. longa* improves overall body energy, relieves gases, improves digestion, regulates menstruation, dissolves gallstones, and relieves arthritis. In Traditional Chinese Medicine (TCM), *C. longa* and three other plants from the genus *Curcuma*, namely, *C. phaeocaulis*, *C. kwangsiensis*, and *C. wenyujin*, were included in the latest version of the Chinese Pharmacopoeia (2010). These herbs remove blood stasis, improve vital energy, eliminate stagnated food, and relieve pain. In the last ten years, turmeric became a popular anti-cancer health food in Taiwan, China, Japan, Korea, Malaysia, and Singapore. It exerts chemopreventive, chemosensitization and radiosensitization effects. In our previous study, we performed an agriculture survey on turmeric cultivars in Nantou. We continued our work to identify morphologically and microscopically three different turmeric cultivars in Nantou, with the common names Spring Turmeric (TN1: *C. aromatica*), Purple Turmeric (TN2: *C. phaeocaulis*), and Autumn Turmeric (TN3: *C. longa*). The phytochemical constituents of these cultivars were identified using RP-HPLC-UV analysis.

Key words: turmeric, *Curcuma*, Nantou, identification, HPLC

Secondary Metabolites Isolated from the Root Bark of *Dictamnus dasycarpus*

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Dictamnus dasycarpus Turcz. (DD) classified in the family of Rutaceae is distributed throughout Europe and North Asia. The root bark of DD is widely used as traditional Chinese medicine for treatment of skin diseases such as eczema, pruritus and urticaria in China, Japan and Korea. However, the whitening effect of DD has not been reported. Therefore, this study was conducted to investigate the secondary metabolites isolated from DD on melanogenesis. The methanolic extract of DD (DDM) was partitioned into ethyl acetate (DDE), *n*-butanol (DDB), and aqueous (DDW) soluble fractions, respectively. In our preliminary research, DDE showed significantly anti-melanogenesis properties. Seven known compounds including obacunone, limonin, rutaevine, limonin diosphenol, fraxinellone, dictamnine and beta-sitosterol were isolated from DDE. The structures of all isolates were identified by nuclear magnetic resonance (NMR). Currently, the chemical isolation and bioassay of DD are still undergoing.

Keywords: *Dictamnus dasycarpus*, Rutaceae, Anti-melanogenesis

New 8-Hydroxybriaranes from the Gorgonian Coral *Junceella fragilis* (Ellisellidae)

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Three new 8-hydroxybriaranes—fragilides R–T (**1**–**3**), were obtained from a sea whip gorgonian coral *Junceella fragilis*. The structures of briaranes **1**–**3** were elucidated by using spectroscopic methods. Fragilides S and T (**2** and **3**) are the only briaranes known to possess 8α-hydroxy and 17β-methyl groups, respectively. Briarane **2** exerted an inhibition effect on iNOS release from RAW264.7, a macrophage cell line that originated from a mouse monocyte macrophage, stimulated with lipopolysaccharides.

Keywords: *Junceella fragilis*; fragilide; briarane; anti-inflammatory; iNOS

2-Acetoxybriaranes from *Briareum violaceum*

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Five 2-acetoxybriaranes, including two known analogues, excavatolides B (**1**), E (**2**), along with three new metabolites, briaviolides V–X (**3**–**5**), have been obtained from the octocoral *Briareum violaceum*. The absolute configurations of **1** and **2** were determined by X-ray analysis for the first time and the structures of **3**–**5** were established by spectroscopic methods. Bioactivity study showed that briarane **3** decreased the release of elastase from human neutrophils.

Keywords: *Briareum violaceum* , Briaviolide , Excavatolide , Elastase

Studies on the Terpenoids from the Octocorals *Paralemnalia thyrosides* and *Cladiella* sp.

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This study focused on the investigation of the chemical constituents of two octcorals identified as *Paralemnalia thyrsoides* and *Cladiella* sp., collected in the waters of Southern Taiwan. From the alcoholic extract of P. thyrsoides two nor-sesquiterpenes were isolated, including a new natural product, (+)-pathylactone (**1**), and a known compound napalilactone (**2**). The analysis of *Cladiella* sp. extract led to the isolation of 14 eunicellin-based diterpenoids, including four new compounds, cladieunicellins T (**3**), U (**4**), W (**6**), X (**7**); a new natural product, cladieunicellin V (5); along with nine known eunicellins, sclerophytins A (**8**), B (**9**), E (**10**), sclerophytin F methyl ether (**11**), cladiellisin (**12**), klysimplexin G (**13**), 6,14-diacetyloxy-10-hydroxy-6,10,14-trimethyl-3-propan-2-yl-15-oxatricyclo pentadecan acetate (**14**), palmonine F (**15**), and klymollin Y (**16**). The structures of 1─16 were established by spectroscopic methods and comparison of the spectroscopic data with those of known related compounds. In anti-inflammatory activity assay, and cytotoxicity, cladieunicellin W (**6**) showed significant inhibitory effects against the generation of superoxide anion and the release of elastase with IC_{50} values 7.18 and 7.83 μM, respectively. It also exhibited cytotoxicity against human leukemia Molt-4 and K562 cells with IC_{50} values 35.09 and 38.92 μM, respectively.

Keywords: *Paralemnalia thyrsoides*, *Cladiella*, eunicellin, anti-inflammatory, cytotoxicity, superoxide anion, elastase release.

Chemical Investigation on the Root Bark of *Bombax malabaricum*

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Bombax malabaricum DC syn. *Bombax ceiba* L. (Bombacaceae), known as cotton tree or silk cotton tree, is one of about 50 species of the *Bombax* genus in the world and distributed widely in tropical regions. Its flower, stem bark, and root are used as folklore medicine in the treatment of enteritis, rheumatism, analgesia, and hemostasis. Our preliminary study indicated the CH2Cl2 and BuOH soluble fractions of the EtOH extract of the root bark of *B. malabarica* to be active against *α*- glucosidase. Separation of these two fractions via various chromatographic methods led to the isolation of ten compounds were isolated from the root bark of *B. malabarica*. Two new compounds, bombamalin (**1**) and 3,4,5-trimethoxyphenol-1-[*β*-xylopyranosyl-(1→2)]-*β*- glucopyranoside (**3**), and shorealactone (**4**), a rare dehydroascorbic acid fused *l*-*ε*-viniferin. Compound **1** is an unusual bissesquiterpene, containing a 1,4-dioxene ring formed by fusing isohemigossypol with *ent*-cadinen-2-one. Their structures were elucidated by extensive spectroscopic analysis. This chemical reinvestigation is of value for chemotaxonomy of the *Bombax* genus, in particular the finding of the unusual **1** and rare **4**.

Keywords: *Bombax malabarica*; *α*-glucosidase; bissesquiterpene; shorealactone

Chemical Constituents and Bioactivities from the Roots of *Physalis peruviana*

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The genus of *Physalis* have been used for a long time in the ethnomedical folk traditions of Asian and American to treat different illnesses, such as malaria, hepatitis, dermatitis, and liver disorders. *P. peruviana* L. is an herbaceous, semi-shrub, upright perennial plant in subtropical zones and belongs to the family Solanaceae. Due to their diverse chemical structures and bioactivities, withanolides have been study extensively for their biological and pharmacological activities. Seven new withanolides (**1**–**7**) and one new androstane (**8**) together with twenty-four known compounds (**9**–**33**) were isolated from the ethanolic extract of *P. peruviana* roots. The structures of all isolated compounds were determined by the interpretation of spectroscopic methods, especially NMR analyses. In biological activities tests, the 75% MeOH layer of *P. peruviana* showed cytotoxic activity and moderate anti-inflammatory activity. This research not only provide surplus value of *P. peruviana* to farmers, but also benefit new drug development.

Keyword: *Physalis peruviana*; ergostane lactones; withanolides

The Metabolites from a Red Sea Sponge of *Spongia* sp.

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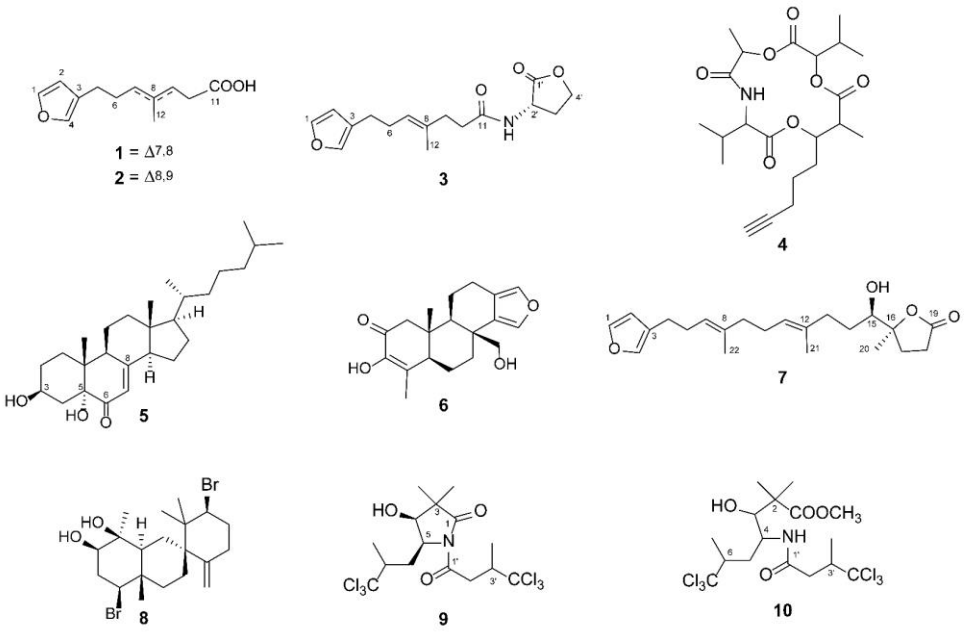
The dichloromethane-soluble fraction of the organic extract of a Red Sea sponge of *Spongia* sp. has been afforded four new compounds, including two isomeric isoprenoid-derived carboxylic acids (**1** and **2**), an isoprenoid-derived amide (**3**) and alkynyl-containing cyclic peptide (**4**), along with known metabolites: cholest-7-ene-3β,5α-diol-6-one (**5**), 18-nor-3,17-dihydroxyspongia-3,13(16),14-trien-2-one (**6**), irciformonin G (**7**), a brominated diterpene (**8**), and two polychlorinated pyrrolidinone derivatives (**9** and **10**). The structures of new compounds were elucidated on the basis of spectroscopic analyses including 2D NMR (COSY, HSQC, HMBC, and NOSEY) correlations. The stereochemistry of **4** and the biological activity of these compounds will be further studied.



Keywords: Red Sea sponge; isoprenoid-derived amide; alkynyl-containing cyclic peptide

Chemical Constituents and Bioactivities of *Cupressus macrocarpa*

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Cupressus macrocarpa Hartw., commonly known as Monterey cypress, belong to the family Cupressaceae, is evergreen tree. The plant is native to the California, and now distributes in Europe, Australia, and Africa. Cypress was reported to produce various natural products such as flavonoids, lignans, and terpenoids. The current study is to explore the chemical constituents of *C. macrocarpa* and evaluate the cytotoxicity and anti-inflammatory activity.

Three new labdane-type diterpenoid compounds (**1**−**3**), together with seven known compounds (**4**−**10**) were isolated from *C. macrocarpa*. All the structures were determined by analyzing their mass and NMR spectroscopic data. In regard to bioactivities, isolated compounds exhibited moderate to strong cytotoxicity inhibition against three cancer cell lines (HepG2, MDA-MB-231, and A549) with IC_{50} values between 0.0039 and 19.9 μM. In the anti-inflammatory assay, compounds **7** and **8** inhibited superoxide anion generation with IC_{50} = 2.7 ± 0.3 and 4.8 ± 0.2 μM, respectively. Compound **8** suppressed the formation of elastase release with IC_{50} = 6.6 ± 0.7 μM.

Keywords: *Cupressus macrocarpa*, cytotoxicity, anti-inflammatory

Study on Polysaccharides with Selectively Inhibitory Effect on Podoplanin-induced Platelet Aggregation from *Artemisia argyi*

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Tumor metastasis is a major treatment challenge in caner. "Tumor cell-induced platelet aggregation, TCIPA" is the interaction between platelets and tumor cells in the process of haematogenous metastasis, which will cause platelet activated and aggregated. It has been confirmed that TCIPA associated with tumor cell metastases. Accordingly, tumor cell metastasis would be reduced through inhibiting platelet aggregation and TCIPA. In recent, a glycoprotein podoplanin (PDPN), found on the cellular surface of various malignant tumor cells, could induce TCIPA through specifically binding to the C type lectin-like receptor 2 (CLEC-2) on the surface of platelet. Since anti-CLEC-2-therapy might be associated with little adverse effect, interruption of specific binding between CLEC-2 and PDPN has been considered as a potential molecular target to inhibit TCIPA and caner metastasis. In attempt to identify blocker between CLEC-2 and PDPN from traditional Chinese medicine (TCM), the water extracts of TCMs were prepared and evaluated on platelet aggregation induced by rPDPN, collagen, thrombin and U46619, respectively. The results showed the water extracts of *Artemisia argyi* selectively inhibited platelet aggregation caused by PDPN. Using the bioactivity-guided fractionation, an acid-insoluble part (CHE-3-WPUUAP) which is derived from a polysaccharide-rich fraction from *A. argyi* water extracts selectively and potently inhibited TCIPA and PDPN-induced platelet aggregation. It shows non- toxicity to either platelets or tumor cells, and can irreversibly inhibit the interaction between PDPN and CLEC-2. Additionally, current data of Western blot reveals that CHE-3-WPUUAP can inhibit the phosphorylation/activation of CLEC-2 signaling proteins such as Akt, p38, cPLA2, and PKCμ.

Keywords: TCIPA, PDPN, *Artemisia argyi*, polysaccharides

Simple Sesquiterpenoids with Good Anti-inflammatory Activity from *Fomitopsis pinicola*

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Bioassay-guided fractionation of the extract of *Fomitopsis pinicola* fruiting body led to isolate and characterize twelve novel and simple sesquiterpenoids, fomitopins A−L (**1**−**12**). The absolute configuration was determined via ECD simulation. The anti-inflammatory activities of the isolated compounds were examined, and among them, **11** exhibited the most effective inhibition of superoxide anion generation and elastase release with IC_{50} values of 0.8 ± 0.2 and 0.7 ± 0.1 μM. These newly purified sesquiterpenoids could be potential candidates for further developing to new anti-inflammatory agents.

Keywords: *Fomitopsis pinicola*, sesquiterpenoid, ECD simulation

Study on the Reproduction and Quality Specifications of *Hedyotis diffusa* Willd.

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Hedyotis diffusa Willd. (*Oldenlandia diffusa* (Willd) Roxb), also known as "Bai-Hua-She-She-Cao"(白花蛇舌草), is the traditional Chinese medicine (TCM) used for the treatment of inflammation-linked diseases, such as hepatitis, appendicitis and urethritis. And the recent pharmacology study showed that *H. diffusa* has the activity of anti-cancer. In addition, *H. diffusa* is usually confused with other plants of *Hedyotis* genus (*e.g. Hedyotis corymbosa, Hedyotis tenelliflora).* Thus, it is important to verify the origin of the herb. In this study, we collected the 10 samples of *H. diffusa* from Chinese medicine shop to determine the percentage of total ash, acid insoluble ash, dilute ethanol extractive, water extractive and loss of drying to make the quality control. Besides, the micropropagations of *H. diffusa* were treated with different concentration of Murashige and Skoog (MS) basal medium and induced the callus by different kinds of growth regulators in dark condition. Further, we examined the growth rate of callus on different medium by different growth regulators. Finally, the collected samples, cultured plant and calluses were applied to HPLC to determine the content of constituents.

Keywords: *Hedyotis diffusa*, quality control, micropropagation

Acylated Flavonoid Glycosides from the Twigs and Leaves of *Gleditsia rolfei* and Their Anti-influenza Activity

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Gleditsia rolfei Vidal., a plant classified in Fabaceae, have never been studied on its chemical constituents and bioactivities. Previous studies demonstrated that triterpenoid saponins isolated from plants of *Gleditsia* genus showed significant cytotoxicity against some cancer cell lines. In this work, crude extracts and partitioned fractions of the *G. rolfei*. were submitted to evaluate their bioactive potentials. Both anti-fatty liver disease (FLD) and anti-influenza activities were discovered in the methanol partitioned fraction. Investigations focused on the exact bioactive constituents were further carried out. Separation jobs were relying on the utilization of column chromatography and high performance liquid chromatography (HPLC). Structural identifications of all these compounds were elucidated by using nuclear magnetic resonance (NMR), mass, and optical rotation equipment. Stereochemistry of these isolates had been determined by comparing data of chemical shifts and coupling constants in the previous studies. Totally, 6 new acylated flavonoid glycosides, Rolfeoside A–F (**1**–**6**), a new monoterpenoid **7**, and 20 known compounds were isolated from *G. rolfei*. **1**–**6** have been submitted to neuraminidase (NA) inhibition assay, and compounds **1** and **5** exhibited NA inhibition activity. Bioactive confirmations of known compounds are still under evaluating.

Keywords: *Gleditsia*, Anti-influenza, Anti-virus, neuraminidase, NA inhibition assay, acylated flavonoid glycoside

Development of Natural Product-aspired Dual Inhibitors of HDAC6 and β-amyloid (Aβ) Aggregation

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Histone deacetylases (HDAC) that contain eighteen isoforms control the acetylation of histone to regulate the epigenetic process. Of these isoform enzymes, HDAC6 is associated with tubulin acetylation, which suggested it to be a drug target to treat neurodegenerative diseases. Additionally, β-amyloid (Aβ) aggregation is a leading cause for Alzheimer‘s disease. To explore the potential anti-Alzheimer’s disease agents, this study develops a series of compounds that had acridine moiety derived from natural products. The resulting compounds (**7a-i**) were identified as dual inhibitors of HDAC6 and β-amyloid (Aβ) aggregation. Most compounds were assayed for enzyme-inhibiting activity in a panel of HDAC isoforms. Furthermore, they were investigated the ability for inhibiting $A\beta 1_{-42}$ aggregation by using thioflavin T (ThT) fluorescence assay. Several compounds showed potent activity against these two target. These experimental results indicated that they have the potential for treating Alzheimer's disease.

Keywords: acridine, HDAC6, $A\beta_{1-42}$

Metabolomics Analysis of *Beauveria bassiana* Revealing the Role of Polyketide Synthase in Fungal Pathogenesis

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Entomopathogenic fungus *Beauveria bassiana* has been used as a biological control agent to manage pest insects. *B. bassiana* infects the insect host by penetration through the external cuticle. The hypha penetrates the insect and invades inside the hemolymph of insect. *B. bassiana* can produce numerous low molecular weight metabolites that play an important role in determining their virulence. Polyketide synthases are multi-domain or enzyme complexes that produce polyketide, which involves the formation of secondary metabolites. In the previous study, we found *pks14*, which only expresses *in vivo* (infected insect) rather than *in vitro* cultural condition, is important for fungal pathogenesis. Here we revealed the metabolic profiles of *pks14* gene overexpression strain and *pks14* gene disrupted strain. The fungal cells and culture filtrate of the two strains were extracted using different solvents follow by LC-MS/MS analysis. The MS data were further analyzed using XCMS and Global Natural Products Social Molecular Networking to explore the metabolic profiling difference between the overexpression strain and the disrupted strain. Our results demonstrated that the *pks14* gene expression would enhance the biosynthesis of fungal virulence factors.

Keywords: *Beauveria bassiana*, polyketide synthase, GNPS

Research on the Chemical Constituents and Bioactivities of *Epicoccum sorghinum* Isolated from *Arundo donax* L.

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In the current study, ethyl acetate extract from the liquid culture medium of an endophyte, *Epicoccum sorghinum* (Sacc.) Aveskamp, isolated from stem of *Arundo donax* L., exhibited anti-inflammatory and cytotoxic activities. In accordance to bioactivity-guided separation, one new compound, named epicorepoxydon A (**1**), along with six known benzyl-skeleton derivatives (**2**–**7**) and one known ethyl phenyl-skeleton derivative (**8**), were obtained. The structural elucidations of all the isolates were decoded by the spectroscopic data, i.e., NMR and MS spectra. The relative configuration of **1** was deduced by the NOESY spectrum. Moreover, the absolute configuration was determined by X-ray single crystal analysis. Furthermore, all isolates were evaluated with various biological assays, including cytotoxicity, anti-inflammatory, anti-platelet aggregation, and anti-angiogenesis activities. Compound **2** demonstrated cytotoxic activity against three human cancer cell lines e.g. MDA-MB-231, HepG2, and A549. Anti-angiogenesis and anti-platelet aggregation potential was also discovered. Compounds **4** and **6** possessed anti-inflammatory activity. Additionally, we proposed a biosynthesis pathway of polyketide secondary metabolites from this fungus. Investigations on the structure-activity relationship (SAR) of those key isolates were carried out as well.

Keywords: *Epicoccum sorghinum*, cytotoxicity, anti-platelet, anti-aggregation, anti-angiogenesis, biosynthesis pathway

Taimordisins A and B, Two Novel Triterpene Glycosides with an Unusual Skeleton from the Fruits of *Momordica charantia*

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The Cucurbitaceae plant *Momordica charantia* is widely cultivated as a vegetable crop in Taiwan, China, India, and Japan. The fruit of the title plant were used in Chinese folk medicine for treatment of liver-fire and diabetes mellitus. In the course of our search for potential anti-inflammatory and anti-diabetes agents, we have isolated two novel cucurbitane-type triterpene glycosides, taimordisins A (**1**) and B (**2**) from the fresh fruits of *M. charantia*. Compounds **1** and **2** possess an unprecedented C36 skeleton with a glycose moiety incorporated into a cucurbitane nucleus at C-24 forming unique di/tricyclic ring moieties. Their chemical structures were elucidated by spectroscopic analysis, including 2D NMR techniques. Compounds **1** and **2** were also evaluated for anti-inflammatory activities at NO productions by LPS-induced on RAW264.7 macrophage cell.

Keywords: *Momordica charantia*, Taimordisin, Cucurbitane glycoside, Anti-inflammatory activity.

Chemical Constituents Isolated from *Lycopodium serratum*

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Thirty-two compounds were isolated from the *Lycopodium serratum*, including seventeen serratene triterpenes, three diterpenes, eight chorophylls, three steroids and one tocopherol. Their structures were determined by 1D and 2D NMR spectral data, and were identified by comparison of their spectral data with those reported in the literature. Among these isolates, four new serratene triterpenes, lycoserratiol A, lycoserratiol B, lycoserratiol C and lycoserratiol D were reported for the first time from the natural sources. In addition, the structures one dimeric abietane-type diterpenoid was established on the basis of 2D-NMR spectroscopic analysis and X-ray diffraction. The bioactivity evaluation of the isolated compounds is in progress.

Keywords: *Lycopodium serratum*, Lycopodiaceae, serratene triterpene, diterpenoid, lycopobiterpene;

Bioassay-guided Isolation of Anti-tumor and Anti-NO Flavonoid Compounds from *Millettia pulchra*

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In Vietnamese folk medicine, *Millettia pulchra* has been used to treat the diseases relating to inflammation, fever and cancer etc. In our searching for potential anti-inflammatory and anti-cancer agents, we found that EtOAc layer of *M. pulchra* Radix showed the significant anti-inflammatory activity by anti-NO production (IC_{50} = 3.22±2.26 μg/mL). Basing on column chromatography with silica gel, six fractions were furnised; in which fraction 4 was proved to possess the most promising anti-NO efffects and was further purified by crystalized method to obtain the remarkable amount karanjin (**1**) (0.1%). Employing semi- preparative HPLC for the other fractions, nine compounds were isolated and identified as flavonoid or chalcone derivatives by spectroscopic analyses and compared with the referenced data. Of the isolates, lanceolatin B (**2**), pongamol (**3**) and 2’’,2’’-dimethyl [5”,6”:7,8] chromene (**4**) were demonstrated to have anti-NO activities, and would be availably yielded via our unique semi-preparative HPLC method. Furthermore, compound **4** also had the anti-tumor activity against human tumor cell lines (549, MCF-7 and WiDr). The above evicences revealed that *M. pulchra* Radix is the well source for isolating anti-inflammatory and anti-tumor flavonoid derivatives.

Keywords: *Millettia pulchra*, anti-tumor, anti NO, 2’’,2’’-dimethyl [5”,6”:7,8] chromene

Diterpenoids and Sequiterpenoids from a Formosan Soft Coral *Cespitularia* sp.

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Soft corals belonging to the genus *Cespitularia* have been found to be a rich source of secondary metabolites with biological activity, and many of these metabolites are terpenoid-type compounds. In this study, the EtOAc extract of a Formosan soft coral *C.* sp. was chemically investigated in order to discover bioactive substances, as it was known to exhibit strong inhibition on superoxide anion generation and elastase release in human neutron-philsstimulatedby *N*-formyl-methionyl-leucyl-phenylalanine/cytochalasin B (fMLF/CB). This study has led to the isolation of twenty compounds, including nine new cespitularane diterpenoids **1**–**9** and one new sequiterpenoid **10** along with ten known compounds **11**–**20**. These pure compounds will be screened for their pharmacological activities for the purpose of future medicinal application.

Keywords: *Cespitularia*, cespitularane diterpenoid, sequiterpenoid, superoxide anion generation, elastase release

Briaviodiols B–E, New Anti-inflammatory Hydroperoxyfurancembranoids from *Briareum violaceum*

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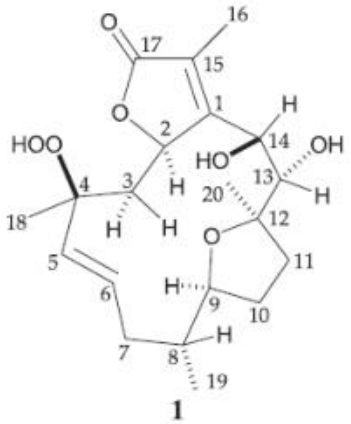
Four new hydroperoxyfurancembranoids, briaviodiols B–E (**1**–**4**), were obtained from an octocoral identified as *Briareum violaceum*. The structures of cembranoids **1**–**4** were established by using spectroscopic methods and comparing the spectroscopic data with those of known related analogues. Compounds **1**, **3**, and **4** were found to exhibit significant in vitro anti-inflammatory activity in LPS-induced RAW 264.7 macrophage cells by inhibiting the expression of iNOS protein.



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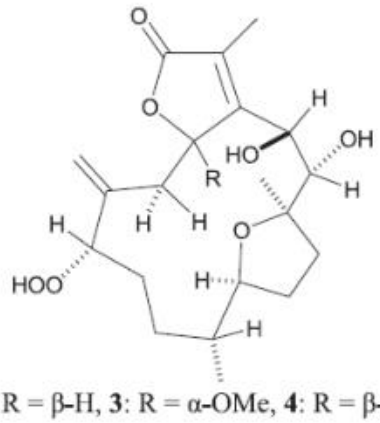

2: R = β-H, **3**: R = α-OMe, **4**: R = β-OMe

Keywords: hydroperoxyfurancembranoid, *Briareum violaceum*, anti-inflammatory, iNOS

Pterostilbene Down-regulates Hypoxia-inducible Factors in Hepatoma Cells Under Hypoxic Conditions

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Transarterial chemoembolization (TACE) is one of the main treatments for hepatocellular carcinoma (HCC) patient. Previous studies have been demonstrated that TACE induced the protein expression of hypoxia-inducible factor-1α (HIF-1α), vascular endothelial growth factor (VEGF), plasma membrane tissue proteins Caveolin-1, -3 (CAV-1, -3) and B-cell lymphoma-2 (BCL-2) and led to tumor proliferation, angiogenesis and metastasis. Pterostilbene (PTS), a stilbenoid compound, is widely distributed in foods and herbs, such as blueberry and Pterocarpus indicus. PTS has many pharmacological effects including antioxidant, anti-inflammation, anticancer and anti-diabetes. However, the molecular biological mechanisms of PTS on hypoxia-induced hepatoma cells have not been investigated yet. Aim of this study was investigated the anti-HCC mechanism of PTS under hypoxic conditions. The cell viability assay showed that HepG2 cells proliferated in the hypoxia, and 40 μM PTS caused cells death. The results showed that the expression of CAV-3, HIF-1α and BCL-2 proteins was induced and the MAPK signaling was activated including phospho-ERK (p-ERK) and phospho-p38 (p-p38) in HepG2 under hypoxia. Administration of PTS inhibited the expression of HIF-1α, pERK, p-p38 and BCL-2 to achieve anti-HCC cells activity. In addition, PTS reduced the expression of metastatic marker such as matrix metallopeptidase 9 (MMP9) and VEGF in HepG2. In summary, PTS has good anti-hepatocarcinoma activity in cancer cell proliferation, angiogenesis and metastasis under hypoxic conditions.

Keywords: transarterial chemoembolization (TACE), hypoxia, hypoxia-inducible factor-1α (HIF-1α), caveolin, proliferation

Antimicrobial Activities of the Endophytic Fungi Isolated from the Medicinal Plant *Atriplex maximowicziana* Makino at Kinmen

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A total of 550 fungal isolates were cultured from leaves of the medicinal plant *Atriplex maximowicziana* Makino collected in November (winter) 2017 at Kinmen County, Taiwan. Among these, culture extracts of 45 isolates were found to exhibit bioactivities against one of the following pathogenic microorganisms: the Gram-positive bacteria, *Staphylococcus aureus* and *Lactococcus garvieae*, the Gram-negative bacteria, *Escherichia coli* and *Edwardsiella tarda*, and the fungi, *Candida albicans* and *Cryptococcus neoformans*. These positive extracts were mostly active against the *S. aureus* and *C. neoformans. Fusarium* sp. KM1549 and *Alternaria* sp. KM1737 inhibited the growth of all 2 test bacteria. These results indicate that the endophytic fungi associated with *Atriplex maximowcziana* Makino can be a potential source of novel natural active substance.

Keywords: *Atriplex maximowicziana* Makino, endophytic fungi, anti-microbial activity

Chemical Constituents from a Littoral Plant-derived Fungus *Chaetomium globosum* Km1225

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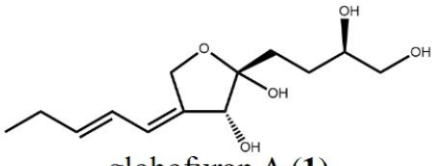
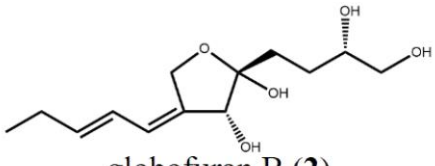
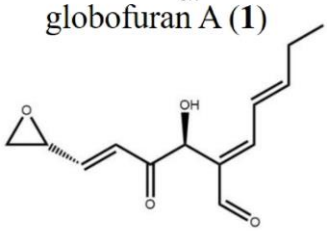
Littoral plant-derived fungi are able to produce lots of secondary metabolites with highly structural diversity. The discovery of new natural products from littoral plant-derived fungi has increased dramatically over the past few decades, and some of them revealed great potentials for drug developments. In our preliminary screening, the bioactivities of 1,249 fungal strains, isolated from littoral plant collected from Kinmen coast, were tested intensively. Of these, the ethyl acetate extract of the fermented broth of *Chaetomium globosum* Km1225, isolated from *Atriplex maximowicziana*, was found to exhibit significant antimicrobial activities against *Staphylococcus aureus*, *Candida albicans* and *Cryptococcus neoformans*. Therefore, bioassay-guided separation of the active principles from liquid- or solid-state fermented products of *C. globosum* Km1225 were carried out, and which has led to the isolation and purification of compounds **1**-**10**. Their structures were elucidated by spectroscopic analysis to be two new compounds, namely globofurans A and B (**1** and **2**), together with eight previously reported aureonitol (**3**), mollipilin A (**4**), chaetoglobosin A (**5**), chaetoglobosin C (**6**), chaetoglobosin D (**7**), chaetoglobosin F (**8**), chaetoglobosin E (**9**), and cytoglobosin C (**10**). Among these, mollipilin A (**4**) exhibited significant NO production inhibitory activity with an IC50 value of 0.7 ± 0.1 μM in microglial BV-2 cells, and chaetoglobosin A (**5**) showed potent cytotoxic activity against the same cells.



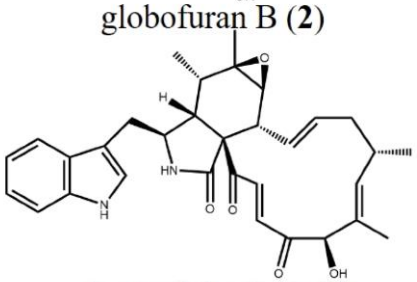
globofuran A (**1**)



globofuran B (**2**)



mollipilin A (**4**)



chaetoglobosin A (**5**)

Keywords: *Chaetomium globosum*; anti-inflammatory; cytotoxicity; globofuran

Bioactive Potential of Culturable Fungi Isolated from the Endemic Plant *Acanthus xiamenensis*

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The plant *Acanthus xiamenensis* is known for its traditional usage in Indian and Chinese system of medicine. In this study, a total of 168 fungal isolates were cultured from leaves and stems of the mangrove plant collected in January and July 2014 at Kinmen County, Taiwan. Spent culture extract of twenty-eight isolates were found to have bioactivities against one of the following pathogenic microorganisms: the bacteria *Bacillus subtilis*, *Staphylococcus aureus* (Gram-positive) and *Escherichia coli* (Gram-negative) and the fungi *Candida albicans* and *Cryptococcus neoformans*. These positive extracts were mostly active against the Gram-positive bacteria and *C. albicans*. *Corynespora cassiicola* NTOU4889 and *Xylaria* sp. NTOU4900 inhibited growth of all
3 test bacteria whereas *Phellinus noxius* NTOU4917 inhibited both test fungi. A further anti-inflammatory study of culture extracts of these 28 isolates revealed that extracts with a high iNOS inhibition caused a low viability of cells, and those with a low iNOS inhibition had a high cell viability. Three extracts showed low cytotoxicity (i.e. >100% cell viability) and high iNOS inhibition (<15% of NO production) of cells and they were *Phoma* sp. 2 NTOU4338, *Nodulisporium* sp. NTOU4868 and *Guignardia* sp. NTOU4871. These results indicate that the endophytic fungi associated with *Acanthus xiamenensis* can be a potential source of novel natural active substance.

Keywords: *Acanthus xiamenensis*; Endophytic fungi; Mangrove; Anti-microbial activity; iNOS inhibitory

Antcin A Induced Glucocorticoid Receptor-Mediated miR-708 Activation Regulates Breast Cancer Tumorigenesis and Metastasis via Downregulation of NF-κB Signaling Pathway

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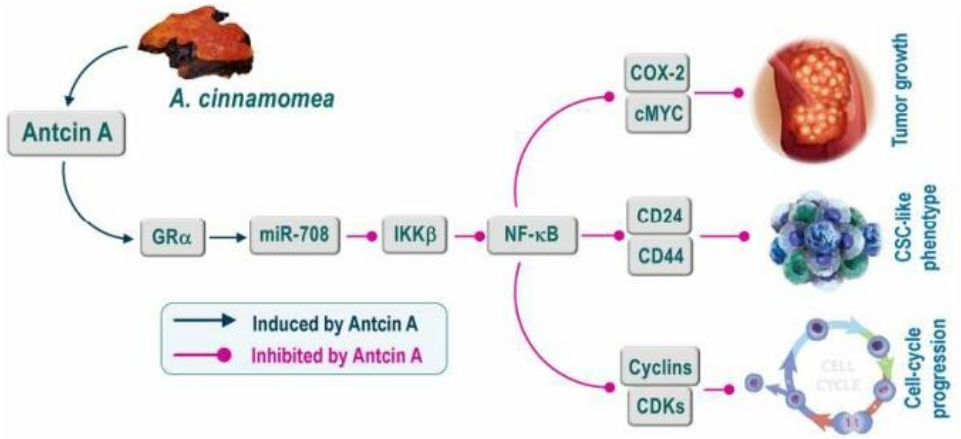
Antcin-A (ATA) is a steroid-like phytochemical isolated from the fruiting bodies of a precious edible mushroom *Antrodia cinnamomea*. We previously reported that ATA has strong anti- inflammatory effects on human lung epithelial cells via activation of glucocorticoid receptor (GR); however, other possible bioactivities of this unique compound remain unexplored. Since, glucocorticoids (GC) are frequently used as add-on chemotherapy for palliative purposes during breast cancer treatment. In this study, we found that treatment with antcin A (ATA), a natural glucocorticoid mimic significantly increased miR-708 expression by transactivation of GRα in MCF-7 and MDA-MB-231 human breast cancer cells (BCCs). Induction of miR-708 by ATA resulted in inhibition of cell proliferation, cell-cycle progression, cancer stem cell (CSC)-like phenotype and metastasis of BCCs. In addition, ATA treatment or miR-708 mimic transfection remarkably inhibited IKKβ expression and suppressed nuclear factor-kappaB (NF-κB) activity and its downstream target genes, including *COX-2*, *cMYC*, *cyclin D1*, Matrix metalloproteinase *(MMP)-2*, *MMP-9*, CD24, CD44 and increased $p21_{CIP1}$ and $p27_{KIP1}$ that are known to be involved in proliferation, cell-cycle progression, metastasis and CSC marker protein. BCCs xenograft models indicate that treatment with ATA significantly reduced tumor growth, weight and volume. Overall, our data strongly suggest that ATA induced miR-708 and downstream suppression of NF-κB signaling, which may be applicable as a novel therapeutic intervention in breast cancer treatment.

Keywords: Antcin A, *Antrodia cinnamomea*, glucocorticoid receptor, breast cancer, microRNA- 708



Pharmacological Effects of CDK4/6 Inhibitor on Neutrophilic Inflammation

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Neutrophils play an important role in the human immune system. However, excessive inflammatory reaction of neutrophils may threat human health. Recently a cyclin dependent kinase 4/6 inhibitor, CDK-0620, has been shown to reduce the formation of neutrophil extracellular traps. However, the pharmacological effects of CDK-0620 on neutrophilic inflammation are still unclear. In this study, we explore the detail effects and underlying mechanism of CDK-0620 in human neutrophils. Herein, CDK-0620 significantly inhibited superoxide anion generation, reactive oxygen species formation, and elastase release in activated human neutrophils. The adhesion of human neutrophils on endothelial cells was also reduced by the treatment of CDK-0620. Additionally, CDK-0620 suppressed the phosphorylation of AKT but not MAPKs and calcium mobilization. Interestingly, our further studies suggested that these anti-neutrophilic inflammatory effects of CDK-0620 were PI3K-dependent but CDK4/6-independent. Moreover, CDK-0620 showed inhibitory effect on PI3K activity and PIP_3 formation. In the *in vivo* study, CDK-0620 ameliorated psoriasis-like skin symptoms in imiquimod-treated mice. In summary, our data indicate that CDK-0620 targets PI3K and inhibits neutrophil activation. We suggest that CDK-0620 may have therapeutic potential for neutrophilic inflammatory diseases.

Keywords: anti-inflammation; CDK4/6; CDK inhibitor; neutrophil; PI3K/AKT; psoriasis

Kansuinine A Against Reactive Oxygen Species-Injury via IKK Pathway in Human Aortic Endothelial Cell

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Atherosclerosis is the main cause of cardiovascular disease and the apoptosis of human aortic endothelial cell (HAECs) causes the formation of early atherosclerosis. In the past studies, it has been found that Kansui has a good therapeutic prospect in anti-virus and anti-inflammatory. In this study, we proposed to exam the effects of Kansuinine A, a natural organic component of Kansui, on the H_2O_2-induced apoptosis of HAECs. In HAECs, our study indicated 0.1-1 μM Kansuinine A inhibited H_2O_2-induced apoptosis in a dose-dependent manner by MTT assay. Hoechst 33342 and Calcein-AM stain explored that elevated intracellular oxidative stress and apoptosis in HAECs. The results of immunoblotting showed that Kansuinine A reduced the protein levels of IKKβ, NFκB, and caspase-3 in HAECs induced by H_2O_2. Moreover, Kansuinine A also arrested the intracellular reactive oxygen specie (ROS) generation. In conclusion, Kansuinine A protects HAECs against H_2O_2-mediated apoptotic death cascade via IKK pathway.

Keywords: Atherosclerosis, Apoptosis, Human Aortic Endothelial Cells (HAECs), Kansuinine A, Reactive oxygen species (ROS)

Carnosic Acid Attenuates Acute Respiratory Distress Syndrome

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The mortality rate of acute respiratory distress syndrome (ARDS) patients is as high as 34.9%. Hence developing novel therapeutic strategies is a matter of great importance. Targeting neutrophilic inflammation is the latest strategy for the treatment of ARDS because pulmonary infiltration of neutrophils is a key feature of ARDS.
Carnosic acid (CA), a phenolic diterpene, is abundant in plants of the Lamiaceae family. In previous studies, CA exhibited antioxidant and antibacterial properties. In our current investigation, we found that CA significantly inhibited superoxide anion generation, elastase release, CD11b expression, and adhesion in human neutrophils. CA also decreased the formation of neutrophil extracellular traps (NETs). Further experiments confirmed that CA inhibited neutrophilic inflammation by inhibiting the MAPKs signaling pathway. Moreover, CA effectively scavenged reactive oxygen species (ROS) and competitively antagonized formyl peptide receptor 1. In ARDS animal model, CA improved lung tissue damage by significantly decreasing the infiltration and inflammatory response of neutrophils in the lungs. Together, these results demonstrate that CA exhibits anti-inflammatory potential via scavenging ROS and suppressing respiratory burst, degranulation, chemotaxis, and NET formation in human neutrophils.
According to our findings, CA could be used to treat or attenuate the symptoms of ARDS, and thus could be developed as a dietary supplement or serve as a lead natural compound for the adjuvant treatment of pulmonary inflammatory diseases.

Keywords: carnosic acid, neutrophil, ARDS, ROS, inflammation

Pharmacological studies of pyrazolo[4,3-*c*]quinoline compound in human neutrophils

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Neutrophilic inflammation plays a critical pathogenic role in acute lung injury (ALI). Overwhelming activation of neutrophils generates numerous harmful substances, including reactive oxygen species (ROS), proteases, and neutrophil extracellular traps (NETs), which cause damage to surrounding tissues. In this study, we identified a pyrazolo[4,3-*c*]quinoline compound, HTL-1866, that significantly inhibited human neutrophil inflammatory responses, including superoxide anion production, ROS generation, elastase release and adhesion. In contrast, HTL-1866 did not show cytotoxicity and inhibit NETs formation in human neutrophil. HTL-1866 did not have superoxide anion scavenging and elastase enzymatic inhibitory activity in cell-free assays. In addition, HTL-1866 did not affect calcium peak intensity but increased the time required for $[Ca^{2+}]i$ to return to half of its peak value in *N*-formyl-L-methionyl-L-leucyl-L-phenylalanine (fMLF)-activated human neutrophils. HTL-1866 inhibited fMLF-induced phosphorylation of Akt, p38, and JNK, but not ERK, in human neutrophils. Importantly, HTL-1866 attenuated the lipopolysaccharides- and hydrochloride-induced ALI in mice, including inhibiting neutrophil infiltration, alveolar destruction, alveolar space enlargement, and myeloperoxidase expression. Together, HTL-1866 exhibits therapeutic potential against neutrophilic inflammatory lung diseases and may serve as a lead compound for the development of novel anti-inflammatory drugs.

Keywords: pyrazolo[4,3-*c*]quinoline, neutrophils, inflammation, acute respiratory distress syndrome

Novel *Antrodia cinnamomea* Extract Reduced Cancer Stem-Like Phenotype Changes and Resensitized KRAS Mutant Colorectal Cancer via a microRNA-27a Pathway

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Colorectal cancer (CRC) is one of the most common causes of death in Taiwan. Previous studies have shown that *Antrodia cinnamomea* (AC) can treat poisoning, diarrhoea and various types of cancer. Therefore, we purified a novel ubiquinone derivative, AC009, and investigated its antitumour effects. A cell viability assay revealed that AC009 reduced the viability of several human CRC cell lines. AC009 treatment resulted in cell cycle arrest/apoptosis, and these effects may occur via caspase and Bcl-2 signalling pathways. We demonstrated that AC009 could significantly inhibit in vivo tumour growth in xenograft mouse models. Using mRNA and microRNA (miRNA) microarrays, we found that KRAS gene expression was also regulated by AC009, possibly through specific miRNAs. AC009 also reduced cancer stem cell marker CD44+/CD24+ expression and restored the tumour inhibition effect of cetuximab in KRAS mutant CRC. Moreover, we found that miRNA-27a could restore the tumour inhibition effect of cetuximab in KRAS mutant CRC cells. Taken together, our results suggest that AC009 has therapeutic potential against human wild-type and KRAS mutant CRC.

Keywords: colorectal cancer, *Antrodia cinnamomea*, KRAS, resensitization, miRNA-27a

Osthole Ameliorates Cartilage Degradation by Downregulation of NF-κB and HIF-2α pathways in an Osteoarthritis Murine Model

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Osteoarthritis (OA) is a common and disabling joint disease mainly characterized by cartilage degradation, with the knees most commonly affected. No effective treatment for the cartilage degradation of OA exists. Preliminary studies have revealed the protective and osteogenic effects of osthole, a natural coumarin first isolated from *Cnidium monnieri* (Fructus Cnidii); however, no evidence of osthole in an OA-related model has been published to date. This study further explored the effects of osthole in a monoiodoacetate (MIA)-induced OA-related animal model and focused on the molecular mechanism(s) behind the anti-inflammatory and cartilage protective effects of osthole. Our study revealed that the cartilage protective effect of osthole in a MIA-induced osteoarthritis (OA) murine model could be explained by downregulation of COX-2 and RUNX2 by inhibition of NF-κB and HIF-2α up-expressed by OA induction, resulting in downregulation of MMP-13, Syndecan IV and ADAMTS-5. In addition, osthole might have anti-inflammatory and analgesic effects due to COX-2 inhibition. We *conclude that* osthole can be considered as a potential component of the treatment of OA, for it possesses a cartilage protective effect, as well as inflammation, analgesic, and movement improving effects. Further preclinical and human clinical studies are needed to examine the efficacy and safety profile of long-term therapy.

Keywords: cartilage degradation; HIF-2α; inflammation; osteoarthritis, osthole, NF-κB

Phytogalactolipid dLGG Inhibits Melanoma Brain Metastasis Through Re-programming Macrophage Polarity in Tumor Microenvironment

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The current conventional cancer therapies for melanoma brain metastasis (MBM) remain ineffective. This study, an acclimated mouse brain-seeking melanoma cell line carrying luciferase reporter gene (B16BM4$^{COX\text{-}2/Luc}$) was used to establish MBM in syngeneic mouse model using intracarotid injection. The in vivo bioefficacy of a bioactive plant glycerol-glycolipid 1,2-di-*O*-α-linolenoyl-3-*O*-β-galactopyranosyl-sn-glycerol (dLGG) alone or in combination with liposomal doxorubicin (Lip-DOX) or anti-angiogenesis drug Avastin were investigated. On the basis of bioluminescence results, dLGG−25 (25 mg/kg, *p.o.*), dLGG−10 (10 mg/kg, *p.o.*)+Avastin−5 (5 mg/kg, *i.p.*) and Lipo-DOX−2 (2 mg/kg, *i.p.*)+Avastin−5 suppressed 59.1%, 55.7% and 72.4% respectively, MBM in mice, relative to tumor control. Immunohistochemistry data showed that infiltration of M2-like macrophages in the tumor microenvironment (TME) was significantly detected in the tumor control. dLGG treatment attenuated M2-like macrophages and increased M1-like resident microglia population, and promoted the cytotoxic T cells recruitment in the TME. Moreover, dLGG significantly inhibited the expression level of PD-L1 in TME. Serum oxylipins metabolome analysis revealed that 15-lipoxygenase derived HETEs were decreased by dLGG treatment. dLGG and 15-LOX inhibitor PD146176 suppressed B16BM4 cells invading into brain tissue evident by an ex vivo 3D-culture assay. In vitro assays showed that dLGG inhibited proliferation and colony formation, and induced apoptosis of B16BM4 cells in a dose- or and time-dependent manner. dLGG also inhibited VEGF-stimulated tube formation in primary HUVEC cells. This report provides a novel therapeutic strategy combating MBM by using dLGG alone or in combination with Lip-DOX or Avastatin through targeting M1/M2 polarization and inhibiting angiogenesis in mouse TME.

Keywords: Brain metastatic melanoma, galactolipid, oxylipin metabolome, macrophage polarization

Antifungal Mechanism Study of Unstable Conjugated Polyynes Targeting to Mevalonate Biosynthesis Pathway in *Candida albicans*

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Plant polyynes have been widely studied, such as ichthyothereol, but the conjugated polyynes were rarely found in microbial sources. Collimonins C and D, the microbial conjugated polyynes isolated from *Massilia* sp. YMA4, are extremely unstable in solid-phase because of the terminal alkyne. Previously, we found that Collimonins C and D exhibited a promising antifungal activity to Fluconazole-resistant *Candida* clinical isolates. In this study, we revealed the detailed antifungal mechanism of Collimonins C and D. The results showed that Collimonins C and D cause fungal cell membrane disruption and then induce fungal apoptosis and necrosis. Further investigation indicated that the overexpression of acetyl-CoA C-acetyltransferase (ERG10) in fungal cells would rescue the inhibition phenotype. Additionally, the bottom-up protein mass spectrometry together with docking analysis showed that Collimonins C and D would form a covalent bond between the terminal alkyne and the activated cysteine residues of ERG10 to block the enzyme activity irreversibly. Our results suggest that Collimonins C and D have the potential to develop as antifungal drugs with a novel target on the mevalonate biosynthesis pathway.

Keywords: antifungal, Collimonin, acetyl-CoA C-acetyltransferase, *Candida albicans*

Phytogalactolipid dLGG Suppresses Triple Negative Breast Cancer Relapse and Metastasis by Regulating Oxylipin-Mediated FABP Signaling Network

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Triple negative breast cancer (TNBC) is a highly aggressive and metastatic BC subtype lacking clinically targetable receptors. Untangling the multi-layered signaling networks in TNBC may offer new directions towards developing effective therapeutic tools for this disease. In our previous work, we showed that elevated expression levels of CYP450 epoxygenases and their AA-derived oxylipin products, epoxyeicosatrienoic acids (EETs), are unique signatures of metastatic TNBC tissues and cell lines. We have also demonstrated that adipocyte signaling-related fatty acid binding proteins (FABP4 and FABP5) are associated with EET-mediated metastasis in TNBC tumors. In this study, we investigated the potential of the plant-derived bioactive compound, dLGG (1,2-di-O-α-linolenoyl-3-O-β-galactopyranosyl-sn-glycerol), which have potent immunomodulatory and anti-metastatic activities, in targeting the FABP-EET axis in TNBC. Our in vitro data show that dLGG (40 μM) inhibited the migration and invasion potential of metastatic TNBC cells grown in mono- or co-cultured with stromal cells. We further investigated the efficacy of dLGG, alone (25 mg/kg daily, *o.p.*; dLGG25) or in combination (DOX5+dLGG25) with the chemotherapeutic drug, doxorubicin (5 mg/kg every 3 days, *i.p.*; DOX5) against TNBC primary tumor growth, local relapse, and lung metastasis, using a tumor-resection orthotopic xenograft model. The rate of primary tumor or relapsed growth for mice with mono or combinational treatments were significantly slower ($P < 0.05$), compared with the doxorubicin or tumor control groups. Animals treated with DOX5 lost a significant amount of weight, which were not seen in the dLGG25 or DOX5+dLGG25 treatment groups, suggesting that dLGG treatment reverses this side effect. Synergism was not observed for the anti-tumor effect in the combination treatment. At tumor resection time point, expression levels of Ki67, FABP4 and FABP5 were attenuated by dLGG. Oxylipin dynamics in the tumors and lungs of tumor-inoculated mice were also perturbed by dLGG-treatment, with the levels of all the EETs lower in the treated mice compared with the tumor control. Notably, dLGG-treatment prolonged mice survival (55 days) and combination treatment with dLGG (dLGG25+DOX5; 75 days) have longer life span than DOX monotherapy (52 days). Together, these findings demonstrate that dLGG attenuates TNBC aggressiveness by regulation of FABP-EET signaling axis, and may have potential for future drug development for metastatic TNBC patients.

Keywords: Triple negative breast cancer, tumor relapse, metastasis, fatty acid binding protein, phytogalactolipid, doxorubicin

Sesamol Protects Apolipoprotein C3-rich LDL-Induced Cell Damage and Cerebral Ischemia-Reperfusion Injury

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Cerebral ischemia is the situation when the blood vessel to the brain is blocked, reperfusion will be damaged by oxidant production and increased microvascular permeability. Endothelial cells (ECs) dysfunction trigger by oxidative stress has been identified as a major risk factor of the development of cell damage. However, the relationship between high oxidative stress-apolipoprotein C3-rich LDL (AC3RL) induces ECs damage and cerebral ischemia-reperfusion injury still remain unknown. The aim of this study is to investigate whether AC3RL-induced ECs damage by increasing intracellular oxidative stress and its underlying mechanism. In vitro studies showed that AC3RL increased intracellular oxidative stress and decreased cell viability of human arterial endothelial cells (HAECs) in dose-dependent. Hoechst 33342 and Calcein-AM stain explored that elevated intracellular oxidative stress caused apoptosis in HAECs. In vivo, C57BL/6 (B6) and Apo E gene knockout mice (APOE-/-) were fed with high fat diet (HFD) supplement with 50mg/kg of Sesamol via oral gavage for 14 days. TTC stains of brain tissue for mice after cerebral ischemia and the quantification of corresponding brain infarct volumes. The results of immunoblotting showed that AC3RL has a higher content in APOE-/- mice. However, pretreatment with Sesamol inhibitor AC3RL-induced cell viability in a dose-dependent manner and protect cerebral ischemia-reperfusion injury. In conclusion, Sesamol protect against cerebral ischemia-reperfusion injury by AC3RL-induced intracellular oxidative stress. This may be a study of the efficacy of Sesamol and the potential aspects of the disease.

Keywords: Apolipoprotein C3-rich LDL, Cerebral ischemia, Human Arterial Endothelial Cells, MCAO, Sesamol

Antrodia cinnamomea Extract Attenuates Methionine/Choline-deficient Diet Induced Steatohepatitis Through Suppressing NLRP3 Inflammasome Activation

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Blockade of NOD-like receptor protein 3 (NLRP3) inflammasome has been shown the promising effect in the progression of non-alcoholic steatohepatitis (NASH). *Antrodia cinnamomea* is a well-known indigenous medicine in Taiwan aboriginal tribes. However, its effect on NASH remains unclear. This study aims to examine the mechanistic insight of *Antrodia cinnamomea* mycelium extract (ACE) in vitro and in vivo models of NASH. The murine macrophage RAW264.7 and human hepatocellular carcinoma HepG2 cells were treated with the indicated concentration of ACE 30 min prior to stimulation with 0.1 μg/ml lipopolysaccharide (LPS) for 24h. Levels of NLRP3, ASC, IL-1β, and caspase-1 were analyzed by western blotting. In vivo model, male C57BL/6 mice weighting 21-25 g were fed with methionine/choline-deficient (MCD) diet along with vehicle or ACE (100 mg/kg) for 10 consecutive days. The plasma levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured. The liver tissues were analyzed for histology (hematoxylin and eosin stain), oxidative stress markers, and proteins levels involved in NLRP3 inflammasome, lipogenesis, autophagy, and inflammatory markers. We found that ACE significantly inhibited NLRP3 inflammasome activation in vitro and in vivo. In addition, ACE attenuated the severity of MCD-induced steatohepatitis and inhibited the activation of lipogenesis related proteins (sterol regulatory element binding protein-1; SREBP-1, CCAAT/enhancer binding protein; C/EBP, acetyl-CoA carboxylase; ACC, and fatty acid synthase; FAS), oxidative stress markers, inflammatory markers, and autophagy system. Based on these findings, *Antrodia cinnamomea* might be a potential candidate for development of anti-NAFLD/NASH agent.

Keywords: *Antrodia cinnamomea* mycelium, MCD diet, NAFLD/NASH, NLRP3 inflammasome

The Effect of Imperator Against Allergic Airway Inflammation in Mice

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Imperatorin is reported to express good expectorant and analgesic anti-inflammatory effects, but its effect on allergic airway inflammation has not been studied. In this study, we explored the protective effect of imperatorin against airway inflammation in asthmatic mice. Allergic asthma in mice was sensitized and challenged by *Dermatophagoides pteronyssinus* (*Der p*) and given three doses of imperatorin at 1 mg/kg, 5 mg/kg and 10 mg/kg for 4 weeks. The inflammatory cell count and classification in bronchoalveolar lavage fluid (BALF) was analyzed. The levels of IgE, IgG1 and IgG2a in serum and Th1 / Th2 cytokines and eotaxin in BALF were measured by enzyme-linked immunoassay (ELISA). The results showed that treatment with imperatorin significantly decreased the inflammatory cell numbers in BALF and production of IgE, IgG1 and IgG2a in serum while IgG2a was significantly increased. Imperatorin reduced the production of Th2 cytokines IL-4 and IL-5 in BALF and promoted the production of Th1 cytokine IFN-γ and IL-12. From the above results, it was found that imperatorin has a significant anti-inflammatory effect on allergic asthma induced by *Der p* in mice and is worthy of further research as a protective agent for allergic asthma.

Keywords: Imperatorin, Asthma, Airway Inflammation

Phytochemicals Activate the Gene Expression of Human GSTM2 and GSTM3 in Bladder Cancer Cells

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Bladder cancer is the ninth most common type of cancer worldwide. Although the mortality of bladder cancer is not high, however, the recurrence after treatment is very common in clinical. It's known that glutathione S-transferase Mu 1 (*GSTM1*)-null status is associated with a modestly increased risk of bladder cancer and this gene is found deleted in approximately 50% population. Since other members of *GSTM* family have great potential to compensate for the lack of antioxidant capacity caused by the deletion of *GSTM1* gene, therefore, the purpose of this study is to find out the phytochemicals which can up-regulate *GSTM* family, thereby increasing the antioxidant ability as well as reducing the risk of bladder cancer. In BFTC 905 bladder cancer cell, it was shown that some phytochemicals, including Wogonin, Chalcone and Baicalein, could up-regulate *GSTM2* promoter activity and protein expression, while Chalcone and Baicalein could enhance *GSTM3* promoter activity. In another cell 5637, we also found that Berberine and Resveratrol upregulated *GSTM*2 protein and mRNA expression. Furthermore, Resveratrol dose-dependently increased the protein level of *GSTM2* and *GSTM3* in 5637 cells, while the promoting effect of Berberine reached saturation when the dosage exceeds 10 μM. Taken together, based on current study, the *GSTM2* and *GSTM3* gene expression could be increased by Resveratrol and Berberine which may provide a rational for phytochemical chemo-prevention in urinary bladder cancer.

Keywords: bladder cancer, chemo-prevention, gene regulation, glutathione S-transferase Mu, phytochemicals

Antiviral Effects of Herbs from Ukraine against Influenza and Enterovirus

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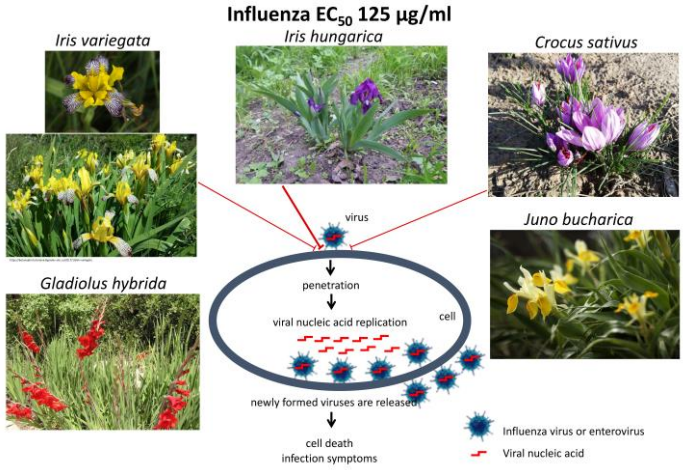
The antiviral activity of 15 plant extracts, 6 volatile oils and 4 pure compounds from Ukraine and Egypt was evaluated against influenza and enteroviruses. We focused on testing herbs from Iridaceae family such as irises (*Iris hungarica* and *I. variegata*), saffron (*Crocus sativa*), gladiolus (*Gladiolus hybrida*), or juno (*Juno bucharica*). Many of these plants are utilized in Chinese and European traditional medicine for the treatment of infections, cancer, and inflammatory diseases. In addition, some of the selected species were scarcely studied before. Among the tested samples, the ethanolic extract of saffron corms and the water extract of *Iris hungarica* rhizomes protected MDCK epithelial cells against influenza infection (EC_{50} 125 µg/ml). Additionally, the water extract of *Iris variegata* rhizomes and the ethanolic extract of *Iris hungarica* rhizomes exerted protective effects against enterovirus D68 infection. The most active herbal extracts of *Iris hungarica* rhizomes were analyzed by HPLC and the obtained fingerprint revealed the presence of iristectorigenin B, irigenin, nigricin, and its glycoside as the major components. The antiviral potency of these herbal natural products may be utilized in the development of drugs or healthy food products for the treatment of influenza and enteritis.



Keywords: Ukraine herbs, *Iris*, saffron, HPLC fingerprint, influenza, enterovirus

Mentha aquatica var. _citrata Lime Mint_ Essential Oil and its Major Components Inhibit _HRASQ61L_ Mutant Keratinocyte Activity and Prevent Chemically Induced Skin Carcinogenesis

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Clinically, 20%-30% of melanoma patients treated with BRAF inhibitor drug vemurafenib (PLX4032) developed cutaneous keratoacanthomas and squamous cell carcinomas as side effects. In the 7,12-dimethylbenz[*a*]anthracene (DMBA) and 12-*O*-tetradecanoylphorbol-13-acetate (TPA) induced two-stage skin carcinogenesis model, PLX4032 could accelerate growth of skin papillomas harboring *HRAS* mutation. That is considered as a representative animal model mimicking the PLX4032-induced cutaneous side effects in human patients. In this study, the effect of mint essential oil on cancer chemoprevention and PLX4032-induced cutaneous side effects were investigated. Essential oil from *M. aquatica* var. *citrata Lime Mint* (LM-EO) exhibited significant anti-proliferation effect against PDV cells, a DMBA transformed mouse keratinocyte bearing *HRASQ61L* mutation. The bioactivity of the combination of two major compounds presenting in LM-EO, *i.e.*, limonene and carvone (L+C) was also evaluated in parallel. LM-EO and L+C treatment suppressed colony formation, cell motility and induced G2/M cell-cycle arrest and apoptosis in PDV cells. We observed that PLX4032 was indeed facilitated papilloma production in the two-stage skin carcinogenesis animal model, and treatment with either LM-EO or L+C attenuated the papilloma formation in the DMBA+TPA and DMBA+TPA+PLX4032 irritated animals. Histopathological data showed that paradoxical activation of MAPK protein, abnormal proliferation of keratinocytes and inflammatory immune cells that were alleviated after LM-EO and L+C topical application. This study demonstrates that LM-EO and L+C have great potential to prevent PLX4032-induced cutaneous side effects in cancer patients.

Keywords: mint essential oil, squamous cell carcinoma, BRAF inhibitor, two-stage skin carcinogenesis, chemoprevention

Taiwanese Plant-derived Constituents Induced Osteogenic Differentiation in Primary Human Osteoblasts

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Osteoporosis is a bone metabolic disorder, which leads to bone loss leaving bone susceptible to fractures. Osteoblasts play a major role in bone remodeling, such as secretion of collagen, alkaline phosphatase (ALP), bone sialoprotein, and osteopontin, aggregation of bone matrix, and bone formation. WTA extract sourced from the dried leaves of the Taiwanese plant. There are few studies demonstrating compound isolation and activity of WTA. Therefore, the aim of the present study was to investigate the osteogenic properties of WTA extract and its active constituents in primary human osteoblasts (HObs). Results showed that bio-guided fractions WTA 1-2 to 1-5 which were found to be non-toxic by cell viability assay significantly promoted ALP activity in HObs. Hence, active fractions were further isolation, purification and identification to obtain five compounds, **1**–**5**. Two flavonoid compounds, **1** and **2**, explored significantly ALP activity and mineralization in a dose-dependent manner. WTA extract and its isolated active compounds have the potential for further investigation as a candidate drug to treat osteoporosis.

Keywords: osteoporosis, Taiwanese plant, osteogenic, primary human osteoblasts, flavonoid

Sesquiterpene Lactone Deoxyelephantopin (DET) Isolated from *Elephantopus Scaber* and Its Derivative DETD-35 Suppress Melanoma Lung Metastasis in Mice

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Melanoma is the most aggressive skin cancer with increasing incidence worldwide. It is treatment refractory and highly metastatic. Metastatic melanoma patients have a poor prognosis with the median survival of less than a year. New preventive or therapeutic modalities for metastatic melanoma are therefore urgently needed. Our lab previously demonstrated that a sesquiterpene lactone deoxyelephantopin (DET) isolated from Chinese medicinal plant *Elephantopus scaber* and its novel derivative DETD-35 reduced human orthotropic A375 BRAFV600E mutant melanoma growth in xenograft mice. In this study we aimed to explore the anti-metastatic activity of DET and DETD-35 against in- house established lung metastatic human melanoma (A375LM5) *in vitro* and *in vivo*. Our data show that DET and DETD-35 treatment inhibited A375LM5 melanoma cells proliferation and induced G2/M phase arrest and apoptosis in a dose-dependent manner. Furthermore, DET and DETD-35 treatment significantly inhibited migration, invasion and colony formation and modulated the EMT markers expression in A375LM5 cells. Most importantly, DET and DETD-35 significantly inhibited lung metastasis in the A375LM5 lung metastasis melanoma model including the number of melanoma foci in the lung and lung/body organ index. In vivo DET and DETD-35 anti-metastatic effect in the mouse lung was observed concomitantly with reduction of the expression of melanoma marker Mel-A, proliferation marker Ki67, metastatic marker N-cadherin, angiogenesis marker VEGF and increased expression of apoptosis-related marker cleaved caspase-3. Interestingly, we observed marked reduction of macrophages and neutrophils infiltration into lung metastatic tissues of DET and DETD-35 treated animals, which implies a potential tumor microenvironment modulation by both compounds. In depth mechanistic studies are in progress. Taken together, this results indicate that phyto-sesquiterpene lactones DET and DETD-35 may be useful in the intervention of lung metastasis of BRAFV600E mutant melanoma.

Keywords: Melanoma, $BRAF_{V600E}$ inhibitor, deoxyelephantopin, DETD-35, lung metastasis

Amelioration of the GDAP1L1-dependent Mitochondrial Dynamics by 2,4-Dimethoxy-6-methylbenzene-1,3-diol (DMD) Unveils a Novel Therapy for Imiquimod-induced Psoriasis- like Skin Inflammation

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Macrophages have long been thought to play an important role in the innate immune system, which is stimulated to produce many inflammatory cytokines that affect acute, chronic inflammatory and autoimmune diseases, such as psoriasis and atopic dermatitis. *Antrodia camphorata* is a precious Chinese herbal medicine in Taiwan, and is used for food supplement, detoxification, hypertension and cancer. Studies recently have shown that *Antrodia camphorata* extract has better anti-inflammatory, antioxidant and immunomodulatory properties. We investigated whether the extract of *Antrodia camphorata* can inhibit the major producers of IL-23/IL-17 axis, and have a therapeutic effect on the imiquimod (IMQ)-induced animal model. In a mouse model of psoriasis-like skin inflammation, application of *Antrodia camphorata* extract and its component 2,4-dimethoxy-6-methylbenzene-1,3-diol (DMD) improved acanthosis, thickening of the epidermis; hyperkeratosis, parakeratosis, microabscesses, neutrophil aggregates in the stratum corneum and expression of inflammatory factors. In tissue immunostaining was observed to inhibit the infiltration of immune cells, particularly macrophages. Microarray chip analysis further found that DMD suppressed the expression of inflammatory factors, including: IL-23, IL-6, TNF, IL-24, CCR7 and GDPA1L1 in the THP-1 cell line model. Here we showed that GDAP1L1 has a pivotal function in Toll-like receptor-regulated mitochondrial morphology switching from fusion to fission through a translocation of GDAP1L1 and DRP1 to mitochondria, which promoted inflammatory factors production. Taken together, DMD suppressed the proinflammatory response of activated macrophages via inhibition of GDAP1L1/Drp1-dependent mitochondrial fission.

Keywords: *Antrodia camphorata*, psoriasis, macrophages, IL-23/IL-17 axis, GDAP1L1, mitochondria.

Blood-brain Barrier Penetrant and Orally Bioavailable Antidotes to Organophosphate Poisoning

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We have developed a series of antidotes to organophosphate (OP) poisoning, hydroxyiminoacetamido alkylamines, that ionize as cations, anions, zwitterions and form appreciable neutral species at physiologic pH values. As such they cross the blood-brain barrier (BBB) and are orally bioavailable. We examine here the blood and tissue dispositions of a lead agent, RS 194B, in the absence of organophosphate to ascertain pharmacokinetic profiles and achieve optimal loading and maintenance dosing of this family of antidotes. Our data show comparable absorption and tissue distribution after tail vein and retro-orbital injection with only a slight delay when the antidote is administered intramuscularly. Hence, systemic distribution can be rapidly achieved to reverse acute toxicity. Initial studies of tissue disposition show both rapid transfer into the brain, along with rapid clearance from tissues and blood through likely transport mechanisms. To prolong the half-life of antidotes in brain, we demonstrated that P-glycoprotein inhibitor can prolong the half-life of RS194B, which can further increase its' availability during OP poisoning treatment. The antidote also appears to be effective in mice and macaques in reversing organophosphate toxicity from accumulating sarin and paraoxon. Such studies enable one to consider effective antidote treatment schemes for longer acting pesticides and acute exposure to the volatile sarin and related nerve agents through respiratory and dermal absorption.

Keywords: pharmacokinetics, zwitterionic oximes, organophosphate poisoning, blood-brain barrier, p-glycoprotein

Physicochemical Properties of Isoflavone Nanofibers and its Antioxidant Activity in PM-Induced HaCaT Keratinocytes Injury

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In recent years, many studies have been demonstrated that soy isoflavones derivative (8THI) possesses a lot of biological activities, including antioxidant, anti-inflammatory, and tyrosinase-inhibiting activities. However, the poor solubility of 8THI decreased the poor skin absorption and limited its application in medicine and cosmetic. The aim of the present study was investigated the improvement mechanism of water solubility and skin penetration of 8THI and its nanofiber (8THIN) using electrospinning process. For analysis of physicochemical properties, the surface morphology of 8THI and 8THIN was observed by scanning electron microscopy (SEM) and the particle size of their suspension was determined by particle size analyzer. The yield and solubility of various 8THIN formulations were analyzed by HPLC. Crystalline structure was analyzed by X-ray diffractometry. In addition, the present study also used the particulate matter (PM)-induced HaCaT keratinocytes oxidative stress model for confirming the antioxidant activity of 8THIN. The results of the present study revealed that 8THIN can effectively increase the water solubility of 8THI by particle size reduction and surface area increase, crystalline transform to amorphous of 8THI. Moreover, 8THIN can also decrease PM-induced ROS content in HaCaT keratinocytes. Therefore, the molecular biological mechanism of 8THIN in PM-induced oxidative stress will be investigating in the further study. We also expect that 8THIN can also use as an cosmetic ingredient in antipollution skin care product in the future.

Keywords: soy isoflavones derivative (8THI), electrospinning, nanofiber, particulate matter, cosmetic

Physicochemical Properties and Antioxidant Activity of Chrysin Nanoparticles

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Chrysin (5,7-dihydroxy-2-phenyl-4*H*-chromen-4-one, Chr), a natural flavone, has many pharmacological activities such as antioxidant, anti-inflammation, anti-hypertension and antidiabetic actions. Unfortunately, the poor water solubility and skin penetration of chrysin caused the bad cutaneous bioavailability, resulting in limitation of clinical applications. The aim of the present study was investigated the improvement of water solubility and skin penetration of chrysin nanoparticles (ChrN). The physicochemical properties were characterized for elucidating the mechanism of solubility improvement, including determinations of water solubility, drug loading and encapsulation efficiency, particle size, crystalline change, drug-excipient interaction and in vitro skin penetration. In the results of this study, we prepared nine batches, ChrN1 to ChrN9 and our results revealed that ChrN1 displayed best drug loading among the different batches and which also present best improvement of water solubility of chrysin. In conclusion, we suggested that ChrN1 has potential to use as a pharmaceutical and cosmetic ingredient in the medicine and cosmetic industries.

Keywords: chrysin, water solubility, skin penetration, nanoparticles

Photoprotective activity of *Artocarpus communis* methanol extract inclusion complex

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1. Background/ Objectives and Goals

As is known, many antioxidants from plant extracts have been used as additives in skincare products to prevent skin damage from environmental pollutants. In the past decades, *Artocarpus communis*, possesses various bioactivities, including anticancer, antioxidation, skin whitening and photoprotective. Nonetheless, the poor aqueous solubility of raw *A. communis* methanol extract (ACM) was limited its application in medicine, food and cosmetic.

2. Methods

For the past few years, cyclodextrin inclusion complex is one of the drug delivery system commonly used to overcome the water solubility of raw materials. The present study used 2-hydroxypropyl-beta-cyclodextrin (HPBCD) and polyvinylpyrrolidone (PVP) as carriers to inclusion the ACM (AHP) for improving the aqueous solubility of ACM. Furthermore, we use scanning electron microscope (SEM) to observed the surface morphology, powder X-ray diffraction to indicate the crystallinity and HPLC to analysis the improvement of water solubility. In addition, the present study also used the UV-induced HaCaT keratinocytes damage model for confirming the photoprotective activity of AHP.

3. Expected Results/ Conclusion/ Contribution

The results indicated that AHP present better antioxidative and skin penetration ability due to improving the aqueous solubility of raw ACM. Therefore, we suggested that AHP can be used as a cosmeceutical additive in cosmetic product.

Keywords: *Artocarpus communis* methanol extract, cyclodextrins, inclusion complex, solubility, polyvinylpyrrolidone, cosmeceutical

Anti-Inflammatory Effect of *Lophatherum gracile* in Human Neutrophils is Mediated Through JNK and Calcium Inhibition

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Activated neutrophils play a crucial pathogenic role in inflammatory diseases. Therefore, the development of drugs for inhibiting neutrophils activation may possess interesting therapeutic potential. *Lophatherum gracile* has been long used as a single formula in traditional Chinese medicine. It is used clinically to clear heat, disinhibit dampness and to treat inflammation. *L. gracile* exhibited several pharmacological effects such as anti-inflammatory, anti-viral, and anti-oxidative activities. However, the effect of *L. gracile* on the activation of human neutrophils remains unclear. In the current study, we investigated the anti-inflammatory properties of *L. gracile* ethanolic extract (LGEE) in *N*-formyl-methionyl-leucyl-phenylalanine (fMLF)-induced activation of human neutrophils. The results indicated that LGEE significantly inhibited fMLF-induced superoxide anion generation, elastase release, CD11b expression, cell adhesion, and cell migration in human neutrophils. Additionally, LGEE inhibited calcium mobilization and the phosphorylation of JNK, but not p38 MAPK, ERK, and Akt, in fMLF-activated human neutrophils. Our results suggested that LGEE holds the potential to be developed as an anti-inflammatory herbal medicine.

Keywords: *Lophatherum gracile*, superoxide, elastase, CD11b, JNK, calcium

Crotonoside Inhibits Dendritic Cell Maturation and Has Therapeutic Effects in Collagen-Induced Arthritis in Mice

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Dendritic cells are antigen-presenting cells (APCs) as a bridge between innate immunity and adaptive immunity. Therefore, dendritic cells are considered to be a significant regulatory target in the development of immunomodulatory. This study is mainly to investigate the effect of crotonoside on the lipopolysaccharide (LPS) induced maturation of murine bone marrow-derived dendritic cells (BMDCs) and treatment collagen-induced arthritis mice. This result discovered that crotonoside inhibits LPS-induce cytokines secreted by BMDCs, TNF-α, IL-6, IL-12 p40, and the release of nitric oxide and reactive oxygen species. At the same time, crotonosdie was also reduction the co-stimulatory molecules CD80 and CD86. Further confirming its molecular mechanism, crotonoside can inhibit the activation of MAPKs-p38 and ERK induced by LPS-stimulated BMDCs and inhibit NF-κB pathway into the nucleus. Also, investigate its molecular mechanism, crotonoside can inhibit the activation of MAPKs induced by LPS-stimulated BMDCs and inhibit NF-κB pathway into the nucleus. We found that crotonoside can slow the joint swelling of type 2 collagen-induced arthritis mice, reduce the proportion of Th1 cells, and increase the level of regulatory T cells in lymph node cells. In summary, this result was the first time found that crotonoside can regulate dendritic cell maturation and has the efficacy in the arthritic mouse model, suggesting that crotonoside has the potential therapeutic for the treatment of human rheumatoid arthritis.

Keywords: Crotonoside, Dendritic cell, Maturation,Collagen-induced arthritis

A Novel PDE4 Inhibitor Impedes Psoriasis-like Lesions Via Restricting Neutrophilic Inflammation

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Psoriasis is a long-lasting and non-radical curing inflammatory skin disease. Inflammatory infiltration of neutrophils is a major pathogenic immune response in psoriasis; therefore, restriction of neutrophilic inflammation is a profitable strategy for alleviating psoriasis. Phosphodiesterase (PDE)4, an intracellular enzyme, critically modulates inflammatory responses of neutrophils via elevating the levels of cyclic adenosine monophosphate (cAMP). Here, we identified a clinical-used anti-cancer drug as a novel PDE4 inhibitor (PDE4i) to attenuate psoriasis-like lesions via mitigating neutrophilic inflammation. PDE4i significantly inhibited various inflammatory responses in activated human neutrophils, including superoxide anion and reactive oxidants generation, CD11b expression and neutrophil adhesion, and extracellular signal-regulated kinase (ERK) and c-JUN N-terminal kinase (JNK) phosphorylation. Noticeably, PDE4i increased the levels of cAMP and protein kinase A (PKA) activity in activated human neutrophils. PDE4i selectively blocked the enzymatic activity of cAMP-specific PDE4 but not PDE3 and PDE7 in vitro. The PDE4i-inhibited inflammatory responses were also reversed by PKA inhibitors in activated human neutrophils, suggesting that PDE4i acts as a PDE4 inhibitor to attenuate neutrophilic inflammation via cAMP/PKA signaling. In the mouse model, topical application of imiquimod (IMQ) induced psoriasis-like symptoms, including epidermal hyperplasia, desquamation, and neutrophil infiltration. PDE4i apparently impedes psoriasis-like lesions and the transepidermal water loss was ameliorated from 28.6 to 14.3 g/m2/h. Together, PDE4i serves as a selective PDE4 inhibitor and exhibits potent anti-inflammatory activity in human neutrophils and psoriasis-like lesions. Our findings provide a therapeutic potential of targeting neutrophilic inflammation for curing psoriasis. PDE4i may have an alternative clinical application as novel adjunct therapy to treat inflammatory skin diseases.

Keywords: inflammatory skin disease; psoriasis; phosphodiesterase 4 inhibitor; neutrophilic inflammation

Phomaketide A Inhibits Lymphangiogenesis in Human Lymphatic Endothelial Cells

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Phoma sp. NTOU4195 was isolated from the edible red alga *Pterocladiella capillacea* sampled in the intertidal zone of northern Taiwan. Phomaketide A was isolated and identified from endophytic fungal strain *Phoma* sp. NTOU4195. Phomaketide A has been reported to exhibit anti-angiogenic and anti-inflammatory effects. However, the effect of phomaketide A on lymphangiogenesis has not yet been clarified. Here, we indicated that phomaketide A exerted the promising anti-lymphangiogenic activity in human lymphatic endothelial cells (LECs). Our data showed that phomaketide A inhibited LECs migration and tube formation in a concentration-dependent manner. Mechanistic investigations discovered that phomaketide A may suppress the phosphorylation and expression of VEGFR-3, and its downstream signals PKCδ, mTOR as well as eNOS. Moreover, phomaketide A impeded tumor growth and lymphangiogenesis by decreasing the expression of LYVE-1, the specific marker of lymphatic vessels, in A549 xenograft animal model. Collectively, we document for the first time that phomaketide A inhibits lymphangiogenesis both *in vitro* and *in vivo*. Phomaketide A may serve as a potential lymphangiogenesis inhibitor for treatment of cancer metastasis.

Keywords: phomaketide A, lymphangiogenesis, lymphatic endothelial cells, vascular endothelial growth factor receptor-3

Garcimultiflorone K Inhibits Angiogenesis *In vitro* and *In vivo*

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Based on bioassay-guided fractionation, we isolated garcimultiflorone K (GMK) from the stem of *Garcinia multiflora*. We found GMK exhibits the promising anti-angiogenic activity in human endothelial progenitor cells (EPCs). GMK inhibited EPCs migration and tube formation in a concentration-dependent manner. Moreover, GMK suppressed *in vivo* angiogenesis in zebrafish embryo assays. Mechanistic investigations revealed that garcimultiflorone K suppressed EPCs angiogenesis through Akt, mTOR, p70S6K, and eNOS signaling cascades. This study is the first to indicate that garcimultiflorone K exhibits the anti-angiogenic effect both *in vitro* and *in vivo*. Our findings provide evidence that GMK is the potential natural product worthy of further development for the treatment of angiogenesis-related pathologies

Keywords: angiogenesis, human endothelial progenitor cells, garcimultiflorone K

Growth Inhibition Effect of Meliaceae Ethanolic Extract Against Breast Cancer Cells

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The antibreast cancer effect of Meliaceae ethanolic extract (MCT) is rarely reported. The subject of this study is to evaluate the regulating effect for growth inhibition of MCT against breast cancer cells. MCT inhibits cell growth of breast cancer (MCF7 and MDA-MB-231) cells but shows little effect on breast normal (M10) cells using MTS assay. Cell cycle analysis shows that MCT induces polyploidy for breast cancer MCF7 cells. Detailed mechanisms were explored by annexin V/7AAD analysis showing necrosis is inducible by MCT. Furthermore, MCT induces reactive oxygen species (ROS) generation, mitochondrial superoxide (MitoSOX) production, mitochondrial membrane potential (MitoMP) deplorization. Therefore, MCT is a potential antibreast cancer agent with growth inhibition and oxidative stress effects.

Keywords: Meliaceae, antibreast cancer, growth inhibition, oxidative stress

Study of the Impact on Steroid Induced Insulin Resistant Rat by Electroacupucture Combined with *Antrodia cinnamomea*

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Objective: This study will investigate the electroacupuncture (EA) combined with *Antrodia cinnamomea* (AC) in two different types of rats: Normal Wistar Rat and steroid-induced insulin-resistant (SIIR) rat by observing and comparing the hypoglycemic effects, in order to became a new therapeutic method for improving plasma blood glucose levels.
Methods: The animal model including normal Wistar rats and SIIR rats induced by that the Wistar rats were given daily intraperitoneal injection of Dexamethasone 1 mg/kg for 5 days. The experimental parameters include plasma biochemical values by feeding the *Antrodia cinnamomea* mycelium powder and combining with EA intervention. The randomized and control experiment will be applied to this study. The animals will be randomized divided into control, electroacupuncture (EA), *Antrodia cinnamomea* (AC), EA combined with *Antrodia cinnamomea* (AC+EA) and TZD (Rosiglitazone) groups.
R**esults and Conclusions:** It has been experimentally confirmed that steroid-induced insulin resistance (SIIR) rats after treatment EA and AC combined therapy can significantly reduce plasma glucose concentration, also it is better than the EA group and the AC group, the single therapy. the relevant mechanisms of hypoglycemic effect will be further explored in the future, expected to become a new medical therapy of acupuncture combined with medicine to treat diabetes mellitus.

Keywords: Electroacupuncture (EA), *Antrodia cinnamomea* (AC), Hyperglycemia, Steroid, Insulin Resistance

Comparison of the Analgesic Effects of *Trametes versicolor* on Different Doses of Formalin Test

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Object: Pain has always been the goal of clinical treatment. Western medicine is often used to relieve pain in the clinic. It has also been found that long-term use of such painkillers can cause side effects such as gastrointestinal discomfort, nausea and vomiting. According to researches, *Trametes versicolor* (Tv) had anti-tumor, anti-bacterial, immune-modulating, anti-inflammatory and other effects. Therefore, this experiment used Tv by two different doses of formalin test in rats, used Saline and Aspirin as a control to explore its effects on the analgesic effects, to find the optimal formalin test dose

Materials and Methods: The Wistar rats were randomly divided into three groups: (1) the saline group: feeding saline 1 ml/kg; (2) the Tv group: feeding Tv 500 mg/ml/kg; (3) the Aspirin group: feeding Aspirin 100 mg/ml/kg. Under formalin test(N=8): After feeding for 30 minutes, 2.5 % Formalin 50 μl (Lower dose) was injected into the hind leg, and the licking frequency and the duration were counted every ten minutes, 60 minutes in total. Finally, the results were compared with 1 % Formalin 0.2 ml (Higher dose).

Conclusion: Feeding Tv 500 mg/kg can effectively relieve the pain caused by 2.5% of formalin 50 μl (Lower dose) and reduce flinching number in rats, both early phase and late phase had the effect of relieving pain. In the licking time of the early phase, there was a significant decrease in the effect of Aspirin compared with Saline, but in the late phase due to the dose was lower there was no significant difference between the groups. In the 1% 0.2 ml Formalin test (Higher dose), Tv has a significant decrease the licking time to compared with Saline in the late phase, so it is recommended to use a higher dose of 1% formalin 0.2 ml for the experimental observation.

Keywords: *Trametes versicolor*, Aspirin, formalin test, dose, analgesic

Formosan Plant Extract Inhibits ATG4B to Hamper Cancer Cells Growth and Metastasis

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Autophagy is an evolutionarily conserved pathway to degrade damaged proteins and organelles for subsequent recycling in cells during times of nutrient deprivation. This process plays an important role in tumor development and progression, allowing cancer cells to survive in nutrient-poor environments. The plant kingdom provides a powerful source for new drug development to treat cancer. Several plant extracts induce autophagy in cancer cells. However, little is known about the role of plant extracts in autophagy inhibition, particularly autophagy-related (ATG) proteins. In this study, we employed S-tagged gamma-aminobutyric acid receptor associated protein like 2 (GABARAPL2) as a reporter to screen forty-eight plant extracts for their effects on activity of autophagy protease ATG4B. *Xanthium strumarium* and *Tribulus terrestris* fruit extracts were validated as potential ATG4B inhibitors by another reporter substrate MAP1LC3B-PLA2. The inhibitory effects of the extracts on cellular ATG4B and autophagic flux were further confirmed. Moreover, the plant extracts significantly reduced colorectal cancer cell viability and sensitized cancer cells to starvation conditions. The fruit extract of *X. strumarium* consistently diminished cancer cell migration and invasion. Taken together, the results showed that the fruit of *X. strumarium* may have an active ingredient to inhibit ATG4B and suppress the proliferation and metastatic characteristics of colorectal cancer cells.

Keywords: plant extract, ATG4B, inhibitor, cancer

Loganin Improves Neuropathic Pain by Reducing CXCL12/CXCR4-Mediated NLRP3 Inflammasone Activation

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Neuropathic pain is associated with abnormal sensory conduction after nervous system injuries and it greatly affected patients' quality of life. NOD-like receptor protein 3 (NLRP3) inflammasome axis has been reported to be a direct target to modulate neuropathic pain. Loganin is isolated from Corni Fructus, a well-known herb with glucose-lowering action and neuroprotective activity. This study aimed to investigate the molecular mechanisms of loganin in a rat model of chronic constriction injury (CCI)-induced neuropathic pain. Sprague-Dawley rats were randomly divided into four groups: Sham, CCI, Sham+loganin and CCI+loganin. Loganin (5 mg/kg/day) was administered intraperitoneally starting at day 1 after surgery. Paw withdraw threshold (PWT) and paw withdrawal latency (PWL) were assessed at day 0, 1, 3, 7, 14 after CCI. Next, rats' spinal cords were collected for western blots and immunofluorescences. The behavioral data showed that loganin could improve CCI-induced mechanical allodynia and thermal hyperalgesia. The spinal NLRP3 inflammasome signaling proteins were increased at day 3,7,14 after CCI, and they were decreased after loganin treatment. Dual immunofluorescent staining further demonstrated that chemokine axis chemokine C-X-C motif ligand 12 (CXCL12), chemokine CXC receptor 4 (CXCR4), thioredoxin-interacting protein (TXNIP) and NLRP3 were colocalized with NeuN (a neuron marker), GFAP (an astrocyte marker) and Iba1 (a microglial marker). These proteins in the spinal dorsal horn were reduced at day 7 after CCI in loganin-treated rats. Loganin was suggested to prevent CCI-induced neuropathic pain via the suppression of CXCL12/CXCR4-mediated NLRP3 inflammasome signaling pathway. These findings could provide a potential therapeutic target in the treatment of peripheral nerve injury-elicited neuropathic pain.

Keywords: Loganin, chronic constriction injury, neuropathic pain, NLRP3 inflammasome, CXCL12/CXCR4

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Bioactive Constituents from the Aerial Part of *Hypericum sampsonii*

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Hypericum sampsonii Hance (Hypericaceae) is a perennial herb widespread in East and Southeast Asia. In the genus *Hypericum*, secondary metabolites such as anthraquinones, flavonoids, biflavonoids, benzophenones, biphenyls, xanthones, and polyprenylated polycyclic acylphloroglucinols are isolated, and many of them have shown significant effects in anti-oxidant, anti-inflammatory, anti-tumor, anti-HIV, anti-microbial, anti- depressant, and anti-neurodegenerative activities. Fractions of the MeOH extract of the aerial part of *Hypericum sampsonii* have undergone screening for anti-inflammatory effects in lipopolysaccharide (LPS)-induced murine macrophage cell line RAW264.7. Among all the fractions, the CH_2Cl_2-soluble fraction has shown significant effect on the NO production, with IC_{50} value of 8.95 μg/ml. A new benzophenone, hypericusampsone (**1**), has been isolated from the CH_2Cl_2-soluble fraction of the MeOH extract of the aerial part of *Hypericum sampsonii*, together with eight known compounds, sampbenzophenoneD (**2**), sampbenzophenone G (**3**), 2,4,6-trihydroxy-benzophenone 4-*O*-geranyl ether (**4**), 1-hydroxy-7-methoxyxanthone (**5**), 2-hydroxyxanthone (**6**), 1,7-dihydroxyxanthone (**7**), stigmasterol (**8**), and β-sitosterol (**9**). Among the isolates, compound **4** inhibits LPS-induced NO production in murine macrophage cell line RAW264.7, with IC_{50} value of 87.92 μM. In addition, compound **7** exhibited cytotoxic effects against human colon cancer cell line HT-29 and murine leukemia cell line P-388, with ED_{50} values of 3.94 and 1.21 μg/ml, respectively. As blood vessels mainly consist of human endothelial cells, which are directly derived from endothelial progenitor cells, inhibition on the growth of endothelial progenitor cells eventually leads to anti-angiogenesis effect. Compounds **4**, **6**, and **7** had shown potent inhibition effects, with IC_{50} values of 13.8, 29.1, and 25.4 μM, respectively, against human endothelial progenitor cells. Structural elucidation of the new compound **1** and anti-angiogenesis activities of the above compounds will be discussed in this symposium.

Keywords: *Hypericum sampsonii,* Hypericaceae, hypericusampsone, anti-inflammatory activity, anti-angiogenesis activity

Identify the Binding Targets of Capsaicin in Colon Cancer Cells by Proteome-wide CETSA

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Non-toxic or low-toxic natural compounds have recently been considered as a promising therapy for their potential pharmacological-like effect that suppresses the cancer progression. Capsaicin is one of these functional compounds that induce apoptosis and cell-cycle arrest in colon cancer cells. However, the underlying mechanism of therapeutic effect of capsaicin remains unclear. In order to clarify the mechanism for developing effective therapies, it is demanding to identify the direct binding targets of capsaicin with a proteomic-wide investigation. In our study, we selected HCT116 colon cancer cell as our test cell line. Cellular thermal shift assay (CETSA) was then combined with two-dimensional electrophoresis (2DE) to identify the direct binding targets of capsaicin in HCT116. To overcome the inconvenience of complicated processing, we also incorporated a recently developed “one-pot analysis” for monitoring the change of protein stability in the presence of capsaicin. In the present results, we found 6 proteins that could be the direct binding targets of capsaicin. Western Blot was subsequently used to verify the interactions between capsaicin and proteins. Our study suggests that capsaicin may interact with proteins related to translational regulation, cell-cycle progression, and cytoskeleton organization. These identifications may clarify the mechanisms of capsaicin on the cancer treatment. Further investigation could be the underpinning for drug design and development.

Keywords: capsaicin, ligand binding, cellular thermal shift assay (CETSA), protein stability

Sulfated Polysaccharides from *Antrodia cinnamomea* Cultured with Sodium Thiosulfate Synergistically Enhanced Clinical Drug-induced Cytotoxic Effects in TKI-resistant Lung Cancer H1975 Cells

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Sulfated polysaccharides (Ac-SPSs) from *Antrodia cinnamomea* present immuno-modulation and anticancer activities. However, the yield of Ac-SPSs isolated from *A. cinnamomea* cultured on normal condition is low. This study aimed to increase the sulfate content and yield of Ac-SPSs in *A. cinnamomea* through sulfate feeding. Using the sodium thiosulfate (ST) and ammonium sulfate (AS) to treat *A. cinnamomea*, we found that ST increased yields of PSs and SPSs but inhibited growth of mycelium in *A. cinnamomea*. AS neither induce changes in yields of PSs and SPSs nor affect growth curve of *A. cinnamomea*. Moreover, ST enhanced appreciate 2-fold sulfate content in the SPSs (denoted ST-SPS) isolated from *A. cinnamomea* treated with ST compared to that cultured in AS-treated and conditional medium. The molecule mass distribution of ST-SPS was further determined. ST induced changes in molecular weight from 320 kDa to 1342 kDa, and area percentage of low-molecular-weight ST-SPS (< 20 kDa) was decreased. Functional studies revealed that ST increased the ST-SPS anticancer efficacy in cancer cells via inhibition of EGFR/AKT signaling in tyrosine kinase inhibitor (TKI)-resistant lung cancer H1975 cells. Moreover, the ST-SPS synergistically enhanced cisplatin- and gefitinib-induced cytotoxic effects. ST-SPS combined with cisplatin and gefitinib increased the expression of apoptotic molecules such as PARP and caspase 3. This study demonstrated that ST significantly induced changes in properties of *A. cinnamomea*. Moreover, the ST-SPS from *A. cinnamomea* treated with ST presented the anticancer activity via inhibition EGFR signaling.

Keywords: Sodium thiosulfate, *Antrodia cinnamomea*, sulfated polysaccharides, lung cancer, synergistic effect

The Attenuating Effects of Allantoin on Amyloid β-peptide Induced Memory Impairment in Rats

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Amyloid β (Aβ) peptide can cause neurotoxicity in Alzheimer's disease (AD). The aim of the present study was to evaluate the effect of allantoin on Aβ1-42 induced impairment of cognitive function in rats. In this study, we found that allantoin (1, 5 or 10 mg/kg, ip, for 4 weeks) could reduce the escape latency and the distance travel and prolong the crossing platform time induced by the Aβ1–42 (5 μL, icv.) in rats in the Morris water maze test. On last day, the rats were sacrificed by decapitation, and the brains were quickly removed. The hippocampal tissues were carefully dissected on ice. To extract the protein, frozen tissues were homogenized in RIPA buffer. According to the results of Western blot analysis, allantoin treatment also increased the expression of p-PI3K, p-Akt, p-GSK-3β and p-tau (Ser396) in rats' hippocampus with the total PI3K, Akt and GSK-3β remained constant. In conclusion, allantoin possessed memory-enhancing effect. This effect may be partly mediated by the PI3K/Akt/GSK-3β signal pathway. These findings suggest that allantoin may be a potential therapeutic agent for this neurodegenerative disease.

Keywords: Alzheimer's disease (AD), $A\beta_{1-42}$, allantoin, cognitive function, PI3K/Akt/GSK-3β signaling

Bioactive Natural Products with Anti-inflammatory and Anti-angiogenic Effects from Formosan Plants

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Garcinia mangostana L. (Guttiferae) is an evergreen tree, distributed in tropical Southeast Asia and contained abundant xanthones. Investigation of EtOAc-soluble fraction of pericarp of *G. mangostana* has led to the isolation of three new xanthones, garcimangone A (**1**), garcimangone B (**2**), and garcimangone C (**3**), together with 18 known compounds (**4**–**21**). Among the isolates, garcinone D (**6**), β-mangostin (**8**), ananixanthone (**14**), morusignin J (**15**), fuscaxanthone C (**16**) and pruniflorone R (**17**) significantly decreased NO production at 25 μM in lipopolysaccharide (LPS)-stimulated RAW264.7 macrophages. Compounds **15** and **16** could also reduce the production of pro-inflammatory cytokines (TNF-α and IL-6) in LPS-stimulated macrophages. Furthermore, compound **15** inhibited the expression of iNOS through reduction of NF-κB activation as well as phosphorylation of ERK and JNK in LPS-stimulated macrophages. On the other hand, compound **15** could also polarize the M1 phenotype macrophages induced by LPS to become M2 phenotype through increasing the expression of M2 markers (KLF4 and arginase 1) and showed its anti-inflammatory potential.

Garcimultiflorone K is a novel polyprenylated polycyclic acylphloroglucinol isolated from the stems of *Garcinia multiflora* that exhibits promising anti-angiogenic activity in human endothelial progenitor cells (EPCs). Our investigations revealed that garcimultiflorone K suppressed EPCs angiogenesis through Akt, mTOR, p70S6K, and eNOS signaling cascades. Notably, garcimultiflorone K dose-dependently impeded angiogenesis in zebrafish embryos. Garcimultiflorone K appears to have potential in the treatment of angiogenesis-related diseases.

Keywords: *Garcinia mangostana*, morusignin J, anti-inflammatory effect, *Garcinia multiflora*, garcimultiflorone K, anti-angiogenic activity

The Antitumor Effect of 13-Acetoxysarcocrassolide, a Cytotoxic Cembranolide Derivative, Against Oral Cancer Cells is Through the Regulation of Nrf2/Keap1/p62/SQSTM1 pathway

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Previous reports showed that the marine cytotoxic product 13-acetoxysarcocrassolide (13-AC), isolated from the alcyonacean coral *Lobophytum crassum*, exhibited potent antitumor and immunostimulating effects. In this study, 13-AC induced apoptosis in oral cancer cells Ca9-22 through the disruption of mitochondrial membrane potential (MMP) and the stimulation of reactive oxygen species (ROS) generation. On the protein level, 13-AC increased the expression of apoptosis-related proteins such as the cleaved caspases-3 and -9 as well as the cleaved PARP in a dose- and time-dependent manner. 13-AC exerted potent antitumor effect against oral cancer cells as demonstrated by the *in vivo* xenograft animal model. It significantly reduced tumor volume (55.29%) and tumor weight (90.33%). In addition, the pretreatment of Ca9-22 cells with *N*-acetylcysteine (NAC), an antioxidant, inhibited ROS production resulting in the attenuation of the cytotoxic activity of 13-AC. Under stressful conditions, Ca9-22 cells which were treated with 13-AC showed a rapid induction of Keap1-Nrf2 pathway and an increase in the expression of p62/SQSTM1, but a suppression in the antioxidative function of Nrf2 as demonstrated by the immunoprecipitation, immunocytofluorecent and Western blotting analysis. The inhibition of p62 expression by siRNA significantly attenuated the growth-inhibition by 13-AC treatment. Taken together, the results suggested that 13-AC exerted its cytotoxic activity through the promotion of ROS generation and the suppression of the antioxidant enzyme activities. The apoptotic effect of 13-AC was found to be mediated through the interruption of Keap1/Nrf2/p62/SQSTM1 pathway suggesting its potential future application as an anticancer agent.

Keywords: Apoptosis, Anticancer, 13-Acetoxysarcocrassolide, Oxidative stress, Keap1/Nrf2/p62/SQSTM1 pathway

Antileukemia Effect of Xestoquinone, Induced Apoptosis via Oxidative Stress Combined with Inhibition of Hsp90 and Topoisomerase II Activities

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Xestoquinone (XQ), a polycyclic quinone-type metabolite, was isolated from the marine sponge *Petrosia* sp. which were found to inhibit a variety of cancer cell proliferation. The marine polycyclic quinone-type metabolite, xestoquinone (XQ) was found to inhibit the proliferation of Molt 4, K562, SupT1 and U937cancer cell lines, with IC_{50} of 1.69, 4.71, 5.87, and 11.65 μM, respectively. It exhibited the most potent activity against leukemia Molt 4 cells. To fully understand the mechanism of XQ, we further explored the precise molecular targets in leukemia Molt 4 cells. We found that the use of XQ increased apoptosis by 20.8%-63.0% and caused disruption of mitochondrial membrane potential (MMP) by 30.3%-88.7% in a dose-dependent manner, as demonstrated by annexin-V/PI and JC-1 staining assays, respectively. Moreover, our findings indicated that the pretreatment of Molt 4 cells with *N*-acetyl-L-cysteine (NAC), a reactive oxygen species (ROS) scavenger, diminished MMP disruption and apoptosis induced by XQ, suggesting that ROS overproduction plays a crucial rule in the cytotoxic activity of XQ. The results of a cell-free system assay indicated that XQ could act as HDAC and topoisomerase inhibitor through the inhibition of pan-HDAC and topoisomerase IIα expression, respectively. On the protein level, the expression of the anti-apoptotic proteins p-Akt, HDAC, XIAP and p-GSK were inhibited by the use of XQ. Taken together, our results suggested that the antileukemic effect of XQ is ROS-mediated mitochondrial apoptosis combined with the inhibitory effect on Hsp90 and topoisomerase activities.

Keywords: reactive oxygen species (ROS), Xestoquinone, Toposiomerase, heat shock protein 90(HSP90)

The Anti-inflammatory Effects of 3'-Hydroxygenkwanin from *Aquilaria sinensis* in Human Neutrophils

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Neutrophils play an important antimicrobial role in the immune system. However, inappropriate neutrophil functions and hyperactivity lead to pathological inflammation and tissue damage. This study investigates anti-inflammatory effect of the underlying mechanism of 3'-hydroxygenkwanin (ASSB-21) from *Aquilaria sinensis* in human neutrophils. Neutrophils were activated with *N*-formyl-methionyl-leucyl-phenylalanine (fMLP) and phorbol 12-myristate 13 acetate (PMA) in this study. Briefly, ASSB-21 inhibited fMLP-induced reactive oxygen species (ROS) production (IC50: 6.03±1.03 μM), cathepsin G released (IC_{50}: 27.51±6.80 μM) and neutrophil chemotaxis in a concentration dependent manner without affecting these induced by PMA. ASSB-21 (5-20 μM) inhibited fMLP-induced Akt phosphorylation. ASSB-21 (10-20 μM) inhibited fMLP-induced PIP3 levels indicated that ASSB-21 affected the activity of PI3K. In addition, ASSB-21 (20-50 μM) did not scavenge oxygen free radical in the xanthine/xanthine oxidase system. The neutrophil viability and toxicity did not affect by ASSB-21 (20-50 μM). Furthermore, ASSB-21 (20 μM) inhibited PMA-induced neutrophil extracellular traps (NETs) formation. ASSB-21 (5-20 μM) inhibited PMA-induced Akt phosphorylation. However, ASSB-21 (20 μM) did not inhibit fMLP-induced and PMA-induced CD11b expression, intracellular calcium mobilization, phosphorylation of ERK1/2 and p38. Thus, ASSB-21 inhibited fMLP-induced neutrophils ROS production, cathepsin G released and chemotaxis through inhibiting PI3K pathway.

Keywords: 3'-hydroxygenkwanin; neutrophil; anti-inflammatory; ROS; PI3K; fMLP

Ursolic Acid Sensitizes Gastric Cancer to 5-fluorouracil via Targeting CYP19A1

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Ursolic acid is a bioactive triterpenoid acid and exhibits the promising anti-inflammation and anti-cancer activities. However, the mode of action underlying ursolic acid-mediated anti-cancer effects is not fully understood. Our previous findings demonstrated that degradation of CYP19A1 by irreversible inhibitor exemestane but not enzymatic inhibitor letrozole improve the efficacy of 5-fluorouracil treatment in GCa. Here, we found that natural products ursolic acid can act as a CYP19A1 inhibitor for treating gastric cancer (GCa). Ursolic acid has ability against GCa, and the expressions of CYP19A1 in GCa cells were inhibited by ursolic acid. Add-on treatment of ursolic acid significantly enhanced the anti-cancer effects of 5-fluorouracil in GCa. Consistently, ursolic acid containing herbal plant *Hedyotis diffusa* showed the similar activities against GCa cells. Additionally, treatment with E2, a CYP19A1 substrate, did not alter the anticancer activity of ursolic acid in GCa, suggesting the role of non-enzymatic mechanism of CYP19A1 in ursolic acid mediated acitivties. Molecular simulation of ursolic acid-CYP19A1 interaction revealed the similar binding mode with exemestane-CYP19A1. Finally, using in vivo xenograft model, ursolic acid exhibited anticancer activity and also improved the antitumor effects of 5-fluorouracil treatment in the GCa tumor. Taken together, these results provide a new therapeutic opinion by combing 5-fluorouracil and ursolic acid containing herbal medicines in CYP19A1 positive GCa.

Keywords: Ursolic acid, CYP19A1, gastric cancer, 5-fluorouracil

In Vitro Evaluation of Galla Chinensis extract in Antibacterial Effect

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Some of the hundreds of *Candida* species can cause infection in humans; the most common is *Candida albicans*. Once the skin is compromised, secondary infection by *C. albicans* is common. Between 40% and 75% of diaper rashes are colonized with *C. albicans*. Several studies have shown that antibiotic use can lead to increased growth of *Candida* species. In this study, gallnut, traditional Chinese medicine is evaluated its effect to inhibit the growth of *C. albicans*. Gallnut has been reported to obtain antibacterial effect. The major ingredient in antibacterial is gallic acid. Disc diffusion assay was performed to screen for the effective drug, and the minimum inhibitory concentration test and cytotoxicity assay were also evaluated. Then the Chinese medicine was loaded into the non-woven fabric. The drug release rate and anti-microbial effect of the non-woven fabric loaded with gallnut extract were evaluated. The results of disc diffusion assays showed that gallnut extract presented the inhibition zone against *C. albicans*, *Staphylococcus aureus*, *Pseudomonas aeruginos*a, and *Escherichia coli* were 20±3 mm, 18±3 mm, 22±3 mm, and 18±3 mm respectively. The minimum inhibitory concentrations of gallnut extract against *C. albicans*, *S. aureus*, *P. aeruginosa*, and *E. coli* were 0.05 mg/ml, 0.03 mg/ml, 0.3 mg/ml, and 1.2 mg/ml respectively. The aim of this study is to evaluate the inhibitory effect of gallnut on *C. albicans* and other strains causing skin infections. It might be utilized for potential products to prevent diaper rash.

Keywords: *Candida albicans*, gallnut, diaper rashes, Chinese medicine

12-Deoxyphorbol Ester Derivatives Induce Growth Arrest and Apoptosis in Human Non-small Lung Cancer A549 Cells

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Prostratin, a non-tumor promoting 12-deoxyphorbol ester, has been reported as a PKC activator and shows anti-proliferative activity in certain cancer cell types. In this study, a natural derivative of 12-deoxyphorbol ester, compound **3**, was investigated for its anticancer effect on NSCLC A549 cells. Both 12-deoxyphorbol esters reduced cell viability of A549 cells that was accompanied by induction of cell cycle arrest and apoptosis. Compound **3** was 10-fold more potent than prostratin on inhibiting cell growth of A549 cells with an IC_{50} value of 300 nM. Compound **3** also showed a greater potency to induce activation and nuclear translocation of PKC-δ as well as to activate its downstream effectors PKD, p38 and ERK compared with prostratin. Knockdown of PKC-δ, but not PKC-α, rescued A549 cells from compound **3**- or prostratin-induced cell cycle arrest and apoptosis, indicating that PKC-δ is a major PKC isoform responsible for the anticancer effect of both compounds. In addition, knockdown of either PKD or MAPK led to similar results to those obtained in PKC-δ-downregulated cells.
Our data have demonstrated that prostratin and a more potent analogue compound **3** inhibit cell viability of NSCLC A549 cells, and this effect is dependent on the PKC-δ/PKD/MAPK pathway.

Keywords: prostratin, lung cancer, PKC-δ, PKD, MAPK

The Antiplatelet Effect of Natural PAR4 Inhibitors

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Platelets play an important role in hemostasis and thrombosis. Abnormal activation of platelets in pathological conditions is the main cause of thrombotic diseases. Currently antiplatelet drugs in clinical have been prove effective in reducing thrombus formation and decreasing the morbidity and mortality of cardiovascular diseases, such as myocardial infarction and stroke. However, using such drugs can lead to increased risk of bleeding. Thus, the development of more effective and safer antithrombotic strategies is necessary. Thrombin, a serine protease, is the most potent platelet activator. Activation of human platelets by Thrombin is primarily meditated by both protease-activated receptor (PAR) 1 and 4. PAR1 is involved in the early platelet activation process while PAR4 contributes to the stability of platelet aggregation. Selective inhibition of PAR4 may not affect the initial process of hemostasis and thus reduces the risk of bleeding complications. As a result, the purpose of this study is to find potential PAR4 inhibitors from natural resources.

In this study, we have found that a natural compound (compound **1**) inhibited platelet aggregation caused by PAR4-activating peptide (IC_{50} = 2.23 μM), but had no inhibitory effect on that induced by PAR1-activating peptide or U46619 (IC_{50} > 20 μM). Compound **1** selectively inhibited PAR4-activating peptide-induced intracellular Ca^{2+} mobilization and ATP release in human platelets. Furthermore, compound **1** selectively reduced PAR4-madiated p47, Akt, p38 MAPK and ERK phosphorylation. In conclusion, our results suggest that compound **1** can selectively inhibit PAR4-mediated platelet activation and be used as a lead compound for the development of PAR4 antagonist.

Keywords: platelets, protease-activated receptor 4, thrombin

Reactive Oxygen Species Mediate the Chemopreventive Effects of Syringin in Breast Cancer Cells

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Syringin (Syr), a phenylpropanoid glycoside extracted from *Eleutherococcus senticosus*, possesses various biological properties, including anticancer activities. However, the cytotoxicity effects of Syr on breast cancer have not yet been elucidated. In this study, we evaluated the anticancer potential of Syr on breast carcinoma and the mechanism involved. Non-tumorigenic (M10), tumorigenic (MCF7) and metastatic (MDA-MB-231) breast cancer cell lines as well as xenograft model were treated with Syr. Proliferation and cell cycle distribution were evaluated using the MTT, the colony formation assay and flow cytometry. The expression levels of cytotoxicity-related proteins were detected by Western blot. Here, we found that colony formation inhibition, cell cycle arrest in the G2/M phase, down-regulation of X-linked inhibitor of apoptosis protein (XIAP), cleaved poly (ADP-ribose) polymerase (PARP) and caspase-3/9 activation were observed in MCF7 and MDA-MB-231 cells treated with Syr. Moreover, pretreatment with a pan-caspase inhibitor (Z-DEVD-FMK) inhibited Syr-induced apoptosis. In addition, treatment with Syr also increased the production of reactive oxygen species (ROS). However, the antioxidant *N*-acetyl-cysteine (NAC) reversed the ROS levels and rescued the apoptotic changes. Meanwhile, Syr inhibited the growth of breast cancer xenograft models and dramatically decreased tumor volume without any obvious body weight loss in vivo. Our findings suggest that Syr induces oxidative stress to suppress the proliferation of breast cancer and thus might be an effective therapeutic agent to treat breast cancer.

Keywords: syringin, breast cancer, reactive oxygen species, X-linked inhibitor of apoptosis protein, apoptosis

Antimetastatic Potentials of Black Tea Extract on Human Melanoma Cells by Targeting the MMP and u-PA Pathway

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Modern people in order to pursue the bronzer skin, so that the trend of tanning is prevailing. Long-term exposure to the sun increases the chance of skin cancer. By the time skin cancer is found, it has mostly metastasized to other organs, making it harder to treat. In addition to pursuing a tan, modern people also have a drink. The most popular beverages are black and green tea, so the amount of tea used is quite large. Among tea, there are many studies on green tea. However, limited studies are available concerning the effect of black tea in human melanoma cells. In this experiment, melanoma cells A 375 and A2058 were treated with black tea ethanol extract (BTEE). In this study, MTT assay was used to assay cell activity. Zymography was also observed for changes in matrix metalloproteinase (MMP)-2, MMP-9, and urokinase-type plasminogen activator (u-PA) activity. The Wound-healing assay and Boyden Chamber observed the migration and invasion ability of cells. Colony formation observed the formation of cell communities. The Adhesion ability of cells was observed. Western blot to observe which pathway was inhibited. The results showed that with the increasing concentration of BTEE treatment A 375 and A2058, cells would not be directly killed in the MTT assay, while under the non-killing condition, the Wound healing assay and Boyden Chamber both found that with the increasing concentration of drugs, cell metastasis and invasion could be inhibit effectively. It can be seen that MMP-2, MMP-9 and u-PA are all decreased in Zymography experiment, of which u-PA is the most obvious. In the colony formation experiment, the community formation decreased with the increase of drug concentration. In the Adhesion assay, it can be seen that the Adhesion force of A 375 decreases with the increase of BTEE concentration. These results suggest that BTEE may effectively inhibit the metastasis and invasion of melanoma A 375 and A2058 cells. But it remains to be determined which ingredients in black tea are truly effective against melanoma A 375 and A2058 cells.

Keywords: black tea, melanoma, matrix metalloproteinase, urokinase-type plasminogen activator, invasion

The Inhibitory Effect of Mentha on Proliferation and Migration of Human Osteosarcoma 143 B Cells

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Bone cancer is a rare malignant tumor, which is a kind of cancer invading bone. The most common type of primary bone cancer is osteosarcoma, which usually occurs in children and adolescents. *Mentha* is a genus of plants in the family Lamiaceae whose essential oils has long been used in various forms and is widely added in food and drink to add flavor, also originally used as a medicinal herb to treat stomachache and chest pains in traditional medicine. However little research has been done on the anti-cancer effects of *Mentha* that are so widely used in our lives, so we wanted to explore whether *Mentha arvensis* extract (MAE) has the ability to inhibit the growth and motility of osteosarcomas 143 B cells. In this study, we used the MTT assay to determine whether MAE would toxically kill human osteosarcoma 143 B cells, use zymography to demonstrate if MAE inhibits enzyme activity of 143 B cells, colony formation assay to demonstrate if MAE inhibits 143 B formed colony, and then used wound healing and boyden chamber assay to explore whether MAE inhibits the migration and invasion of osteosarcoma cells. MAE inhibit the proliferation and colony formation of human osteosarcoma cells. The results of chamber and wound healing assay showed that MAE can inhibit the invasion and migration of 143 B cells. In conclusion, MAE may be effective in inhibiting the proliferation and migration of osteosarcoma 143B cells.

Keywords: osteosarcoma, *Mentha arvensis* , migration

Cinnamaldehyde Induces Apoptosisin Human Osteosarcoma Cells

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Osteosarcoma is the most common primary malignant bone tumor that occurs in adolescents. This type of malignance often occurs in the knees,that with a high potential for metastasis. The most common site of metastasis is the lungs. While metastasis is the most vital cause of death.Since ancient times, plant extracts have been used in the treatment of diseases, even today. *Cinnamomum cassia* is an important traditional Chinese medicine, and also used as spices.Cinnamaldehyde was the main component. Recent studies have indicated that cinnamaldehyde have anti-inflammatory, antibacterial and anticancer effects. In this study, we demonstrate that cinnamaldehyde has cytotoxic effect toward a malignant osteosarcoma cell line, HOS. Cinnamaldehyde reduced the viability and colony formation of human osteosarcoma cells. Further, cinnamaldehyde changed the cell cycle. The results of PI staining indicated that cinnamaldehyde caused the apoptosis of HOS cells. We will further research the effects and mechanisms of cinnamaldehyde on human osteosarcoma cells. In the future, cinnamaldehyde may be used in cancer chemoprevention and adjuvant therapy.

Keywords: cinnamaldehyde,osteosarcoma,apoptosis, cell cycle

The Anti-MRSA Infection and Anti-inflammatory Activity of 2,4-Dimethoxy-6-methylbenzene-1,3-diol from *Antrodia cinnamomea* for Treating Atopic Dermatitis Lesion

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Atopic dermatitis (AD) is an inflammatory skin disease with an associated barrier dysfunction and *Staphylococcus aureus* infection. The mainstay steroid and calcineurin inhibitor therapy shows some adverse effects. 2,4-Dimethoxy-6-methylbenzene-1,3-diol (DMD) is a benzenoid isolated from *Antrodia cinnamomea*. We investigated the inhibitory effect of DMD on methicillin-resistant *S. aureus* (MRSA), the chemokine production in stimulated keratinocytes, and the AD-like lesion found in ovalbumin (OVA) sensitized mice. The antimicrobial effect and cutaneous barrier function were evaluated using an in vitro culture model and an in vivo mouse model of AD-like skin. DMD exhibited a comparative minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) against MRSA with nalidixic acid, a conventional antibiotic. The MIC and MBC for DMD was 78.1 and 156.3 mg/ml, respectively. DMD also showed the ability to eliminate the clinical bacteria isolates with resistance to methicillin and vancomycin. The DNA polymerase and gyrase inhibition evoked by DMD for bacterial lethality was proposed. In the activated keratinocytes, DMD stopped the upregulation of chemokines (CCL5 and CCL17) and increased the expression of differentiation proteins (filaggrin, involucrin, and integrin β-1). Topical application of DMD facilely penetrated into the skin, with AD-like skin displaying 2.5-fold greater permeation than healthy skin. The in vivo assessment using the mouse model with OVA sensitization and MRSA inoculation revealed a reduction of transepidermal water loss (TEWL) and bacterial burden by DMD by about 2- and 100-fold, respectively. Differentiation proteins were also restored after topical DMD delivery. Our data demonstrated an advanced concept of AD treatment by combined barrier repair and bacterial eradication with a sole agent for ameliorating the overall complications.

Keywords: 2,4-dimethoxy-6-methylbenzene-1,3-diol, *Antrodia cinnamomea*, atopic dermatitis, *S. aureus*

Adenosine Analog from *Gastrodia elata* Ameliorates Aging in Mice

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Aging is a natural human process. It is uniquely individual, taking into account experiences, lifestyle habits and environmental factors. However, many disorders and syndromes, such as osteoporosis, neurodegenerative disorders, cognitive decline etc., often come with aging. The present study aimed to investigate the anti-aging effect of *N6*-(4-hydroxybenzyl)adenine riboside (**1**), one of the active components isolated from the rhizomes of *Gastrodia elata*, in D-galactose (D-gal)-induced aging mice and explored the underlying mechanism. Compound **1** suppressed D-gal- and BeSO4-induced cellular senescence. *In vivo* results in mice revealed that **1** abated D-gal- induced reactive oxygen species generation and ameliorated cognitive decline by inducing neurogenesis and lowering D-gal-caused neuron death. Therefore, compound **1** could be a potent agent for postponing senility and preventing aging-related neuroinflammation and neurodegeneration.

Keywords: adenosine analog, senescence, neurogenesis, anti-neuroinflammation

The Fungus Natural Compound LB53 Attenuates Retinal Inflammation in Dry Form-like AMD

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Activated retinal pigment epithelium (RPE), which increases the production of matrix metalloproteinases (MMPs) and pro-inflammatory cytokines, are the essential mechanisms for the progression of age-related macular degeneration (AMD). Thi study focused on the retinoprotective effects and the mechanisms of a natural fungal compound, theissenlactone B (LB53) isolated from *Theisseno cinerea*. It could inhibit tumor necrosis factor-α (TNF-α)-induced activation in ARPE-19 cells. First, LB53 concentration-dependently suppressed MMP-9-mediated gelatinolysis induced by TNF-α in RPE cells. Moreover, LB53 significantly inhibited both MMP-9 protein and mRNA expressions without cellular toxicity. Nevertheless, LB53 did not attenuate the blue light-induced phototoxicity in photoreceptor 661W cells. For the signaling studies, LB53 had significant effects on LPS/TLR4 downstream signaling pathways, such as the NF-κB signaling. Especially, phosphorylation of p65 was significantly inhibited by LB53. In addition, *in vivo* study indicated that LB53 attenuated dysfunction of combined rod-cone response by electroretinogram (ERG) and geographic atrophy by optical coherence tomography (OCT) in dry form-like AMD mice induced by sodium iodate treatment. In conclusion, the present study demonstrated that fungus-derived LB53 could be a potential agent for treating retino-inflammation in dry-form AMD.

Keywords: tumor necrosis factor-α (TNF-α), matrix metalloproteinases (MMPs), nuclear factor-κb (NF-κB), age-related macular degeneration (AMD), sodium iodate (NaIO3)

Biological Activities and Mechanism of Methyl Gallate on ER-positive Breast Cancer Cells

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The incidence of breast cancer has risen year by year in Taiwan and become one of the most important health issues for women. In addition to surgery, the radiation therapy and traditional chemotherapy have many side effects on the human body. Now there are many natural medicines have been used in clinical treatment. Methyl gallate is a component in many plants, including *Bauhinia*, *Toona sinensis*, and mango. Methyl gallate is known to have anti-oxidation, anti-inflammatory, antibacterial and anti-cancer effects. Methyl gallate can also increase the effects of various chemotherapy drugs. Previous studies indicated that methyl gallate may inhibit human liver cancer cell line (HepG2), prostate cancer cell line (PC-3), human colon cancer cell line (HT-29), and Hela cells. However, there is a lack of research on the treatment of human ER-positive breast cancer cells. This study will be discussed about the inhibitory effect and mechanism of methyl gallate in ER-positive breast cancer cells, and the improved effect of hormone therapy.

Keywords: Methyl gallate, Breast cancer, Apoptosis

The Molecular Mechanisms of Rutin on ER Positive Breast Cancer Cells

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Rutin, from native cereal plant *Chenopodium formosanum* in Taiwan, is reported the pharmacological activities, including antioxidant, cytoprotective, vasoprotective, anticarcinogenic, neuroprotective and cardioprotective activities. The aim of this study was to provide potential compounds against breast tumor cell lines. The result in this study showed that rutin had no significant toxicity in mammary cancer cell lines. However, it inhibited the proliferation of mammary cancer cell lines. In further study, the result demonstrated that rutin inhibited the proliferative effect of E2 on ER-positive mammary cancer cells.

Keywords: Rutin, ER positive breast cancer cells, E2

Xanthine Derivative Prevents Monosodium Iodoacetate-induced Osteoarthritis in Rats

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Osteoarthritis (OA) is a chronic and degenerative joint disease, which is the most frequent musculoskeletal disorder in the aging. Pharmacological treatments of OA include non-steroidal anti-inflammatory drugs (NSAID), such as diclofenac and ibuprofen, and long-lasting glucocorticoids or hyaluronic acid. Therefore, decreasing inflammation will likely be beneficial in OA management. KMUP-1, a xanthine derivative has been shown to have anti-inflammatory, cardioprotective and antioxidant properties. However, the beneficial effect of KMUP-1 related anti-inflammatory responses in osteoarthritis have not been addressed. The anti-inflammatory effect of KMUP-1 was evaluated in vitro in lipopolysaccharide (LPS)-treated RAW264.7 cells. The anti-osteoarthritic effect of KMUP-1 was investigated in an *in vivo* rat model of monosodium iodoacetate (MIA)-induced osteoarthritis in rats. *In vitro*, KMUP-1 reduced the LPS-induced cytotoxicity by MTT assay in the dose dependent manner. The LPS-induced nitric oxide production and inflammatory cytokines were inhibited by KMUP-1. Furthermore, the proteins expression of inflammatory mediators such as TNF-α, IL-6, COX-2 and MMPs were inhibited by KMUP-1 in the dose dependent manner. The measurement of hind limb paw withdrawal time indicated that KMUP-1 protected the joints of rats from MIA-induced damage. Additionally, MIA-injected rats treat with KMUP-1 were reduced the joints of cartilage erosion and bone resorption by macroscopic observation and histological examination. MIA-injected rats increased serum level of TNF-α, IL-6 were inhibited by KMUP-1. Our data suggest that KMUP-1 has an anti-inflammatory effect and may have potential as an agent for the treatment of osteoarthritis associated symptoms.

Keywords: Osteoarthritis, monosodium iodoacetate, inflammation, xanthine derivative

Metabolomics Approach on the Effects and Mechanisms of Natural Products on Nonalcoholic Fatty Liver and Diabetes Mice

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Gallic acid (GA), a naturally abundant plant phenolic compound has been shown to have potent anti-oxidative and anti-obesity activity. However, the effects and mechanisms of GA on diabetes and nonalcoholic fatty liver disease (NAFLD) are not clear. In this presentation, we investigated the beneficial effects of GA administration on NAFLD and diabetes mice induced by high fat diet (HFD) followed by streptozotocin (STZ) injections. A holistic view approach using 1H NMR-based metabolomics was used to examine the metabolites changes in serum, urine, liver, and muscle tissues to obtain the information that might lead to a better understanding of the mechanisms of GA in mitigating diabetes and NAFLD. The results indicated that severe metabolic disturbance were observed in the diabetes and NAFLD mice. The metabolic disorders under the disease model included glucose, amino acids, lipids, purines, and pyrimidines. Inerestesting, metabolites changes related to intestinal microbiota also observed. GA oral adminatration slow down the progression of NAFLD, alleviated the high blood glucose and partially reversed the disturbance of metabolic pathways in the diabetes mice. Further liver lipid metabolite gene expressions studies indicated that mechanism in alleviating lipid accumulation was related to the upregulations of β-oxidation and ketogenesis. These results suggested that metabolomics approach is a useful platform for natural product functional evaluation. The selected metabolites are potentially useful as preventive action biomarkers and could also be used to help our furthe identifying new mechanisms of GA in alleviating metabolic diseases.

Keywords: Gallic acid, NAFLD, Diabetes, Metabolomics, Metabolic diseases

Oleic Acid Nanoparticles Combined with Cilomilast for Inhibiting Neutrophilic Inflammation in Psoriasis-like Mouse Model

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Psoriasis is a common chronic inflammatory skin disease characterized by itchy red scaly skin lesions. Current forms of therapy for this disease are relatively ineffective, as there are no drugs available that can considerably reduce the disease progression. GlaxoSmithKline had invented cilomilast as an oral phosphodiesterase (PDE)4 inhibitor. Cilomilast failed for drug approval with the US FDA since the patients can not accept the nausea, vomiting and other side effects.We loaded cilomilast with lipid nanoparticles containing polyunsaturated fatty acids (PUFAs)-oleic acid (OA) as the lipid phase for improving the therapeutic efficiency and reducing the adverse effects of the drug. OA is reported to suppress neutrophil activation by inhibiting superoxide anion and elastase production. Our results show that OA combined with cilomilast can inhibit neutrophil superoxide generation and elastase release. The cilomilast loaded nanocarriers can also reduce endoplasmic reticulum calcium release. In the in vivo study of inducing psoriasis-like skin in mouse. The combination of cilomilast and OA in the lipid nanoparticles demonstrate a synergistic activity to ameliorate the inflammation response caused by imiquimod (IMQ).

Keywords: cilomilast, oleic acid, neutrophils, nanostructured lipid carriers, anti- inflammation

The Effects of Linalool, A Major Constituent of Essential Oils in Aromatic Plants, on the GABAergic Signaling and Sleep-Wake Cycle in Sprague-Dawley Rats

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The role of aromatherapy for sleep quality has been underexplored and scientific evidence remains insufficient. Gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the brain, plays important role in sleep-wake regulation. The aim of this study is to investigate the effects of linalool (3,7-dimethyl-1,6-octadien-3-ol, LNL), a major constituent of essential oils in aromatic plants, on the GABAergic receptors and sleep-wake cycle in Sprague-Dawley (SD) rats. The sleep-wake stages of the rats were evaluated by using the electroencephalography (EEG) for brain activity and electromyography (EMG) for muscle activity. Protein expressions of the cortical neuron separated from the E16 rat embryos were analyzed by western blots. In primary cortical neurons, LNL upregulated the protein expressions of GABAA-α1/GABAB receptors. In sleep-wake cycle of SD rats, LNL altered sleep-wake and EEG spectral composition, especially non-rapid eye movement (NREM) sleep enhancement. These results suggest that LNL possesses sleep-promoting benefits via enhancement of the GABAergic signaling and NREM sleep.

Keywords: linalool, sleep-wake cycle, GABAergic signaling. non-rapid eye movement

Anti-inflammatory and Adipogenesis Studies on Agri-food Residues

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Taiwan is a biodiversity island. The circular agriculture and agri-food residues managements and applications are popular topics. Agri-food residues such as flowers of *Abelmoschus esculentus*, peels of *Hylocereus undatus*, and peels of *Citrus limon* were extracted and studied the anti-inflammatory and adipogenesis effect with different extract method. Inflammatory bowel disease (IBD) is characterized by chronic inflammation of the gastrointestinal tract. While the precise etiology still remains unknown, understanding of the pathophysiology of IBD has advanced. The typical features of these diseases have been shown in various studies and especially for intestinal immune cells and intestinal epithelial cells of IBD. It had been reported that intestinal epithelial cells and macrophages secrete large amounts of chemokines and pro-inflammatory cytokines in the inflamed intestine of IBD patients. To assess the gut anti-inflammatory activity of agri-food residues, the co-culture system with intestinal epithelial Caco-2 cells and RAW264.7 macrophages was applied to imitate IBD in vitro and IL-8 expression was detected. In adipogenesis, 3T3-L1 cells exhibit a fibroblast-like morphology before differentiation but become rounded and accumulate lipid droplets several days after the initiation of differentiation, therefore, 3T3-L1 cells differentiation into adipocyte cells were applied to imitate anti- adipogenesis. In anti-inflammatory activity results, water extract for flowers of *Abelmoschus esculentus* and peels of *Hylocereus undatus* could inhibit 26.8~40.6% of IL-8 expression. But all of extracts have no significant difference on anti-adipogenesis capacity.

Keywords: *Abelmoschus esculentus, Hylocereus undatus,* IBD, Caco-2, RAW264.7, IL-8

Anti-inflammatory Constituents of *Helicteres angustifolia*

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Helicteres angustifolia L. (Sterculiaceae) is a shrub distributed in South East Asia, and has been used as a traditional Chinese medicine for the treatment of fever and inflammation. Flavonoids, triterpenes, coumarins, tannins and their derivatives were isolated from this plant in previous studies. Many of these isolates exhibit antioxidant, antimicrobial, hypoglycemic, anti-inflammatory, and cytotoxic activities. In our studies on the anti-inflammatory constituents of Formosan plants, many species have been screened for *in vitro* anti-inflammatory activity, and *H. angustifolia* has been found to be an active species.

Investigation on active EtOAc-soluble fraction of this plant provided fourteen known compounds, methyl helicterate (**1**), vanillin (**2**), methyl helicterilate (**3**), vanillic acid (**4**), syringaldehyde (**5**), 3β-acetoxy-27- *trans*-caffeoyloxyolean-12-en-28-oic acid methyl ester (**6**), 3β-acetoxy-27-[(4-hydroxybenzoyl)oxy]lup- 20(29)-en-28-oic acid (**7**), mansonone M (**8**), mansonone E (**9**), mansonone H (**10**), mansonone F (**11**), helicteric acid (**12**), 3β-acetoxy-27-*cis*-caffeoyloxyolean-12-en-28-oic acid methyl ester (**13**), and protocatechuic acid (**14**). Their anti-inflammatory effects were evaluated by measuring the suppression of the NO production by LPS-treated RAW 264.7 macrophage, and compounds **8**, **9**, **11** and **12** significantly reduced LPS-induced NO production by 100.00, 47.16, 21.00, and 88.82 %, respectively, at 25 μM. This symposium describes the anti-inflammatory activities of the isolates.

Keywords: *Helicteres angustifolia*, anti-inflammatory activity, RAW 264.7 macrophage

Rottlerin, A Natural Polyphenol, Inhibits Up-regulation of Matrix Metalloproteinase-9 and Brain Astrocytic Migration by Reducing PKCδ-Dependent ROS Signal

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Up-regulation of matrix metalloproteinase-9 (MMP-9) has been indicated as one of the inflammatory biomarkers. In the central nervous system (CNS), the MMP-9 is induced by several proinflammatory mediators and participates in the CNS disorders, including inflammation and neurodegeneration. Several phytochemicals are believed to reduce the risk of several inflammatory disorders including the CNS diseases. In addition, protein kinase Cs (PKCs) has been shown to be involved in regulation of various inflammatory factors like MMP-9 by several stimuli in many cell types. The rottlerin, a principal phenolic compound of the Kamala plant *Mallotus philippinensis*, has been shown to possess an array of medicinal properties, including anti-PKCδ, antitumor, anti-oxidative, and anti-inflammatory activities. Herein, we first demonstrated the signaling mechanisms of phorbol 12-myristate 13-acetate (PMA)-induced MMP-9 expression in rat brain astrocytes (RBA). Then, we evaluate the effects of rottlerin on PMA-induced MMP-9 expression in RBA and its influencing mechanism. In the results, we first demonstrated that PMA stimulated activation of various types of PKC, including PKCδ in RBA. Subsequently, PMA induced MMP-9 expression via PKCδ-mediated ROS generation, extracellular signal-regulated kinase 1/2 (ERK1/2) activation, and then induced c-Fos/AP-1 signaling pathway. Finally, up-regulation of MMP-9 by PMA via the pathway may promote astrocytic migration and the event could be attenuated by rottlerin. These data indicated that rottlerin may have anti-inflammatory activity by reducing these related pathways of PKCδ-dependent ROS-mediated MMP-9 expression in brain astrocytes.

Keywords: rottlerin, PKCδ, MMP-9, ROS, brain astrocytes, neuroinflammation

To Evaluate the Effect and Mechanism of Epigallocatechin Gallate on Brain Microvascular Endothelial Cell-Dependent Brain Inflammation

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As the population of the world ages, the elderly population and aging-related disorders are also increasing, including the central nervous system (CNS) degenerative diseases. It is known that endothelial cells of blood-brain barrier (BBB) in patients with neurodegenerative diseases usually have an inflammatory state, but the mechanisms are still unclear. Here, we use the brain microvascular endothelial cells (bEnd.3) as a cell model to investigate the inflammatory responses induction by proinflammatory factors IL-1β and then the effects of Epigallocatechin Gallate (EGCG) on the responses. The results showed that IL-1β can induce inflammatory proteins' expression, including matrix metalloproteinase-9 (MMP-9) in bEnd.3 cells. IL-1β induced MMP-9 expression via a reactive oxygen species (ROS)-dependent pathway and then activated many signaling molecules, such as c-Src, EGFR, Akt, and MAPKs (ERK1/2, p38, and JNK1/2) linking to activation the transcriptional factors NF-κB and AP-1. Finally, we found that IL-1β induced the configurational change of ZO-1, as a cell tight junction protein. The induction of MMP-9 by IL-1β may be involved in the event. Furthermore, many previous studies have indicated that EGCG have anti-inflammatory effects, which may have fewer side effects. Therefore, we evaluated the effects of EGCG in the event. The result showed that EGCG can attenuate IL-1β-induced MMP-9 expression and ZO-1 configurational change in bEnd.3 cells, suggesting that EGCG may contain anti-inflammatory components to protect the brain BBB from inflammatory damage.

Keyword：Interleukin-1β、Matrix metalloproteinase-9、Blood-brain barrier、Endothelial cells、Neuroinflammation

Studies on Plant Tissue Culture and Activities Evaluation of *Ophioglossum petiolatum* HOOK.

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Ophioglossum petiolatum HOOK. belongs to the Ophioglossaceae family and *Ophioglossum* genus. It is a folk medicine and has long been used as an endemic plant in Taiwan. *O. petiolatum* can be used for antipyretic treatment in children, sore throat, snake injury and epidermoid cyst. And it was previously studied for diverse pharmacological activities, including anti-inflammatory, anti-viral, anti-HBV and anti-oxidation. Because *O. petiolatum* is really expensive, we hope that establish a plant tissue culture technique for the propagation of *O. petiolatum.*

In the study, we found that we could use the rhizome explants to make the shoot formation. We cultured on Woody Plant Medium (WPM) supplemented with potato and 2% sucrose. In addition, the culture medium used the 3M tape to increase air permeability. Furthermore, we measured the antioxidant activities including total phenol content, total flavonoid content and DPPH free radical scavenging activity. The results revealed that total phenolic content of *O. petiolatum* was equivalent to 136.283 ± 1.991 mg gallic acid/g, total flavonoid content was 17.391 ± 0.606 mg catechin/g and IC_{50} value of DPPH scavenging activity was 0.748 ± 0.026 mg/mL.

After that, we also use the High Performance Liquid Chromatography (HPLC) to analysis the indicator component. The detection of indicator component can help us to know the quality control about *O. petiolatum.*

Because *O. petiolatum* has the antioxidant activities, it may have protective ability to against reactive oxygen species (ROS) which is the main causes of diseases. Therefore, we will perform more relevant measurements in the future.

Keywords: *Ophioglossum petiolatum,* plant tissue culture, antioxidant activity

Creating a Chemical Networking Database for the Metabolome of Traditional Chinese Medicine

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Traditional Chinese medicine (TCM) has been widely used for improving human health for a long history. Due to the high variety of TCM's medicinal nature and pharmacological effects, TCM possesses diverse functions in the treatment and prevention of diseases. The metabolites in TCM predominantly dominate its medicinal nature and pharmacological effects. Each TCM material may contain unique bioactive components, while different TCM materials may also share various common metabolites or structurally-similar metabolites. In practical applications, TCM is mainly used in the form of a combination formula, and its ideal therapeutic efficacy is achieved through the synergistic and antagonistic interactions between different metabolites in the medicinal materials. Traditionally, the common strategy for TCM metabolite analysis is bioactivity-guided isolation and identification. However, this approach may lead to redundant re-identification of known metabolites from different medicinal materials, and it hardly provides comprehensive information on the metabolome profile and tends to neglect the potential regulatory effects of minor components on the bioactivity. Therefore, an integrative TCM whole metabolome information consisting of structural similarity-based clusters may facilitate the TCM resource mining and new drug discovery processes, and it also can act as a scientific reference for TCM quality control. This study aims to develop an analytical platform for TCM metabolome profiling and to establish a systematic database of TCM chemical networking. We selected 24 TCM materials for investigation, and their hexane, ethyl acetate, methanol, 50% methanol and 50% ethanol extracts were prepared and analyzed by standardized LC-MS/MS and GC-MS methods. The metabolites were identified by comparing the MS and MS/MS data with mass spectral library and natural product library. For the unknown analogs, we applied the Global Natural Products Social Molecular Networking (GNPS; http://gnps.ucsd.edu) approach to predict their structures based on the MS/MS spectral similarity. Furthermore, we used ClassyFire (http://classyfire.wishartlab.com) to automatically classify the metabolites in networking based on their structural features. In conclusion, through the standardized metabolite data collection and analysis strategy, as well as the construction of the molecular networking of 24 TCM materials, this study will establish a fundamental model of chemical networking database for TCM metabolome.

Keywords: TCM, LC-MS/MS, GNPS, molecular networking, metabolome mining, database

Study on the original investigation and identification of confused and mistaken used *Portulaca oleracea* L. in Taiwan Market

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Portulaca oleracea L., also known as "Ma-Chi-Xian" (馬齒莧), which belongs to the Portulacaceae family. *P. oleracea* is the traditional Chinese medicine (TCM) to use for the diuretic and treatment of inflammation-linked diseases, dysentery and mammary abscess. And especially people use it as the edible vegetable and fed it to pigs for stimulating lactation in Taiwan. Besides, the recent pharmacology study showed that *P. oleracea* has the activity of anti-cancer. In Taiwan market, *P. oleracea* is usually confused with other plants (e.g. *Bacopa monnieri*, which belongs to Scrophulariaceae). Thus, it is important to verify the origin of the herb. In this study, we collected the dried medicine and fresh plants of *P. oleracea* and confused medicine from Chinese medicine shop and field. Then, we proceed the microscopic identification, DNA sequencing and HPLC analysis. Investigated the differences between *P. oleracea* and its confused medicine and the origin plant of the confused and mistaken medicine in Taiwan market. Finally we determined the total flavonoids content of the ethanol extract of *P. oleracea* for the study of the active constituents.

Keywords: *Portulaca oleracea*, original identification, Traditional Chinese Medicines

Functional Characterization of Nociceptive Mechanisms Involved in Fibromyalgia and Electroacupuncture

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Chronic pain has a definitive lack of objective parameters in the measurement and treatment efficacy of diseases such as Fibromyalgia (FM). Persistent hyperalgesia and allodynia are characteristic symptoms. This disease has indicated a refractory tendency to conventional treatment ventures, largely resultant from a lack of etiological and pathogenic understanding of the disease development. Emerging evidence indicates that the central nervous system (CNS) plays a critical role in the amplification of pain signals and the neurotransmitters associated therewith. It remains unclear whether or not electroacupuncture (EA) can attenuate the chronic pain associated with FM. We examined the contribution of the transient receptor potential vanalloid 1 (TRPV1) channel and the major nociceptive components of pPI3K, pAkt, pmTOR, pERK, pp38, pJNK, pNFκB, Nav1.7, Nav1.8, pPKCε and pPKAIIα in response to fibromyalgia-like pain in an intermittent cold-stress (ICS) model, in the pre-frontal cortex, somatosensory cortex, hippocampus and thalamus areas of the brain. The potential therapeutic benefits of electroacupuncture (EA) at bilateral ST36 acupoint was analysed in order to identify the analgesic effects and mechanism associated with this therapy. The results suggest that TRPV1 upregulation is central to the FM induced hyperalgesia and the treatment of EA showed a decrease in this FM induced nociceptive sensitization, suggesting TRPV1 and related nociceptive conduit upregulation and overexpression can be attenuated by EA at bilateral ST36. The results indicate that EA treatment successfully attenuated both mechanical and thermal hyperalgesia. A majority of proteins associated with the nociceptive signalling cascade indicated overexpression in FM, which was rescued through the use of EA. The use of TRPV1 knockout mice allowed for a successful blockade of TRPV1 expression, and further served to elucidate the role of the TRPV1 receptor in the development and expression FM-like pain. Moreover, the use of non-functional sham acupoints demonstrated that TRPV1 is abundantly expressed at ST36 and possibly participates in acupuncture related analgesia. This evidence strongly suggests that the TRPV1 signalling pathway and related components may represent promising therapeutic targets for FM treatment. Furthermore, the treatment of EA showed a decrease in this FM induced nociceptive sensitization, suggesting TRPV1 upregulation and overexpression can be attenuated by EA at bilateral ST36, and that EA can provide analgesic benefits to patients suffering from FM.

Keywords: Fibromyalgia, Electroacupuncture, TRPV1, Analgesia

Murraya paniculata (L.) Jack Leaf Extract Suppresses LPS-induced Inflammatory Responses in RAW264.7 Cells through NF-κB Pathway Inhibition and Nrf2/HO-1 Pathway Activation

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It has been suggested that the agents aiming at decreasing cytokines and oxidative stress might prevent or attenuate the pathological cascade of inflammation induced by lipopolysaccharide (LPS). Natural products represent a rich source for the discovery of anti-inflammatory and anti-oxidant agents. The traditional Chinese medicine, *Murraya paniculata* (L.) Jack, is the most popular flavor plants and is well-known due to its therapeutic efficacy also. In the present study, the crude extract of *M. paniculata* (L.) Jack leaves was tested for the anti-inflammatory properties using cell model and molecular techniques were used to evaluate macrophage biomarkers expression and specific proteins in the related signaling pathways. The crude extract down-regulated the protein and mRNA levels of LPS-stimulated macrophage biomarkers (e.g., IL-6, IL-1β, TNF-α, iNOS). The underlying mechanisms were investigated in cell culture. We demonstrated that the crude extract of *M. paniculata* (L.) Jack leaves suppressed LPS-induced NF-κB translocation while activated Nrf2 and subsequently inducing HO-1 expression. Taken together, *M. paniculata* (L.) Jack exhibited a promising protection against LPS-induced damage via anti-oxidative and anti-inflammatory functions. Thus, we anticipate that *M. paniculata* (L.) Jack is a potential candidate for the resolution of inflammation.

Keywords: *Murraya paniculata* (L.), lipopolysaccharide, inflammation

Protective Effects and Network Analysis of Natural Compounds Obtained from Dipsaci Radix, Eucommiae Cortex, and Drynariae Rhizoma Against RANKL-induced Osteoclastogenesis *in Vitro*

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Osteoporosis is a common bone diseases; it is a risk factor for hip fracture. Chinese herbal medicines (CHMs) and their related natural compounds have been used for treating bone diseases, since ancient times in China and are regarded as a cost-effective complementary therapy. The goal was to investigate the osteoprotective mechanisms of the three Chinese herbs and related natural compounds. The effects of CHMs and compounds on RANKL-induced osteoclastogenesis *in vitro* were investigated. A network pharmacology method was applied to study CHM-related natural compounds and their osteoporosis targets. In addition, their effect on RANKL-induced osteoclastogenesis in RAW264.7 cells was also investigated *in vitro*. Dipsaci radix, Eucommiae cortex, and Drynariae rhizoma exhibited protective effects against mortality in hip fracture patients. Furthermore, these herbs inhibited RANKL-induced TRAP activities and reduced the expression of bone resorption-related genes in RAW264.7 cells. Network analysis of natural compound (ingredient)-target interactions identified 11 compounds. Signal pathway analyses suggested that these compounds may target cytokine-cytokine receptor interactions, including RANKL-induced osteoclastogenesis. Five compounds exhibited reduced RANKL-induced TRAP activities and bone resorption-related gene expression. The clinically used CHMs, Dipsaci radix, Eucommiae cortex, and Drynariae rhizoma, and compounds obtained from them may suppress RANKL-induced osteoclastogenesis *in vitro*.

Keywords: Hip fracture, Chinese herbal medicine, natural compound, osteoclastogenesis.

Ethnopharmacological Investigation of Breast Milk Secretion Prescriptions in the Middle of Taiwan

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Breastfeeding is beneficial for both mother and infant. Nevertheless, not all mothers have enough breast milk to feed their infants. Nowadays, they tend to seek help from Traditional Chinese Medicine because they believe it is mild and harmless. Therefore, this study was conducted a field investigation, recorded and analyzed breast milk secretion prescriptions, and discussed their efficacy and safety. In this study, twenty-one prescriptions were bought in eighteen traditional Chinese pharmacies, and forty-three kinds of raw materials were sorted out. This study was the first systematic ethnobotanical study on breast milk secretion prescriptions. It provided the results of the ingredients that serve as a reference for breast milk secretion prescriptions and can be used by the public and regulatory agencies.

Keywords: breastfeeding, breast milk secretion, field investigation, the middle of Taiwan, Traditional Chinese Medicine

Study on Probing the Anti-Inflammatory Compositions of *Lonicera japonica*

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Neutrophils play a significant role in regulating inflammatory diseases. Activated human neutrophils generate superoxide anion and release elastase to the traumatic tissues, causing the inflammatory response. Therefore, the development of drugs for inhibiting neutrophils activation may possess interesting therapeutic potential. *Lonicera japonica* is a single formula in traditional herbal medicine. In the traditional Chinese clinical treatment, it is usually used for clearing heat and resolving toxic. Although chlorogenic acid is considered as the marker component of *L. japonica* in Chinese and Taiwanese Pharmacopoeia, the other anti-inflammatory compositions and their mechanism of action remain unclarified. In this study, the high-performance liquid chromatography (HPLC)-based high-resolution bioassay profiling techniques were applied, the active constituents were isolated and purified from ethanolic extract of *L. japonica* and their anti-inflammatory effects were explored. The results showed that the components other than chlorogenic acid exhibited the inhibition of superoxide anion generation, CD11b expression, cell adhesion, and cell migration in fMLF-activated human neutrophils. Moreover, these compounds also inhibited fMLF-induced calcium mobilization. In conclusion, it is suggested that the compounds apart from chlorogenic acid can be referred as the anti- inflammatory indicators in *L. japonica.*

Keywords: *Lonicera japonica*, neutrophils, fMLF, superoxide, calcium

Protective Effects of Fucoxanthin on Ultraviolet B-Induced Corneal Denervation and Inflammatory Pain in a Rat Model

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Fucoxanthin is a carotenoid with many pharmaceutical properties that is found in brown seaweed. However, the effects of fucoxanthin on corneal innervation and intense eye pain have not been extensively examined. To clarify the protective roles and underlying mechanisms of fucoxanthin on ocular lesions, we investigated the beneficial effects and mechanisms by which fucoxanthin ameliorates ultraviolet B (UVB)-induced corneal denervation and trigeminal pain. Treatment with fucoxanthin enhanced the expression of nuclear factor erythroid 2-related factor 2 in the cornea. Inhibition of typical denervation and epithelial exfoliation in the cornea were observed in rats treated with fucoxanthin following UVB-induced nerve disorders. Moreover, the active phosphorylated form of p38 MAP kinase (pp38) and the number of glial fibrillary acidic protein (GFAP)-positive neural cells were significantly reduced. Decreased expression of neuron-selective transient receptor potential vanilloid type 1 (TRPV1) in the trigeminal ganglia neurons was also demonstrated in rats treated with fucoxanthin after UVB-induced keratitis. Symptoms of inflammatory pain, including difficulty in opening the eyes and eye wipe behavior, were also reduced in fucoxanthin-treated groups. Pretreatment with fucoxanthin may protect the eyes from denervation and inhibit trigeminal pain in UVB-induced photokeratitis models.

Keywords: fucoxanthin; ultraviolet B; denervation

Lonicera japonica Extracts Inhibit Cells Growth, Migration and Cancer Stem-like Properties by Downregulating PI3K-AKT and PLC-γ1 Signaling in Non-muscle Invasive Bladder Cancer

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Non-muscle invasive bladder cancer (NMIBC) has highly rate of overall survival comparison with muscle invasive bladder cancer (MIBC). However, up to 70% NMIBC relapse after following therapy and even 10-20% recurrent NMIBC progress into MIBC. *Lonicera japonica* is classified as heat clearing medicine to treat with less Yang syndrome which related to inflammation and abscess in Chinese medicine theory. In this study, *L. japonica* ethanol extracts containing dicaffeoylquinic acid which was found is the mainly component of this herbal suppresses NMIBC cell line proliferation, migration and cancer stem-like properties in vitro. Additionally, *L. japonica* extracts downregulate PI3K-AKT and PLC-γ1 signaling pathway which abnormal activate in bladder cancer and promote cancer stem cell formation. These findings suggest this herbal extract can be used as a treatment strategy for NMIBC recurrent. The active fraction and components are currently under studied and identified for botanical drug development.

Keywords: *Lonicera japonica*, PI3K-AKT, PLC-γ1

Dietary Supplement of *Fagopyrum tataricum* Gaertn (Taichung No.2) Attenuates Diabetic Conditions of C57/BL6 Mice Induced by High Fat Diet-streptozocin via Enhancing Serum GLP-1 levels

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Diabetes is a chronic metabolic disease affecting 424.9 million people in the world. *Fagopyrum tataricum* Gaertn (Taichung No.2), so called buckwheat, is one of the important crops in the middle of Taiwan. It contains rich flavons, especially rutin. In the present, we employed experimental type 2 diabetes mice model to evaluate the anti-diabetic effect of buckwheat and rutin is used as reference compound.

Type 2 diabetic mice were induced by high fat diet (60% of calorie from fat) plus 100mg/kg streptozotocin. Once fasting blood sugar over 200mg/dl, mice were grouped and fed with high fat diet supplemented with 0, 3% and 10% buckwheat powder and 0.1% rutin for 4 weeks. At the end, fasting blood sugar, HbA1c, glucose tolerance, pyruvate tolerance, HOMA-index, endocrine profiles, islet pathology were measured and compared. As a result, fasting blood sugar of diabetic mice was significantly reduced when mice fed with 10% buckwheat (consisting of 0.7% rutin) and 0.1% rutin, respectively. Glucose tolerance, HOMA-B%, and islet pathology in diabetic mice were also improved by 10% buckwheat consumption. However, 10% buckwheat supplementation provided less potency comparing to that of 0.1% rutin. In terms of endocrine profile analysis, insulin, GLP-1, Ghrelin, adiponectin were increased in diabetic mice in dose-dependent manner. The elevation of GLP-1 levels is also associated with directly stimulatory effect of rutin on stc-1 L cells and inhibition of DPPIV activity.

Therefore, we concluded that rutin may play an important role for anti-diabetic effects of buckwheat. Modulation of GLP-1 levels with dual actions may indicate the underlying mechanisms of actions of consumption of buckwheat.

Keywords: *Fagopyrum tataricum* Gaertn (Taichung No.2), type 2 diabetes, islet function, glucagon like peptide-1 (GLP-1), dipeptide 4 (DPP4)

The Correlation between Components and Bioactivities of Processed Hedysari Radix

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In Taiwan, Hong Qi (*Hedysarum polybotrys* Hand.-Mazz.) was more widely used than Huang Qi (*Astragalus membranaceus* (Fisch.) Bunge.). for a long time. However, the processed method of Hong Qi was not standardized in traditional Chinese medicine. Therefore, the suitable processed method for Hong Qi with honey would be established in this study. In the first part, the effects of anti-inflammatory, inhibition of oxaliplatin-induced myotubes damage, inhibition of alcohol-induced gastric mucosal cells damage and promotion of iron uptake in Caco-2 cells were used to investigate the difference in bioactivity between Hong Qi and Huang Qi. According to the results, the Huang Qi more strongly inhibited the production of nitric oxide on LPS-induced macrophage than Hong Qi. However, Hong Qi more significantly promoted iron uptake than Huang Qi.

In the second part, the Orthogonal experimental test was used to evaluate the best condition of processed Hong Qi with honey. At first, vanillic acid, ferulic acid, ononin and formononetin were isolated from the methanol extract of Hong Qi. Then, the concentrations of honey, immersion time, temperature and duration of stir-fry were as the factor of the Orthogonal experimental test. According to the results, the concentrations of honey is major impact factor of the total content of polysaccharides and the four major components in Hong Qi, while the temperature of stir-fry was the impact factor of total polyphenols. The comparison among the raw material and the processed Hong Qi, the processed products had the weak effect on inhibition of LPS-induced nitric oxide production on macrophage and inhibition of oxaliplatin-induced myotube damage than the raw material. However, raw and processed products promoted iron uptake, and based on correlation analysis indicated that vanillic acid was positively correlated with iron uptake, while it was negatively correlated with fructose. In addition, the inhibition of oxalipltin-induced myotube damage was positively correlated with the content of monosaccharide. It was speculated that processed Hong Qi with honey can enhance proliferation of myotubes.

Keywords: Hedysari Radix, Inflammatory, Myogenesis, Iron-uptake, Peptic ulcer disease

New Formula from Pu-Ji-Fang Enhances Wound Healing in Rats

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The Traditional Chinese Medicine (TCM) formula has been used to treat patients for a long time. We used the prescription of the Ming Dynasty medical book "Pu-Ji- Fang" to establish a database of Chinese medicine prescriptions for data exploration to find out the relevance, in order to facilitate the verification of drug predictions. We selected the traumatic drugs that are convenient for experiment, and established drug- related modules. Many literatures also mentioned that the traumatic drugs of traditional Chinese medicine can not only accelerate wound healing, but also reduce the scar production. Then we organize Jin-Chuang-Phylum, Zhang-Chuang- Phylum and Chih-Chuang- Phylum data, contain 6 volumes and 410 formula, using Apriori Algorithm to identify two formulations of traumatic drugs, which were divided into oral and external application. The cytology experiment and the wound healing test proved that the traumatic formulation really contributed to the growth rate of fibroblasts. Finally, we conducted rats experiment with a predictive drug-mixed hydrogel. The external wound medicine (74.36%) has better recovery degree than control group (70.14%) for deeper wounds, and the drugs have a significant recovery within 6 days. It can be seen that the predicted drug formula has better effects than the experimental group of pure hydrogel. In the future, we will use these modules to predict the formulation of various major prescriptions, and we can find more novel core prescriptions.

Keywords: Pu-Ji-Fang, wound healing, Traditional Chinese Medicines

A Study on the Folk Botany of Taiwan Bitter Tea

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Herbal tea is made up of a variety of plants other than *Camellia sinensis* (L.) Kuntze. It is brewed or boiled in water. It is often taken from locally visible plants. There are many different formulas in tea, among which qīng-cǎo-chá, commercial herbal tea and kǔ- chá (bitter tea) are more common, but Taiwan's research in this area is not enough. The raw material formula has always been the heart of the store, there is no systematic sorting and record, many are just secret recipes of each family, the composition, safety and effectiveness of the raw materials have to be confirmed. This study continued the previous investigation of herbal tea, focusing on the investigation of bitter tea, and conducting interviews through a semi-structured questionnaire. The survey was conducted by traditional vendors of traditional herbal teas, and then the statistics were compiled and documented. In this study, a total of 86 stores were visited, and 73 kinds of bitter tea materials were sorted out. Although these materials have long been used as tea drinks, more research is needed to clarify their efficacy and safety. Traditional methods, phytochemistry, nutrition, physiology and toxicity should also be analyzed. This study will provide preliminary information on these plants. Investigate for future research.

Keywords: Herbal tea, qīng-cǎo-chá, kǔ-chá, bitter tea

A Feasibility Study on the Separation of Protopanaxadiol (PPD) and Protopanaxatriol (PPT) in *Panax quinquefolius* L. (American ginseng) by Simulated Moving Bed Chromatography

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In this study, the separation of protopanaxadiol (PPD) and protopanaxatriol (PPT) in an American Ginseng (*Panax quinqueflius* L.*)* root hair was achieved by a simulated moving bed chromatography (SMB). PPD and PPT were extracted by 95% ethanol. After removing polysaccharide from the crude extract, a clear and stable feedstock solution was obtained for the separation. A packed column with C18 modified silica was selected as the stationery phase for the chromatography. It is found that 50% of ethanol can effectively separate the PPD and PPT with the selected stationery phase. Effect of ethanol content on the extraction of Ginsenoside from the root hair is also reported in this presentation. A feedstock solution, which was obtained from 2 L of 95% ethanol and 300 g of root hair, contains Re(1.741 mg/mL), Rb1 (1.560 mg/mL), Rc (0.875 mg/mL), and Rd (0.647 mg/mL) is used for the SMB separation. Among the ginsenosides, Rb1, Rc, and Rd are categorized as PPT, and Re is PPD. A preliminary result shows that PPD and PPT can be separated by the SMB. Future study on the separation of ginsenoside isolate is also undergoing.This study will provide useful information for developing large scale SMB and its needs for pretreatment and post processing for isolating each ginsenoside.

Keywords: *Panax quinqueflius* L., SMB, Ginsenoside, protopanaxadiol (PPD), protopanaxatriol (PPT)

Bioactive Natural Products from *Eupatorium fortunei* with Inhibitory Activity on Melanin Generation and MMP-1 expression

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The family Asteraceae, belongs to the class of eudicotyledons, is one of the largest families of angiosperm plants. *Eupatorium fortunei* is a plant species in this family, distributed in fields or at riversides in Japan and China, and also is a common Chinese traditional medicine. Several researchers have found the plant have some bioactivity, such as anti-inflammatory, anticancer, antiviral, and decreased melanin production. In a preliminary screening, the EtOAc extract of *E. fortunei* significantly decreased melanin production and inhibited metalloproteinase-9 (MMP-9) expression. Investigation of EtOAc-soluble fraction of *E. fortunei* has led to the isolation of a new acetophenone derivative, eupatofortunone (**1**) and 7 known compounds (**2-8**). Among the isolates, *o*-coumaric acid (**4**) decreased melanin production with IC_{50} value of 18.5 μM in alpha-melanocyte-stimulating hormone (α-MSH) stimulated B16F10 melanoma cell, and taraxasterol (**6)** inhibited MMP-1 expression with IC_{50} value of 25.2 μM in Hs68 fibroblast cell stimulated with tumor necrosis factor alpha (TNF-α).

Keywords: *Eupatorium fortunei*, eupatofortunone, melanin, MMP-1, inhibitory activity