第三十三屆天然藥物研討會

The 33rd Symposium on Natural Products

議程及論文摘要集
AGENDA AND ABSTRACTS

主辦單位：高雄醫學大學藥學院天然藥物研究所
中華天然藥物學會

協辦單位：科技部生命科學研究推動中心
科技部生科司藥學及中醫藥學門
衛生福利部
衛生福利部國家中醫藥研究所
國立海洋生物博物館
國立中山大學
財團法人工業技術研究院
財團法人高醫藥學文教基金會

時　　間：中華民國 107 年 10 月 6 日至 10 月 7 日(星期六-日)
地　　點：高雄醫學大學第一教學大樓地下室演藝廳
地　　址：807 高雄市三民區十全一路 100 號

The 33rd Symposium on Natural Products

AGENDA AND ABSTRACTS

Organizations:

Graduate Institute of Natural Products, College of Pharmacy, Kaohsiung Medical University

The Society of Chinese Natural Medicine, Taiwan

Sponsor Organizations:

Ministry of Science and Technology, Life Science Research Promotion Center

Department of Science and Technology, Department of Pharmacy and Chinese Medicine

Ministry of Health and Welfare, Taiwan

National Research Institute of Chinese Medicine, Ministry of Health and Welfare

National Museum of Marine Biology & Aquarium

National Sun Yat-Sen University

Industrial Technology Research Institute

The Pharmacy Alumni Foundation for Culture and Education, Kaohsiung Medical University

Date: Oct. 6-7, 2018

Location: Performing Center, 1st Teaching Building, Kaohsiung Medical University

Address: 100, Shih-Chuan 1st Road, Kaohsiung, 80708, Taiwan

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壹、籌備委員會
Organizing Committee

主　任　委　員：鐘育志 校長

委　　員：**中華天然藥物學會 名譽理事長**
吳天賞、吳永昌、洪傳岳、陳介甫、謝明村

中華天然藥物學會 理事長
黃聰龍

中華天然藥物學會 理事
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中華天然藥物學會 監事
吳志中、陳益昇、黃文田、郭曜豪、謝伯舟
(依中文姓名筆劃排列)

高雄醫學大學藥學院 院長
黃耀斌

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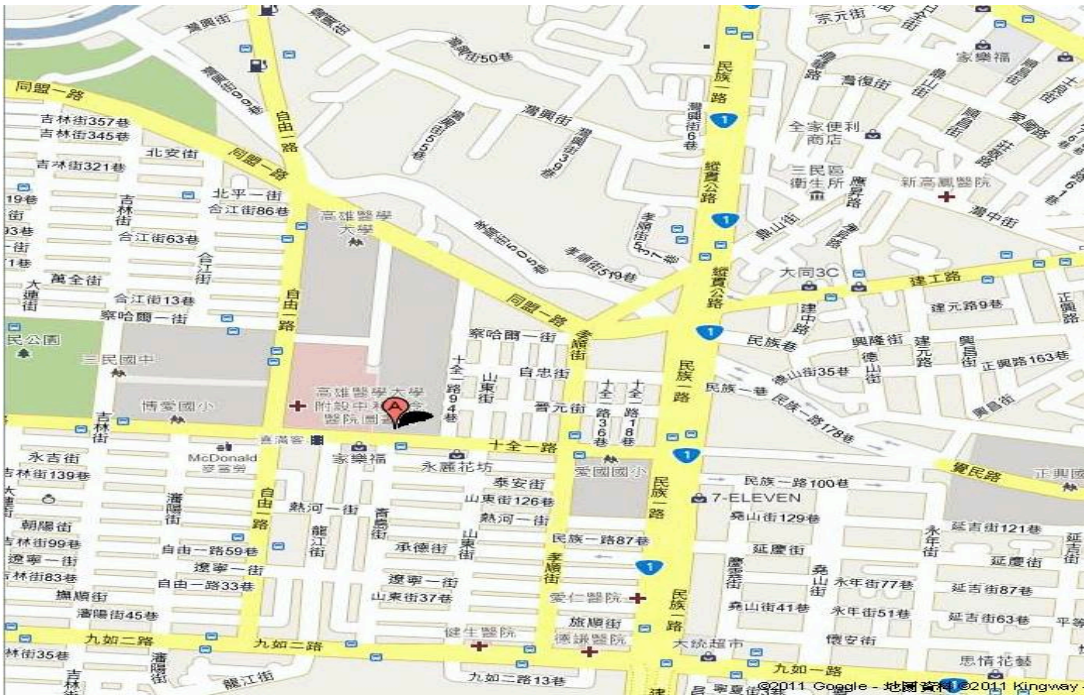
聯　絡　地　址：高雄市三民區十全一路 100 號

電　　話：07-3121101 轉 2685

傳　　真：07-3114773

貳、 高雄醫學大學校區位置圖
The Map of KMU Campus



參、研討會議程
AGENDA

地點: 高雄醫學大學第一教學大樓 B1 演藝廳

研討會日期：民國 107 年 10 月 6 日（週六）至 7 日（週日）

10 月 6 日 （六）

時間	講題	主講人	主持人
08:20～08:50	註冊/報到		
08:50～09:20	開幕典禮 貴賓致詞		
09:20～10:10	Keynote Speech： Learn from nature and target to need: development of first-in class GSTO inhibitor	吳永昌 講座教授/ 高雄醫學大學	張芳榮 所長/ 國家中醫藥研究所
10:10～10:30	大合照 & 茶敘		
10:30～11:00	Total synthesis of gymnocin-A, a polycyclic ether marine natural product	Prof. Yuji Mori (Meijo University, Japan)	許志宏 教授/ 中山大學 張永勳 教授/ 中國醫藥大學
11:00～11:30	Role of NRF2 signaling in the stress response of cancer stem cells	Prof. Mi-Kyoung Kwak (The Catholic University of Korea, Korea)	
11:30～12:00	*Avicennia marina* extract and its active compound as potential anti-androgenic alopecia hair loss agents	Prof. Wanchai De-Eknamkul (Chulalongkorn University, Thailand)	
12:00～13:40	午餐（勵學大樓 A3 教室） 中華天然藥物學會會員大會（勵學大樓 A3 教室） 科技部藥學暨中醫藥學門業務報告暨計畫撰寫分享（勵學大樓 A3 教室）		
13:40～14:10	Studies on the bioactive constituents from Formosanous plants	吳天賞 教授/ 成功大學	沈雅敬 教授/ 台灣大學 郭曜豪 教授/ 國家中醫藥研究所
14:10～14:40	Cancer chemopreventive effects and underlying molecular mechanisms of citrus polymethoxyflavones	潘敏雄 教授/ 台灣大學	
14:40～15:10	Targeting Axl/EZH2 for glioblastoma multiformis: from bench to IND approved	韓鴻志 教授/ 慈濟大學	

時間	講題	主講人	主持人
15:10～15:40	Phytomedicine polypharmacology: Modulation of multiple signaling mediators and networking for cancer therapy	徐麗芬 教授/ 中央研究院	
15:40～16:00	茶敘		
16:00～16:30	Target identification and mechanistic study of anti-cancer compounds in medicinal plants	楊文欽 教授/ 中央研究院	宋秉鈞 教授/ 東華大學 李美賢 教授/ 台北醫學大學
16:30～17:00	The turnover rates of marker substances in Huang-Chin-Tang from herbs to final products	王靜瓊 教授/ 台北醫學大學	
17:00～17:30	Biofunctional natural products from marine resources	廖志中 教授/ 中山大學	

10 月 7 日 （日）

時間	講題	主講人	主持人
09:00～9:30	Evaluate the essential active ingredients from Buyang Huanwu Decoction to become a botanic new drug for treatment of ischemic stroke	沈郁強 教授/ 國家中醫藥研究所	謝珮文 教授/ 長庚大學
09:30～10:00	From genomics to metabolomics, exploring bioactive polyynes from bacterial sources using an integrated strategy	楊玉良 助研究員/ 中央研究院	
10:00～12:00	Poster Flash		
12:00～13:30	午餐		
13:30～13:50	Phytochemical study on the folk medicine of Southeast Asia	鄭源斌 副教授/ 高雄醫學大學	柯宏慧 教授/ 高雄醫學大學
13:50～14:10	Antitumor bufadienolides and flavonol glycosides from Crassulaceae plants	黃慧琪 副教授/ 中國醫藥大學	
14:10～14:30	Establishment of plant extract libraries for high-throughput drug screening	顏嘉宏 助理教授/ 高雄醫學大學	
14:30～14:50	頒獎與閉幕典禮		

AGENDA

Oct. 6 (SAT)

Time	Title	Speaker	Modulator
08:20～08:50	Registration		
08:50～09:20	Opening Ceremony		
09:20～10:10	Keynote Speech： Learn from nature and target to need: development of first-in class GSTO inhibitor	Chair Prof. Yang-Chang Wu (Kaohsiung Medical University)	Prof. Fang-Rong Chang (National Research Institute of Chinese Medicine)
10:10～10:30	Group Photo & Coffee Break		
10:30～11:00	Total synthesis of gymnocin-A, a polycyclic ether marine natural product	Prof. Yuji Mori (Meijo University, Japan)	Prof. Jyh-Horng Sheu (National Sun Yat-sen University) Prof. Yuan-Shiun Chang (China Medical University)
11:00～11:30	Role of NRF2 signaling in the stress response of cancer stem cells	Prof. Mi-Kyoung Kwak (The Catholic University of Korea, Korea)	
11:30～12:00	*Avicennia marina* extract and its active compound as potential anti-androgenic alopecia hair loss agents	Prof. Wanchai De-Eknamkul (Chulalongkorn University, Thailand)	
12:00～13:40	Lunch		
13:40～14:10	Studies on the bioactive constituents from Formosanous plants	Prof. Tian-Shung Wu (National Cheng Kung University)	Prof. Ya-Ching Shen (National Taiwan University) Prof. Yao-Haur Kuo (National Research Institute of Chinese Medicine)
14:10～14:40	Cancer chemopreventive effects and underlying molecular mechanisms of citrus polymethoxyflavones	Prof. Min-Hsiung Pan (National Taiwan University)	
14:40～15:10	Targeting Axl/EZH2 for glioblastoma multiformis: from bench to IND approved	Prof. Horng-Jyh Harn (Tzu Chi University)	
15:10～15:40	Phytomedicine polypharmacology: Modulation of multiple signaling mediators and networking for cancer therapy	Prof. Lie-Fen Shyur (Academia Sinica, Taiwan)	

Time	Title	Speaker	Modulator
15:40～16:00	Coffee Break		
16:00～16:30	Target identification and mechanistic study of anti-cancer compounds in medicinal plants	Prof. Wen-Chin Yang (Academia Sinica, Taiwan)	Prof. Ping-Jyun Sung (National Dong Hwa University) Prof. Mei-Hsien Lee (Taipei Medical University)
16:30～17:00	The turnover rates of marker substances in Huang-Chin-Tang from herbs to final products	Prof. Ching-Chiung Wang (Taipei Medical University)	
17:00～17:30	Biofunctional natural products from marine resources	Prof. Chih-Chuang Liaw (National Sun Yat-sen University)	

Oct. 7 (SUN)

Time	Title	Speaker	Modulator
09:00～9:30	Evaluate the essential active ingredients from Buyang Huanwu Decoction to become a botanic new drug for treatment of ischemic stroke	Prof. Yuh-Chiang Shen (National Research Institute of Chinese Medicine)	Prof. Pei-Wen Hsieh (Chang Gung University)
09:30～10:00	From genomics to metabolomics, exploring bioactive polyynes from bacterial sources using an integrated strategy	Dr. Yu-Liang Yang (Academia Sinica, Taiwan)	
10:00～12:00	Poster Flash		
12:00～13:30	Lunch		
13:30～13:50	Phytochemical study on the folk medicine of Southeast Asia	Prof. Yuan-Bin Cheng (Kaohsiung Medical University)	Prof. Horng-Huey Ko (Kaohsiung Medical University)
13:50～14:10	Antitumor bufadienolides and flavonol glycosides from Crassulaceae plants	Prof. Hui-Chi Huang (China Medical University)	
14:10～14:30	Establishment of plant extract libraries for high-throughput drug screening	Dr. Chia-Hung Yen (Kaohsiung Medical University)	
14:30～14:50	Closing Ceremony		

肆、論文目錄

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天然物藥理(Natural Products Pharmacology)

傳統中藥(Traditional Chinese Medicine)

伍、 廣告、展覽及贊助廠商
EXHIBITIONS AND FINANCIAL SPONSORS

一、 贊助廣告廠商

三津科技股份有限公司
台塑生醫科技股份有限公司
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尚博生物科技有限公司
進階生物科技股份有限公司
俊懋企業股份有限公司
博大科學儀器股份有限公司
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二、 參加展覽廠商

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勁因科技有限公司
莊松榮製藥廠有限公司
喬璞科技有限公司
德碁科技有限公司
錫德斯生醫科技股份有限公司
鴻洺科技有限公司

三、 其他贊助廠商

昶安科技有限公司
康寧生物科技股份有限公司
賣艸人家有限公司

(依筆劃順序排列)

邀請演講

INVITED LECTURES

Yang-Chang Wu

Personal Profile

Name/ Position title	Yang-Chang Wu / Chair Professor
Nationality	Taiwan

Contact Information

Email Address	yachwu@kmu.edu.tw Phone 07-312-1101 ext. 5347
Mailing Address	100, Shih-Chuan 1st Road, Sanmin Dist., Kaohsiung, 80708, Taiwan

Education & Training Background

Higher Education (University or other degree-awarding institute)

From(yr)	To(yr)	Degree	University/ Institute	Country	Subject
1987	1987	Postdoctoral Fellow	University of North Carolina at Chapel Hill	U.S.A.	Pharmacy
1986	1987	Postdoctoral Fellow	Meijo University	Japan	Pharmacy
1982	1986	Doctor of Philosophy	Kaohsiung Medical University	Taiwan	Pharmacy
1979	1982	Master of Science	Kaohsiung Medical University	Taiwan	Pharmacy
1971	1975	Bachelor of Science	Kaohsiung Medical University	Taiwan	Pharmacy

Employment History

From(yr)	To (yr)	Department	Position/ professional status
2017	now	Graduate Institute of Natural Products, KMU, Taiwan	Chair Professor
2017	now	Research Center for Natural Products and Drug Development, KMU, Taiwan	Director
2017	now	Taiwan Institute of Economic Research, Taiwan	Consultant
2012	now	Academia-Industry Consortium for Agricultural Biotechnology Park, Taiwan	Executive director
2014	now	Niu-Chang-Chih Industry Association, Taiwan	Executive director
2014	now	National Standards Technical Committee, Niu-Chang-Chih Industry Association, Taiwan	Chairman
2014	2017	School of Pharmacy, College of Pharmacy, CMU, Taiwan	Chair Professor/ Vice President
2014	2016	Division of Pharmacy and Chinese medicine, Department of Life Science, Ministry of Science and Technology, Taiwan	Chairman
2012	2014	School of Pharmacy, College of Pharmacy, CMU, Taiwan	Chair Professor /Dean/Vice President
2010	2015	Experts on East Asian Herbal Medicine of the United States Pharmacopoeia Committee, USA	Member
2010	2012	Graduate Institute of Integrated Medicine, College of Chinese Medicine, CMU, Taiwan	Chair Professor/ Vice President
2009	2010	Graduate Institute of Natural Products, KMU, Taiwan	Chair Professor
2006	2009	Department of Research and Development, KMU,	Provost

		Taiwan	
1996	2010	Committee on Chinese Medicine and Pharmacy, Department of Health, Executive Yuan, Taiwan	Member
1992	2006	Graduate Institute of Natural Products, College of Pharmacy, KMU, Taiwan	Professor/Director
1990	1992	College of Pharmacy, KMU, Taiwan	Professor

Awards & Honors

Member of the American Society of Pharmacognosy and 10 more other association members. The member of 6 editorial board and ca. 30 referee member of journals

2017 Outstanding Venturing Award- Innovation and Startups Program

2015 12th National Innovation Award

2010 Outstanding Medical and Pharmaceutical Technology award of TienTe Lee Biomedical Foundation, Taiwan

2009 Outstanding research award of National Science Council, Taiwan

2007 Outstanding merit and high scholastic achievement to medical and pharmaceutical research award of Wang Ming-Ning Foundation

Selected Inventions & Patents

Title COMPOUND FOR INHIBITING GLUTATHIONE S-TRANSFERASE OMEGA 1 ACTIVITY, PHARMACEUTICAL COMPOSITION CONTAINING THEREOF, AND METHOD FOR SYNTHESIZING THE SAME

Inventors **Yang-Chang Wu**, Kuo-Hsiung Lee, Fang-Rong Chang, Da-Wei Chuang, Juan-Cheng Yang

Country	Patent type	Patent number	Date of Patent
Taiwan	Utility Patent	I503315	Aug. 16, 2014
USA	Utility Patent	8,969,406	Aug. 07, 2014
China	Utility Patent	1944383	Aug. 13, 2014
Japan	Utility Patent	5778301	Aug. 25, 2014
European union	Utility Patent	3081562	Feb. 28, 2018

Selected Publications

1. Chen HM, Chang FR, Hsieh YC, Cheng YJ, Hsieh KC, Tsai LM, Lin AS, **Wu YC***, Yuan SS *, 2011, "A Novel Synthetic Protoapigenone Analogue, WYC02-9, Induces DNA Damage and Apoptosis in DU145 Prostate Cancer Cells through Generation of Reactive Oxygen Species.", *Free Radical Biology & Medicine*, 50, 1151-1162.
2. Lu MC, El-Shazly M, Wu TY, Du YC, Chang TT, Chen CF, Hsu YM, Lai KH, Chiu CP, Chang FR***** and **Wu YC***, 2013, "Recent Research and Development of *Antrodia cinnamomea*", *Pharmacology & Therapeutics*,139, 124-156.
3. Lai KH, Lu MC, Du YC, El-Shazly M, Wu TY, Hsu YM, Henz A, Yang JC, Backlund A, Chang FR* and **Wu YC***, 2016,"Cytotoxic Lanostanoids from *Poria cocos*", *Journal of Natural Products*, 79, 2805-2813.
4. Li CC, Yang JC, Lu MC, Lee CL, Peng CY, Hsu WY, Dai YH, Chang FR, Zhang DY, Wu WJ* and **Wu YC***, 2016, "ATR-Chk1 Signaling Inhibition as a Therapeutic Strategy to Enhance Cisplatin Chemosensitivity in Urothelial Bladder Cancer", *Oncotarget* , 7, 1949-2553
5. Lee CC, Chang WH, Chang YS, Liu TY, Chen YC, **Wu YC*** and Chang JG*, 2017, "4β-Hydroxywithanolide E Modulates Alternative Splicing of Apoptotic Genes in Human Hepatocellular Carcinoma Huh-7 Cells", Scientific Reports, 7: 7290.

※ More than 581 research articles in SCI refereed journals and authorships of several book chapters. More than 40 patents granted or in application. More than 20 industry-academic cooperation. More than 6 patent/tech transfer practices.

Learn from Nature and Target to Need: Development of first-in-class GSTO inhibitor

Yang-Chang Wu (吳永昌)

1. Research Center for Natural Products & Drug Development, 2. Graduate Institute of Natural Products and 3. Department of Medical Research, Chung-Ho Memorial Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan

The Omega class glutathione s-transferases (GSTO) have distinct function that plays a novel role unrelated to the function of other GSTs family. The signaling pathway of GSTO, an enzyme of cell oxidative stress, plays an important role in cancer progression. The up-regulation of GSTO has been linked to several human cancer diseases. Recently, we have demonstrated that GSTO1 has an ability to affect the levels of cisplatin in tumor. In addition, overexpression of GSTO1 is widely observed in many cancer types and several cancers such as bladder, lung, colon, and kidney are significantly associated with poor prognosis. These findings highlight a new therapeutic option for the development of the new anti-cancer drug. We pay more attention to discover and develop the natural products-modified structure as GSTO inhibitor. Our teams consolidated research and development to fulfill the project of the preclinical studies including A) Manufacture of drug substance, B) Preformulation and formulation, C) PK/Range-finding/Toxicokinetic, D) Efficacy, MOA of GSTO inhibitors, E) Development of New Generation Inhibitors and Patent application. Collectively, development of GSTO inhibitor will be a new add-on (adjuvant) therapeutic agent for improving the efficacy of platinum-based chemotherapy.

Yuji Mori

Personal Profile

Name/Position title	Yuji Mori (森　裕二) / Professor
Nationality	Japan

Contact Information

Email Address	mori@meijo-u.ac.jp	Phone	+81-52-834-2658
Mailing Address	Faculty of Pharmacy, Meijo University (名城大学) 150 Yagotoyama, Tempaku-ku, Nagoya 468-8503, Japan		

Education & Training Background

Higher Education (University or other degree-awarding institute)

From (yr)	To (yr)	Degree	University/ Institute	Country	Subject
1969	1973	B. S.	Gifu Pharmaceutical University	Japan	Pharmacy
1973	1978	Ph. D.	Faculty of Pharmaceutical Sciences, Kyoto University	Japan	Organic chemistry

Employment History

From (yr)	To (yr)	Department	Position/ professional status
1978	1991	Faculty of Pharmacy, Meijo University	Assistant Professor
1983	1985	Department of Chemistry, Columbia University	Postdoctoral researcher
1991	1993	Faculty of Pharmacy, Meijo University	Senior Lecturer
1993	2000	Faculty of Pharmacy, Meijo University	Associate Professor
2000	present	Faculty of Pharmacy, Meijo University	Professor
2002	2005	Graduate School of Environmental and Human sciences, Meijo University	Dean
2003	2005	Faculty of Pharmacy, Meijo University	University Councilor
2004	2004	Kyoto Pharmaceutical University	Visiting Lecturer
2009	2011	Graduate School of Environmental and Human sciences, Meijo University	Dean
2011	2015	Research Institute of Meijo University	Director
2012	2012	Graduate School of Pharmaceutical Sciences, Nagoya City University	Visiting Lecturer
2015	2017	Graduate School of Environmental and Human sciences, Meijo University	Dean
2016	2017	Graduate School of Pharmaceutical Sciences, Kyoto University	Visiting Lecturer

Awards & Honors

1990 The Pharmaceutical Society of Japan Tokai Branch Award
1993 The Pharmaceutical Society of Japan Award for Young Chemists
2018 The Pharmaceutical Society of Japan Award

Selected Publications

1. Sakai, T.; Ishihara, A.; Mori, Y. Synthesis of the KLMN Fragment of Gymnocin-A from the FGH Fragment. *J. Org. Chem.* **2017**, *82*, 3976−3981.
2. Sakai, T.; Mori, Y. Strategies for Brevisamide Synthesis Based on the Method for Constructing the Tetrahydropyranyl Core. *Heterocycles*, **2017**, *95*, 81–115.
3. Sakai, T.; Matsushita, S.; Arakawa, S.; Mori, K.; Tanimoto, M.; Tokumasu, A.; Yoshida, T.; Mori, Y. Total Synthesis of Gymnocin‐A. *J. Am. Chem. Soc.* **2015**, *137*, 14513–14516.
   Top 20 Most Read Articles during 2015–2016
4. T.; Sakai, A.; Fukuta, K.; Nakamura, M.; Nakano, Y.; Mori: Total Synthesis of Brevisamide Using an Oxiranyl Anion Strategy. *J. Org. Chem*. **2016**, *81*, 3799–3808.
5. Sakai, T.; Asano, H.; Furukawa, K.; Oshima, R.; Mori, Y. Synthesis of the KLMN Fragment of Gymnocin-A Using Oxiranyl Anion Convergent Methodology. *Org. Lett.* **2014**, *16*, 2268−2271.
6. Sakai, T.; Matsushita, S.; Arakawa, S.; Kawai, A.; Mori, Y. Synthetic Study of Gymnocin-A: Synthesis of the ABC Ring Fragment. *Tetrahedron Lett.* **2014**, *55*, 6557–6560.
7. Sakai, T.; Sugimoto, A.; Tatematsu, H.; Mori ,Y. Divergent Synthesis of *trans*-Fused Polycyclic Ethers by a Convergent Oxiranyl Anion Strategy. *J. Org. Chem*. **2012**, *77*, 11177–11191.
8. Sakai, T.; Sugimoto, A.; Mori, Y. A Convergent Strategy for the Synthesis of Polycyclic Ethers by Using Oxiranyl Anions. *Org. Lett*. **2011**, *13*, 5850–5853.
9. Furuta, H.; Hasegawa, Y.; Hase, M.; Mori, Y. Total Synthesis of Gambierol by Using Oxiranyl Anions. *Chem. Eur. J*. **2010**, *16*, 7586–7595.
10. Furuta, H.; Hasegawa, Y.; Mori Y. Total Synthesis of Gambierol. *Org. Lett*. **2009**, *11*, 4382–4385. Top 10 Most Read Articles during mid 2009.

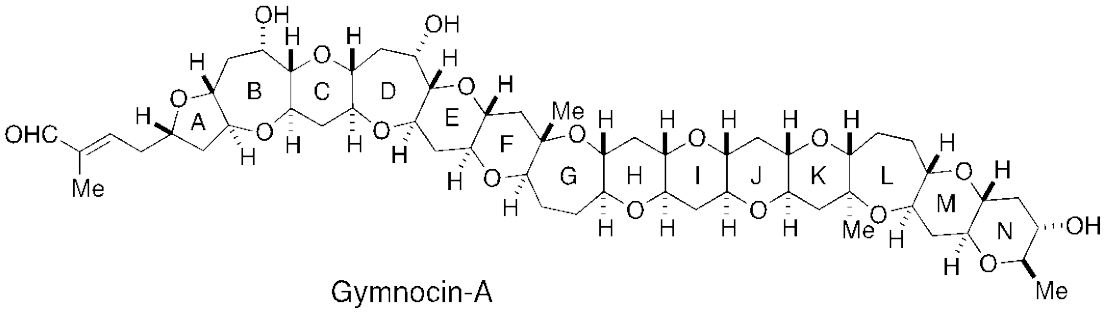
Total Synthesis of the Red-Tide Toxin Gymnocin-A

Yuji Mori（森　裕二）

Faculty of Pharmacy, Meijo University
150 Yagotoyama, Tmepaku-ku,Nagoya 468-8503, Japan

Marine polycyclic ether biotoxins produced by dinoflagellates are interesting targets for synthetic chemists as they have unique biological activities and complex structures. Gymnocin-A was isolated from a culture of the red-tide dinoflagellate *Karenia mikimotoi* as a potent cytotoxic principle, which is characterized by a stunning array of 14 contiguous ether rings containing four seven-membered rings.

Our longstanding interest in synthetic chemistry on marine polycyclic ethers led to the recent development of a new [X+2+X]-type convergent oxiranyl anion strategy, which opens a pathway for the synthesis of large polycyclic ethers. We report here the total synthesis of gymnocin-A based on this convergent strategy. The successful implementation of the synthesis highlights the efficient assembly of three ABC, FGH, and KLMN polyether fragments by iterative coupling of triflates and highly reactive oxiranyl anions generated from epoxy epoxy sulfones.



Gymnocin-A

Key words: polycyclic ether, red-tide toxin, synthesis, oxiranyl anion

Mi-Kyoung Kwak

Personal Profile

Name/Position title	Mi-Kyoung Kwak / Professor / Dean
Nationality	Republic of Korea

Contact Information

Email Address	mkwak@catholic.ac.kr	Phone	+82-2-2164-6532
Mailing Address	43 Jobong-ro, Bucheon, Gyeonggi-do 14662, The Catholic University of Korea, College of Pharmacy		

Education & Training Background

Higher Education (University or other degree-awarding institute)

From (yr)	To (yr)	Degree	University/ Institute	Country	Subject
1987	1991	B.S.	Seoul National University	ROK	College of Pharmacy
1991	1993	M.S.	Graduate School of Seoul National University	ROK	Pharmacology
1993	1997	Ph.D.	Graduate School of Seoul National University	ROK	Pharmacology

Employment History

From (yr)	To (yr)	Department	Position/ professional status
1997	1998	Korea Research Institute of Bioscience and Biotechnology	Postdoctoral Fellow
1999	2001	Johns Hopkins University	Postdoctoral Fellow
2002	2004	Johns Hopkins University	Research Faculty
2004	2001	Yeungnam University, College of Pharmacy	-Associate Professor
2011	2018	The Catholic University of Korea, College of Pharmacy	-Professor / Dean (2017 ~)

Selected Publications

1. Kim D, Choi BH, Ryoo IG, Kwak MK, High NRF2 level mediates cancer stem cell-like properties of aldehyde dehydrogenase (ALDH)-high ovarian cancer cells: inhibitory role of all-trans retinoic acid in ALDH/NRF2 signaling. Cell Death Dis. (2018) 9(9):896.
2. Ryoo IG, Choi BH, Ku SK, Kwak MK, High CD44 expression mediates p62-associated NFE2L2/NRF2 activation in breast cancer stem cell-like cells: Implications for cancer stem cell resistance. Redox Biol. (2018) 17: 246.
3. Choi BH, Ryu DY, Ryoo IG, Kwak MK,NFE2L2/NRF2 silencing-inducible miR-206 targets c-MET/EGFR and suppresses BCRP/ABCG level in cancer cells. Oncotarget (2017) 8(63):107188.
4. Jung KA, Lee S, Kwak MK, NFE2L2/NRF2 activity is linked to mitochondria and AMP-activated protein kinase signaling in cancers through miR-

181c/mitochondria-encoded cytochrome c oxidase regulation Antioxid Redox Signal (2017) 27(13): 945.
5. Kim DH, Choi BH, Ku SK, Park JH, Oh E, Kwak MK, Beneficial effects of sarpogrelate and rosuvastatin in high fat diet/streptozotocin-induced nephropathy in mice PLoS One (2016) 11(4):e0153965.
6. Song MG, Ryoo IG, Choi HY, Choi BH, Kim ST, Heo TH, Lee JY, Park PH, Kwak MK, NRF2 Signaling Negatively Regulates Phorbol-12-Myristate-13-Acetate (PMA)-Induced Differentiation of Human Monocytic U937 Cells into Pro-Inflammatory Macrophages PLoS One. (2015) 29;10(7):e0134235
7. Ryoo IG, Choi BH, Kwak MK, Activation of NRF2 by p62 and proteasome reduction in sphere-forming breast carcinoma cells Oncotarget (2015) 6(10):8167.
8. Jung KA, Choi BH, Kwak MK, The c-MET/PI3K signaling is associated with cancer resistance to doxorubicin and photodynamic therapy by elevating BCRP/ABCG2 expression Mol Pharmacol (2015) 87(3):465.
9. Choi BH, Ryoo IG, Kang HC, Kwak MK, The Sensitivity of Cancer Cells to heophorbide a-Based Photodynamic Therapy Is Enhanced by NRF2 Silencing PLoS One (2014) 16;9(9):e107158
10. Ryoo IG, Ha H, Kwak MK, Inhibitory Role of the KEAP1-NRF2 Pathway in TGFβ1-Stimulated Renal Epithelial Transition to Fibroblastic Cells: A Modulatory Effect on SMAD Signaling. PLoS One. (2014) 9(4):e93265.
11. Manandhar S, Choi BH, Jung KA, Ryoo IG, Song M, Kang SJ, Choi HG, Kim JA, Park PH, and Kwak MK, NRF2 inhibition represses ErbB2 signaling in ovarian carcinoma cells: Implications for tumor growth retardation and docetaxel sensitivity. Free Radic Biol & Med (2012) 52: 1773.
12. Kim TH, Hur EG, Kang SJ, Kim JA, Thapa D, Lee YM, Ku SK, Jung Y, Kwak MK, NRF2 blockade suppresses colon tumor angiogenesis by inhibiting hypoxia-induced activation of HIF-1α (2011). Cancer Res. 71(6): 2260.
13. Shin DH, Park HM, Jung KA, Choi HG, Kim JA, Kim DD, Kim SG, Kang KW, Ku SK, Kensler TW, Kwak MK, The NRF2-heme oxygenase-1 system modulates cyclosporin A-induced epithelial-mesenchymal transition and renal fibrosis. Free Radic Biol Med (2010) 48(8):1051.
14. Shim GS, Manandhar S, Shin DH, Kim TH, Kwak MK, Acquisition of doxorubicin resistance in ovarian carcinoma cells accompanies activation of the NRF2 pathway. Free Radic Biol Med (2009) 47: 1619.

Role of NRF2 signaling in the stress response of cancer stem cells

Mi-Kyoung Kwak*, In-geun Ryoo, Donghyeok Kim
The Catholic University of Korea, College of Pharmacy,
Gyeonggido, Republic of Korea

Abstract

Cancer stem cells (CSCs) are believed to be responsible for tumor recurrence after chemotherapy. Cluster of differentiation 44 (CD44) is the most common CSC marker and high CD44 expression has been associated with anticancer drug resistance, tumor recurrence, and metastasis. In this study, we aimed to investigate the molecular mechanism by which CD44 and nuclear factor, erythroid 2-like 2 (NFE2L2; NRF2), a key regulator of antioxidant genes, are linked to CSC resistance using $CD44^{high}$ breast CSC-like cells. NRF2 expression was higher in $CD44^{high}$ cell populations isolated from doxorubicin-resistant MCF7 (ADR) than in corresponding $CD44^{low}$ cells. High NRF2 expression in the $CD44^{high}CD24^{low}$ CSC population (ADR44P) established from ADR cells depended on standard isoform of CD44. Silencing of *CD44* or overexpression of CD44 resulted in the reduction or elevation of NRF2, respectively. As functional implications, *NRF2* silencing rendered ADR44P cells to retain higher levels of reactive oxygen species and to be sensitive to anticancer drug toxicity. Moreover, *NRF2*-silenced ADR44P cells displayed tumor growth retardation and reduced colony/sphere formation and invasion capacity. In line with these, CD44 significantly colocalized with NRF2 in breast tumor clinical samples. In addition to CD44, we observed that the aldehyde dehydrogenase (ALDH)-enriched ovarian cancer stem-like cells expressed high levels of NRF2 and its target genes, and stable silencing of *NRF2* led to the reductions in CSC markers expression, colony formation, sphere formation, doxorubicin resistance, and tumor growth in xenografts model. Collectively, These results provide insight into the molecular basis of the CD44/ALDH-mediated development of CSC-like properties such as stress/treatment resistance, and suggest that NRF2 might be a promising therapeutic target for the control of CSC.

Key words: Cancer stem cells, drug resistance, NRF

Wanchai De-Eknamkul

Personal Profile

Name/Position title	Wanchai De-Eknamkul / Professor
Nationality	Thai

Contact Information

Email Address	dwanchai@chula.ac.th	Phone	+6686 318 5309
Mailing Address	Department of Pharmacognosy and Pharmaceutical Botany Faculty of Pharmaceutical Sciences Chulalongkorn University Phayathai Road, Pathumwan District, Bangkok 10330, Thailand		

Education & Training Background

Higher Education (University or other degree-awarding institute)

From (yr)	To (yr)	Degree	University/ Institute	Country	Subject
1982	1987	Ph.D.	University of Guelph	Canada	Plant Biochem.
1989	1990	Post. Doc	University of Munich (LMU)	Germany	Plant Nat. Products

Employment History

From (yr)	To (yr)	Department	Position/ professional status
1980	Present	Pharmacognosy and Pharmaceutical Botany	Faculty member, from Lecturer to Professor

Awards & Honors

Germany's Alexander von Humboldt Research Fellowship, 1989-1990

Japan's JSPS-UNESCO Visiting Scientist (The University of Tokyo), 1994, 2000, 2006

The Thailand Research Fund's "Best Research Award 1999" on Plaunotol biosynthetic studies in *Croton sublyratus* (US patent no. 5, 879, 916, March 9, 1999)

Thailand's BIOTEC Research Group Development Grant, 2003-2008 (20-million Baht)

Thailand's National Innovation Agency's "Innovation Ambassador Award 2008"

Technology Licensing on "Innovative Analysis of Artemisinin in *Artemisia* Leaves" to *Artemisinin and Farming International Company*, February 2009

National Research Council of Thailand's Invention Award 2010 on a new analytical technique for determination of artemisinin in *Artemisia* leaves

Inventions & Patents

1. De-Eknamkul W. and P. Tansakul. Geranylgeraniol-18-hydroxlase from *Croton sublyratus* US patent no. 5, 879, 916, March 9, 1999
2. De-Eknamkul W. and P. Tansakul. Production of an Anti-Peptic Ulcer Plaunotol by an Enzymatic Reaction, Thai Patent no. 9858, September 15, 2000
3. Koobkokkruad, T., C. Kerdmanee, W. De-Eknamkul. Development of *Artemisia*

annua Strains for y Yield Improvement of Artemisinin by Gamma Irradiation. Submitted for patenting, No. 0901001074, on March 12, 2009, and advertisement since August 2012

Selected Publications

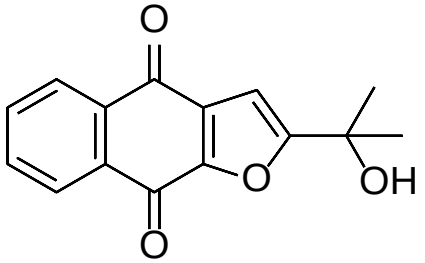
1. Promden, W., Viriyabancha, W., Monthakantirat, O., Umehara, K., Noguchi, H., De-Eknamkul, W. Correlation between the Potency of Flavonoids on Mushroom Tyrosinase Inhibitory Activity and Melanin Synthesis in Melanocytes. *Molecules* 2018, 23 (6), 1403
2. Wunnakup, T., Vimolmangkang, S., De-Eknamkul, W. 2017. Transient expression of the homogentisate phytyltransferase gene from Clitoria ternatea causes metabolic enhancement of a-tocopherol biosynthesis and chlorophyll degradation in tomato leaves. *J. Plant Biochem. Biotechnol*. (27):55–67
3. Karnsomwan, W., Rungrotmongkol, T., De-Eknamkul, W., Chamni, S. 2016. In Silico Structural Prediction of Human Steroid 5α-Reductase Type II, Medicinal Chemistry Research, 25, (6):1049-1056
4. Jain R, Monthakantirat O, Tengamnuay P, De-Eknamkul W. 2016. Identification of a new plant extract for androgenic alopecia treatment using a non-radioactive human hair dermal papilla cell- based assay. Jain et al. BMC Complementary and Alternative Medicine, 16, (1):18
5. Sintupachee S, Promden W, Ngamrojanavanich N, Sitthithaworn W, De-Eknamkul W. 2015. Functional expression of a putative geraniol 8-hydroxylase by reconstitution of bacterially expressed plant CYP76F45 and NADPH-cytochrom*e P45*0 reductase CPR I from *Croton stellatopilosus* Ohba. *Phytochemistry*. 118:204-215.
6. Sintupachee S, Ngamrojanavanich N, Sitthithaworn W, De-Eknamkul W. 2014. Molecular cloning, bacterial expression and functional characterisation of cytochrome P450 monooxygenase, CYP97C27, and NADPH-cytochrome P450 reductase, CPR I, from *Croton stellatopilosus* Ohba. *Plant Science : An International Journal of Experimental Plant Biology* 229:131-141.
7. Jain R, De-Eknamkul W. 2014. Potential targets in the discovery of new hair growth promoters for androgenic alopecia. *Expert Opin Ther Targets* 18:787-806.
8. Promden W, Monthakantirat O, Umehara K, Noguchi H, De-Eknamkul W. 2014. Structure and antioxidant activity relationships of isoflavonoids from *Dalbergia parviflora*. *Molecules* 19:2226-2237.
9. Jain R, Monthakantirat O, Tengamnuay P, De-Eknamkul W. 2014. Avicequinone C isolated from Avicennia marina exhibits 5alpha-reductase-type 1 inhibitory activity using an androgenic alopecia relevant cell-based assay system. *Molecules* 19:6809-6821

From Simple Screening of Natural 5-α Reductase Inhibitors to Discovery of an Anti-Hair Loss Compound with Complete Effects on Androgenic Alopecia-Causing Mechanism

Wanchai De-Eknamkul[1*], Sukanya Numsawat[1,2], Woraanong Prugsakij[1,3], Parkpoom Tengamnuay[3]

[*1]Natural Product Biotechnology Research Group, Department of Pharmacognosy and Pharmaceutical Botany, [2]Department of Biochemistry and Microbiology, [3]Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok 10330, Thailand

Steroid 5α-reductase (5α-R) is an enzyme catalyzing the conversion of testosterone (T) to 5α-dihydrotestosterone (DHT). Overexpression of 5α-R has been known to affect the balance between T and DHT causing androgenic disorders, such as prostate cancer, hirsutism, and androgenic alopecia. Androgenic alopecia (AGA) is a major type of scalp hair loss caused by the over-production of DHT, a potent androgen located in the hair follicles. Therefore, 5α-R has been considered as an important target for searching potential inhibitors as anti-AGA agents. An HPTLC method was developed as part of a new non-radioactive cell-based assay for detecting the formation of DHT. Among randomly selected 50 plant extract samples, only the one of *Avicennia marina* was found to exhibit the 5α-R inhibitory activity. The active constituent was subsequently isolated and identified as a known furanonaphthaquinone, namely avicequinone C. Interestingly, mechanistic studies revealed that avicequinone C not only inhibits the 5α-R activity in hair dermal papilla cells, but also inhibits the subsequent step of translocation of DHT-androgen receptor complex from the cytoplasm to the nucleus, with concomitant expression of hair growth-promoting factors. These results suggested that avicequinone C has a potential for developing as a natural anti-AGA agent.



Avicequinone C

Key words: avicequinone C; *Avicennia marina*; androgenic alopecia, anti-hair loss, 5α-reductase inhibitor

Tian-Shung Wu

Personal Profile

Name/Position title	Tian-Shung Wu/ Emeritus Professor
Nationality	Taiwan

Contact Information

Email Address	tswu@mail.ncku.edu.tw	Phone	+886-6-2757575#65333
Mailing Address	No.1, University Road, Tainan City 701, Taiwan (R.O.C)		

Education & Training Background

Higher Education (University or other degree-awarding institute)

From (yr)	To (yr)	Degree	University/ Institute	Country	Subject
1981	1984	Degree	Meijo University	Japan	Pharmacy

Employment History

From (yr)	To (yr)	Department	Position/ professional status
2018		National Cheng Kung University	Emeritus Professor
2014		Tajen University	Adjunct Chair Professor
2009	2013	China Medical University	Dean & Chair Professor
2004	2007	National Research Institute of Chinese Medicine	Director
2001	2004	Center for General Education	Director
1997	2000	Department of Chemisty	Chairman

Awards & Honors

1987-1994	Excellent Research Award, National Science Council R.O.C.
1993	The 1st Author Prize, The Ministry of Education, R. O. C.
1985-1986, 1995-1996, 1998-2000	The 1st Research Award, National Science Council R.O.C.
2002	Distinguished Professor, National Cheng Kung University.
2003	The 13th Annual Wang Ming-Ning Award.
2006	Adjunct Chair professor, Providence University.
2006	The 2nd Yung-Shin Li Tian-De Medical and Pharmaceutical Technolgy Excellence Award.
2007	Awarded the Honor of KT Li Honorary Scholar Award.

Selected Publications

The papers published in the natural products chemistry and related field are more than 500 and 31 patents.

Studies on the Bioactive Constituents from Formosan Plants

Tian-Shung Wu[1, 2]

[1].School of Pharmacy, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[2].Department of Pharmacy and Graduate Institute of Pharmaceutical Technology, Tajen University, Pingtung 907, Taiwan, R.O.C.

1. Traditional Chinese medicine is one of the most valuable heritage of Chinese culture. It is a Chinese quintessence and also called as traditional medical science, which resulted from the experience accumulation and of many physicians in all ages and passing from generation to generation. Some analysis indicated that although Chinese people faced various wars and natural disasters, it did not appear serious public health problems such as plague and smallpox occurred in medieval Europe. The key point maybe that the traditional Chinese medicine provided the whole Chinese people a physiological defense. However, traditional Chinese medicine could only be inherited by mentoring system before the development of modern science. And usually the disciples could not learn the essence from the master in depth. Therefore, this system was almost collapsed in several timings.
2. Various modern scientific experimental instruments were developed successively and applied to explore the new drugs. Nowadays, extraction and analysis of the small molecules, and identification of the active principles in Chinese herbal medicines are more and more popular. It is well established and holds a place in treating diseases and preserving health. But there are still several troublesome diseases such as cancer, dementia, neurodegeneration, and Parkinson's disease, which are very difficult to be cured. Thus it leaves the space for the alternative therapies.
3. Although the modern advance of traditional Chinese medicine science was declared for a long time, it was not improved so much since many Chinese medicinal theories could not be identified by modern scientific methods. For example, the meridians and acupuncture points could not be corresponded in modern anatomy. In the post-genetic era, the new drug discovery is still a severe challenge. However, the direct human clinical data left by past physicians provide us an important blueprint, such as that Prof. You-you Tu explored the antimalarial drug "artemisinin" based on the traditional Chinese medicine clinical experiences. The development of traditional Chinese medicine should follow the strategy of reviewing past and planning future, and therefore to explore new plant medicines maybe the best shortcut. Hopefully, the new plant medicines could overcome various diseases and prolong the human’s age, and thus it could be kept pace with the modern medicines.
4. Several abundant and potent bioactive principles in natural medicinal plants were characterized and applied to be clinical drugs. However, these drugs were so few and not proportional to the quantity of natural medicinal plants commonly used in traditional Chinese medicine. In addition, although the research on the active principles from traditional Chinese medicine has continued for more than one hundred years and the development of experimental instrument is so fast, the advance of new plant medicines is still slow. Why? It means that we all should change our thinking and make a fresh start to yield good results of traditional Chinese medicine in 21st century.
5. In the present symposium, chemical constituents from the stems of *Machilus philippinensis* and the roots of *Lindera aggregata* along with their bioactivities would be reported.

Min-Hsiung Pan

Personal Profile

Name/Position title	Min-Hsiung Pan / Distinguished Professor
Nationality	Taiwan

Contact Information

Email Address	mhpan@ntu.edu.tw	Phone	02-3366 4133
Mailing Address	No. 1, Sec. 4, Roosevelt Road, Taipei, 10617 Taiwan (R.O.C) Institute of Food Science and Technology R408		

Education & Training Background

Higher Education (University or other degree-awarding institute)

From	To	Degree	University/ Institute	Country	Subject
1996	2000	Ph.D	College of Medicine, NTU	Taiwan	Biochemistry and Molecular Biology
1993	1995	Master	Department of Food Science, NTOU	Taiwan	Food Chemistry
1991	1993	Bachelor	Department of Food Science, NTOU	Taiwan	Food Chemistry

Employment History

From (yr)	To (yr)	Department	Position/professional status
2015/08	Now	Institute of Food Science and Technology, NTU	Distinguished Professor
2018/08	Now	Institute of Food Science and Technology, NTU	Graduate Chair
2013/08	2015/07	Institute of Food Science and Technology, NTU	Professor
2012/08	2013/07	Research & Development Affairs, NKMU	Dean/Professor
2011/08	2012/07	Academic Affairs, NKMU	Associate Dean/Professor
2009/07	2011/01	Interns and Alumni Service Division, NKMU	Director/Professor
2007/08	2008/07	Department of Seafood Science, NKMU	Director/ Professor
2005/08	2007/07	Department of Seafood Science, NKMU	Director/ Associate Professor
2005/06	2005/09	Department of Food Science at Rutgers SEBS - Rutgers University	Visiting Scholar
2004/08	2007/07	Department of Seafood Science, NKMU	Associate Professor
2001/08	2004/07	Department of Seafood Science, NKMU	Assistant Professor
2000/08	2001/07	Institute of Biochemistry, College of Medicine, NTU	Postdoctoral Associate

Awards & Honors

2015, Outstanding reviewer Award of Journal of Agriculture and Food Chemistry
2015, National Taiwan University, Food Safety Center, Health and safety Visit External experts. (2015/6/17-2016/12/31)
2014, Fellow, Agricultural & Food Chemistry Division, American Chemistry Society
2013, Outstanding Research and Technology Development Award of Health Food Society of Taiwan
2011, Outstanding Research Award of National Science Council
2009, Outstanding Research Award of National Kaohsiung Marine University, Taiwan

Inventions & Patents

Application of polymethoxyflavonoids on medicine prepared for treating skin papillomatosis
Curcumin Herbal Extract and Its Usage of Improving Sperm Function
Herbal natural complex for improving sperm function and manufacturing method thereof
Hydroxylated Polymethoxyflavone Compositions
Method use of polymethoxyflavones (PMFs) in body composition management.
Pharmaceutical composition with liver-protecting effect and preparation method thereof
Trans-2-nonadecyl-4-hydroxymethyl-1,3-dioxolane and method for producing thereof
The uses of hydroxyl polymethoxylflavones and/or derivative thereof
Use of tea polyphenols for treating and/or preventing nicotine or nicotine-derived compounds or estrogen induced breast cancer
Uses of hydroxyl polymethoxylflavones (HPMFs) and derivatives thereof
Method use of polymethoxyflavones (PMFs) in body composition management.

Selected Publications

1. Wu, JC, Tsai, ML, Lai, CS, Lo, CY, Ho, CT, Wang, YJ, Pan, MH*. Polymethoxyflavones prevent benzo[a]pyrene/dextran sodium sulfate-induced colorectal carcinogenesis through modulating xenobiotic metabolism and ameliorate autophagic defect in ICR mice. International Journal of Cancer. 2018. 142(8):1689-1701.
2. Chiou, YS, Huang, Q, Ho, CT, Wang, YJ, Pan, MH*. Directly interact with Keap1 and LPS is involved in the anti-inflammatory mechanisms of (-)-epicatechin-3-gallate in LPS-induced macrophages and endotoxemia. 2016. Free Radical Biology and Medicine. 94:1-16.
3. Lai, CS., Liao, SN, Tsai, ML, Kalyanam, N, Majeed, M, Majeed, A, Ho, CT, **Pan, MH***. Calebin-A inhibits adipogenesis and hepatic steatosis in high-fat diet-induced obesity via activation of AMPK signaling. Molecular Nutrition and Food Research. 2015. 59(10):1883-1895.
4. Tsai ML, Chiou YS, Chiou LY, Ho CT, **Pan MH***. Garcinol suppresses inflammation -associated colon carcinogenesis in mice. Molecular Nutrition and Food Research. 2014. 58(9):1820-1829.
5. Wu, JC, Wang, FZ, Tsai, ML, Lo, CY, Badmaev, V, Ho, CT, Wang, YJ, **Pan, MH***. Se-Allylselenocysteine Induces Autophagy by Modulating the AMPK/mTOR Signaling Pathway and Epigenetic Regulation of PCDH17 in Human Colorectal Adenocarcinoma Cells. 2015. Molecular Nutrition & Food Research. 59 (12) 2511-2522.

Cancer chemopreventive effects and underlying molecular mechanisms of citrus polymethoxyflavones

Min-Hsiung Pan

Institute of Food Science and Technology, National Taiwan University.
Email: mhpan@ntu.edu.tw

Abstract

Chemoprevention been recognized as a promising strategy to prevent human disease by using natural compounds to prevent, block, inhibit, reverse, or retard the process of disease. Polymethoxyflavone (PMFs) and hydroxyl PMFs (OH-PMFs) are a unique class of flavonoids that almost exclusively exists in citrus genus, especially in the peel. Moreover, OH-PMFs can be formed from their corresponding PMFs counterparts by hydrolysis during storage. Our studies have revealed both PMFs and OH-PMFs exhibit a broad spectrum of biological activity, such as inhibition of cancer cells growth, suppression of inflammatory mediators and skin carcinogenesis as well as colonic tumorigenesis. In addition, we found OH-PMFs exhibit epigenetics regulation properties. Understanding of the chemopreventive mechanisms of PMFs and OH-PMFs might promote further application for prevention and treatment of various human diseases. Moreover, investigation of chemopreventive property of OH-PMFs and elucidate the structural feature on the type of functional group of PMFs will be useful for further application of functional food. Finally, we also expect to promote the people's health and the utilization of citrus peel.

Keyword: *Chemoprevention, polymethoxyflavones, cancer development*

Horng-Jyh Harn

Personal Profile

Name/Position title	Horng-jyh Harn 韓鴻志 MD PhD/Professor
Nationality	Taiwan

Contact Information

Email Address:	arthewduke@gmail.com	Phone	0983-301-805
Mailing Address:.	Department of Pathology**,** Buddhist Tzu Chi General hospital ,707, Sec.3, Chung yang Rd Hualien 970, Taiwan		

Education & Training Background

Higher Education (University or other degree-awarding institute)

From (yr)	To (yr)	Degree PhD	University/ Institute
1987	1991		Duke University/ Durham, USA

Employment History

From (yr)	To (yr)	Department	Position/ professional status
1986	1987	Chief Resident, Pathology Department	Tri-Service General Hospital, Taiwan
1997	1998	Director of Surgical Pathology	Tri-service General hospital, Taipei, Taiwan
2002, Aug	2007, Oct	Director of Molecular Medicine	Tzu-Chi Buddhist General Hospital, Hualien, Taiwan
2007, Oct	2011, Apr	Chairman, Professor, Pathology department	China Medical University Hospital, Taichung, Taiwan
2011, Oct	2016, Oct	Professor, Pathology department	China Medical University Hospital, Taichung, Taiwan
2016, Oct	now	Professor, Associate vice president	Bioinnovation Center, Tzu Chi foundation, Attending Physician of Anatomical Pathology. Buddhist Tzu Chi General hospital, Tzu Chi University, Hualien, Taiwan

Awards & Honors

National Innovation Award, distinguished technique transfer Award; National Science Institute Research Award; Research Awards for Medical Practitioners, Institute of Biomedical Science, Taiwan, Award; The Japanese Society of Pathology, Kitakyushu Award; Asian Conference on Emergency Medicine Certificate of Award; and The Professors' Yeh foundation Prize in Pathology Award. He is selected as a National Academy of Invenstors, Fellow USA 2018.

Inventions & Patents

—New Drug Development—

1. Entitled: Method for Extracting Antineoplastic Components from Bupleurum Scorzonerifolium**(USA JAPAN TAIWAN)**

Patent No: US7,348,032 B2
Patent period: 2003/10/21-2023/10/21

2. Entitled: Angelicae sinensis extracts useful for treatment of cancers **(USA,CHINA,HONG KONG SINGAPORE)**
Patent No: US7,455,861 B2
Patent period: 2006/11/20-2026/11/24

Selected Publications

1. Tsai NM, Lin SZ, Lee CC, Chen SP, Su HC, Chang WL, **Harn HJ***. The anti-tumor effects of Angelicae Sinensis on malignancy brain tumor in vitro and in vivo. ***Clinical Cancer research, 2005 May 1;11(9):3475-84.***

2. Lin PC, Chen YL, Chiu SC, Yu YL, Chen SP, Chien MH, Chen KY, Chang WL, Lin SZ, Chiou TW, **Harn HJ***. Orphan nuclear receptor, Nurr-77 was a possible target gene of butylidenephthalide chemotherapy on glioblastoma multiform brain tumor.

3. ***Journal of Neurochemistry. 2008 Aug;106(3):1017-26.***

4. Chen YL, Jian MH, Lin CC, Kang JC, Chen SP, Lin PC, Hung PJ, Chen JR, Chang WL, Lin SZ, **Harn HJ***. The induction of orphan nuclear receptor Nur77 expression by n-butylenephthalide as pharmaceuticals on hepatocellular carcinoma cell therapy.

5. ***Molecular Pharmacology. 2008 Oct; 74(4):1046-58. 2008 Jun 24.***

6. **Harn HJ***, Lin SZ, Lin PC, Liu CY, Liu PY, Chang LF, Yen SY, Hsieh DK, Liu FC, Tai DF, Chiou TW. Local interstitial delivery of z-butylidenephthalide by polymer wafers against malignant human gliomas. ***Neuro-Oncology 2011 Jun;13(6):635-48.***

7. N-butylidenephthalide attenuates Alzheimer's disease-like cytopathy in Down syndrome induced pluripotent stem cell-derived neurons.Chang CY, Chen SM, Lu HE, Lai SM, Lai PS, Shen PW, Chen PY, Shen CI, **Harn HJ**, Lin SZ, Hwang SM, Su HL. ***Sci Rep. 2015 Mar 4; 5:8744.***

8. Yen SY, Chen SR, Hsieh J, Li YS, Chuang SE, Chuang HM, Huang MH, Lin SZ, **Harn HJ***, Chiou TW*. Biodegradable interstitial release polymer loading a novel small molecule targeting Axl receptor tyrosine kinase and reducing brain tumour migration and invasion.

9. ***Oncogene. 2016 Apr 28; 35(17):2156-65.*** doi: 10.1038/onc.2015.277.

10. Hsueh KW, Chiou TW, Chiang SF, Yamashita T, Abe K, Borlongan CV, Sanberg PR, Huang AY, Lin SZ*, **Harn HJ***. Autophagic down-regulation in motor neurons remarkably prolongs the survival of ALS mice.

11. ***Neuropharmacology. 2016 Sep; 108:152-60.***

12. Tsai SF, Tao M, Ho LI, Chiou TW, Lin SZ, Su HL, **Harn HJ***. Isochaihulactone-induced DDIT3 causes ER stress-PERK independent apoptosis in glioblastoma multiforme cells.**Oncotarget. 2017 Jan 17;8(3):4051-4061.**

13. Rajamani K, Liu JW, Wu CH, Chiang IT, You DH, Lin SY, Hsieh DK, Lin SZ, **Harn HJ***, Chiou TW. n-Butilydenephthalide exhibits protection against neurotoxicity through regulation of tryptophan 2, 3 dioxygenase in spinocerebellar ataxia type 3. **Neuropharmacology. 2017 Feb 18.**

***: First or corresponding author.**

Targeting Axl/EZH2 for Glioblastoma Multiformis From Bench to IND approved
生技產業中 臨床醫師的角色

韓鴻志教授

花蓮慈濟醫學中心/慈濟大學 病理部

惡性腫瘤持續高居國人十大死因之首，根據美國癌症協會 (American Cancer Society, ACS)以及美國腦瘤病例登錄中心 (Central brain tumor registry, CBTRUS)的統計報告顯示，每年估計約有兩萬筆的腦瘤患者新病例產生，台灣每年約有四百名惡性膠質腦瘤新病例。 多型性神經膠母細胞瘤 (glioblastoma multiformis; GBM) 是相當惡性的腦部腫瘤，腫瘤最快 1 個月內可長大 16 倍，是惡化快速的原發性腦瘤，切除後的復發率也非常高，一般確診為 4 級 GBM 後的病患，平均存活時間只有 12 至 18 個月。惡性腦瘤擴散程度迅速又難以根除，一旦確診後，通常已是晚期，見圖 1.，患者平均壽命往往只有 1 年左右，5 年存活率更只有 3.4%。

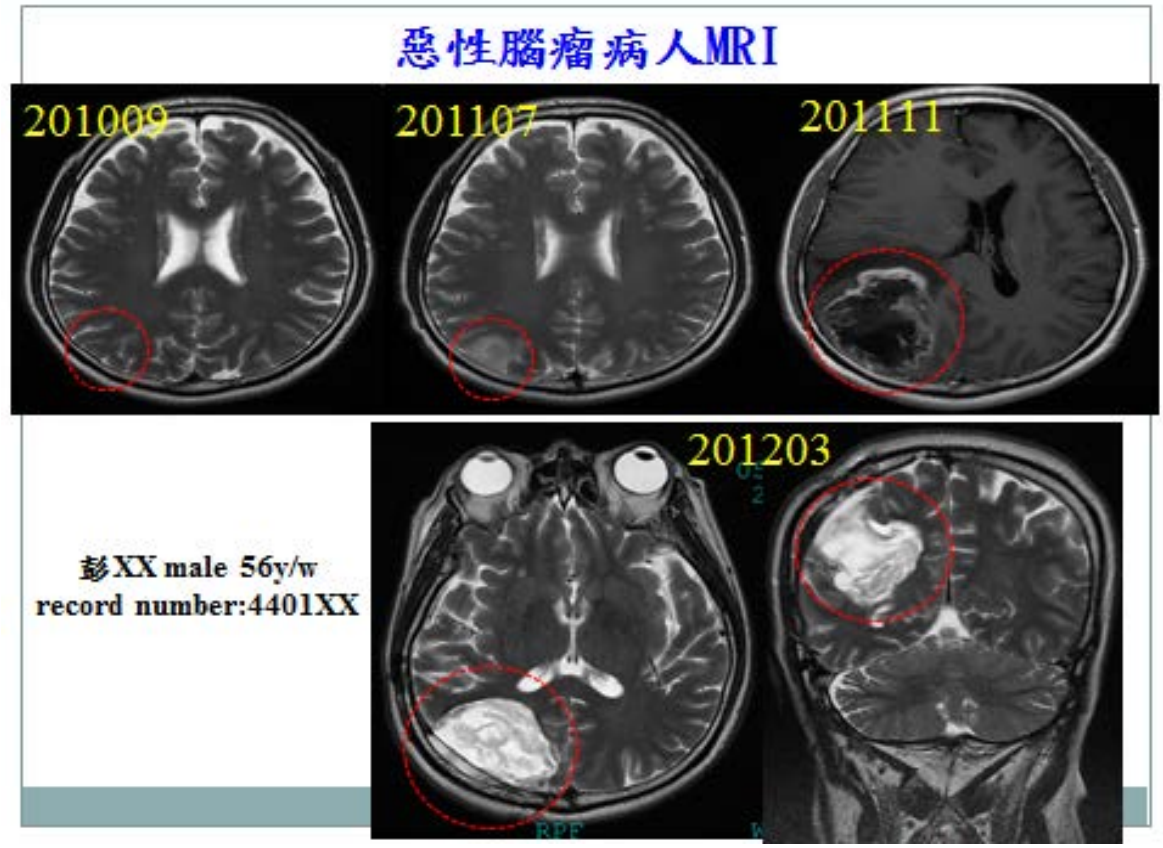
目前醫學上有三種治療方式，手術治療、放射線治療及化學治療。在化學藥物輔助治療上，於 1996 年美國食品藥物管理局已核准利用生物可降解的 p(CPP-SA)聚酸酐生醫材料攜帶化學藥物 Carmustine (BCNU) 之局部給藥裝置，稱之為格立得貼片 GLIADEL Wafer， 植入於外科手術切除惡性腦瘤後所產生之空腔中， BCNU 會緩慢釋放擴散至周邊腦組織，而增強 BCNU 通過血腦障壁的效率，然而 BCNU 此烷基化藥物具有延遲性骨髓抑制、噁心、嘔吐與肺臟纖維化等副作用，且與安慰組之存活時期中位數 11.6 月做比較，GLIADEL Wafer 存活時期中位數為 13.8 月，其延長病患僅兩個多月。

由林欣榮 韓鴻志 邱紫文教授領導的新藥開發團隊 以正丁烯基苯酞(z-Butylidenephthalide, z-BP)，簡稱 BP，開發標靶抗癌藥物，以生醫材料 p(CPP-SA) 聚酸酐，但攜帶此有效成分正丁烯基苯酞(Butylidenephthalide, BP)，兩者合併之給藥裝置 BP-Wafer (Cerebraca ® wafer)，此給藥裝置為圓形淡黃色錠片，每片總重 200 毫克，共包含 30 毫克的 BP，亦用於治療惡性腦瘤，如附圖 2。

研究以大鼠為實驗對象，將標靶小分子藥物 BP 藉由控制緩釋型化學晶片將藥物釋放至腦瘤區，比不接受治療，平均存活時間延長 2.55 倍 (55.78 Vs 21.83 見附圖 3.)，標靶基因是 Axl/EZH2/SOX2，telomerase 及 DNA 修復酶 MGMT,目前已完成動物實驗無任何副作用，並且已獲得美國、大陸、日本、歐盟、台灣之專利，相關論文在 Journal of Neurochemistry, Neuro-Oncology、Biochemical pharmacology 及 Clinical Cancer Research, Oncogene 等，著名 SCI 期刊發佈共 19 篇。並有台灣，大陸，美國，日本， 歐盟等八國專利，分別由花蓮慈濟醫院，花蓮東華大學及台中中醫大擁有，並已技轉長弘生技公司，並已委託台灣台耀公司完成：藥物化學製造(CMC)及美國 Pharmaron 公司完成藥動及 GLP 動物毒理，台灣東洋公司完成錠片製劑，見下附圖 3.。 2016 八月已通過美國 FDA 及台灣 TFDA 之 IND (investigate new drug; 新藥臨床試驗許可) ，見圖 5.，長弘公司將委託花蓮慈濟醫院 及 台北三軍總醫院 展開第一到二 a 期臨床實驗 現已完成

三例病人 安全性沒問題 預計今年年底完成 12 例 phase I 明年 (2019)正式進入 phase II 12 例病人

圖 1. 惡性腦瘤擴散程度迅速又難以根除，且手術後容易復發。



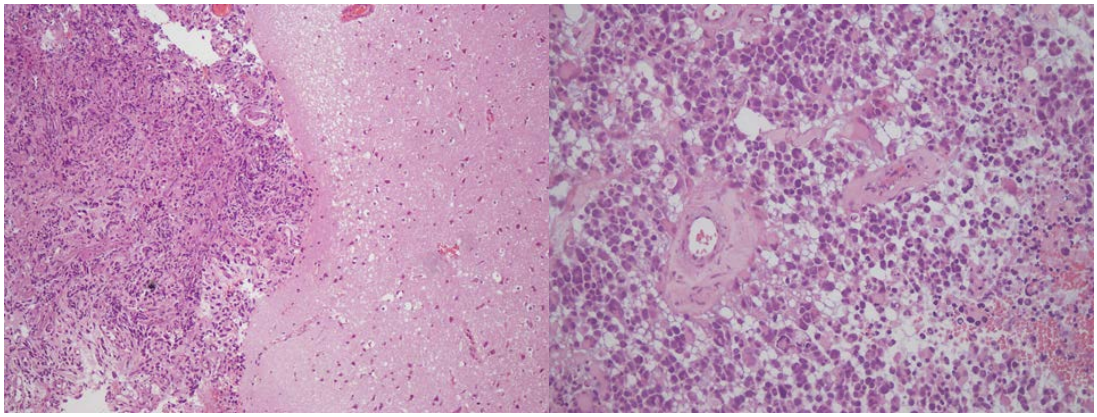


圖 2. 標靶小分子藥物正丁烯基苯酞(z-Butylidenephthalide, z-BP,Cerebraca ® wafer)結構及藥物投遞裝置：生醫材料 p(CPP-SA) 聚酸酐

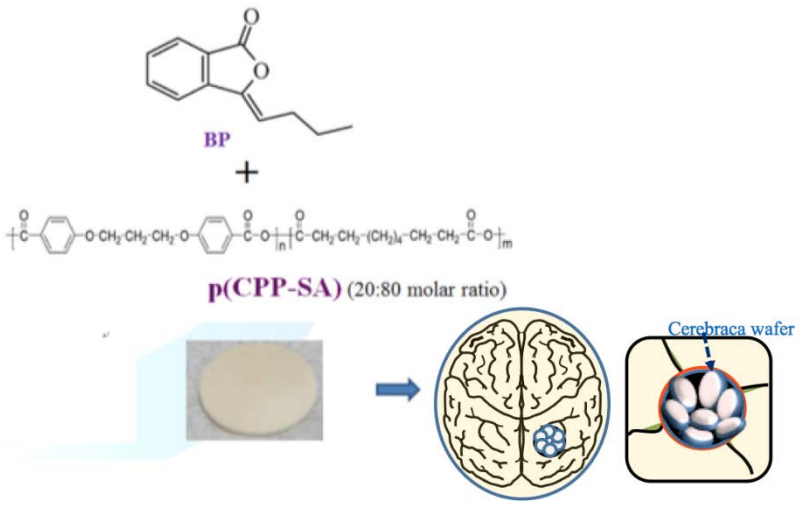
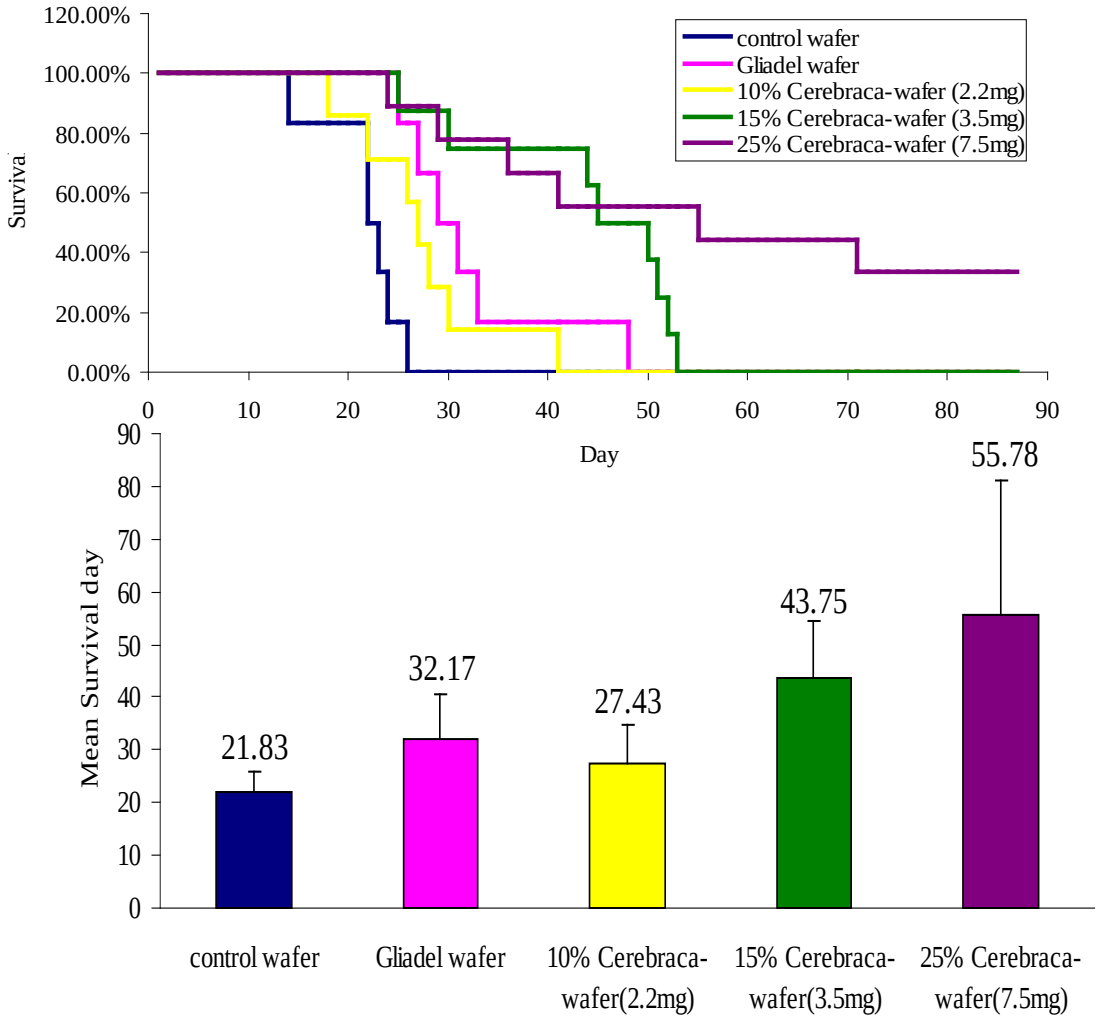


圖 3. 標靶藥物暨投遞裝置 Cerebraca ® wafer 在動物模式內可延長 2.55 倍存活天數 (多延長 34 天)



Lie-Fen Shyur

Personal Profile

Name/Position title	Lie-Fen Shyur / Distinguished Research Fellow
Nationality	Taiwan

Contact Information

Email Address	jaclyn@gate.sinica.edu.tw	Phone	02-27872102
Mailing Address	No 128, Academia Road Sec 2, Nankang, Taipei		

Education & Training Background

Higher Education (University or other degree-awarding institute)

From (yr)	To (yr)	Degree	University/ Institute	Country	Subject
1986	1990	PhD	National Taiwan University/ Agricultural Chemistry	Taiwan	Plant Molecular Biology

Employment History

From (yr)	To (yr)	Department	Position/ professional status
2008	2016	Agricultural Biotechnology Research Center (ABRC), Academia Sinica	Vice Director

Awards & Honors

2018 永信李天德醫藥卓越科技獎
National Invention and Creation Award, Invention Silver Award, 2014
The 10th National Innovation Award on Agricultural Biotechnology, 2013

Inventions & Patents (Selected)

1. **Shyur, L.-F.***, Yang, C.-C., and Chang, M.-T. (2018) Use of *Crassocephalum Rabens* extract in the suppression of cancer metastasis. (US patent pending)
2. **Shyur, L.-F.***, Apaya, K. M., and Chang, M.-T. (2018) Use of *Crassocephalum Rabens* extract in the treatment of breast cancer. (US Patent pending)
3. **Shyur, L.-F.***, Lee, K.-H., Nakagawa-Goto, K., Feng, J.-H., Chen, J.-Y., Lee, W.-L., Cheng, Y.-T., and Huang, J.-Y (2018) Novel sesquiterpene derivatives and their use in inflammation or cancer treatment. (US, PCT, and China patent pending)
4. **Shyur, L.-F.***, Feng, J.-H., and Apaya, K. M. (2018) Galactolipids-enriched plant extracts and the uses thereof. (US and European patent pending; Japan patent issued 6033255; ROC patent issued 2016)
5. **Shyur, L.-F.***, Lee, K.-H., Nakagawa-Goto, K., Feng, J.-H., Chen, J.-Y., Lee, W.-L., Cheng, Y.-T., and Huang, J.-Y (2016) Novel sesquiterpene derivatives and compositions comprising the same for treating inflammation and/or neoplasm related disorders. (ROC patent issued I535725)
6. **Shyur, L.-F.***, Chao, W.-W., and Cheng, Y.-W. (2016) Use of deoxyelephantopin (DET) and analogues thereof for reducing side effects of an anti-cancer agent. (US patent issued 9173868).
7. **Shyur, L.-F.*** and Liu, W.-C. (2016) Dual-functional hybrid glucanases. (US patent issued 9,493,751)
8. **Shyur, L.-F.***, Chao, W.-W., and Cheng, Y.-W. (2014) Use of deoxyelephantopin (DET) for treatment of melanoma. (US patent issued US 8,754,121 B2).
9. **Shyur, L.-F.*** and Hsu, C.-A. (2013) Novel laccases from white-rot fungi. (US Patent issued 8,492,131)
10. **Shyur, L.-F.***, Hsu, C.-A., and Su, Yu-Chang (2013) Novel fungal laccases and uses thereof 新穎真菌漆化酵素及其用途 (ROC patent issued TW I 410492).
11. **Shyur, L.-F.***, Hou, C.-C., Wu, J.-H., Chen, Y.-P., Wang, S.-Y., Huang, C.-C., and

Yang, N.-S. (2011) Treatment of cancer and inflammatory disorder (US patent issued 8048455 B2)

Selected Publications

1. Yang, C.-C., Chang, C.-K., Chang, M.-T. , and **Shyur, L.-F.*** (2018) Plant galactolipid dLGG suppresses lung metastasis of melanoma through deregulating TNF-α–mediated pulmonary vascular permeability and circulating oxylipin dynamics in mice. **International Journal of Cancer** DOI:10.1002/ijc.31663
2. Shiau, J.-Y., Nakagawa-Goto, K., Lee, K.-H., and **Shyur, L.-F.*** (2017) Phytoagent deoxyelephantopin derivative inhibits triple negative breast cancer cell activity by inducing oxidative stress-mediated paraptosis-like cell death. **Oncotarget** *25*, 56942-56958.
3. Shiau, J.-Y., Chang, Y.-Q., Nakagawa-Goto, K., Lee, K.-H., and **Shyur, L.-F.*** (2017) Phytoagent deoxyelephantopin and its derivative inhibit triple negative breast cancer cell activity through ROS-mediated exosomal activity and protein functions. **Frontiers in Pharmacology** *8*, Article 398 (doi.org/10.3389/fphar.2017.00398).
4. Shang, K.-M., Su, T.-H., Lee, W. L., Hsiao, W.-W., Chiou, C.-Y., Ho, B.-Y., Wang, S.-Y., and **Shyur, L.-F.*** (2017) Novel effect and the mechanistic insights of fruiting body extract of medicinal fungus *Antrodia cinnamomea* against T47D breast cancer. **Phytomedicine** *24*, 39-48.
5. Feng, J.-H., Nakagawa-Goto, K., Lee, K.-H., and **Shyur, L.-F.*** (2016) A novel plant sesquiterpene lactone derivative DETD-35 suppresses $BRAF^{V600E}$ mutant melanoma growth and overcomes acquired vemurafenib resistance in mice. **Molecular Cancer Therapeutics** *15*, 1163-1176. (**Selected as the highlights of the issue**)
6. Cheng, Y.-T., Yang, C.-C., and **Shyur, L.-F.*** (2016) Phytomedicine – Modulating oxidative stress and the tumor microenvironment for cancer therapy. **Pharmacological Research** *114*, 128-143.
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8. Nakagawa-Goto, K., Chen, J.-Y., Cheng, Y.-T., Lee, W.-L., Takeya, M., Saito, Y., Lee, K.-H., and **Shyur, L.-F.*** (2016) Novel sesquiterpene lactone analogues as potent anti-breast cancer agents. **Molecular Oncology** *10*, 921-937.
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10. *Lee, W.-L., Huang, J.-Y., and **Shyur, L.-F.*** (2013) Phytoagents for cancer management: regulation of nucleic acid oxidation, ROS, and related mechanisms. **Oxidative Medicine and Cellular Longevity** 2013, doi.org/10.1155/2013/925804.*
11. *Chou[#], T.-W., Feng[#], J.-H., Huang, C.-C., Cheng, Y.-W., Chien, S.-C., Wang, S.-Y.*, and **Shyur, L.-F.*** (2013) A plant kavalactone desmethoxyyangonin prevents inflammation and fulminant hepatitis in mice. **PLoS ONE** 8, e77626.*
12. *Liao, G.-S., Apaya, M. K., and **Shyur, L.-F.*** (2013) Herbal medicine and acupuncture for breast cancer palliative care and adjuvant therapy. **eCAM** 2013, Article ID 437948, 17 pages.*
13. Huang, C.-C., Lin, K.-J., Cheng, Y.-W., Hsu, C.-A., Yang, S.-S., and **Shyur, L.-F.*** (2013) Hepatoprotective effect and mechanistic insights of deoxyelephantopin, a phyto-sesquiterpene lactone, against fulminant hepatitis. **Journal of Nutritional Biochemistry** *24*, 516-530.

Phytomedicine polypharmacology: Modulation of multiple signaling mediators and networking for cancer therapy

Lie-Fen Shyur

Agricultural Biotechnology Research Center, Academia Sinica, Taipei, Taiwan

The perspective of holism in traditional herbal medicine is used in the treatment of various diseases through modulating multiple networking or targets during different disease states. While anecdotal claims are used to backup years of ethnopharmacology of herbal medicines, the evidence-based information aids scientists to evaluate the merit of molecular pharmacological networks modulated by medicinal herbal extracts or derived bioactive compounds in particular disease. Herbal formulations are emerging as a source for discovery of new phyto-therapeutics for human health care in the past two decades. We have been conducting in phytomedicine research, aiming to identify bioactive phytocompounds from Formosan plants for developing botanical supplements or drugs for inflammatory diseases, including breast cancer and cutaneous melanoma. By using the state-of-the-art “Omics” technological platforms, we explored on several Asteraceae medicinal plants and identified a phyto-galactolipid dLGG from *Crassocephalum rabens* (called Zhaohe Cao in mandarin) effective to preventing cancer in preclinical mouse tumor models through modulating the dynamics of lipid mediators (namely oxylipins) and attenuating pulmonary vasculature permeability in mice bearing metastatic melanoma. Phyto-sesquiterpene lactone DET and its derivative from *Elephantopin scaber* are effective in inhibiting triple negative breast tumor and melanoma metastasis. A school of sophisticated molecular mechanisms and signaling networks defined as phytomedicine polypharmacology are elucidated. The Zhaohe Cao-based botanical drug was approved by US FDA for an Investigational New Drug (IND) for cancer therapy in 2017.
.

Key words：polypharmacology, phytomedicine, galactolipids, Omics, oxylipins

Wen-Chin Yang

Personal Profile

Name/Position title	Wen-Chin Yang / Research fellow/Deputy director
Nationality	Taiwan

Contact Information

Email Address wcyang@gate.sinica.edu.tw Phone 0937923842
Mailing Address 128, Academia Rd. Sec. 2,
Nankang, Taipei, 11529 Taiwan

Education & Training Background

Higher Education (University or other degree-awarding institute)

From (yr)	To (yr)	Degree	University/ Institute	Country	Subject
1994	1998	PhD	Universite de la Mediterranee	France	Immunology

Employment History

From (yr)	To (yr)	Department	Position/ professional status
2001	Present	Agricultural Biotechnology Research Center	/Research fellow/Deputy director

Awards & Honors

1994 - 1998	France-Taiwan Exchange Student Fellowship.
1998	Very Honorable Thesis in Mediterranean University (Tres honorable).
2000 - 2003	Post-doctoral Fellowship (3 years) of Cancer Research Fund DamonRuyon-Walter Winchell Foundation, USA.
2010-	MOST subsidy for distinguished talents
2007 –	Mentor of Brands million thesis award (Brands, Inc.)
2008 –	National Innovation Award (Institute for Biotechnology and Medicine Industry)
2010 – 2014	Career Development Award (Academia Sinica)
2012	International Inventor prize (Taiwan International Invention Award Winners Association)
2013	Best Poster Award (2013 SCBA International Symposium)
2013	National Invention and Creation Award (IPO, Ministry of Economic Affairs, Taiwan)
2015	Taiwan Healthcare and Agricultural Biotech Industries Innovation and Excellence Award (Epoch Foundation, Taiwan)
2016	Best Poster Award (2016 CGCM International Symposium)

Inventions & Patents

Over 20 patents and technology transfer/licensing fee over 13.45 million NTD

Selected Publications

1. Chang, S.C., **Yang, W.C.**, and Lee, Y.H.* (1992). The 16S rRNA gene of Streptomyces lividans TK64 contains internal promoters. Biochim. Biophs. Acta. 1129, 219-222 (IF=5.083；R/C= 11/72)
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6. **Yang, W.C.**, Ching, K.A., Tsoukas, C.D., Berg L.J.* (2001). Tec kinase signaling in T cells is regulated by phosphatidylinositol 3-Kinase and the Tec PH domain. J. Immunol.,166(1), 387-395 (IF=4.985；R/C= 32/151)
7. Garçon, F., Ghiotto, M., Gérard, A., **Yang, W.C.**, Olive, D. and Nunès, J.A.* (2004) The SH3 domain of Tec kinase is essential for its targeting to activated CD28 costimulatory molecule. Eur J Immunol., 34.1972-1980 (IF=4.179；R/C=42/151)
8. Chang C.L.T., Yang C.Y., Muthamilselvan, T.*, **Yang W.C.*.** (2016) Field trial of medicinal plant, *Bidens pilosa*, against eimeriosis in broilers, Scientific Reports, 6 :24692. (IF=5.228；R/C= 7/63)
9. Liang, Y.C., Yang, M.T., Lin, C.J., Chang, C.L.T.*, **Yang W.C.*.** (2016) *Bidens pilosa* and its active compound inhibit adipogenesis and lipid accumulation via down-modulation of the C/EBP and PPARγ pathways, Scientific Reports, 6:24285. (IF=5.228；R/C= 7/63)
10. Wei, W.C., Lin, S.Y., Lan, C.W., Huang, Y.C., Lin, C.Y., Hsiao, P.W., Chen, Y.R., **Yang, W.C.** and Yang*, N.S. (2016) Inhibiting MDSC differentiation from bone marrow with phytochemical polyacetylenes drastically impairs tumor metastasis. Scientific Reports, 6:27917. (IF=5.228；R/C= 7/63)
11. Kuo, T.F., Chen, T.Y., Jiang, S.T., Chen, K.W., Chiang, Y.M., Hsu, Y.J., Liu, Y.J., Chen, H.M., Yokoyama, K.K., Tsai, K.C., Yeh, H.H., Chen, Y.R., **Yang W.C.*.** (2017) Protein disulfide isomerase a4 as a novel therapeutic target of cancer, Oncogene, 36: 5484–5496 (IF=7.932；R/C= 15/213)

A multi-disciplinary approach to characterizing the phytochemicals for the prevention and therapy of breast cancer

楊文欽(Wen-Chin Yang) [1,#*] ，郭恬峉(Tien-Fen Kuo)[1] ，陳宗彥(Tzung-Yan Chen) [1,2]

[1]Agricultural Biotechnology Research Center, Academia Sinica, Taipei, 11529 Taiwan.
[2]Institute of Biotechnology, National Taiwan University, Taiwan

Protein disulfide isomerase a4 (PDIA4) is implicated in the growth and death of tumor cells; however, its molecular mechanism and therapeutic potential in cancer are unclear. Here, we found that PDIA4 expression was upregulated in a variety of tumor cell lines and human lung adenocarcinoma tissues. Knockdown and overexpression of PDIA4 in tumor cells showed that PDIA4 facilitated cell growth via the reduction of caspase 3 and 7 activity. Consistently, Lewis lung carcinoma (LLC) cells overexpressing PDIA4 grew faster than did parental cells in tumor-bearing mice, as shown by a reduced survival rate, increased tumor size and metastasis, and decreased cell death and caspase 3 and 7 activity. PDIA4 knockdown resulted in opposite outcomes. Moreover, results obtained in mice with spontaneous hepatoma indicated that PDIA4 deficiency significantly reduced hepatic tumorigenesis and cyst formation and increased mouse survival, tumor death, and caspase 3 and 7 activity. Mechanistic studies illustrated that PDIA4 negatively regulated tumor cell death by inhibiting degradation and activation of procaspases 3 and 7 via their mutual interaction in a CGHC-dependent manner. Finally, we found that cytopiloyne aglycone (CPA), a PDIA4 inhibitor, reduced tumor development via enhancement of caspase-mediated cell death in TSA tumor-bearing mice. These findings characterize PDIA4 as a negative regulator of cancer cell apoptosis and suggest that PDIA4 is a potential therapeutic target for cancer.

Key words: PDIA4, tumorigenesis, (pro)caspases 3 and 7 and PDIA4 inhibitor

Ching-Chiung Wang

Personal Profile

Name/Position title	Ching-Chiung Wang/ Professor /Director
Nationality	Taiwan

Contact Information

Email Address	crystal@tmu.edu.tw	Phone	886-2-2736-1661 ext. 6161
Mailing Address	11031 No. 250 Wu-Xing Street, Taipei, Taiwan		

Education & Training Background

Higher Education (University or other degree-awarding institute)

From	To	Degree	University/ Institute	Country	Subject
1996	1999	Doctor of Philosophy	Taipei Medical University School of pharmacy	Taiwan	Pharmacognosy
1993	1995	Master	Taipei Medical University Master of Graduate Institute of Pharmacognosy	Taiwan	Pharmacognosy
1988	1993	Bachelor of Science	Taipei Medical University School of pharmacy	Taiwan	Pharmacy

Employment History

From (yr)	To (yr)	Department	Position/ professional status
2016	—	Graduate Institute of Pharmacognosy	Director
2012	2014	Professional Master Program in Pharmaceutical and Biotechnology Management, College of Pharmacy, Taipei Medical University	Director
2012	2013	College of Pharmacy, Taipei Medical University	Vice president
2010	2011	Industry-Academia Collaboration and Incubation Operation Center, Taipei Medical University	Director

Awards & Honors

2008 and 2014, The Faculty Award of Taipei Medical University

Selected Publications

1. Tseng SH, Sung CH, Chen LG, Laie YJ, Chang WS, Sung HC, **Wang CC***. Comparison of chemical compositions and osteoprotective effects of different sections of velvet antler. **Journal of Ethnopharmacology**. 2014, 151, 352-360.
2. Lee YW, Chen TL, Shih YR Vernon, Tai CL, Chang CC, Liang HH, Tseng SH, Chien SC, **Wang CC***.Adjunctive traditional Chinese medicine therapy improves survival in patients with advanced breast cancer. Cancer, 2014, 1338-1344.
3. Tsai CF, Wang KT, Chen LG, Lee CJ, Tseng SH, **Wang CC***. Anti-Inflammatory effects of *Vitis thunbergii* var. *taiwaniana* on knee damage associated with arthritis. ***Journal of Medicinal Food***. 2014, 17 (4) 479-786.

4. Shih YC D, Lee YW, Tseng SH, Chien SC, **Wang CC*.** Learning the fundamentals of traditional Chinese medicine by using computer courseware: A preliminary study. ***Indian Journal of Pharmaceutical Education and Research***. 2015, 49 (1), 18-25.
5. Tseng SH, Chen LG, Lai YJ, Wang KT, **Wang CC*.** Effects of different forage on the chemical compositions and antiosteoporotic activities of velvet antlers. ***Anim. Sci. J.*** 2015, doi: 10.1111
6. Huang GC, Chen SY, Tsaie PW, Ganzone JG, Shiah HS, **Wang CC*.** Effects of Dang-Gui-Bu-Xue-Tang on iron uptake in iron-deficient anemia. ***Drug Design, Development and Therapy***. 2016 (10), 949-957.
7. Chien TY, Huang Steven KH, Lee CJ, Tsai PW, **Wang CC*.** Antinociceptive and Anti-inflammatory effects of zerumbone against mono-iodoacetate-induced arthritis. ***Int. J. Mol. Sci.*** **2016**, *17*, 0000; doi:10.3390
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9. Chen LG, Jan YS, Tsai PW, Norimoto H, Michihara S, Murayama C, **Wang CC*.** Anti-inflammatory and antinociceptive constituents of *Atractylodes japonica* Koidzumi. ***J Agric Food Chem***, 2016, 64(11):2254-62. doi: 10.1021
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11. Lee CJ, Chen LG, Liang WL, **Wang CC***. Multiple activities of *Punica granatum* Linne against *Acne vulgaris*. ***Int. J. Mol. Sci.*** **2017**, 7, 18, 141; doi:10.3390
12. Chang CH, Lee CY, Lu CC, Tsai FJ, Hsu YM, Tsao JW, Juan YN, Chiu HY, Yang JS, **Wang CC***. Resveratorl-induced autophagy and apoptosis in cisplatin-resistant human oral cancer CAR cells: A key role of AMPK and Akt/m TOR signaling. ***Int. J. Oncology*** 2017, 50:873-882.
13. Lee CJ, Chen LG, Liang WL, Hsieh MS, **Wang CC*.** Inhibitory effects of punicalagin from *Punica granatum* against type II collagenase-induced osteoarthritis. ***Journal of Functional Foods***. 2018, 41:216-222.

The Turnover Rates of Marker Substances in Huang-Chin-Tang from Herbs to Final Products

陳立耿(Lih-Geeng Chen)[a]，李佳蓉(Chia-Jung Lee)[b]，張家榕(Chia-Jung Chang)[c]，王靜瓊(Ching-Chiung Wang)[b,c,d,#,*]

Department of Microbiology, Immunology and Biopharmaceuticals, National Chiayi University, 300 University Road, Chiayi 60004, Taiwan. [a]
Ph.D Program for the Clinical Drug Discovery from Botanical Herbs[b]*. Graduate Institute of Pharmacognosy* [c]*, School of Pharmacy* [d]*, Taipei Medical University, 250 Wu-Hsing Street, Taipei 11031, Taiwan.*

Objective: In this study we used Huang-Chin-Tang (HCT) as a model material to explore the guidance on how to define the marker substances in the commercial extract product (CEP), based on the marker substances transfers (turnover rate) from raw material to decoction. **Methods:** HCT consists of *Scutellaria baicalensis* Georgi, *Glycyrrhiza uralensis* Fisch., *Paeonia lactiflora* Pall. and *Ziziphus jujuba* Mill. The three lots of raw materials were collected and the contents of baicalin in *S. baicalensis*, paeoniflorin in *P. lactiflora* and glycyrrhizin in *G. uralensis* contents were quantitative by high-performance liquid chromatography (HPLC), respectively. The contents of baicalin, paeoniflorin, and glycyrrhizin in HCT and CEP were also analysing with HPLC. All the analysis conditions, such as extraction condition, HPLC analysis method and turnover rate calculation, are based on the Taiwan Herbal Pharmacopeia (THP) regulations. **Results:** Base on the THP, baicalin in *S. baicalensis* is not less than 8 %. Three lots of *S. baicalensis* raw materials were all accredited. The average turnover rate of baicalin was 68.81% from raw material to decoction. Paeoniflorin in *P. lactiflora* was not less than 1% and the average turnover rate was 80.86%. Glycyrrhizin in *G. uralensis* was not less than 2% and the average turnover rate was 62.45%. However, the average turnover rates of baicalin, paeoniflorin and glycyrrhizin were 78.21%, 78.46 and 37.79%, respectively. According to the concentrated TCMs guidance of Taiwan, we suggested baicalin in CEP should be more than 4.38% (8.0% × 0.78 × 0.7), paeoniflorin should be more than 0.42% (1%× 0.6× 0.7) and glycyrrhizin should be more than 0.51% (2%× 0.36× 0.7). Moreover, paeoniflorin was stable as marker substance in HCT, secondly was baicalin. In Taiwan marketing, we collected 7 kinds of HCT-CEPs and analysed their marker substances. There were 50% CEPs could fulfil the standards. **Conclusions:** The characteristics of the marker substances in Chinese Medicine Formulas-CEPs should be soluble in water and stable without being affected by other herbs, paeoniflorin is the best choice. Secondly, the major component also was important, such baicalin. Therefore, we suggested paeoniflorin and baicalin could be the marker substances in HCT.

Key words：turnover rate, marker substance, Huang-Chin-Tang

Chih-Chuang Liaw

Personal Profile

Name/Position title	Chih-Chuang Liaw / Professor/Director
Nationality	Taiwan

Contact Information

Email Address	ccliaw@mail.nsysu.edu.tw	Phone	07-5252000#5058
Mailing Address	70, Lien-Hai Rd, Kaohsiung City, Taiwan. Department of Marine Resources, National Sun Yat-sen University		

Education & Training Background

Higher Education (University or other degree-awarding institute)

From (yr)	To (yr)	Degree	University/ Institute	Country	Subject
2000	2004	PhD	Kaohsiung Medical University/ Graduate Institute of Pharmaceutical Sciences	Taiwan	Natural Products
1992	1995	Ms	National Sun Yat-sen University/ Institute of Marine Resources	Taiwan	Marine Natural Products
1988	1992	Bs	National Sun Yat-sen University/ Department of Marine Resources	Taiwan	Marine Sciences

Employment History

From (yr)	To (yr)	Department	Position/ professional status
2018	now	National Sun Yat-sen University/ Department of Marine Biotechnology and Resources	Director/ Professor
2016	now	National Sun Yat-sen University/ Department of Marine Biotechnology and Resources	Professor
2012	2016	National Sun Yat-sen University/ Department of Marine Biotechnology and Resources	Associate Professor
2010	2012	National Sun Yat-sen University/ Department of Marine Biotechnology and Resources	Assistant Professor
2006	2010	China Medical University/ Graduate Institute of Pharmaceutical Chemistry	Assistant Professor
2005	2006	Chia-Nan University of Pharmacy and Science/ Department of Cosmetic Science	Assistant Professor

Awards & Honors

2004 Outstanding Graduate Student Award, Kaohsiung Medical University
2008 Poster Presentation Award, The 6th International Symposium for Chinese Medicinal Chemists (ISCMC)
2015 NSYSU-KMU Joint Outstanding Research Award, National Sun Yat-sen University

Inventions & Patents

梁家華、廖志中、曾良鵬、易采璇、霍竹芸；Ugonin t 合物用以製備抗皮膚發炎之組成物之用途，中華民國專利證書，發明第 1524892 號，2016。

Selected Publications

1. **Chih-Chuang Liaw**, Jing-Ru Liou, Tong-Ying Wu, Fang-Rong Chang, Yang-Chang Wu.* Acetogenins from Annonaceae. In *Prog. Chem. Org. Nat. Prod.* A. Douglas Kinghorn, Heinz Falk, Simon Gibbons, Jun'ichi Kobayashi, Series Title: Progress in the Chemistry of Organic Natural Products; Springer International Publishing: Switzerland; **2016**, *101*, 113-230. doi: 10.1007/978-3-319-22692-7.
2. Chun-Kuang Lin, Yu-Ting Wang, Er-Mao Hung, Yu-Liang Yang, Jin-Ching Lee, Jyh-horng Sheu, **Chih-Chuang Liaw**,* “Butyrolactones and diketopiperazines from marine microbes: Inhibition effects on Dengue virus type 2 replication”, *Planta Med.* **2017**, *83*, 158-163.
3. **Chih-Chuang Liaw**,* Pei-Chin Chen, Chao-Jen Shih, Sung-Pin Tseng, Ying-Mi Lai, Chi-Hsin Hsu, Pieter C. Dorrestein, and Yu-Liang Yang,* “Vitroprocines, new antibiotics against *Acinetobacter baumannii*, discovered from marine Vibrio sp. QWI06 using mass-spectrometry-based metabolomics approach”, *Sci. Rep.* **2015**, *5*, 12856; doi: 10.1038/srep12856.
4. Chun-Kuang Lin, Chin-Kai Tseng, Kai-Hsun Chen, Shih-Hsiung Wu, **Chih-Chuang Liaw**,* Jin-Ching Lee,* “Betulinic acid exerts anti-hepatitis C virus activity via the suppression of NF-κB and MAPK-ERK1/2-mediated cyclooxygenase-2 expression”, *Br. J. Pharmacol.* **2015**, *172*, 4481-4492.
5. **Chih-Chuang Liaw**,* Yu-Liang Yang, Chun-Kuang Lin, Jin-Ching Lee, Wen-Ying Liao, Chia-Ning Shen, Jyh-Horng Sheu, and Shih-Hsiung Wu,* “New Meroterpenoids from Aspergillus terreus with Inhibition of Cyclooxygenase-2 Expression”, *Org. Lett.* **2015**, *17*, 2330–2333. (IF: 6.364, Chemistry, Organic, 4/57=7.0%)
6. **Chih-Chuang Liaw**,* Wen-Ying Liao, Chien-Sheng Chen, Yang-Chang Wu, Shu-Chuan Jao, Chia-Ning Shen*, and Shih-Hsiung Wu,* “Calcium-chelating Capability of Tetrahydrofuranic Moieties Modulates Cytotoxicity of Annonaceous Acetogenins” *Angew. Chem. Int. Ed.* **2011**, *50*, 7885–7891.

Biofunctional Natural Products from Marine Resources

Chih-Chuang Liaw

Department of Marine Biotechnology and Resources, , National Sun Yat-sen University*;*
Doctoral Program of Marine Biotechnology, National Sun Yat-sen University
E-mail address: ccliaw@mail.nsysu.edu.tw

Marine microorganisms interfere the metabolism system of marine life by producing toxins or anti-feedants/ or directly producing metabolites to store in the organs of marine organisms to protect them from predators and grazers. In the view of natural products chemistry, the biofunctional compounds are regarded as a treasure for drug discovery and organic chemistry.

To efficiently discover novel bioactive natural products from abundant marine microbial resources, we tried to establish a robust and convenient research strategy of de-replication by integrating state-of-the-art analytical techniques. By integrating these analytical technologies, such as imaging mass spectrometry (IMS) and mass spectrometry-based molecular network, and the conventional bioactivity-guided fractionation isolation, we can “target” unknown but bioactive natural products from marine microbes for further performing the isolation of target compounds from the scale-up microbial culture. In this talk, we will show some examples recently done in our lab by the aforementioned integrating strategy, about the elucidation of key enzyme for the biosynthesis of bioactive compounds, vitroprocines, from *Vibrio* sp. QW1-06, the isolation of peptaibols from *Trichoderma resssei* (MR13-TR01), and the development of antifouling pyone-type derivatives from *Trichoderma* sp.

Yuh-Chiang Shen

Personal Profile

Name/Position title	Yuh-Chiang Shen / Research Fellow
Nationality	Taiwan

Contact Information

Email Address	yuhcs@nricm.edu.tw	Phone	+886-2-28201999
Mailing Address	No 155-1, LiNung Street Sec 2, Peitou, 11221, Taipei, Taiwan		

Education & Training Background

Higher Education (University or other degree-awarding institute)

From (yr)	To (yr)	Degree	University/ Institute	Country	Subject
1995	1999	PhD	Yang-Ming U/Pharmacology	Taiwan	TCM in Ischemic Stroke

Employment History

From (yr)	To (yr)	Department (National Research Institute of Chinese Medicine)	Position/ professional status
2012	2018	Clinical Chinese Medicine	Research Fellow/ Division Chief
2008	2012	Basic Research in Chinese Medicine	Associate Research Fellow

Awards & Honors

Invited Speaker: The 27th Symposium on Natural Product and Pharmacy and TCM (2012)

Invited Speaker: International Symposium on Industry Trends and Strategies for Globalization of Chinese Botanic Medicine, held by Ministry of Health and Warfare (2015).

Invited Speaker: International Symposium on Redox Biology and Mitochondrial Medicine and Cross-Strait Free Radical Symposium (2016).

Excellent Poster Award: The 31th Symposium on Natural Product and Pharmacy and TCM (2016)

Invited Speaker: The 33th Symposium on Natural Product and Pharmacy and TCM (2018)

Inventions & Patents

【專利名稱】治療或預防神經性疾病之藥物；國家中醫藥研究所覽號：MP-011-20180529

Selected Publications

1. Wang YH, Liou KT, Tsai KC, Liu HK, Yang LM, Chern CM, Shen YC*, GSK-3 Inhibition through GLP-1R Allosteric Activation Mediates the Neurogenesis

Promoting Effect of P7C3 after Cerebral Ischemic/Reperfusional Injury in Mice, *Toxicol Appl Pharmacol*, Sep, in press, 2018 (SCI).

2. Chien MY, Chuang CH, Chern CM, Liou KT, Liu DZ, Hou YC, Shen YC*, Salvianolic acid A alleviates ischemic brain injury through the inhibition of inflammation and apoptosis and the promotion of neurogenesis in mice, *Free Radical Biology & Medicine*. 99:508-519, 2016 (SCI).
3. Chen HJ, Shen YC†, Shiao YJ, Liou KT, Hsieh PH, Lee CY, Chen YR, Yun-Lian Lin YL, Multiplex brain proteomic analysis revealed the molecular therapeutic effects of **Buyang Huanwu Decoction** on cerebral ischemic stroke mice, *PlosOne* 10(10):e0140823, 2015 (†equal first author; SCI).
4. Shen YC*, Lu CK, Liou KT, Hou YC, Lin YL, Chern CM, Wang YH, Sun HJ, Liao KH, Wang HW, Common and unique mechanisms of **Chinese herbal remedies** on ischemic stroke mice revealed by transcriptome analyses, *J Ethnopharmacology*, 173:370-382, 2015 (SCI).
5. Chern CM, Wang YH, Liou KT, Hou YC, Chen **CC,** Shen YC*, 2-Methoxystypandrone ameliorates brain function through preserving BBB integrity and promoting neurogenesis in mice with acute ischemic stroke, *Biochem Pharmacol* 87:502-14, 2014 (SCI).
6. Chern CM, Liao JF, Wang YH, Shen YC*, Melatonin ameliorates neural function by promoting endogenous neurogenesis through MT2 melatonin receptor in ischemic stroke mice. *Free Radical Biology & Medicine* 52:1634-47, 2012 (SCI).
7. Chen HJ, Shen YC†, Lin CY, Tsai KC, Lu CK, Shen CC, Lin YL, Metabolomics Study of **Buyang Huanwu Tang Decoction** in Ischemic Stroke by 1H NMR. *Metabolomics*, 8:974-84, 2012. (†equal first author; SCI).
8. Wang HW, WangYH, Liou KT, Lu CK, Lin YL, Huang ST, Tsai YH, Cheng YC, Lin HJ, Shen YC*, Deciphering the neuroprotective mechanisms of **Bu-yang Huan-wu Decoction** by an integrative neurofunctional and genomic approach in ischemic stroke mice, *J Ethnopharmacology*, 138:22-33, 2011 (SCI).

Evaluate the essential active ingredients from Buyang Huanwu Decoction to become a botanic new drug for treatment of ischemic stroke

盧重光 (Chung-Kuang Lu) ，蔡耿彰 (Keng-Chang Tsai)，
劉國同 (Kuo-Tong Liou)，沈郁強 (Yuh-Chiang Shen)*

National Research Institute of Chinese Medicine, Ministry of Health and Welfare, Taipei City, Taiwan

Acute ischemic stroke (AIS) is one of the leading causes of mortality, disability, and morbidity worldwide. *I*t is our strength to develop a botanic new drug from Traditional Chinese Medicine (TCM) for the treatment of AIS. In this project, we intend to evaluate the mechanisms of action and SAR of the most essential component, i.e., medicarpin from Buyang-Huanwu Decoction (BHD), using a cerebral ischemic/reperfusional (CI/R) injury murine model. Treating CI/R mice using medicarpin (1.0–2.0 mg/kg, i.v.) significantly improved tracking distance and walking behavior, and reduced brain damage. Specifically, medicarpin promoted the expression of neurogenesis-associated proteins, including doublecortin, beta tubulin III (β-tub3), adam11 and adamts20, near the peri-infarct cortex, accompanied by glycogen synthase kinase 3 (GSK-3) inhibition and β-catenin upregulation. The application of a specific inhibitor against g*lucagon-like peptide 1 receptor (GLP-1R)*, exendin (9-39), revealed that the beneficial effects of medicarpin involved triggering the activation of *GLP-1R*-associated PKA/Akt signaling. Medicarpin elicited the *GLP-1R*-dependent intracellular cAMP increment and the insulin secretion in cellular models. Surface plasmon resonance (SPR) assay of medicarpin showed a Kd value of around μM for *GLP-1R* binding, and *the docking of* medicarpin *to the putative active site on GLP-1R was successfully predicted by molecular modeling.* Our findings indicate that medicarpin promotes neurogenesis by activation of the cAMP/PKA-dependent and Akt/GSK3-associated β-catenin through positive orthosteric stimulation of GLP-1R.

Key words: acute ischemic stroke, β-catenin, glycogen synthase kinase 3, g*lucagon-like peptide 1 receptor,* medicarpin, neurogenesis, orthosteric stimulation, surface plasmon resonance.

Yu-Liang Yang

Personal Profile

Name/Position title	Yu-Liang Yang / Assistant Research Fellow
Nationality	Taiwan

Contact Information

Email Address	ylyang@gate.sinica.edu.tw	Phone	02-27872089
Mailing Address	A730, Agricultural Biotechnology Building, Academia Sinica		

Education & Training Background

Higher Education (University or other degree-awarding institute)

From (yr)	To (yr)	Degree	University/ Institute	Country	Subject
1999	2004	PhD	Kaohsiung Medical University	Taiwan	Pharmacy
1995	1999	B. Pharm	Kaohsiung Medical University	Taiwan	Pharmacy

Employment History

From (yr)	To (yr)	Department	Position/ professional status
2011	now	Agricultural Biotechnology Research Center, Academia Sinica	Assistant Research Fellow
2009	2011	Skaggs School of Pharmacy and Pharmaceutical Science, UC San Diego	Postdoctoral Fellow
2004	2008	Institute of Biological Chemistry, Academia Sinica	Postdoctoral Fellow

Awards & Honors

Ta-You Wu Memorial Award (2016)
On *the Analytical Scientist*'s 2014 Top 40 Under 40 list of researchers (2014)
Li Foundation Heritage Prize for "Excellence in Creativity" (40,000 USD) (2012)

Selected Publications

1. Pi-Yu Chen, Chi-Ying Hsieh, Chao-Jen Shih, Yuan-Jing Lin, Chia-Wen Tsao, **Yu-Liang Yang***, **2018**, "Exploration of Fungal Metabolic Interactions Using Imaging Mass Spectrometry on Nanostructured Silicon", ***J. Nat. Prod.***, 81, 1527-1533.
2. Yi-Shu Chiu, Pi-Yu Chen, Tung Kuan, Po-Chuan Wang, Ying-Ju, Chen, **Yu-Liang Yang***, Hsin-Hung Yeh*, **2018**, "A Polysaccharide Derived from *Trichosporon* sp. Culture Metabolite Strongly Primes Plant Resistance to Viruses", ***Mol. Plant Microbe. Interact.***, in press.

3. Ying-Ning Ho, Han-Jung Lee, Chi-Ting Hsieh, Chia-Chi Peng, **Yu-Liang Yang***, **2018**, "Chemistry and Biology of Salicyl-capped Siderophores", ***Stud. Nat. Prod. Chem.***, *59*, 431-490.
4. Lin-Jie Shu, **Yu-Liang Yang***, **2017**, "*Bacillus* Classification Based on Matrix-Assisted Laser Desorption Ionization Time-of-Flight Mass Spectrometry-Effects of Culture Conditions", ***Sci. Rep.***, 7, 15546.
5. Ying-Ning Ho, Lin-Jie Shu, **Yu-Liang Yang***, **2017**, "Imaging Mass Spectrometry for Metabolites: Technical Progress, Multimodal Imaging and Biological Interactions", ***Wiley Interdiscip. Rev. Syst. Biol. Med.***, 9, e1387.
6. Wen-Jen Chen, Tzu-Yen Kuo, Feng-Chia Hsieh, Pi-Yu Chen, Chang-Sheng Wang, Yu-Ling Shih, Ying-Mi Lai, Je-Ruei Liu, **Yu-Liang Yang***, Ming-Che Shih*, **2016**, "Involvement of Type VI Secretion System in Secretion of Iron Chelator Pyoverdine in *Pseudomonas taiwanensis*", ***Sci. Rep.***, 6, 32950.
7. Chao-Jen Shih, Sheng-Chung Chen, Chieh-Yin Weng, Mei-Chin Lai*, **Yu-Liang Yang***, **2015**, "Rapid Identification of Haloarchaea and Methanoarchaea Using the Matrix Assisted Laser Desorption/ionization Time-of-flight Mass Spectrometry", ***Sci. Rep.***, 5, 16326.
8. Chih-Chuang Liaw*, Pei-Chin Chen, Chao-Jen Shih, Sung-Pin Tseng, Ying-Mi Lai, Chi-Hsin Hsu, Pieter C. Dorrestein, **Yu-Liang Yang***, **2015**, "Vitroprocines, New Antibiotics against *Acinetobacter baumannii*, Discovered from Marine *Vibrio* sp. QWI-06 Using Mass-spectrometry-based Metabolomics Approach", ***Sci. Rep.***, 5, 12856.
9. Chao-Jen Shih, Pi-Yu Chen, Chih-Chuang Liaw, Ying-Mi Lai, **Yu-Liang Yang***, **2014**, "Bring Microbial Interactions to Light Using Imaging Mass Spectrometry", ***Nat. Prod. Rep.***, 31, 739-755. **(Selected as the cover picture)**
10. **Yu-Liang Yang**, Yuquan Xu, Roland Kersten, Wei-Ting Liu, Michael Meehan, Bradley S. Moore, Nuno Bandeira, Pieter C. Dorrestein*, **2011** "Connecting Chemotypes and Phenotypes of Cultured Marine Microbial Assemblages by Imaging Mass Spectrometry", ***Angew. Chem. Int. ed.***, 50, 5839-5842. **(Selected as the cover picture)**
11. Wei-Ting Liu, **Yu-Liang Yang**, Yuquan Xu, Anne Lamsa, Nina M Haste, Jane Y. Yang, Julio Ng, David Gonzalez, Craig D. Ellermeier, Paul D. Straight, Pavel A. Pevzner, Joe Pogliano, Victor Nizet, Kit Pogliano, Pieter C. Dorrestein*, **2010**, "Imaging Mass Spectrometry of Intraspecies Metabolic Exchange Revealed the Cannibalistic Factors of *Bacillus subtilis*", ***Proc. Natl. Acad. Sci. U.S.A.***, 107, 16286-16290. **(Equal contribution as first author, selected by Faculty of 1000 Biology "Must Read")**
12. **Yu-Liang Yang**, Yuquan Xu, Paul Straight*, Pieter C. Dorrestein*, **2009**, "Translating Metabolic Exchanging with Imaging Mass Spectrometry", ***Nat. Chem. Biol.***, 5, 885-887. **(Selected by Faculty of 1000 Biology "Recommended")**

Discovery of conjugated polyynes against drug-resistant *Candida* from a bacterial source using integrated Omics analyses

楊玉良 (Yu-Liang Yang)

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

Conjugated polyynes are unstable secondary metabolites with various biological functions that are mainly identified from plant, marine organism and fungal sources. However, only a few polyynes have been identified from bacteria. Through the genome mining analysis, we found that only six genera of bacteria have the potential to produce conjugated polyynes. The phylogenetic analysis of bacterial polyyne BGCs demonstrated that *Massilia* sp. YMA4 is a unique source for the production of novel conjugated polyyne structures. Since the production of conjugated polyynes from *Massilia* sp. YMA4 was unstable, here we employed an integrated Omics approach, including RNA-seq transcriptomics, *in situ* metabolomics, together with gene inactivation to discover massilicins, the silent and unstable antifungal agents, from dual-culture of *Massilia* sp. YMA4 *versus Candida albicans*. The click reaction was then employed to trap massilicins from *Massilia* sp. YMA4 extract for further isolation and structure elucidation. The mechanism of antifungal activity was exposed in this study as well.

Yuan-Bin Cheng

Personal Profile

Name/Position title	Yuan-Bin Cheng / Associate Professor
Nationality	Taiwan

Contact Information

Email Address	jmb@kmu.edu.tw	Phone	07-3121101 ext. 2197
Mailing Address	Room 717, First Teaching Building, No. 100, Shih-Chuan 1st Road, Kaohsiung, 80708, Taiwan.		

Education & Training Background

Higher Education (University or other degree-awarding institute)

From (yr)	To (yr)	Degree	University/ Institute	Country	Subject
2002	2007	Ph. D	Sun Yat-sen University	Taiwan	Marine Biotechnology and Resources
1997	2001	B. Sc	Kaohsiung Medicinal University	Taiwan	Chemistry

Employment History

From (yr)	To (yr)	Department	Position/ professional status
2016	present	Graduate Institute of Natural Products, KMU	Associate Professor
2012	2016	Graduate Institute of Natural Products	Assistant Professor
2012	2012	Agricultural Biotechnology Research Center, Academia Sinica	Post-Doctoral Fellow
2010	2011	Center for Marine Biotechnology and Biomedicine, SIO, UCSD	Post-Doctoral Fellow
2008	2010	School of Pharmacy, NTU	Post-Doctoral Fellow

Awards & Honors

Outstanding young scholar program of the Ministry of Science and Technology (2014)

Outstanding young scholar program of the Ministry of Science and Technology (2018)

Inventions & Patents

Formyl Peptide Receptor 1 Antagonists and Uses Thereof (US9,895,329B1)

Selected Publications

1. Bioactive Phenolic Components from the Twigs of *Atalantia buxifolia*, *J. Nat. Prod.* **2018**, *81*, 1534–1539.
2. Ethyl Acetate Extract of *Scindapsus* cf. *hederaceus* Exerts the Inhibitory Bioactivity on Human Non-Small Cell Lung Cancer Cells through Modulating ER Stress, *Int. J. Mol. Sci.* **2018**, *19*, 1832.
3. Anti-Lymphangiogenesis Components from Zoanthid *Palythoa tuberculosa*, *Marine Drugs* **2018**, *16*, 47.
4. Bioactive Triterpenoids from the Leaves and Twigs of *Lithocarpus litseifolius* and *L. corneus*, *Planta Medica*, **2018**, *84*, 49–58.
5. Isolation and absolute configuration determination of alkaloids from *Pandanus amaryllifolius*, *Tetrahedron* **2017**, *73*, 3423–3429.
6. Inflammation Modulatory Phorbol Esters from the Seeds of *Aquilaria malaccensis*, *J. Nat. Prod.* **2017**, *80*, 1421–1427.
7. Zoanthamine-Type Alkaloids from the Zoanthid *Zoanthus kuroshio* Collected in Taiwan and Their Effects on Inflammation. *J. Nat. Prod.* **2016**, *79*, 2674–2680.
8. Diterpenes from *Grangea maderaspatana*, *Phytochemistry* **2016**, *129*, 124–129.
9. Anti-Dengue Virus Constituents from Formosan Zoanthid *Palythoa mutuki*, *Marine Drugs* **2016**, *14*, 151.
10. Ecdysones from *Zoanthus* spp. with inhibitory activity against dengue virus 2, *Bioorg. & Med. Chem. Lett.* **2016**, *26*, 2344–2348.
11. Alkylamides of *Acmella oleracea*, *Molecules* **2015**, *20*, 6970–6977.
12. New alkaloids from Formosan zoanthid *Zoanthus kuroshio*, *Tetrahedron* **2015**, *71*, 8601–8606.
13. Limonoids from the Seeds of *Swietenia macrophylla* with Inhibitory Activity against Dengue Virus 2, *J. Nat. Prod.* **2014**, *77*, 2367–2374.
14. Kuroshines A and B, new alkaloids from *Zoanthus kuroshio*, *Tetrahedron Lett*. **2014**, *55*, 5369–5372.
15. Cytotoxic and Antimicrobial Napyradiomycins from Two Marine-Derived *Streptomyces* Strains, *Eur. J. Org. Chem.* **2013**, 3751–3757.
16. Nortriterpene Lactones from the Fruits of *Schisandra arisanensis*, *J. Nat. Prod.* **2010**, *73*, 1228–1233.
17. Arisandilactone A, a New Triterpenoid from the Fruits of *Schisandra arisanensis*, *Org. Lett.* **2010**, *12*, 1016–1019.
18. Oxygenated Lignans from the Fruits of *Schisandra arisanensis*, *J. Nat. Prod*. **2009**, *72*, 1663–1668.
19. Cembrane Diterpenoids from the Taiwanese Soft Coral *Sarcophyton stolidotum*, *J. Nat. Prod*. **2008**, *71*, 1141–1145.
20. Kadsuphilols A-H, Oxygenated Lignans from *Kadsura philippinensis*, *J. Nat. Prod*. **2007**, *70*, 1139–1145.
21. Xenicane-Type Diterpenes with Cytotoxicity from *Xenia florida*, *J. Nat. Prod.* **2006**, *69*, 675–678.
22. New Prostanoids with Cytotoxic Activity from Taiwanese Octocoral *Clavularia viridis*, *J. Nat. Prod.* **2004**, *67*, 542–546.

Phytochemical Study on the Folk Medicine of Southeast Asia

鄭源斌 (Yuan-Bin Cheng) [#,*]

[#]Graduate Institute of Natural Products, Kaohsiung Medical University, Kaohsiung 807, Taiwan.

In our bioactive screening for folk medicine of Southeast Asia, more than 50 plant materials were screening for antibacterial, anti-inflammatory, antiviral, and cytotoxic activities. Consequently, the methanol extracts of *Clinacanthus nutans*, *Pandanus amaryllifolius*, *Aleurites moluccanus*, and *Hippobroma longiflora* were found to have anti-inflammatory, antiviral, and Nrf2 activity. Herein, the phytochemical investigation of *A. moluccanus*, and *H. longiflora* are reported.

A. moluccanus (family Euphorbiaceae), the candlenut, is native to Polynesia and Malaysia. The boiled nut of *A. moluccanus* is a kind of food source in Indonesia. Besides, the leaf of candlenut is also regarded as a folk medicine for the treatment of arthritis, hemorrhage, and ulcer in East Asia. *H. longiflora*, a perennial herb, is a species of toxic plants in the monotypic genus *Hippobroma* (family Campanulaceae). This plant is native to the West Indies, and now widely distributes in the tropical to temperate regions of the world. *H. longiflora* is an important folk medicine for treatment of wounds, eye diseases, asthma, bronchitis and cancer in Indonesia.

In our natural product study, 16 new compounds including three novel skeletons were identified from the above two plant materials. The structures of these isolates were elucidated through extensive 1D and 2D NMR (COSY, HSQC, HMBC, NOESY) spectroscopic data analyses. The absolute stereochemistry of three novel skeletons was confirmed by X-ray diffraction analyses and the Mosher's method. The biosynthetic pathways of those unprecedented compounds were also proposed. Pharmacological study performed by collaborators showed that those new compounds possessed anti-angiogenic, anti-inflammatory, and cytotoxic activities.

Key words：*Aleurites moluccanus*; *Hippobroma longiflora*; anti-inflammatory; anti-angiogenic; cytotoxic

Hui-Chi Huang

Personal Profile

Name/Position title	Hui-Chi Huang / Associate Professor
Nationality	Taiwan

Contact Information

Email Address hchuang@mail.cmu.edu.tw Phone 04-22053366 ext.5211or 5709
Mailing Address 91, Hsueh-Shih Road, Taichung 404, Taiwan

Education & Training Background

Higher Education

From (yr)	To (yr)	Degree	University/ Institute	Country	Subject
2001	2006	Ph.D.	Kaohsiung Medical University/ Pharmacy	Taiwan	Natural Products Chemistry
1997	1999	M.S.	Kaohsiung Medical University/ Graduate of Natural Products	Taiwan	Natural Products Chemistry

Employment History

From(yr)	To (yr)	Department	Position/ professional status
2013	present	Department of Chinese Pharmaceutical Sciences and Chinese Medicine Resources, China Medical University	Associate Professor/ Natural Products Chemistry
2008	2013	Department of Chinese Pharmaceutical Sciences and Chinese Medicine Resources, CMU	Assistant Professor/ Natural Products Chemistry
2007	2008	Tsuzuki Institute of Traditional medicine, CMU	Postdoctoral Fellow/ Natural Products Chemistry
2006	2007	National Research Institute of Chinese Medicine	Postdoctoral Fellow/ Natural Products Chemistry

Inventions & Patents

1. 專利名稱:強效天然植物性除螺劑之組成物，中華民國發明第 I294270 號
2. 專利名稱:金線連(蓮)經微生物發酵之混合物及其用途，中華民國發明第 4849 號

Selected Publications

1. Huang, HC, Yang, CP, Wang, SY, Chang, CI,Sung, PJ, Huang, GJ, Chien, SC, Kuo, YH, Anti-inflammatory flavonol acylglycosides from the aerial part of *Lindera akoensis* Hayata, RSC Advances, 2017, 7, 50868-50874.
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3. Chang CT, Hseu YC, Thiyagarajan V, Huang HC, Hsu LS, Huang PJ, Liu JY, Liao JW, Yang HL. *Antrodia salmonea* induces G2 cell-cycle arrest in human triple-negative breast cancer (MDA-MB-231) cells and suppresses tumor growth in athymic nude mice. ***J Ethnopharmacol*** 20;196:9-19, 2017.
4. Huang HC, Chuang SH, Wu YC, Chao PM. Hypolipidemic function of Hsian-tsao tea (Mesona procumbens Hemsl.): working mechanisms and active components. **J Func Food** 26; 217-227, 2016.

5. Liaw CC, Huang HC, Hsiao PC, Zhang LJ, Lin ZH, Hwang SY, Hsu FL, Kuo YH. 5β,19-epoxycucurbitane triterpenoids from *Momordica charantia* and their anti-inflammatory and cytotoxic activity. ***Planta Med*** 81(1):62-70, 2016.
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Antitumor Bufadienolide and Flavonol Glycosides from Crassulaceae plants

Hui-Chi Huang

Department of Chinese Pharmaceutical Sciences and Chinese Medicine Resources, China Medical University, Taichung, Taiwan

We focus on study of the anti-cancer compounds from Taiwanese medicinal plants. Our preliminary experimental tests showed that the methanol extracts from *Kalanchoe tubiflora* (Harvey) Hamet. and *Kalanchoe laetivirens* Desc. of Crassulaceae family plants exhibited promising bioactivities. The phytochemical investigation of the EtOH extracts of *K. tubiflora* (Harvey) Hamet. resulted in the isolation and identification of two new cardenolides, kalantubolide A (**1**) and kalantubolide B (**2**), two new bufadienolide glycosides, kalantuboside A (**3**) and kalantuboside B (**4**), and one new megastigmane, tubiflorone (**5**) together with twenty-one known (**6**-**26**) compounds. We examined the *in vitro* or *in vivo* anti-melanoma cancer effects of low concentration of **4** (KB, 5-20 ng/mL; 8.7-34.8 nM), a novel naturally occurring bufadienolide compound and revealed its molecular mechanism of action. In conclusion, **4**-induced apoptosis was preceded by the induction of cytoprotective autophagy in human melanoma cells. *In vivo* data showed that **4** significantly delayed the tumor incidence and inhibited the tumor growth in A2058-xenografted nude mice. The novelty and significant contribution of the other report are describing for the first time that **3**, **4** and **5**, isolated from *K. tubiflora* (Harvey) Hamet. activate autophagy process to induce cell death in CL1-5 highly metastatic human lung cancer cells. In addition, **4** exhibits a better autophagy induction and cytotoxicity. This study provided evidence for the possibility of treating highly metastatic human lung cancer with bufadienolide glycosides.

Four new flavonoid glycosides, crenatosides A-D (**FG1-4**) and six known flavonoid glycosides (**FG5-10**), were isolated from *K. laetivirens* Desc. The structures of these compounds were elucidated on the basis of 1D and 2D NMR spectra analyses. Compounds **FG1**, **2**, **4**, **5**, **6**, and **8** were tested for their inhibition of the growth of H226 (lung cancer) cell line. We found that **FG5** significantly impeded the H226 lung cancer cells proliferation in the dose- and time-dependent manners. Additionally, **FG5** treatment triggered apoptosis and autophagy in H226 cells. These results suggest that **FG5** might be a potential candidate for development of antitumor drug targeting lung cancer.

Key words：Crassulaceae, *Kalanchoe tubiflora* (Harvey) Hamet., *Kalanchoe laetivirens* Desc., apoptosis, autophagy

Chia-Hung Yen

Personal Profile

Name/Position title	Chia-Hung Yen / Assistant Professor
Nationality	Taiwan

Contact Information

Email Address	chyen@kmu.eud.tw	Phone	+886-7-312-1101#2558
Mailing Address	No. 100, Shih-Chuan 1st Road, Kaohsiung, 80708,Taiwan.		

Education & Training Background

Higher Education (University or other degree-awarding institute)

From (yr)	To (yr)	Degree	University/ Institute	Country	Subject
2004	2009	PhD	National Yang-Ming University/ Molecular Medicine Program	Taiwan	Tumor biology
1999	2001	MS	National Taiwan University/ Institute of Biochemical Science	Taiwan	Molecular biology

Employment History

From (yr)	To (yr)	Department	Position/ professional status
2009	2012	National Yang-Ming University/ Institute of Microbiology and Immunology	Postdoctoral research associate

Awards & Honors

2009 Excellent Award at the Annual Thesis Competition of National Yang-Ming University

Inventions & Patents

1. Taiwan Patent: A Potential Composition And Its Use For Carcinoma. Patent No. I626051

Selected Publications

1. **Yen CH***, Chang HS, Yang TH, Wang SF, Wu HC, Chen YC, Lin KJ, Wang S. High-Content Screening of a Taiwanese Indigenous Plant Extract Library Identifies Syzygium simile leaf Extract as an Inhibitor of Fatty Acid Uptake. ***Int J Mol Sci.*** 2018 Jul 22;19(7). pii: E2130.
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11. **Yen CH**, Lu YC, Li CH, Lee CM, Chen CY, Cheng MY, Huang SF, Chen KF, Cheng AL, Liao LY, Wu Lee YH and Chen YM. Functional Characterization of Glycine N-methyltransferaseand its Interactive Protein-DEPDC6/DEPTOR in Hepatocellular Carcinoma. ***Mol Med.*** 2012; 18:286-296.
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Establishment of plant extract libraries for high-throughput drug screening

顏嘉宏 (Chia-Hung Yen)[1,2]*

1 Graduate Institute of Natural Products, College of Pharmacy, Kaohsiung Medical University, Kaohsiung, 80708 Taiwan

2 Center for Infectious Disease and Cancer Research, Kaohsiung Medical University, Kaohsiung, 80708 Taiwan

Natural products and their derivatives have historically been used as a source of therapeutic agents. Currently, more than 60% of clinically used drug are originated from natural product. Our team had established two plant extract libraries. First library-the Taiwanese Indigenous Plant Extract Library (TIP Library) is a collection of 3,000 methanolic extracts prepared from the root, stem, leaves, flower, or whole plant of 1,336 plants originating from Taiwan. The second library-the Dr. Cecilia Koo Botanic Conservation Center (KBCC)-Leslie Kuo Plant Drug Library contains 2,592 extracts prepared by different solvents from 845 plants that covers 80 families. We screened these libraries with several bioassays such as luciferase reporter-based assay, image-based assay, and protein-based assay; and several interesting plants that were identified from these platforms are currently under investigation. Furthermore, a library composed of MPLC fractions, which will accelerate drug discovery process, are under construction. These libraries will be unique and useful natural product libraries that can be applied in HTS for new drug discovery.

Key words：High-throughput drug screening, plant extract libraries, KBCC

壁報論文

POSTER PAPERS

Total Synthesis and Metabolic Stability of Hispidulin and Its *d*-Labelled Derivative

陳亮傑 (Liang-Chieh Chen) [#,†,‡], 許凱程 (Kai-Cheng Hsu) [§], 邱麗珠 (Lih-Chu Chiou) [⊥,‖], 曾惠如 (Hui-Ju Tseng) [†,▽], 黃偉展 (Wei-Jan Huang) [*,†,▽,○,⊗]

[†]*Graduate Institute of Pharmacognosy, College of Pharmacy, Taipei Medical University, Taipei 110, Taiwan*

[‡] *School of Pharmacy, College of Pharmacy, Taipei Medical University, Taipei 110, Taiwan*

[§]*Graduate Institute of Cancer Biology and Drug Discovery, College of Medical Science and Technology, Taipei Medical University, Taipei 110, Taiwan*

[⊥]*Graduate Institute of Brain and Mind Sciences, College of Medicine, National Taiwan University, Taipei, 100, Taiwan*

[‖] *Graduate Institute of Pharmacology, College of Medicine, National Taiwan University, Taipei, 100, Taiwan*

[▽]*Ph.D. Program in Biotechnology Research and Development, College of Pharmacy, Taipei Medical University, Taipei 110, Taiwan*

[○]*Ph.D. Program for the Clinical Drug Discovery from Botanical Herbs, College of Pharmacy, Taipei Medical University, Taipei 110, Taiwan*

[⊗]*School of Pharmacy, National Defense Medical Center, Taipei 114, Taiwan*

Hispidulin is a naturally occurring flavone known to have various central nervous system (CNS) activities. Proposed synthetic approaches to synthesizing hispidulin have proven unsatisfactory due to their low feasibility and poor overall yields. To solve these problems, this study developed a novel scheme for synthesizing hispidulin, which had an improved overall yield as well as more concise reaction steps compared to previous methods reported. Additionally, using the same synthetic strategy, *d*-labelled hispidulin was synthesized to investigate its metabolic stability against human liver microsome. This work may produce new chemical entities for enriching the library of hispidulin-derived compounds.

Key words: hispidulin; total synthesis; flavone; microsome stability; deuterium-labelled compound

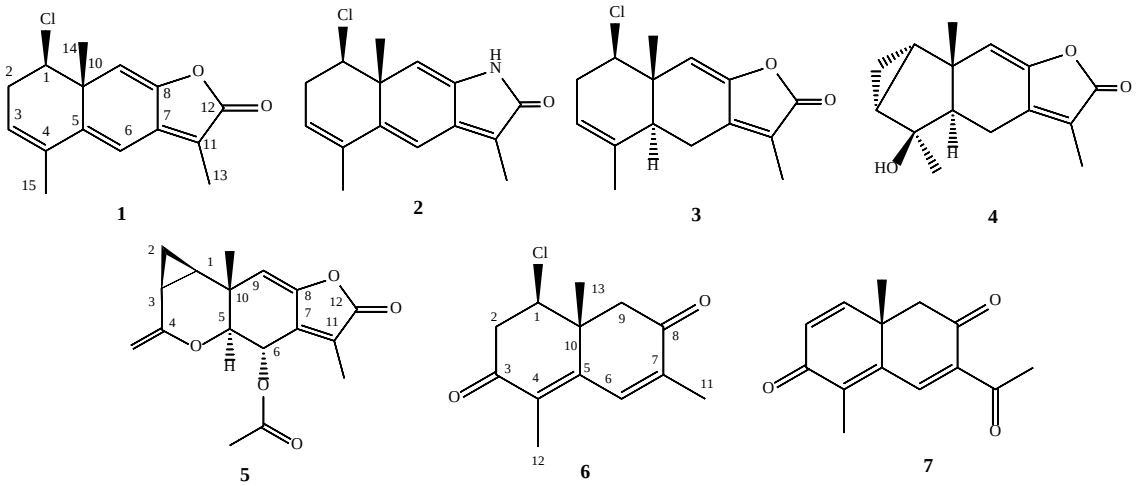
Constituents from the Roots of *Lindera aggregata*

郭賓崇 (Ping-Chung Kuo)[#], 洪欣儀 (Hsin-Yi Hung)[#], 馬國豪 (Guo-Hao Ma)[†], 吳天賞(Tian-Shung Wu)[#,*]

[#] *School of Pharmacy, College of Medicine, National Cheng Kung University, Tainan 701, Taiwan*

[†] *Department of Chemistry, National Cheng Kung University, Tainan 701, Taiwan*

L. aggregata (Lauraceae) is widely distributed in China and extensively used in traditional Chinese medicine for the treatment of various physiological symptoms. Pharmacological studies on *L. aggregata* have reported several significant bioactivities. In the present study, a series of chromatographic separations of the methanol extract of roots of *L. aggregata* has led to the isolation of thirty-nine compounds. Their chemical structures are elucidated by spectroscopic and spectrometric analysis. Among these compounds, linderaggredins A-E (**1**-**5**) are new sesquiterpenoids reported for the first time. In addition, linderaggredins F (**6**) and G (**7**) are characterized with unprecedented carbon skeletons. Other known compounds are identified by comparison of their physical and spectroscopic data with values reported in the literature.



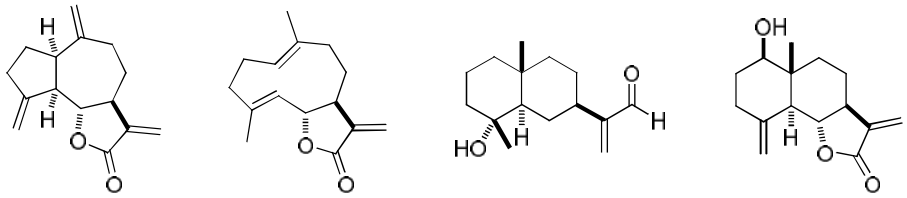
Key words: Lauraceae, sesquiterpenoid, unprecedented carbon skeleton, spectroscopic and spectrometric analysis

Biological Activities of Sesquiterpenoids and Their Derivatives from the Roots of *Saussurea costus*

藍啟涎(Chi-Ting Lan)[#], 林倚銘(Yi-Ming Lin) and 鄭竣亦(Shi-Yie Cheng)*

#Department of Life Sciences, National University of Kaohsiung, Kaohsiung 811, Taiwan

Eighteen sesquiterpenoids, identified as dehydrocostus lactone (**1**), costunolide (**2**), *β*-costic acid (**3**), 4*α*-hydroxyeudesm-11-en-12-al (**4**), ilicic alcohol (**5**), 12- acetoxy-4*α*-hydroxyeudesm-11(13)-ene (**6**), cuicothamnal (**7**), arbusculin A (**8**), 4-*epi*-arbusculin A (**9**), dehydrocostus lactone 10*α*(14)-epoxide (**10**), 10*α*,14- epoxy-11*β*H-guaia-4(15)-ene-12,6*α*-olide (**11**), reynosin (**12**), 11*β*,13-dihydro- reynosin (**13**), santamarine (**14**), 11*β*,13-dihydrosantamarin (**15**), ilicic acid (**16**), 4-*epi*-ilicic alcohol (**17**), 7*α*,12-dihydroxy-eudesm-4(15),11(13)-diene (**18**) were isolated from the MeOH extract of the root of *Saussurea costus*. In previous studies, compound **4** showed powerful gastric cytoprotective effect and antiproliferative against a human ovarian carcinoma cell line (A2780), a human lung carcinoma cell line (SW1573) and a human breast cancer cell line (T-47D) with GI_{50} values of 1.8, 2.0 and 6.5 μM, respectively. Compounds **1**, **2**, **8**, **12** and **14** showed cytotoxicity against a human hepatocellular carcinoma cell line (HepG2) with CD_{50} values of 3.5, 1.6, 10.0, 11.0 and 7.5 μg/mL, cytotoxicity against a human cervical cancer cell line (HeLa) with CD_{50} values of 3.5, 2.0, 7.5, 7.5 and 10.0 μg/mL, and cytotoxicity against a human ovarian carcinoma cell line (OVCAR-3) with CD_{50} values of 2.5, 2.0, 7.5, 7.5 and 10.0 μg/mL,
respectively.



1 **2** **4** **12**

Key word：*Saussurea costus*, Dehydrocostus lactone, Costunolide

Chemical Constituents from the Stems of *Tinospora sinensis* and Their Bioactivity

Sio-Hong Lam[1], Po-Hsun Chen[2], Hsin-Yi Hung[1], Tsong-Long Hwang[3], Tran-Dinh Thang[4], Ping-Chung Kuo[1,*] and Tian-Shung Wu[1,*]

[1] School of Pharmacy, College of Medicine, National Cheng Kung University, Tainan 701, Taiwan
[2] Department of Biotechnology, National Formosa University, Yunlin 632, Taiwan
[3] Graduate Institute of Natural Products, College of Medicine, Chang Gung University; Research Center for Industry of Human Ecology, Research Center for Chinese Herbal Medicine, and Graduate Institute of Health Industry Technology, College of Human Ecology, Chang Gung University of Science and Technology; Department of Anesthesiology, Chang Gung Memorial Hospital, Taoyuan 333, Taiwan
[4] School of Chemistry, Biology and Environment, Vinh University, Vinh City, Vietnam

The genus *Tinospora*, belonged to Menispermaceae, is composed of more than 20 species all over the tropical regions of the Eastern Hemisphere. This genus is traditionally medical used in Southeast Asian countries to treating malaria, skin diseases, gout, and diabetes. A lot of scientific reports of their physiological activities mainly include antioxidation, anti-inflammation, and cytotoxicity, especially with the most extensively explored hypoglycemic activity. However, the bioactive principles of *T. sinensis* remained poorly understood. According to the preliminary screening results, the methanol extract of *T. sinensis* collected from Vietnam displayed IC_{50} values of 6.66 μg/mL and 4.68 μg/mL in the inhibition of superoxide anion generation and elastase release, respectively. Further chromatography purification had resulted in the characterization of nine lignans (**1**-**9**), six pyrrole alkaloids (**10**-**15**), seventeen benzenoids (**16**-**32**), ten terpenoids (**33**-**42**), eight steroids (**43**-**50**), four amides (**51**-**54**), one coumarin (**55**), and two others (**56**-**57**), respectively. The chemical structures of new compounds **1**, **11**, and **17** were established on the basis of 1D and 2D NMR and mass spectrometric analyses.

Key words: *Tinospora sinensis*, Menispermaceae, superoxide anion generation, elastase release

Anti-melanogenesis and Antioxidant Components from *Ampelopsis japonica*

李家琳 (Chia-Lin Lee),[†,‡,*] 詹昀璉 (Yun-Lian Jhan),[†] 江秀梅 (Hsiu-Mei Chiang),[†] 陳朝榮 (Chao-Jung Chen),[§,⊥] 張永勳 (Yuan-Shiun Chang),[‖]

[†] *Department of Cosmeceutics, China Medical University, Taichung 40402, Taiwan*
[‡] *Chinese Medicine Research and Development Center, China Medical University Hospital, Taichung 40447, Taiwan*
[§] *Graduate Institute of Integrated Medicine, China Medical University, Taichung 40402, Taiwan*
[⊥] *Proteomics Core Laboratory, Department of Medical Research, China Medical University Hospital, Taichung 40447, Taiwan*
[‖] *Department of Chinese Pharmaceutical Sciences and Chinese Medicine Resources, China Medical University 40402, Taiwan*

Ampelopsis Radix (*Ampelopsis japonica*) which belongs to the traditional Chinese medicine (TCM) is one of the traditional whitening agents. In our preliminary research, the ethyl acetate- (AJE) and *n*-butanol- (AJB) soluble fractions of this TCM showed significantly anti-melanogenesis and antioxidant properties. Until now, fourteen compounds were isolated from AJE and their structures were identified by NMR and MS. Anti-melanogenesis assay indicated two tannins **8** and **9** derivatives could potentially reduce melanin contents. Two stilbenes **2**, **3**, one lignan **6**, and five tannins **7**–**11** have more antioxidant activities than positive control, vitamin C. Our results demonstrated Ampelopsis Radix and its constituents could be potential botanical resources of cosmeceutical development for skin disorders.

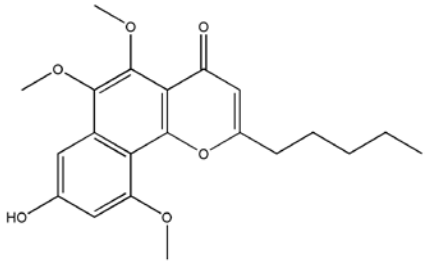
Key words: *Ampelopsis japonica*, Anti-melanogenesis, Antioxidant

Chemical Constituents from the Formosan Crinoid *Colobometra perspinosa*

蕭令琮(Ling-Tsung Hsiao)[1], 李宗祐(Zong-You Li)[2], 施怡茜(Yi-Chien Shih)[1], 柯惠茹(Hui-Ru Ke)[1], 張弘煒(Hong-wei Zhang)[1],韓鎮鴻(Jhen-Hong Han)[1], 許蓮佳(Wei-Jia Syu)[1], 洪名緯(Ming-Wei Hong)[1], 馮渝芸(Yu-Yun Fong)[1], 林鳳瑜(Feng-Yu Lin)[1], 鍾旭銘(Hsu-Ming Chung)[1*]

[1]*Department of Applied Chemistry, National Pingtung University, Pingtung 900, Taiwan.*
[2]*Department of Marine Biotechnology and Resources, National Sun Yat-sen University, Kaohsiung, 804, Taiwan*

In the interest of identifying natural substances from marine invertebrates collected off the waters of Taiwan, we studied the Crinoid *Colobometra perspinosa* for its organic extract showed interesting chemical constituents by NMR data analysis. In this presentation, including twelve compounds **1**–**5** were isolated from Crinoid *Colobometra perspinosa*. The structures of these compounds and their derivatives were established primarily on the basis of NMR spectral analysis and chemical derivatization. The application of NMR techniques included ^{1}H NMR, ^{13}C NMR, DEPT, COSY, HMQC, HMBC, NOESY and so on.



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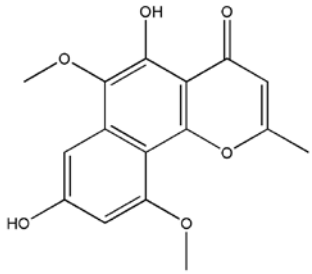

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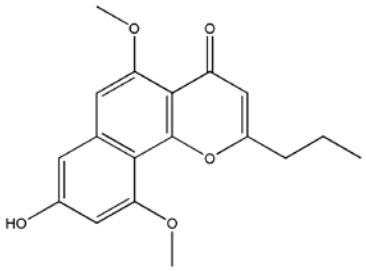

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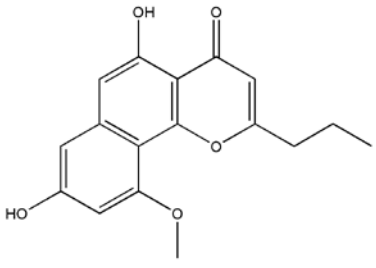

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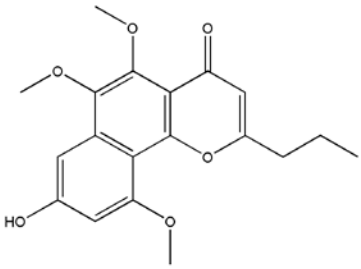

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Key words: Crinoid, *Colobometra perspinosa*, iNOS, COX-2

Design of Diarylheptanoid Derivatives as Dual Inhibitors Against Class IIa Histone Deacetylase and β-amyloid Aggregation

曾惠如 (Hui-Ju Tseng), [#,†] 陳亮傑 (Liang-Chieh Chen), [‡,§] 劉昌邑 (Chang-Yi Liu), [⊥] 黃耘翌 (Yun-Yi Huang), [‡] 顏政昌 (Cheng-Chung Yen), [‡] 翁靖如 (Jing-Ru Weng), [¶] 呂岳霖 (Yeh-Lin Lu), [‡,§] 侯文琪 (Wen-Chi Hou), [‡] 林偉德 (Tony E. Lin), [⊥] 潘一紅 (I-Horng Pan), [▽] 黃國魁 (Kuo-Kuei Huang), [▽] 許凱程 (Kai-Chang Hsu)*, [⊥] and 黃偉展 (Wei-Jan Huang) *, [†, ‡, ○, ⊗]

[†] *Ph.D. Program in Biotechnology Research and Development, College of Pharmacy, Taipei Medical University, Taipei, Taiwan*

[‡] *Graduate Institute of Pharmacognosy, College of Pharmacy, Taipei Medical University, Taipei, Taiwan*

[§] *School of Pharmacy, College of Pharmacy, Taipei Medical University, Taipei, Taiwan*

[⊥] *Graduate Institute of Cancer Biology and Drug Discovery, College of Medical Science and Technology, Taipei Medical University, Taipei, Taiwan*

[¶] *Department of Marine Technology and Resources, College of Marine Sciences, National SunYat-sen University, Kaohisung, Taiwan*

[▽] *Herbal Medicinal Product Division., Industrial Technology Research Institute, Hsinchu, Taiwan*

[○] *Ph.D. Program for the Clinical Drug Discovery from Botanical Herbs, College of Pharmacy, Taipei Medical University, Taipei, Taiwan*

[⊗] *School of Pharmacy, National Defense Medical Center, Taipei, Taiwan*

Alzheimer's disease (AD) is a progressive neurodegenerative disorder with multiple etiologies. Beta-amyloid (Aβ) self-aggregation and overexpression of class IIa histone deacetylases (HDACs) are strongly implicated with AD pathogenesis. In this study, a series of novel diarylheptanoid derivatives were designed, synthesized and evaluated for use as dual Aβ self-aggregation and class IIa HDAC inhibitors. Among these compounds, **4j**, **5c** and **5e** displayed effective inhibitions for Aβ self-aggregation, HDAC5 activity and HDAC7 activity with IC_{50} values of < 10 μM. The compounds contain three common features: (1) a catechol or pyrogallol moiety, (2) a carbonyl linker and (3) an aromatic ring that can function as an HDAC cap and create hydrophobic interactions with $Aβ_{1-42}$. Furthermore, compounds **4j**, **5c** and **5e** showed no significant cytotoxicity to human neuroblastoma SH-SY5Y cells and also exhibited neuroprotective effect against H_2O_2-induced toxicity. Overall, these promising in vitro data highlighted compounds **4j**, **5c** and **5e** as lead compounds that are worthy for further investigation.

Key words: Alzheimer's disease, Aβ aggregation, histone deacetylase, isoform-selective inhibitors, dual inhibitors

Anti-oxidative phenolic derivatives and TNF-α-activated polysaccharides from *Amaranthus caudatus*

黃宏澤 (Hung-Tse Huang)[†], 張世霖 (Stephen S. Chang)[‡], 戴承杰 (Chen-Jei Tai)[‡], 林玉麒 (Yu-Chi Lin)[†], 魏紋祈 (Wen-Chi Wei)[†], 蔡維人 (Wei-Jern Tsai)[†], 盧美光 (Mei-Kuang Lu) *[,†] and 郭曜豪 (Yao-Haur Kuo) *[,†]

[†]*Division of Chinese Materia Medica Development, National Research Institute of Chinese Medicine, Taipei 112, Taiwan*

[‡]*Ph.D. Program in Clinical Drug Development of Chinese Herbal Medicine, College of Pharmacy, Taipei Medical University, Taipei 110, Taiwan.*

Amaranthus caudatus belonging to Amaranthaceae family is one of edible vegetables in Taiwan. Preliminary bioactive screening revealed that the *A. caudatus n*-BuOH extract possessed the promising superoxide radical scavenging ability (by PMS/NADH system). Further isolation by column chromatography and bioactivity-guided fractionations, four phenolic derivatives as 3,4-dihydroxylbenzoic acid, caffeic acid, rutin, and kaempferol-3-rutinoside were isolated and characterized from the active fraction (ACF3) in which the HPLC profile is presented was also established. Moreover, the polysaccharide extracts of *A. caudatus* exhibited immunomodulatory effects by TNF-α activation. Further analysis of the bioactive polysaccharide revealed that myo-inositol**,** sorbitol, fucose, glucosamine, galactosamine, galactose, glucose, mannose and fructose were the major mono-sugars and glucose had the highest amount with the value of 66.72 μmol/g in the *A. caudatus* polysaccharides.

Key words: *Amaranthus caudatus*, polysaccharide analysis, immunomodulatory activities

Chemical constituents and anti-inflammatory activities from the fruit of *Myristica cagayanensis*

Sin-Ling Wang (王馨翎) [1#], Hsiang-Ruei Liao (廖庠睿) [2], Mei-Ing Chung (鍾美英) [1*], Jih-Jung Chen (陳日榮) [3*]

1. School of Pharmacy, College of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan
2. Graduate Institute of Natural Products, College of Medicine, Chang Gung University, Taoyuan, Taiwan
3. Faculty of Pharmacy, School of Pharmaceutical Sciences, National Yang-Ming University, Taipei, Taiwan

The genus *Myristica* contains over 80 species that are distributed in the tropical regions of India, Australia, and Indo-Malaya to the Pacific island. Only three species, *M. simarum*, *M. cagayanensis*, and *M. fragrans* are found in Taiwan. *Myristica cagayanensis* Merr., a medium-sized evergreen tree belonging to the family Myristicaceae, is indigenous to Philippines and Lanyu of Taiwan. Additionally, previous phytochemical research on this genus has led to the isolation of various compounds including diarylnonanoids, isoflavones, and lignans, some of which show valuable antimicrobial, antioxidant, and anticancer activities.

In our studies on the anti-inflammatory constituents of Formosan plants, many species have been screened for *in vitro* anti-inflammatory activity, and *M. cagayanensis* has been found to be one of active species. Investigation on active EtOAc-soluble fraction of this plant afforded a new isoflavone derivative, myristicagayanensis A (**1**), a new diarylnonanoid derivative, myristicagayanensis B (**2**), together with 28 knows compounds, 4',7-dihydroxy-2'-methoxyisoflavon (**3**), formononetin (**4**), daidzein (**5**), 5,7,4'-trihydroxy-2'-methoxyisoflavon (**6**), genistein (**7**), 3'-*O*-methylorobol (**8**), irilone (**9**), (-)-hinokinin (**10**), (-)-pluviatolide (**11**), (-)-dehydroxycubebin (**12**), (+)-dihydrosesamin (**13**), (-)-dihydrocubebin (**14**), (+)-dihydrocubebin (**15**), pluviathilol (**16**), 3,4-(methylenedioxy)toluene (**17**), 4-hydroxybenzenepentanoic acid (**18**), malabaricone A (**19**), malabaricone B (**20**), malabaricone A (**21**), (2*R*,3*R*)-4,4-bis(4'-hydroxy-3'-methoxyphenyl)-2,3-dimethylbutanol (**22**), demthyldactyloidin (**23**), dactyloidin (**24**), otobanone (**25**), cagayanin (**26**), (+)-guaiacin (**27**), (-)-isoguaiacin (**28**), castanone (**29**), and β-sitostenone (**30**). The structure of compounds **1** and **2** were determined through spectral analysis including extensive 2D NMR data. This symposium describes the structural elucidation of **1** and **2** and the anti-inflammatory activities of the isolates.

Key words：*Myristica cagayanensis*, Myristicaceae, isoflavone and diarylnonanoid derivatives, anti-inflammatory activity

Phomaketide A inhibits angiogenesis in human endothelial progenitor cells *in vitro* and *in vivo*

王佳蓉 (Chia-Jung Wang)[1,3]，李宗徽 (Tzong-Huei Lee)[2]，陳裕仁 (Yu-Jen Chen)[3]，王士維 (Shih-Wei Wang)[1,*]

[1]*Department of Medicine, Mackay Medical College, New Taipei City, Taiwan*
[2]*Institute of Fisheries Science, National Taiwan University, Taipei, Taiwan*
[3]*Department of Radiation Oncology, MacKay Memorial Hospital, Taipei, Taiwan*

Many studies have shown that bone marrow-derived endothelial progenitor cells (EPCs) can contribute to postnatal neovascularization and tumor angiogenesis. EPCs have been shown to play a "catalytic" role in metastatic progression by mediating the angiogenic switch. Understanding the pharmacological functions and molecular targets of natural products are critical for drug development. 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 anti-angiogenic mechanism of phomaketide A in human EPCs is mostly unknown. In this study, we found that phomaketide A inhibited migration and tube formation of EPCs. Phomaketide A concentration-dependently repressed the phosphorylation of Akt, Erk, and Src in EPCs. We also showed that phomaketide A markedly inhibits VEGF-induced angiogenesis in the chick embryo chorioallantoic membrane (CAM) model. Moreover, phomaketide A significantly attenuated microvessel formation in the *in vivo* Matrigel plug assay. Overall, our results demonstrate that phomaketide A inhibits angiogenesis in human EPCs through Akt, Erk, and Src signaling pathways. Phomaketide A further exerts promising anti-angiogenic effect *in vivo*. Phomaketide A may serve as a potential angiogenesis inhibitor for treatment of cancer and other angiogenesis-related diseases.

Key words： Phomaketide A, Angiogenesis, Endothelial Progenitor Cells

Discussion on the specification limit of preservatives in cosmetics in Taiwan and other countries

邱怡菁(I-Ching Chiu)[1,2#], 吳建達(Chien-Ta Wu)[2], 江瑩真(Ying-Chen Chiang)[1], 謝伯舟(Po-Chow Hsieh)[1], 劉怡旻(I-Min Liu)[1], 劉崇喜(Shorong-Shii Liou)[1]*

Department of Pharmacy and Master Program, College of Pharmacy and Health Care Tajen University, Pingtung 90741, Taiwan.[1]

Taiwan Shuenn-An Biotechnology Pharmaceutical Co.,Ltd 831, Taiwan.[2]

Due to the global focus on the development of cosmetic materials and attention of process safety formula research, the side effects of chemical preservatives in cosmetics have aroused public concern. As the trend to return to nature, the use of natural materials to replace the synthesis or use of biological technology, making cosmetics more and more nutritious ingredients. In contrast, antiseptic and antibacterial ability of product become another important issue in the safety of cosmetics.

Cosmetic Hygiene and Safety Act Full text was first formulated and promulgated by the Former Department of Health, Executive Yuan on December 28, 1972. From then on, Health authorities began to pay attention to cosmetics related issues. This study consolidation Taiwan government health authority from 1985 to 2017,investigation and research on inspection items, announcements and monitoring data of preservatives in cosmetics, according to the announcement background of time, related characteristics and results, classify the analysis to discuss the specifications direction of cosmetics preservative in Taiwan.

The study integrates and compares the preservatives in cosmetics in the European Union, the United States, Japan, the East Association, China and Korea, and expects to know the direction of Taiwan's research and future development on preservative projects with existing data and background values. It is expected to provide appropriate advice on the development of preservative items and standards. Also, improve the development of the cosmetics industry and quality of products.

Key words：Laws and regulations, preservatives, cosmetics

Analysis on the current trend of the management and supply of opioid in Taiwan

洪金華(Chin-Hua Hung)[1#], 江瑩真(Ying-Chen Chiang)[1], 謝伯舟(Po-Chow Hsieh)[1], 謝博銓(Po-Chuen Hsieh)[1*]

Department of Pharmacy and Master Program, College of Pharmacy and Health Care Tajen University, Pingtung 90741, Taiwan.[1]

The Ministry of Health and Welfare amended and promulgated the Controlled Drugs Act on June 14, 2017. The pharmaceutical plant of the Food and Drug Administration (FDA) shall handle the import, export, manufacture and selling of the Schedule 1 and 2 controlled drugs, as necessary, FDA may commission another pharmaceutical firms to manufacture it. Make good use of Taiwan pharmaceutical environment and enhance drug development. Provide more choices for medication.

Opioid is the milk cutting from the poppy fruit and extracted after drying. As the pain treatment agent with strong analgesic effect in clinical. Due to its height addiction, Taiwan follows the spirit of three major anti-drug conventions of the United Nations, controlled as schedule 1 and schedule 2 controlled drugs by Controlled Drugs Act. Cancer has been the first cause of death for 36 consecutive years since 1982. To relieve pain in patients and the right to healthy living, demand for schedule 1 and schedule 2 controlled drugs of new ingredients, new dosage forms or new doses is increasing.

Taiwan pharmaceutical factory supply 6 kinds main ingredient, 7 dosage forms and 31 items of Schedule 1 and 2 controlled drugs. Tablets, injections and internal liquids dosage form are made by our factory. Capsules and buccal soluble films are import. According to Controlled Drugs Factory Operating Fund Final Statement of TFDA, the total income increasing from 2010 approximately NT 4.8 billion to 2017 about NT 7.8 Billion, grow at least 50%. Analysis of the statistical tables of Schedule 1 and 2 controlled drugs revenue and expenditure in the Ministry of Health and Welfare, Fentanyl injection 0.05mg/ml, 2ml, Jurnista Prolonged-Release Tablets 8 mg, OxyNorm Immediate Release Capsules 5mg and PAINKYL fentanyl (buccal soluble films) 200 μg are star products in the past 2 years. We may commissioned by Controlled Drugs Factory manufacturing, research and development to improve the self-made rate of capsules and buccal soluble films.

This study compared related standards and management of domestic and foreign controlled drugs safety. Review its similarities and differences. Analysis Opioid management and current trend of PIC/S GDP supply implementation. Hope to provide management policy and supply model specific recommendations of Schedule 1 and 2 controlled drugs. As a reference for the revision of Taiwan regulations.

Keywords： Opioid, Controlled Drugs, Controlled Drugs Factory, Controlled Drugs Act, Commissioned manufacturing

Secondary Metabolites Isolated from *Pharbitis nil*

羅珮婷 (Pei-Ting Lo),[†] 李家琳 (Chia-Lin Lee)[†,‡*]

[†] *Department of Cosmeceutics, China Medical University, Taichung 40402, Taiwan*
[‡] *Chinese Medicine Research and Development Center, China Medical University Hospital, Taichung 40447, Taiwan*

Morning glory (*Pharbitis nil* (L) Choisy) is classified in the family of Convolvulaceae which is cultured globally and mainly distributed in the tropical and subtropical regions of Asia and America. Morning glory is an annual crop that are harvested during early July to end of October. The seeds (Qian Niu Zi) of morning glory are well documented to have remedy properties such as elimination of edema, sputum and stasis. According to the coating colors of the seeds, it is separated into two varieties: black (Hei Chou) and white (Bai Chou).

The objective was to investigate antioxidant constituents of Hei Chou. The methanolic extract of Hei Chou were partitioned into hexane- (MPSH), *n*-butanol- (MPSB), and aqueous (MPSW) soluble fractions, respectively. Three compounds, including *trans*-caffeic acid (**1**), 2-(4-hydroxyphenyl) ethyl 6-*O*-D-apio-*β*-D-furanosyl-*β*-D-glucopyranoside (**2**), and 4,5-di-*O*-caffeoyl quinic acid (**3**) were isolated from the active MPSB. The structures of all isolates were identified by nuclear magnetic resonance (NMR). Currently, the compound isolation and antioxidant assay are still undergoing.

Key words: *Pharbitis nil*, Pharbitidis Semen, antioxidant

Anti-melanogenesis LJMEH from *Leonurus japonicus*

呂杰臨 (Chieh-Lin Lu),[†] 江秀梅 (Hsiu-Mei Chiang),[†] 李家琳 (Chia-Lin Lee),[†,‡,*]

[†] *Department of Cosmeceutics, China Medical University, Taichung 40402, Taiwan*
[‡] *Chinese Medicine Research and Development Center, China Medical University Hospital, Taichung 40447, Taiwan*

Leonurus japonicus belongs to the family of Lamiaceae and is commonly known as Chinese motherwort, it is a Chinese herbal plant native to Asia. Motherwort are commonly used as a folk remedy for anti-inflammatory, anti-cancer, anti-oxidation, and treatment of cardiovascular diseases etc. However, the whitening effect of this species has not be reported. In our preliminary studies, the MeOH extract of *L. japonicas* showed anti-melanogenesis and then partitioned into hexane- (LJMEH), EtOAc-, *n*-BuOH-, and aqueous soluble fractions, respectively. The low polar extract LJMEH had potential melanin inhibition without cytotoxicity toward melanoma cell and was chosen to investigate the active chemical composition. Currently, a series of steroid derivatives were found and further compound isolation and bioassay were still ongoing.

Key words: *Leonurus japonicus*, Lamiaceae, Anti-melanogenesis

The war of bacteria and fungi: bio-enzymatic transformation of the siderophore, pyochelin through imaging mass spectrometry and multi-omics analyses.

何攖寧 (Ying-Ning Ho)[#], 謝其庭 (Chi-Ting Hsieh), 彭嘉琪 (Chia-Chi Peng), 王博緯 (Bo-Wei Wang), 林芝 (Chih Lin), 楊玉良 (Yu-Liang Yang)*

Agricultural Biotechnology Research Center, Academia Sinica, Taiwan[#*]

Many species of plant-associated bacteria secrete natural product that inhibit the development or growth of plant pathogens. In turn, pathogens may develop resistance to antagonistic molecules. However, little is known about enzymatic transformations of secreted metabolites that occur during interactions between bacteria and fungi. *Burkholderia cenocepacia* strain 869T2, an endophytic bacterium showed a promising antagonistic effect against plant pathogens. To understand the functional bacterial-fungal interaction comprehensively, it is a good strategy to monitor metabolite secretion and gene expression profiles of both interacting organisms simultaneously. Pyochelin, one of siderophore of *Pseudomonas aeruginosa* and *Burkhoderia* sp. that is able to induce plant ISR (induction of systemic resistance) and has been identified as an antifungal antibiotic. Through IMS, RNA-seq and proteomics analysis, we found that instead of inhibiting the gene expression of pyochelin in 869T2, *P. noxius* could modify pyochelin (*m/z* 325) to *m/z* 383, while *P. noxius* faced to 869T2. This modification resulted in poor ability of iron chelating while *m/z* 325 changed to *m/z* 383. This is first study to show the enzymatic transformation of pyochelin in the battle for iron. In addition, strain 869T2 induced the secretion of oxidoreductases (laccase, copper radical oxidase, aryl-alcohol oxidase, manganese peroxidase and etc.) which are lignin degradation enzymes and virulence factors. We also observed induced antimicrobial compounds in the interaction region by imaging mass spectrometry. In the battle of bacteria and fungi, fungi can use proteins and metabolites to response the stress from antagonistic bacteria. Thorough understanding of this bacterial/fungal interaction might lead to the discovery of a method to control fungi disease.

Keyword: *Phellinus noxius*, siderophore, image mass spectrometry, RNA-seq, proteomics, enzymatic transformation.

A New Xanthone and Anti-inflammatory Constituents from the Pericarp of *Garcinia mangostana*

Cheng-Shin Yang (楊晟鑫)[1#], Tzu-Cheng Chang (張資正)[2], Yu-Jing Wu (吳郁靖)[3], Jhih-Yi Chen (陳志以)[4], Anya Maan-Yuh Lin (林滿玉)[4], Jih-Jung Chen (陳日榮)[1,4*]

[1] Institute of Biopharmaceutical Sciences, National Yang-Ming University, Taipei, Taiwan.
[2] Department of Forestry and Natural Resources, National Ilan University, Yilan, Taiwan.
[3] Department & Institute of Pharmacology, National Yang-Ming University, Taipei, Taiwan.
[4] Faculty of Pharmacy, National Yang-Ming University, Taipei, Taiwan.
(E-Mail: chenjj@ym.edu.tw)

Garcinia mangostana Linn (Guttiferae), as known as mangosteen, is a slow-growing tropical evergreen tree and is mainly found in Southeast Asia. Many studies have shown that this plant is rich in a variety of prenylated xantones and its constituents have displayed many bioactivities. The dry pericarp of mangosteen has been widely used as an anti-inflammatory agent in Southeast Asia for many years.

In our preliminary screening, the EtOAc-soluble part of the pericarp of *Garcinia mangostana* showed anti-inflammatory activities *in vitro*. To isolate anti-inflammatory constituents from it, fifteen compounds including a new xanthone, garcimangone A (**1**), and fourteen known xanthones, α-mangostin (**2**), γ-mangostin (**3**), garcinone D (**4**), gartanin (**5**), β-mangostin (**6**), dulcisxanthone D (**7**), brasilixanthone B (**8**), 8-hydroxycudraxanthone G (**9**), tovophyllin A (**10**), garcinone E (**11**), ananixanthone (**12**), morusiqnin J (**13**), fuscaxanthone C (**14**), and pruniflorone R (**15**) have been isolated and identified. Their anti-inflammatory effects were evaluated by measuring the suppression of the NO production by LPS-treated RAW 264.7 macrophages. The structural elucidation of **1** and the anti-inflammatory property of all isolates are described herein.

Key words: *Garcinia mangostana*, Guttiferae, pericarp, xanthones, anti-inflammatory activity, RAW 264.7 macrophages

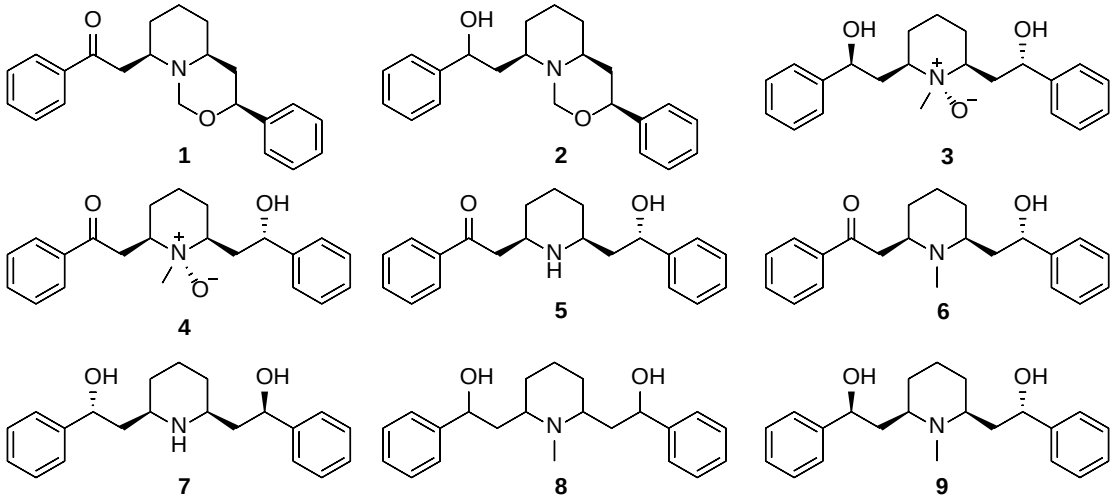
Anti-inflammatory 2,6-Disubstituted Piperidine Alkaloids from *Hippobroma longiflora*

林珏君 (Jue-Jun Lin)[#,†], 張芳榮 (Fang-Rong Chang)[†,‡], 黃聰龍 (Tsong-Long Hwang)[‖], 鄭源斌 (Yuan-Bin Cheng)[*,†]

[†]*Graduate Institute of Natural Products, Kaohsiung Medical University, Kaohsiung 807, Taiwan.*
[‡]*National Research Institute of Chinese Medicine, Taipei 112, Taiwan.*
[‖]*Graduate Institute of Natural Products, College of Medicine, Chang Gung University, Taoyuan 333, Taiwan.*

Hippobroma longiflora is a species of toxic plants in the monotypic genus *Hippobroma* (family Campanulaceae). This plant is an important herbal medicine for treatment of wounds, eye diseases, asthma, bronchitis and cancer in Indonesia. In previous pharmacological studies, *H. longiflora* was proved to have anti-inflammatory, anti-tumor, analgesic, and hemostatic effects.

The methanol extract of *H. longiflora* demonstrated substantial inhibition on superoxide anion generation and elastase release. In the nuclear factor erythroid-2-related factor (Nrf2) activity screening also had well activity of Nrf2 activation. After a series of chromatography, four new 2,6-disubstituted piperidine alkaloids, hipporidines A–D (**1**–**4**), together with five known compounds (**5**–**9**). Their structures were elucidated on the basis of HRESIMS, 1D and 2D NMR spectroscopic data.



Key words: *Hippobroma longiflora*; superoxide anion generation; elastase release; Nrf2; 2,6-disubstituted piperidine alkaloids

Sterols from *Ficus septica*

趙虹筑 (Hong-Chu Chao)[#] and 翁靖如 (Jing-Ru Weng) *

[#,*]*Department of Marine Biotechnology and Resources, National Sun Yat-sen University, Kaohsiung 80424, Taiwan*

Dengue fever is an acute infections disease which transmitted by mosquitoes to humans. *Ficus septica*, a small and green plant in tropical region in Asia, has been used in folk medicine to treat fever, fungal and bacterial diseases for centuries. In our search for potential anti-dengue virus agents, the extract of *F. septica* showed the highest ability, which led us to identify its potential constituents. Two sterols, olean-9(11),12(13)-dien-3β-yl acetate (**1**) and lupeol (**2**), were isolated from the bark of *F. septica*. The structures including relative configurations were elucidated by means of spectroscopic analyses.

Key words：*Ficus septica*; dengue virus; sterol

To Develop an Industrial Process for Producing H-compound, a Flavonoid from Rutaceae Family

廖培茹 Pei Ru Liau[1, 2]#, 賴韋霖 Wei-Lin Lai[1], 趙偉平 Wee-Pin Chao[1], 黃騰漢 Terng-Hoanng Hwang[1], 許振霖 Jennline Sheu[1] *

[1]Biomedical Technology and Device Research Laboratories, Industrial Technology Research Institute; Taiwan, [2] Department of Pharmacognosy, School of Pharmacy, College of Pharmacy, Taipei Medical University, Taiwan

H-compound is a flavonoid isolated from Rutaceae family with many biological activities, such as anti-inflammatory, anti-cancer cell, antioxidation and vascular protect, especially used to treat hypertension and myocardial infarction. Because of the high potential of H-compound, it is important to establish a mass production process for drug development. The general industrial processes to produce H-compound is using sodium hydroxide solution or limewater to extract from plant material, not only producing mass waste water but also low yield. In the study, the optimal solvents were selected to extract H-compound from plant material were based on the specific structure to decrease impurities in crude extract, and also to find the suitable parameters of extraction and purification for obtain H-compound, include the reflux time, number of times of extraction and purification method. This research developed the batch size from gram grade to tens of kilograms grade process to produce H-compound by more efficiency and economically. By the process, the purity of H-compound was more than 95%.

Key words：Flavonoid, Rutaceae, Mass production process

Taiwan Database of Extracts and Compounds (TDEC)

陳冠宇 (Guan-Yu Chen)[a,#], 楊顓丞 (Juan-Cheng Yang)[a], 姚宗佑(Tsung-Yu, Yao)[b,c], 李家琳 (Chia-Lin Lee)[a,d,e,*], 吳永昌 (Yang-Chang Wu) [c,f,g,*]

[a]*Chinese Medicine Research and Development Center, China Medical University Hospital, Taichung 404, Taiwan*

[b]*School of Pharmacy, Kaohsiung Medical University, Kaohsiung 807, Taiwan*

[c]*Research Center for Natural Products & Drug Development, Kaohsiung Medical University, Kaohsiung 807, Taiwan*

[d]*Department of Cosmeceutics, China Medical University, Taichung 404, Taiwan*

[e]*Chinese Medicine Research Center, China Medical University, Taichung 404, Taiwan*

[f]*Graduate Institute of Natural Products, Kaohsiung Medical University, Kaohsiung 807, Taiwan*

[g]*Department of Medical Research, Chung-Ho Memorial Hospital, Kaohsiung Medical University, Kaohsiung 807, Taiwan*

Taiwan Database of Extracts and Compounds (TDEC) is an academic and scientific website which offers a platform for investigators in different fields to share their own research information. Furthermore, the primary aims of TDEC are to preserve the Taiwan's important resources, including crude extracts, pure natural isolates, and chemically synthesized derivatives from Chinese herbal medicines, marine organisms, and microbes; then to integrate aforementioned substances from the academic research institutions, industrial units, and botanic conservation centers to make more drugs and products developments efficiently.

TDEC provides functional services such as drug management, drug search, investigator matching, and data statistics system. Drug information consisted of compounds' structures, physical and chemical properties and biological activities could be shared for every researchers in the world. Especially for the matching function, it could offer a point-to-point link between drug providers and investigators to efficiently help them to cooperate with each other and promote the powerful researches.

TDEC is a new conceptual data sharing platform for drug researches and developments. So far, this platform is developing under system construction. On the timeline, it will be online at 2019. (https://tdec.kmu.edu.tw)

Keywords: Taiwan Database of Extracts and Compounds, Extracts, Compounds

New Indole Alkaloids from Qing Dai

李家琳 (Chia-Lin Lee),[†,‡,§*] 王建旻(Chien-Ming Wang),[§] 胡皓竣(Hao-Chun Hu),[⊥] 陳朝榮 (Chao-Jung Chen),[‖] 吳永昌(Yang-Chang Wu)[⊥,*]

[†] *Department of Cosmeceutics, China Medical University, Taichung 40402, Taiwan*
[‡] *Chinese Medicine Research and Development Center, China Medical University Hospital, Taichung 40447, Taiwan*
§ *Chinese Medicine Research Center, China Medical University, Taichung 40402, Taiwan*
[⊥] *Graduate Institute of Natural Products, Kaohsiung Medical University, Kaohsiung 80708, Taiwan*
[‖] *Graduate Institute of Integrated Medicine, China Medical University, Taichung 40402, Taiwan*

Qing Dai (Indigo Naturalis), derived from the aerial parts of *Baphicacanthus cusia*, *Polygonum tinctorium*, or *Isatis tinctoria*, has been used in traditional Chinese medicine (TCM) to treat various inflammatory conditions. Three new indole alkaloid derivatives, indigodoles A–C (**1**, **2**, and **10**), along with seven known compounds were isolated from this TCM. The structures of **1**–**10** were elucidated from spectroscopic data, including NMR, MS, UV, IR, optical rotation, and ECD.

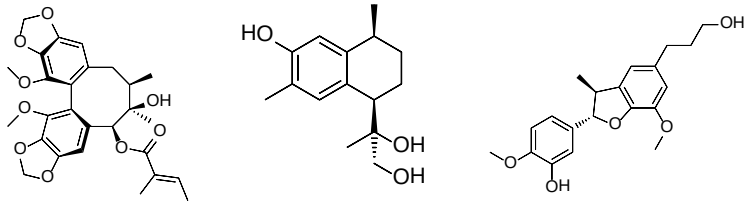
Key words: Qing Dai (Indigo Naturalis); Indole alkaloids

Bioactive Lignans from stems of *Schisandra arisanensis*

Pei-Hsin Li,[a] Yuan-Bin Cheng,[b] Yao-Haur Kuo,[c] Tsong-Long Hwang [d, e, f] and Ya-Ching Shen [a,*]

[a]School of Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan, [b]Institute of Natural Products, Kaohsiung Medical University, Kaohsiung, Taiwan, [c]Division of Chinese Materia Medica Development, National Research Institute of Chinese Medicine, Taipei, Taiwan, [d] Graduate Institute of Natural Products, College of Medicine, Chang Gung University, Taoyuan, Taiwan,[e] Research Center for Chinese Herbal Medicine, Research Center for Food and Cosmetic Safety, and Graduate Institute of Health Industry Technology, College of Human Ecology, Chang Gung University of Science and Technology, Taoyuan, Taiwan, [f] Department of Anesthesiology, Chang Gung Memorial Hospital, Taoyuan, Taiwan

Schisandra arisanensis Hayata, an endemic species in Taiwan was investigated its constituents in our lab previously. Many new and bioactive triterpenoids and lignans have been isolated from the fruits of *S. arisanensis* and reported in the literature. The lignans showed the significant anti-hepatic fibrosis activity and were proved to be inhibitor of alpha-glucosidase and free radical scavenger in vitro. However, the lignans of stems were not fully investigated and reported. Herein, we report the lignans and sesquiterpenes from the stems of *S. arisanensis*. In addition to eighteen known compounds, two new lignans and one sesquiterpene (**1**-**3**) have been isolated from the stems of *S. arisanensi*. The structures of these compounds were established on the basis of spectroscopic methods, especially 2D NMR (COSY, HMQC, HMBC, ROESY). All compounds were tested and evaluated anti-inflammatory bioactivities, anti-tumor cytotoxicities, and anti-oxidation activities. The structural elucidation and biological activities of the isolated lignans and sesquiterpenes will be presented in this conference.



1 **2** **3**

Key words：*Schisandra arisanensis*, lignans, sesquiterpenes, activities

Agricultural Survey, Origin Identification and Phytochemical Analysis of Two Turmeric Cultivars (TN1-2) in Nantou

Yu-Ming Hsu＃[1], Ying-Chi Du[2], Yu-Chuan Huang[3], Mohamed El-Shazly[4,5], Chien-Cheng Huang[2], Ching-Peng Chiu[2], Kuei-Hung Lai[6], Mei-Chin Lu[6,7], Tusty-Jiuan Hsieh[1,8], Lung-Yao Wang[3], Shih-Tsun Liang[9], and Yu-Hsuan Lin＊[9]

＃[1]Research Center for Environmental Medicine, Kaohsiung Medical University, Kaohsiung City 80708, Taiwan. [2]UYOUNG BIOMEDICAL CO., LTD., Taichung City 40255, Taiwan. [3]Instrument Center, National Defense Medical Center, Taipei City 11490, Taiwan. [4]Department of Pharmacognosy and Natural Products Chemistry, Faculty of Pharmacy, Ain-Shams University, Organization of African Unity Street, Abassia, Cairo 11566, Egypt. [5]Department of Pharmaceutical Biology, Faculty of Pharmacy and Biotechnology, German University in Cairo, Cairo 11432, Egypt. [6]National Museum of Marine Biology & Aquarium, Pingtung 94450, Taiwan. [7]Graduate Institute of Marine Biology, National Dong Hwa University, Pingtung 94450, Taiwan. [8]Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung City 80708, Taiwan. ＊[9]Department of Botanicals, Medical and Pharmaceutical Industry Technology and Development Center, New Taipei City 24886, Taiwan

Turmeric (*Curcuma* spp.) is a popular anti-inflammatory and anti-cancer health food in Taiwan, China, Japan, Korea, Malaysia, and Singapore. Very few pharmacognosy and phytochemical studies were reported on the Taiwanese turmeric cultivars. The aim of the present study was to establish a standardization protocol for the Taiwanese turmeric cultivars. As a first step, we travelled to Nantou, one of the most important places of turmeric agriculture in Taiwan. In Nantou, we performed an extensive agriculture survey. Next, two different turmeric cultivars, with common names Spring Turmeric (TN1) and Purple Turmeric (TN2), were collected and investigated microscopically as well as with thin layer chromatography (TLC) and high pressure liquid chromatography (HPLC). According to our results and previous literature, we confirmed that the species of TN1 and 2 are *C. aromatica* and *C. phaeocaulis*, respectively. The isolation and structure elucidation of the major components in TN1-2 extracts are currently under investigation.

Studies on the Secondary Metabolites from the Soft Coral *Briareum violaceum*

黃品彰 (Pin-Chang Huang)[†,‡,#], 彭柏融 (Bo-Rong Peng)[‡,§,⊥],蘇東彬 (Tung-Pin Su), [†,‡] and 宋秉鈞 （Ping-jyun Sung）*[,†,‡]

[†] *Graduate Institute of Marine Biology, National Dong Hwa University, Pingtung 94450, Taiwan*

[‡] *National Museum of Marine Biology & Aquarium, Pingtung 94450, Taiwan*

[§]*Doctoral Degree Program in Marine Biotechnology, National Sun Yat-Sen University, Kaohsiung 80424, Taiwan*

[⊥]*Doctoral Degree Program in Marine Biotechnology, Academia Sinica, Nankang, Taipei 11529, Taiwan*

Twelve cembranolides, including seven new compounds, briaviols A–G (**1**–**7**), as well as five known analogues, briaviodiol A (**8**), pachyclavulariolides E–H (**9**–**11**) and K (**12**), were isolated from a cultured octocoral identified as *Briareum violaceum*. We also discovered three pairs of stereoisomers in these compounds. The structures, including the relative configuration of compounds **1**–**7**, were established by spectroscopic analyses. These compounds were evaluated for their anti-inflammatory activities. In terms of anti-inflammatory test, compounds **2**, **4**–**6**, **8**, **11** and **12** have showed significant inhibitory effects on the iNOS protein expression in LPS-induced mouse macrophage RAW 264.7 at the concentration of 10 μM. In addition, we also discussed these structure-activity relationship (SAR) in this study.

Key words: *Briareum violaceum*, cembranolide, iNOS, SAR

Studies on the chemical constituents and their bioactivity from the Formosan coral *Briareum violaceum*

許景皓 (Jing-Hao Xu)[†,‡,#], 彭柏融 (Bo-Rong Peng)[‡,§,⊥],姚佳妏 (Jia-Wen Yao)[†,‡], 葉姵淇(Pei-Qi Ye)[†,‡] and 宋秉鈞(Ping-Jyun Sung)[*,†,‡]

[†] *Graduate Institute of Marine Biology, National Dong Hwa University, Pingtung 94450, Taiwan*

[‡] *National Museum of Marine Biology & Aquarium, Pingtung 94450, Taiwan*

[§]*Doctoral Degree Program in Marine Biotechnology, National Sun Yat-Sen University, Kaohsiung 80424, Taiwan*

[⊥]*Doctoral Degree Program in Marine Biotechnology, Academia Sinica, Nankang, Taipei 11529, Taiwan*

Studies on the chemical constiuents of the cultured soft coral *Briareum violaceum* had isolated twelve briarane-type diterpenoids, including seven new compounds named briaviolides K–Q (**1**–**7**), along with five know compounds, 2*β* -acetoxy-2-(debutyryloxy) stecholide E (**8**), stecholide C acetate (**9**), excavatoid E (**10**), 2*β*-acetoxy-2-(debutyryloxy)-stecholide E acetate (**11**) and excavatolide Z (**12**). Structures of compounds **1**–**12** were determined by spectroscopic methods, and comparison of the spectroscopic data with other related metadolites. In addition, those compounds are tested for anti-inflammatory activity. As a result, compound 5 was found to display inhibitory effect on the accumulation of the pro-inflammatory iNOS protein in the LPS-stimulated RAW264.7 macrophage cell at a concentration of 10 μM (reduced to10.53±1.38 %).

Keywords: *Briareum violaceum*, briarane, iNOS

Studies on the secondary metabolites from the Formosan gorgonian coral *Junceella fragilis*

鄭立國 (Li-Guo Zheng)[†,‡,#], 胡瓊止 (Chiung-Chih Hu)[‡],張智鈞 (Zhi-Jun Zhang)[†,‡], and 宋秉鈞(Ping-Jyun Sung)[*,†,‡]

[†] *Graduate Institute of Marine Biology, National Dong Hwa University, Pingtung 94450, Taiwan*

[‡] *National Museum of Marine Biology & Aquarium, Pingtung 94450, Taiwan*

In this study, eight briarane-type diterpenoids were isolated from the gorgonian coral *Junceella fragilis* collected from the coast of southern Taiwan. These metabolites include three new compounds, fragilide K (**1**), fragilide L (**2**), and (+)-12-*epi*-fragilide G (**3**), along with five known compounds, gemmacolide X (**4**), praelolide (**5**), juncin P (**6**), juncin ZI (**7**), and gemmacolide V (**8**). The structures of the above metabolites **1**–**8** were established by the spectroscopic methods and comparison of the spectroscopic data with other known related compounds. In terms of anti-inflammatory test, gemmacolide X (**4**) showed significant inhibitory effects on the iNOS and COX-2 protein expressions in LPS-induced mouse macrophage RAW 264.7. Fragilide L (**2**) and juncin ZI (**7**) showed significant inhibitory effects on the iNOS protein.

Keywords: *Junceella fragilis*, iNOS, COX-2

Andrographolide and its derivative reduced the expression of $p53^{R273H}$ and suppressed malignancy of pancreatic cancer cells

Chiao-Ju Liao (廖巧儒)[#], Jia-Ling Syu (許嘉凌) , and Shu-ling Fu (傅淑玲)*
Institute of Traditional Medicine, National Yang-Ming University, Taipei, Taiwan

Andrographolide (Andro) is a diterpenoid compound extracted from *Andrographis paniculata*. Accumulative evidence has demonstrated that Andro and its derivatives exhibit anti-tumor properties. However, the therapeutic effect of Andro on pancreatic cancer is rarely studied. Oncogenic gain-of-function (GOF) missense p53 mutant proteins are commonly identified in pancreatic ductal adenocarcinoma (PDAC). The most common p53 GOF mutations in PDAC is $p53^{R273H}$, which has been proven to promote cancer progression.

The current study investigated the effects of Andro and its derivative NCTU-322 on mutant $p53^{R273H}$ proteins as well as pancreatic cancer malignancy. We found Andro, and NCTU-322 could downregulate the protein level of $p53^{R273H}$ in pancreatic cancer cell PANC-1 without altering the mRNA expression. Notably, NCTU-322 exhibited stronger inhibitory effects than Andro. The interaction between $p53^{R273H}$ and its chaperone Hsp90 was reduced after andrographolide treatment. Moreover, treatment with these compounds could suppress the proliferation and stemness markers of PANC-1.

The gene expression profiles of vehicle-, Andro- or NCTU-322-treated PANC-1 cells were analyzed with microarray. After analyzing microarray data with Ingenuity pathway analysis (IPA), we found that NRF2-related stress signal transduction pathway and cell cycle-related pathway was controlled by Andro treatment. The expression of known $p53^{R273H}$-regulated target genes in our microarray data was further analyzed and a group of $p53^{R273H}$ downstream target genes altered by Andro was identified. The expression of most significantly downregulated genes involved in cell proliferation identified from microarray (*CXCL1, PCNA, CCNA2*) was confirmed by RT-PCR. Furthermore, the gene expression profiles in Andro- and NCTU-322-treated PANC-1 are highly overlapping .

In summary, our data demonstrate that Andro and its derivative NCTU-322 exhibit anti-cancer activity on pancreatic cancer, possibly through inhibiting GOF mutant $p53^{R273H}$. The molecular mechanism underlying anti-cancer activity of Andro and NCTU-322 is currently under investigation.

Key words: andrographolide, missense p53 mutant, pancreatic cancer

Anti-inflammatory Bisnorditerpenoid from *Blumea aromatica*

Lie-Chwen Lin (林麗純)[1,*], Xian-Jun Huang (黃嫻濬)[1], Shu-Ling Fu (傅淑玲)[2]

[1] National Research Institute of Chinese Medicine, Ministry of Health and Welfare, Taipei, Taiwan

[2] Institute of Traditional Medicine, National Yang-Ming University, Taipei, Taiwan

Blumea aromatica DC. (Compositae) is an aromatic hairy herb growing in forest edge from low to mid elevations of Taiwan. *B. aromatica* has been used in folk medicine to treat rheumatoid arthritis, eczema and with anti-bleeding and anti-itching effects. Our preliminary bioassay showed that the ethanolic extract of *B. aromatica* had inhibitory effect on NF-κB activity in LPS-stimulated RAW 264.7/Luc macrophage. Further repeatedly chromatographs led to the isolation of a new bisnorditerpenoid (**1**), sterebin A (**2**), two flavonoids (**3**-**4**) and seven caffeoyl quinic acids (**5**-**11**). Their structure were determined on the basis of spectroscopic evidences. Compound **1** at 30 μM concentration had significantly inhibitory effects on NF-κB activity in LPS-stimulated RAW 264.7/Luc macrophage without causing cytotoxicity.

Key words: *Blumea aromatica;* Bisnorditerpenoid; Anti-inflammatory; NF-κB activity

Classification of Indigenous Thraustochytrids of Taiwan by Matrix-Assisted Laser Desorption Ionization Time-of-Flight Mass Spectrometry

林佳穎 Jia-Ying Lin[1,#], 李澤民 Tse-Min Lee[1,2], 林秀瑾 Hsiu-Chin Lin[1,2], 張欣暘 Hsin-Yang Chang[1,2], 廖志中 Chih-Chuang Liaw[1,2,*]

[1] Department of Marine Biotechnology and Resources, National Sun Yat-sen University, Kaohsiung, Taiwan, [2] Doctoral Degree Program in Marine Biotechnology, National Sun Yat-sen University, Kaohsiung 80424, Taiwan.

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). Besides, our previous research indicated that the ethyl acetate (EtOAc) extracts of several species of thraustochytrids have certain components with a clear inhibitory activity toward acetylcholinesterase (AChE), which is responsible for the breakdown of acetylcholine (Ach) in the neural synapse to lead “cholinergic deficit hypothesis” of Alzheimer's disease.

Although there are some established taxonomic characterization of the thraustochytrids by modern biotechnology for their molecular identification, the procedure of the species identification is still time- and cost-consumed. Recently, MALDI biotyper, based on the analysis of the expressed intrinsic proteins of microbes, is regarded as a powerful and rapid tool for the species identification of the pathogens in hospitals. In the poster, we would try to propose the biotyper database of the strains of thraustochytrids by matrix assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) to facilitate the species identification of indigenous thraustochytrids from mangrove regions of Taiwan.

Constituents from *Monascus pilosus* BCRC 38072 (V)

吳和澄 (Ho-Cheng Wu),[†,#] 吳明德 (Ming-Der Wu),[‡] 陳益昇 (Ih-Sheng Chen),[ǁ] 袁國芳 (Gwo-Fang Yuan),[‡] 張訓碩 (Hsun-Shuo Chang),[†,ǁ*] 鄭銘仁 (Ming-Jen Cheng),[‡,*]

[†]*Graduate Institute of Natural Products, Kaohsiung Medical University, Kaohsiung 807, Taiwan.*
[‡] *Bioresource Collection and Research Center (BCRC), Food Industry Research and Development Institute (FIRDI), Hsinchu 300, Taiwan.*
[ǁ]*School of Pharmacy, College of Pharmacy, Kaohsiung Medical University, Kaohsiung 807, Taiwan*

Monascus spp. have been used in Asia for over 1000 years to color, aromatize and conserve meat, fish and soybean products. It is also applied for medicinal purposes like improved food digestion and blood circulation. Various secondary metabolites useful as food additives and/or pharmaceuticals have report being produced by *Monascus* spp. The whole genome of *Monascus pilosus* BCRC 38072 was sequenced and assembled by our Institute. In this study, we have chemically explored the constituents of a yellow mutant of the mycelia from *Monascus pilosus* BCRC 38072.

In our previous study, several new compounds were reported. As a continuation of the polar fraction of the mycelia from *M. pilosus*, eight compounds as additional constituents were isolated and identified from this fungus. They were characterized as one unprecedented azaphilone, monapilonitrile (**1**), along with seven known metabolites (**2**–**8**). The structure was elucidated by 1D and 2D-NMR spectroscopy together with HR-ESI-MS analysis, and comparison of the spectroscopic data with those reported for structurally related compounds. Further investigation of polar fractions of BCRC 38072 and the antifungal activity of the identified compounds are under proceeding.

Key words: *Monascus* spp., mycelia, azaphilone

Flavonid-type compounds from *Pterocarpus indicus* Willd by Chromatographic analysis

洪茂軒 (Mao-Xuan Hung)#，廖志中 (Chih-Chuang Liaw)*

[1]Department of Marine Biotechnology and Resources, National Sun Yat-sen University, Kaohsiung, Taiwan, [2]Doctor Degree Program in Marine Biotechnology, National Sun Yat-sen University Academia Sinica, Kaohsiung, Taiwan

Pterocarpus indicus Willd is used to treat “sores and minor wound” in Chinese medicine. Literature survey indicated that some procyanidin-type tannins were isolated from the epidermis of *P. indicus*. Those condensed tannins showed the effect of protease inhibitory and antiviral activities companied with the stage of high polymerization. In our previous study, the methanol extract of the bark of *P. indicus* exhibited 52% inhibitory activity against ovarian cancer cells, Hela cells, at the concentration of 50 μg/mL and inhibitory effect toward Dengue virus replication at 40 μg/mL. In the ongoing study, we extracted the bark powder of *P. indicus* by ethanol and then partitioned with methanol and hexane to give MeOH and Hex layers. Later on, the MeOH layer was subjected to flash chromatography high-performance liquid chromatography (HPLC) to give 24 flavonoid-type compounds. Among them, compound 10 is a new compound. All structures of the compounds were elucidated on the basis of spectroscopic methods (NMR, MS, UV, IR etc.) and comparison with literature data. In this poster, we will show the derivatives of flavonoids from *P. indicus.*

關鍵字/Key words：*Pterocarpus indicus* Willd, procyanidin-type tannins, flavonoid, isoflavonoid

Key enzymes for the biosynthesis of bioactive marine natural products

羅麗華 (Li-Hua Lo)#，張欣暘 (Hsin-Yang Chang)，廖志中 (Chih-Chuang Liaw)*

Department of Marine Biotechnology and Resources, National Sun Yat-Sen University, Kaohsiung (*Taiwan*)

In recent decades, antibiotic abuse results in the exponential increasing of the antibiotic-resistant pathogens, which leads to higher medical cost, prolonged hospital stays and increased mortality. It becomes urgent to find new type of antibiotics to treat such infections. In our previous study, we found new antibiotics, vitroprocines from marine *Vibrio* sp. QWI-06 against many pathogen indicators, such as *Acinetobacter baumannii*. Vitroprocines belonged to amino-polyketide derivatives. Moreover, we found that the biosynthesis of vitroprocines is related to the condensation of tyrosine and a polyketide chain catalyzed by a pyridoxal 5´-phosphate (PLP)-dependent enzyme, which is like those biosynthesis of mycotoxins by alanine and sphinganine, and sulfonolipids by serine and the sphingolipids or cysteate. By genome mining of the *vibrio* sp. QWI-06, we found four sets of putative PLP-dependent enzyme genes (PTs-1~4) in those of the *Vibrio*. By recombinant DNA technology, only three proteins (PTs-2~4) were overexpressed in *E. coli* system. To examine the function of enzymes PTs 1-4 with three kinds of amino acids and lauroyl CoA, only enzyme PT-3 works as The PLP-dependent acyl-CoA transferases to synthesize vitroprocines by tyrosine and lauroyl CoA.

Key words：Vitroprocines ; *Vibrio* sp. QWI-06 ; PLP dependent enzyme

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

陳若萱 (Ruo-Syuan Chen) [1,#], 黃聰龍 (Tsong-Long Hwang) [2],
張訓碩 (Hsun-Shuo Chang) [1,3,*]

[1]*Graduate Institute of Natural Products, College of Pharmacy, Kaohsiung Medical University, Kaohsiung 807, Taiwan*
[2]*Graduate Institute of Natural Products, College of Traditional Chinese Medicine, Chang Gung University, Taoyuan 333, Taiwan*
[3]*School of Pharmacy, College of Pharmacy, Kaohsiung Medical University, Kaohsiung 807, Taiwan*

Inflammation is a biological response to invasive stimulation which can cause chronic human diseases, such as diabetes, Crohn's disease, cancer, Alzheimer's disease and so on. With an obvious side effect which leads to treatment limitation, finding new anti-inflammatory drugs is an urgent issue. About sixty species of Formosan indigenous Lauraceous plants have been screened for anti-inflammatory activity by using the platform of fMLP/CB-induced superoxide anion and elastase release in human neutrophils. Among them, the methanolic extract of the root of *Machilus zuihoensis* Hayata showed potent anti-inflammatory effect. This study aims to isolate chemical constituents from the roots of *M. zuihoensis* and to evaluate their anti-inflammatory activity.

M. zuihoensis is a medium evergreen tree and endemic to Taiwan. The methanolic extract of the root of *M. zuihoensis* was partitioned into ethyl acetate layer and water layer. Bioassay-guided fractionation of the active ethyl acetate soluble layer of the root of *M. zuihoensis* led to the isolation of 11 known compounds, including two butanolides, (−)-methyl (2*E*)-2-(1-hydroxyl-2-oxopropyl)eicos-2-enoate (**1**) and isomahubanolide-23 (**2**), one coumarin, scoparone (**3**), five lignans, chicanine methyl ether (**4**), (−)-zuonin A (**5**), zuihonin B (**6**), machilolin-A (**7**) and (−)-styraxin (**8**), one phenylpropanoid, teracosyl *trans*-ferulate (**9**), and two steroids, a mixture of *β*-sitosterol (**10**) & stigmasterol (**11**). The structures of these compounds were elucidated by spectral analysis. The isolation work is still in progress, and the isolates are further evaluated for their anti-inflammatory activity.

The effects of soy bean and coffee extracts on antioxidant activity and emulsion stability

蔡燕鈴 (Taai Yen-Ling)* ，陳奕宇 (Chen I-Yu)

Department of Cosmetic Science, Vanung University

Abstract

The corn germ oil was used as a dispersion phase to prepare the O/W emulsions. For increasing the antioxidant effect of emulsions, the soy bean and coffee extracts were extracted with rotary evaporator then were added to the emulsion respectively. The antioxidant activity was performed by DPPH (1, 1diphenyl-2-picryl hydrazyl) radical scavenging method. The antioxidant effect could be verified by ultraviolet radiation spectrophotometer. The dynamic light scattering (DLS) analyzer was used for measuring the particle size of emulsions. The polarized optical microscope (OM) was utilized to observe the morphology of emulsions.

According to the results of antioxidant assay, it presented both of the soy bean and coffee extracts possess superior antioxidant activity. Even the dispersion phase - corn germ oil has good antioxidant activity. The particle size of emulsion droplets is under 300 nm and the droplets dispersed well. It displays the soy bean and coffee extracts not only possess excellent antioxidant effect but also have good emulsion stability.

Key words：soy bean, coffee, extracts, antioxidant activity, emulsion stability

Investigation of extraction of polysaccharides from southern Taiwan local *Sargassum ilicifoium* and the analysis of its monosaccharide composition

陳榮煌 (Jung-Huang Chen)[#], 鄒旻軒 (Min-Hsuan Tsou)[‡], 林秀美 (Hsiu-Mei Lin)*, 林綉美 (Showe-Mei Lin)[†]

[#‡]**Department of Bioscience and Biotechnology, National Taiwan Ocean University, Keelung 202, Taiwan.*

[†]*Institute of Marine Biology, National Taiwan Ocean University, Keelung 202, Taiwan.*

Fucoidan and alginate are the main polysaccharides in brown algae. Among them, fucoidan is a physiologically active polysaccharide consisting mainly of fucose and sulfate groups. In recent years, it has been explored in the biomedical field to cause cancer cell apoptosis, inhibit cancer cell metastasis, inhibit cancer cell angiogenesis, inhibit inflammatory gene NF-kB, antiviral, immune regulation and antioxidant equivalent. The bioactivities of fucoidan are associated with its structure, monosaccharide composition, the content and the location of sulphate groups. *Sargassum* is a kind of brown algae with high economic value widely distributed in the coastal waters of Taiwan. The main purpose of this study was to extract the fucoidan of *Sargassum ilicifoium* from the southern Taiwan in an optimized method, to identify the yield, monosaccharide composition, sulfate, total sugar and so on. In addition, this study will also identify the alginate yield of *Sargassum ilicifoium*.

Photos of *Sargassum ilicifoium* from Kenting, Taiwan

Key words: *Sargassum ilicifoium* polysaccharide, sulphate groups, Taiwan *Sargassum* spp.

Antimicrobial peptaibols from Marine-derived fungus, *Trichoderma reesi*

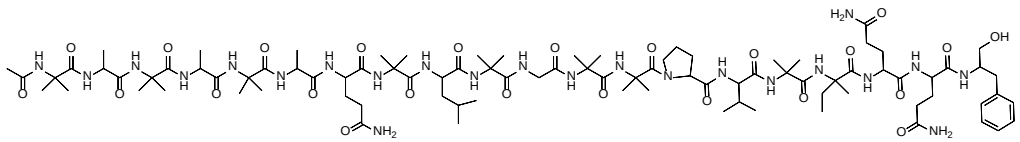
連雅筑 (Ya-Chu Lien)[#], 楊玉良 (Yu-Liang Yang),[‡] 廖志中 (Chih-Chuang Liaw),*,[†]

[#]Department of Marine Biotechnology and Resources, National Sun Yat-sen University, Kaohsiung 804, Taiwan.

[‡]Agricultural Biotechnology Research Center, Academia Sinica, Taipei 115, Taiwan

[†]Doctor Degree Program in Marine Biotechnology and Resources, National Sun Yat-sen University/Academia Sinica, Kaohsiung 804, Taiwan.

Marine organisms are regarded as one of the most notable source for the drugs discovery. In recent years, microorganisms symbiotic with marine invertebrates, such as sponges and soft corals, have been found as real producers of important and unique bioactive metabolites from such resources. In our lab, one of our goals is to search the bioactive natural products from the symbionts of marine invertebrates. We isolated a fungus *Trichoderma reesei* (**MR13-TR01**) from a sponge *Niphates* sp. collected in Wan-Li Tong, Pingtung County. This fungal strain **MR13-TR01** showed an interesting inhibitory activity against Acinetobactor baumannii, an opportunistic pathogen that could be a major cause of nosocomial infections in patients and increase the mortality in hospital. So far, we have isolated 14 peptaibols from ethyl acetate (EtOAc) extract of MR13-TR01. Among them have 9 new and 2 known compounds while remaining 3 peptaibols have a same amino acid sequence compounds. In the poster, we will mention fourteen peptaibols from the EtOAc extract of the strain MR13-TR01. The structures of these isolates will be elucidated on the basis of their spectroscopic analysis (CD, NMR, MS). Known compound named Trichocellin TC-A-II (**2**) was tested in cytotoxic screening against six human oral cancer cell lines (OC-2, HSC-3, Ca9-22, OECM-1, CAL27, SCC9) and possess good activity with IC_{50} value of 8.7~9.7 μM. The bioactivities of others constituents are under investigation.



Trichocellin TC-A-II

Key words: symbionts of marine invertebrates, *Trichoderma reesei*, antimicrobial activity, *Acinetobactor baumannii*, polypeptides, peptaibols, Oral cancer

Studies on the Chemical Constituents and Biological Activities of a Marine-Derived Bacterium, *Pseudoalteromonas elyakovii*

紀政宇 (Zheng-yu, Ji)[#], 廖志中(Chih-Chuang Liaw)*

[1]*Department of Marine Biotechnology and Resources, National Sun Yat-sen University, Kaohsiung, Taiwan*

[2]*Doctor Degree Program in Marine Biotechnology, National Sun Yat-sen University, Kaohsiung,Taiwan*

Secondary metabolites of marine microorganisms are regarded as one of the worthiest treasures for the novel scaffolds of bioactive chemicals. To search for anti-microbial secondary metabolites from marine environment, we isolated a series of symbiotic bacteria from the barnacles, collected from Qigu, Tainan. By the preliminary screening of paper-disc agar-plate method, one strain bar-22, identified as *Pseudoalteromonas elyakovii* by 16S rDNA analysis, showed clear inhibition against *Staphylococcus aureus* (*S.a*), *Salmonella typhimurium* (*S.t*) and *Candida albicans* (*C.a*). Later, the strain bar-22 was scaled up and extracted by the ethyl acetate (EtOAc) and subjected to Sephadex LH-20 column chromatography and reversed-phase high performance liquid chromatography. So far, we isolated four compounds from bioactive fraction of the EtOAc extract of *P. elyakovii* bar-22 by the bioassay-guided fractionation isolation. Among them, compound 1, benzethonium chloride, showed celar inhibitiory activity towards *Candia albican.* All the structures of isolates from *P. elyakovii* bar-22 were determined on the basis of NMR, Mass and also comparison with literature data.

Key words：*Pseudoalteromonas elyakovii,* benzethonium chloride and *Candia albican*

Anti-cancer effects of ethyl acetate extract from *Jaboticaba* on PC-3 prostate cancer cells and presumed its inhibitory potential.

林聖喆 Sheng-Jhe Lin# 詹媛婷 Yuan-Ting Chan 陳懿芬 I-Fen Chen＊

Department of Biomedical Engineering, I-Shou University

Abstract

It is well known that Chinese herbal medicine has good anticancer activity. In this study, we evaluate the anticancer activity of prostate cancer cell line PC-3 with the ethyl acetate extract of *Jaboticaba* seeds.

Treatment with crude ethyl acetate extract of *Jaboticaba* seeds inhibited cell viability and proliferation by MTT assay. The toxicity of various extract concentrations to PC-3 was examined by LDH assay.

The results showed that ethyl acetate extract of *Jaboticaba* seeds reduced cell viability and significant toxicity in PC-3 cells. Therefore, it can be speculated that ethyl acetate extract of *Jaboticaba* seeds may have the ability to cause apoptosis of PC-3 cells, which may be proved by flow cytometry or the like in the future.

Keyword: *Jaboticaba*, prostate cancer, anti- cancer, toxicity

IN VITRO ANTIOXIDANT, α-GLUCOSIDASE AND α-AMYLASE INHIBITORY ACTIVITIES AND IN VIVO ANTI-HYPERGLYCEMIC EFFECTS OF SOME MEDICINAL PLANTS IN DAKLAK PROVINCE, VIETNAM

Nguyen Quang Vinh[1*], Nguyen Anh Dung[1], Nguyen Van Bon[2], San Lang Wang[3], Hoang Van Chuyen[4], Ngo Ngoc Yen[5], Nguyen Thi Dao[4]

[1]Institute of Biotechnology and Environment, Tay Nguyen University, Vietnam
[2]Faculty of Natural Science and technology, Tay Nguyen University, Vietnam
[3]Department of Chemistry, Tam Kang University, Taiwan
[4]Faculty of Agriculture and Forestry, Tay Nguyen University, Vietnam
[5]Faculty of Medicine and Pharmacy, Tay Nguyen University, Vietnam

Recent years, medicinal plants are using for treatment of diabetes mellitus disease partly replacing for synthetic medicines. The aim of this review is to present the in vitro antioxidant activity, α-glucosidase and α-amylase inhibitory, and in vivo anti-hyperglycemic effects of some medicinal plants used as traditional medicine for treatment of diseases by ethnic minorities living in Daklak Province, Vietnam. Amongst the collected medicinal plants, *Terminalia corticosa Pierre* ex Laness, *Terminalia alata*, *Psidium littorale* R., *Syzygium* sp., *Eunonymus laxiflorus* Champ, *Terminalia bellirica* are the potent plants possessed high in vitro antioxidant and α-glucosidase and α-amylase inhibitory activities as well as in vivo anti-hyperglycemic effect. The Isolated compounds from ethyl acetate fraction of *Eunonymus laxiflorus* Champ are Walterolactone A/B β-D-pyranoglucoside, Gallic acid (3,4,5-Trihydroxybenzoic acid), Chatechin, Methyl gallate (Methyl 3,4,5-trihydroxybenzoate), Poly Condensed Tannin, Umbelactone, Phenylalanine, Schweinfurthinol 9-O-β-D-pyranoglucoside, 1-O-(3-methyl)-butenoyl-myo-inositol or Myo-inositol 1-O-3,3-dimethylacrylate, eonuriside, 2-benzoyl myo-inositol, 1-O-Benzoyl-myo-inositol. Poly condensed tannin possessed antihyperglycemia activity in rats induced hyperglycemia by oral starch.

Keywords: α-glucosidase and α-amylase inhibitory, anti-hyperglycemic, *Eunonymus laxiflorus* Champ, *Psidium littorale* R.

Anti-NO and Anti-tumor Components from *Euphorbia neriifolia*

張世霖 (Stephen S. Chang),[#,†] 林玉麒 (Yu-Chi Lin),[†] 魏紋祈 (Wen-Chi Wei),[†] 林志虎 (Zhi-Hu Lin),[†] 戴承杰 (Chen-Jei Tai),[*,‡] 郭曜豪 (Yao-Haur Kuo),[*,†,#]

[#]*Ph.D. Program in Clinical Drug Development of Chinese Herbal Medicine, College of Pharmacy, Taipei Medical University, Taipei 110, Taiwan.*

[†] *Division of Chinese Materia Medica Development, National Research Institute of Chinese Medicine, Taipei 112, Taiwan*

[‡] *Traditional Herbal Medicine Research Center, Taipei Medical University Hospital; Department of Chinese Medicine, Taipei Medical University Hospital, Taipei 110, Taiwan.*

Euphorbia neriifolia, a medicinal herb widely distributed in Asian countries, has been used in the folk herbal medicine for the prevention or management of vast diseases including anti-cancer effects. The aim of this study was to isolate and identify the anti-NO and anti-cancer constituents from *E. neriifolia.* The *E. neriifolia* MeOH extract (ENME) was found to possess potent anti-NO activity with the IC_{50} value of 16.37 μg/mL, as well as the acceptable anti-cancer effect on MCF-7 and A549 cancer cell lines. Further isolation by bioassay-guided fractionations, seven compounds as 3,3',4-tri-*O*-methyl-4'-*O*-rutinosyl ellagic acid (**1**), 7-hydroxy-6-methoxy-2*H*-chromen-2-one (**2**), 6,7,8-trimethoxycoumarin (**3**), kaempferol-3-*O*-rhamnoside (**4**), indole carboxylic acid (**5**), 3,3'-di-*O*-methylellagic acid (**6**) and ellagic acid derivative (**7**) were isolated and characterized. Notably, compound **7** demonstrated potent anti-NO activity (IC_{50} = 5.99 μg/mL) and cytotoxicity against MCF-7 with EC_{50} value of about 20 μg/mL. More investigations of bioactive mechanisms and relationships between inflammation and cytotoxicity for **7** were also presented here.

Key words: *Euphorbia neriifolia*, Antitumor, Anti-NO

Anti-NO, Anti-oxidative and Antitumor Constituents from *Phyllostachys makinoi* Hayata

吳紹瑜 (Shao-Yu Wu),[†,‡] 廖家慶 (Chia-Ching Liaw),[†] 林玉麒 (Yu-Chi Lin),[†] 林志虎 (Chih-Hu Lin),[†] and 郭曜豪 (Yao-Haur Kuo)*[,†,‡]

[†] *Division of Chinese Materia Medica Development, National Research Institute of Chinese Medicine, Taipei 112, Taiwan*

[‡]*Department of Life Sciences and Institute of Genome Sciences, National Yang-Ming University, Taipei 112, Taiwan*

One new chromone analogue, phyllomakin A (**1**), and a new flavonolignan, (–)-quiquelignan C (**2**), along with nine known compounds as vanillin (**3**), tricin 4′-*O*-[*threo*-*β*-guaiacyl- (9″-*O*- acetyl)-glyceryl] ether (**4**), tricin 4′-*O*-(*threo*-*β*-guaiacylglyceryl) ether (**5**), calquiquelignan D (**6**), (–)-(5S,6S)-5,6- dihydro- 3,8,10 - trihydroxy - 5-(4-hydroxy-3- methoxyphenyl)-6-hydroxymethyl- 2,4- dimethoxy- 7H - benzo [c]xanthen-7-one(**7**), tricin (**8**), (–) - (7R,7′R,7″R, 8S,8′S,8″S) - 4′, 4″- dihydroxy - 3,3′,3″,5 - tetramethoxy- 7,9′:7′,9 – diepoxy - 4,8″ - oxy- 8,8′- sesquineolignan - 7″,9″- diol (**9**), (–)- (7R,7′R, 7″S,8S,8′S,8″S)-4′,4″-dihydroxy-3,3′,3″,5-tetramethoxy 7,9′:7′,9-diepoxy - 4,8″- oxy - 8,8′- sesquineolignan- 7″,9″- diol (**10**), syringaresinoal (**11**), as well as two triterpenoids, lupeol (**12**) and betulin (**13**) were isolated from the leaves of *Phyllostachys makinoi* Hayata. The structures of **1-13** were elucidated by majorly application of various spectroscopic analysis (1D & 2D NMR and MS) and comparison with reported data. Biological evaluation showed that **1** exhibited the moderate cytotoxicity against Hep-G2 (ED_{50} = 18.4 μg/mL), **4** showed very potent anti-NO production activity (IC_{50} = 2.7 μg/mL), and **11** had strong anti-oxidative activity (ED_{50} = 11.2 μg/mL) by using DPPH assay.

Key words: *Phyllostachys makinoi*, anti-inflammatory, anti-oxidative

Fomosamines A–G, New Alkaloids from Formosan Zoanthid *Zoanthus vietnamensis*

陳姝蓉 (Shu-Rong Chen)[#], 鄭源斌 (Yuan-Bin Cheng)[#,‡,*]

[#]Graduate Institute of Natural Products, College of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan

[‡]Department of Medical Research, Kaohsiung Medical University Hospital, Kaohsiung 807, Taiwan

Sea anemones of the genus *Zoanthus* (family Zoanthidae) are commonly found in subtropical or tropical coastal area. These marine invertebrates are usually cultured in aquarium because of its various colors. *Z. vietnamensis* Pax & Müller, having a pale pink oral disc with black and white tentacles, was collected in the north coastal area of Taiwan and was identified by its mitochondrial and nuclear sequence-based phylogenies. In previous natural product studies, alkaloids, ceramides, steroids, and sphingolipids were regarded as the major components of zoanthid. Zoanthids are also regarded as rich sources of novel secondary metabolites with diverse bioactivities. For example, ecdysones isolated from *Palythoa tuberculosa* demonstrated anti-lymphangiogenesis effect, while alkaloids purified from *Z. kuroshio* inhibited superoxide anion generation and elastase release.

In our chemical investigation of *Z. vietnamensis*, seven new alkaloids named fomosamines A–G (**1**–**7**), along with ten known compounds, kuroshine A (**8**), kuroshine C (**9**), 7*α*-hydroxykuroshine A (**10**), zoanthenamine (**11**), 3*β*-hydroxyzoanthenamine (**12**), 7*α*-hydroxyzoanthenamine (**13**), 28-deoxyzoanthenamine (**14**), zoanthamine (**15**), oxyzoanthamine (**16**), and epioxyzoanthamine (**17**) were identified. The structures of all isolated compounds were determined by the interpretation of spectroscopic methods, especially 2D NMR analyses (COSY, HSQC, HMBC, and NOESY). Compound **1** is an oxidized analogue of 28-deoxyzoanthenamine (**14**) that contains a keto group at the C-11 position. Compound **2** can be characterized as a new kuroshine A type alkaloid with an additional hemiacetal at C-28. Compounds **3**–**7** are new hydroxy derivatives of compounds **8**, **11**, **14**, and **15**. All compounds were evaluated by MTT assays for cytotoxicity against MDA-MB-231, A549, HepG2 cancer cell lines.

Keywords: alkaloids; *Zoanthus vietnamensis*; marine natural products

Loganin attenuates chronic constriction injury-induced neuropathic pain via the TNF-α/NF-κB signaling pathway

Sin-Lan Chen[1] (陳心蘭), Li-Wen Chu[1] (朱立雯), Yu-Chin Chang[1] (張毓秦)
Su-Ling Hsieh[2] (謝素玲), Bin-Nan Wu[1,*] (吳炳男)

[1]Department of Pharmacology, Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
[2]Department of Pharmacy, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

Background: Neuropathic pain, largely resulting from primary lesions in the peripheral nerve or from malfunctions in the central nervous system, has an extremely negative impact on the quality of life of patients affected by this condition. The chronic constriction injury (CCI) model of peripheral nerve injury has provided a deeper understanding of nociception and the events contributing to the pathogenesis of chronic pain conditions. 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 CCI-induced neuropathic pain.
Methods: Sprague–Dawley rats were randomly divided into four groups: sham, sham+loganin, CCI and CCI+loganin. Loganin (5 mg/kg/day) was injected intraperitoneally starting at day 1 after surgery. Mechanical and thermal responses were assessed before surgery and at day 3, 7, 14 after CCI. Proximal and distal sciatic nerves (SNs) were isolated for western blots, confocal microscopy and enzyme-linked immunosorbent assay to analyze protein expression, immunoreactivity and proinflammatory cytokines.
Results: Behavior data show that thermal hyperalgesia and mechanical allodynia were reduced in loganin treated group as compared to CCI group. The neurobehavioral changes was correlated with the demyelination of Schwann cells, particularly in the distal stump of injured SN. Inflammatory proteins (pNFκB, p-IκB, iNOS) and proinflammatory cytokines (TNF-α, IL-1β) induced by CCI were attenuated in the loganin treated group at day 7 after CCI. Loganin also blocked IκB phosphorylation (p-IκB). Double immunofluorescent staining further demonstrated that p-NFκB protein was reduced by loganin in peripheral glial cells at day 7 after CCI.
Conclusion: Based on these findings, we concluded that loganin has antiinflammatory and antihyperalgesia properties in CCI-induced neuropathic pain via decreases in TNF-α/NF-κB activation.

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Key words: Loganin, chronic constriction injury, sciatic nerve, neuropathic pain

A marine sterol induces apoptosis in breast cancer cells

翁靖如(Jing-Ru Weng),[1,#] Chang-Fang Chiu (邱昌芳),[2,†]
Li-Yuan Bai (白禮源),[3,*] and Jyh-Horng Sheu (許志宏),[1,*]

[1]Department of Marine Biotechnology and Resources, National Sun Yat-sen University, Kaohsiung 80424, Taiwan
[2]Division of Hematology and Oncology, Department of Internal Medicine, China Medical University Hospital, Taichung 40402, Taiwan
[3]College of Medicine, China Medical University, Taichung 40402, Taiwan

Marine natural products have served as sources of therapeutic agents over the past three decades. In our search for potential anti-tumor agonists, a compound library comprising various marine compounds was examined. Among them, a sterol (compound **1**) suppressed the viability of breast cancer cells in a concentration- and time-dependent manner. Cell cycle analysis demonstrated that compound **1** increased the population of sub G1 cells in breast cancer cells. In addition, compound **1** modulated the phosphorylation/expression of cyclin D1, CDK6, and Bcl-2. Furthermore, compound **1** increased ROS generation which could be partially rescued by the pre-treatment with the antioxidant glutathione in breast cancer cells. Taken together, these findings suggest that compound **1** may have therapeutic applications in cancer treatment.

Key words：Sterol; *Apoptosis; Breast cancer*

β-Mangostin suppresses mobility and invasiveness of cervical cancer cells via inhibiting JNK-mediated AP-1/Snail/integrin axis

林佳良(Chia-Liang Lin)[a#], 林君香(Chun-Shiang Lin)[a#], 邱慧玲(Hui-Ling Chiou)[b], 謝逸憲(Yi-Hsien Hsieh)[a,c*]

[a]*Institute of Biochemistry, Microbiology, and Immunology, Chung Shan Medical University, Taichung, Taiwan.*
[b]*School of Medical Laboratory and Biotechnology, Chung Shan Medical University, Taichung, Taiwan.*
[c]*Department of Biochemistry, of School of Medicine, Chung Shan Medical University, Taichung, Taiwan.*

Natural mangostins have been reported to have potent antitumor activity against various types of cancers. In this study, we explored the antitumor activity of β-mangostin (β-mangostin) against cervical cancer. Although cell viability and cell cycle distribution were not significantly altered, β-mangostin dose-dependently inhibited the migration and invasion of the human cervical cancer cell lines, HeLa and SiHa. Further, we found that β-mangostin suppressed the expression of integrin αV and β3 and the downstream focal adhesion kinase (FAK)/Src signaling cascade. Simultaneously, β-mangostin suppressed Snail expression and the nuclear translocation of AP-1, which diminished the migration and invasion of HeLa cells. We demonstrated that AP-1 was directly bound to the Snail promoter to induce gene expression; however, this binding was abolished by β-mangostin. We also discovered that β-mangostin inhibited AP-1 binding to the Snail promoter via the suppression of JNK activation in HeLa cells. In addition, the increased expression of Snail and a positive correlation between AP-1, Snail, and JNK expression was also detected in cervical tumor samples. Collectively, our findings indicated that β-mangostin inhibited the mobility and invasiveness of cervical cancer cells, which contributed to the suppression of the JNK-mediated AP-1/Snail/integrin axis, suggesting that β-mangostin was a potential anti-metastatic agent in cervical cancer.

Key words: β-mangostin; anti-metastatic; Snail; AP-1; JNK; cervical cancer

Natural products-derived from *Mitella formosana* suppress angiogenesis in *vitro* and in *vivo*

陳佩琪(Pei-Chi Chen)[1]，張訓碩(Hsun-Shuo Chang)[2]，陳益昇(Ih-Sheng Chen)[3]，王士維(Shih-Wei Wang)[1,*]

[1]*Department of Medicine, Mackay Medical College, New Taipei City, Taiwan*
[2]*School of Pharmacy, College of Pharmacy, Kaohsiung Medical University, Kaohsiung*

Based on bioassay-guided fractionation, we isolated gallotannins PPG and T-II from the whole plant of *Mitella formosana*. We found these two gallotannins exhibit the promising anti-angiogenic activity in human endothelial progenitor cells (EPCs). PPG and T-II inhibited EPCs migration and tube formation in a concentration-dependent manner. Moreover, T-II suppressed *in vivo* angiogenesis in chick embryo chorioallantoic membrane (CAM) and mice Matrigel plug assay models. Mechanistic investigations found that T-II inhibited angiogenesis by down-regulating the phosphorylation of VEGFR-2 receptor and its downstream signals Erk, Src, and FAK pathways. Taken together, our findings provide evidence that T-II is the potential natural product worthy of further development for the treatment of angiogenesis-related pathologies.

Key words：*Mitella formosana*, Anti-angiogenesis

Kaempferol induced cell growth inhibition and cell death in cisplatin-resistance AGS gastric cancer cells

KENG-MING CHANG[1], CHIEN-JUNG HUANG[2], JAI-SING YANG [3], POCHUEN SHIEH[1]*

[1]Department of Pharmacy, Tajen University, Pingtung, Taiwan
[2]Fuyuan Medical & Biopharm Association
[3]Department of Medical Research, China Medical University Hospital, China Medical University

Abstract

Cisplatin is the leading therapeutic agent for gastric cancer therapy. In our study, Kaempferol suppressed cell viability in cisplatin-resistant AGS gastric cancer cells through inhibiting cell proliferation and causing cell death. The results demonstrated that cisplatin-resistant AGS gastric cancer cells exhibited marked cell shrinkage, cell membrane breakage and apoptotic bodies following treatment with kaempferol. Kaempferol also effectively suppressed cell confluence in a time- and concentration-dependent manner. The DAPI/TUNEL double staining determined that DNA condensation, a characteristic of apoptosis, was enhanced following treatment with kaempferol, which confirmed by the pan-caspase inhibitor. In addition, kaempferol increased caspase-3 and caspase-9 activities in cisplatin-resistant AGS gastric cancer cells. Overview, Kaempferol may elicit an anti-cancer response in cisplatin-resistant AGS gastric cancer cells and may have a good chemotherapeutic adjuvant to treat gastric cancer.

Pterostilbene induced cell growth inhibition and cell death in cisplatin-resistance AGS gastric cancer cells

YI-CHIA LI[1], CHIEN-JUNG HUANG[2], JAI-SING YANG [3], POCHUEN SHIEH[1*]

[1]Department of Pharmacy, Tajen University, Pingtung, Taiwan 907
[2]Fuyuan Medical & Biopharm Association
[3]Department of Medical Research, China Medical University Hospital, China Medical University

Abstract

Pterostilbene is known to possess antioxidant activity and induces cell death in various types of cancer cells. Here, the effects of pterostilbene on cell viability in cisplatin-resistant AGS gastric cancer cells were investigated. This study demonstrated that pterostilbene was able to inhibit cell proliferation and induce cell death in concentration- and time-dependent manners. Pterostilbene-induced cell death was characterized with changes in nuclear morphology, DNA fragmentation by TUNEL staining. The molecular mechanism of pterostilbene induced apoptosis was also investigated. The results show the caspase-9 and caspase-3 are activated, and using the pan-caspase inhibitor carbobenzoxyvalyl-alanyl-aspartyl fluoromethyl ketone by pterostilbene in cisplatin-resistant AGS gastric cancer cells. In summary, pterostilbene induced apoptosis in cisplatin-resistant AGS gastric cancer cells through activating the caspase cascade. The induction of apoptosis by pterostilbene may provide a pivotal mechanism of the anti-cancer effects and for treatment of human gastric cancer.

Piperine-mediated suppression of voltage-dependent Ca^{2+} influx and glutamate release in rat hippocampal nerve terminals involves $5HT_{1A}$ receptors and G protein βγ activation

Ting Yang Hsieh[a#], Yi Chang[b, c], Hsi Lung Hsieh[e] and Su Jane Wang[c, d]*

[a]P.H.D. Program in Neutrition & Food Science, Fu Jen Catholic University No. 510, Chung-Cheng Rd., Hsin-Chuang, New Taipei 24205, Taiwan
[b] Department of Anesthesiology, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan
[c] School of Medicine, Fu Jen Catholic University, No. 510, Chung-Cheng Rd., Hsin-Chuang, New Taipei 24205, Taiwan
[d] Research Center for Chinese Herbal Medicine, College of Human Ecology, Chang Gung University of Science and Technology, Taoyuan City, Taiwan
[e]Department of Nursing, Division of Basic Medical Sciences, Research Center for Chinese Herbal Medicine, and Graduate Institute of Health Industry Technology, Chang Gung University of Science and Technology, Tao-Yuan, Taiwan

Abstract

Piperine is a crucial alkaloid component of black pepper (*Piper nigrum* Linn.) and has neuroprotective effects. Because inhibition of glutamatergic excitatory neurotransmission is a possible mechanism involved in neuroprotection, we investigated the effects of piperine on the 4-aminopyridine (4-AP)-evoked release of glutamate from rat hippocampal synaptosomes. Piperine inhibited 4-AP-evoked glutamate release, and the inhibition was prevented by the chelation of extracellular Ca^{2+} ions and a vesicular transporter inhibitor. Piperine reduced the 4-AP-evoked elevation of intrasynaptosomal Ca^{2+} levels but did not affect the synaptosomal membrane potential. In the presence of ω-conotoxin MVIIC, an N- and P/Q-type channel blocker, the piperine-mediated inhibition of 4-AP-evoked glutamate release was markedly reduced; however, dantrolene and CGP37157, which are intracellular Ca^{2+}-release inhibitors, did not alter the piperine effect. In addition, immunocytochemical analysis confirmed the presence of presynaptic 5-hydroxytryptamine 1A ($5\text{-}HT_{1A}$) receptor proteins. The glutamate release-inhibiting effect of piperine was discovered to be prevented by the $5\text{-}HT_{1A}$ receptor antagonist WAY100635 and the G protein βγ subunit inhibitor gallein; however, it was unaffected by the adenylate cyclase inhibitor SQ22536 or the protein kinase A inhibitor PKI6-22. These results suggest that piperine inhibits glutamate release from rat hippocampal nerve terminals by reducing Ca^{2+} influx through N- and P/Q-type Ca^{2+} channels and that the activation of presynaptic $5\text{-}HT_{1A}$ receptors and G protein βγ subunit is involved in this effect.

A sulfated glucan from *Antrodia cinnamomea* suppresses lung cancer: blockage of TGFβ-mediated signalings controls Slug stability

林東毅 (Tung-Yi Lin)[1,*]，盧美光 (Mei-Kuang Lu)[2,3]

[1] Institute of Traditional Medicine, National Yang-Ming University
[2] National Research Institute of Chinese Medicine, Ministry of Health and Welfare, Taipei, Taiwan
[3] Graduate Institute of Pharmacognosy, Taipei Medical University, Taipei, Taiwan
[*] Corresponding author at: Dr. Tung-Yi Lin, Institute of Traditional Medicine, National Yang-Ming University, 155 Li-Nung St., Sec. 2, Shipai, Beitou, Taipei 112, Taiwan. E-mail: biotungyi@gmail.com or tylin99@ym.edu.tw

Abstract

Sulfated polysaccharides (SPSs) exhibit anti-cancer activity. In this study, we identified a novel sulfated glucan (called SGA) from the medicinal mushroom *Antrodia cinnamomea* B86, and showed that it suppressed tumor progression in an LLC1-bearing mouse model. SGA inhibited cell viability and migration that were correlated with suppression of transforming growth factor beta (TGFβ) receptors expression and inhibition of focal adhesion kinase (FAK) phosphorylation in human lung cancer A549 and H1975 cells. Moreover, we found that SGA potentiated cisplatin-induced cytotoxicity in lung cancer cells. Functional studies revealed that SGA inhibited the TGFβ/FAK/AKT/GSK3β axis via induction of lipid-raft-mediated lysosome-dependent TGFβ receptor degradation. Overexpression of Slug, a transcription factor, is regarded as the critical event in lung tumor progression, drug resistance and metastasis. We found that SGA elimination of TGFβ-mediated intracellular signalings promoted Slug degradation in H1975 cells. Mechanistically, we demonstrated that proteasome- dependent Slug degradation was controlled by TGFβ-mediated downstream signaling pathways; however, inhibitors of AKT and GSK3 abolished Slug degradation. Our findings suggested that SGA targets of TGFβ/AKT/GSK3β axis played a key role in enhancing Slug degradation and suppressing lung cancer cells. In addition, SGA may be a potential therapeutic supplement for lung cancer.

Key words：Sulfated glucan, *Antrodia cinnamomea*, TGFβ, Slug, protein degradation

Evaluate the inhibition mechanisms of 3'- hydroxygenkwanin, an extraction from *Aquilaria sinensin*, on human neutrophils superoxide anion generation

王思媛 (Si-Yuan Wang)[#], 陳日榮 (Jih-Jung Chen), 廖庠睿 (Hsiang-Ruei Liao)[*]

[#, *]*Graduate Institute of Natural Products, Chang Gung University, Taoyuan, Taiwan.*
Institute of Biopharmaceutical Sciences, National Yang-Ming University, Taipei.

Neutrophils play a crucial role in the inflammatory reaction. In this process, neutrophils kill pathogens to protect of the human body by phagocytosis, degranulation, respiratory burst and neutrophil extracellular traps (NETs) release. Neutrophils dysfunction caused abnormal inflammation, such as chronic granulomatous disease (CGD). However, excessive neutrophils activation caused tissue damage, such as ischemia / reperfusion injury.

This study investigates the effect and the underlying mechanism of 3'-hydroxygenkwanin (ASSB-21), extracted from the stem bark of *Aquilaria sinensis*, on N-formyl-methionyl-leucyl-phenylalanine (fMLP) -induced respiratory burst in human neutrophils. Briefly, ASSB-21 inhibited fMLP-induced superoxide anion production (IC_{50} : 6.03 ± 1.03 μM), cathepsin G release (IC_{50} : 10.23 ± 0.27 μM) in a concentration dependent manner. However, ASSB-21 (50 μM) minor inhibited PMA-induced superoxide anion production and cathepsin G. ASSB-21 did not scavenge oxygen free radical in the xanthine / xanthine oxidase system. The cell viability did not affect by ASSB-21. In another set of experiments, ASSB-21 (50 μM) inhibited fMLP-induced CD11b expression and fMLP-induced neutrophil chemotaxis. However, ASSB-21 did not inhibited fMLP-induced intracellular calcium release. ASSB-21 inhibited PMA-induced NETs release. In conclusion, ASSB-21 plays ROS in neutrophil function and could be further developed for the effect and the underlying mechanism on fMLP-induced superoxide anion generation in human neutrophils.

Key words: 3'- Hydroxygenkwanin; neutrophil; ROS; inflammation; fMLP

Sesamol Reduces the Senescence Induced by Apolipoprotein C3-rich LDL *in Vivo* and *in Vitro*

陳莉蓁 (Li-Zhen Chen)[#], 蔡秉宣 (Ping-Hsuan Tsai)[‡], 陳芳玉 (Fang-Yu Chen)[†], 沈明毅 (Ming-Yi Shen)[*,†]

[#]*Graduate Institute of Biomedical Science, China Medical University, No. 91 Hsueh-Shih Road, Taichung 40402, Taiwan*

[‡]*Department of Biological Science and Technology, China Medical University, No. 91 Hsueh-Shih Road, Taichung 40402, Taiwan*

[†] *Department of Pharmacology, School of Medicine, China Medical University, Taichung, Taiwan; No. 91 Hsueh-Shih Road, Taichung 40402, Taiwan*

Apolipoprotein C3-rich LDL (AC3RL) induces endothelial cell (EC) senescence, which leads to the development of atherosclerosis. We examine the effects of sesamol, a natural organic component of sesamol oil, on the AC3RL-induced senescence of ECs. In human aortic ECs, 0.3-3 μM sesamol blocked AC3RL-induced senescence in a dose-dependent manner. Further mechanism studies showed that sesamol inhibited the AC3RL-induced FBXO31-dependent p53 upregulation and activation of senescence signaling pathway. Syrian hamsters, which have an LDL profile similar to that of human, were fed a normal chow diet (control), a high-fat diet (HFD), or an HFD supplemented with 50 or 100 mg/kg of sesamol via oral gavage for 16 weeks (n=8 per group). Senescence-associated β-galactosidase (SA-β-gal) staining showed that cardiovascular senescence was markedly reduced in the thoracic aortic tissue of hamsters in the HFD supplemented with sesamol groups when compared with that in the HFD group. Our findings suggest that sesamol protects against atherosclerosis by reducing AC3RL-induced endothelial cell (EC) senescence.

Key words: Sesamol, Apolipoprotein C3-rich LDL, senescence, atherosclerosis

Pterostilbene-triggered ER stress-mediated autophagy with suppression of eIF2α dephosphorylation induced autophagic apoptosis in human hepatocellular carcinoma cells

尤振霖 Chen-Lin Yu[1,#], 楊順發 Shun-Fa Yang[1], 林佳良 Chia-Liang Lin[2], 謝逸憲 Yi-Hsien Hsieh[2*], 邱慧玲 Hui-Ling Chiou [3*]

[1]Insitiute of Medicine, Chung Shan Medical University, Taichung, Taiwan
[2]Institute of Biochemistry, Microbiology and Immunology, Chung Shan Medical University, Taichung, Taiwan
[3]School of Medical Laboratory and Biotechnology, Chung Shan Medical University, Taichung, Taiwan

Hepatocellular carcinoma (HCC) is the one of the most common cancer worldwide and the leading cause of cancer-related death. Due to the poor response rate and severe side effect of current treatment, new effective therapeutic strategies are urgently needed. Pterostilbene (PT), a natural analog of resveratrol, is known to have diverse pharmacologic activities including antioxidant, anti-inflammation and anti-proliferation. However, the molecular mechanism underlying PT as an anti-HCC agent is not yet fully understood. Here we show that PT inhibited HCC cell proliferation without the induction of apoptosis while simultaneously induced autophagy and ER stress. Mechanistic investigations suggested that PT modulated the ER stress related autophagy through p-eIF2α/ATF4/LC3 pathways and further inhibition of dephosphorylation of eIF2α with salubrinal leads to increased cytotoxicity due to increased induction of autophagy and sequential induced apoptosis. In vivo xenograft analysis revealed that PT significantly reduced tumor growth in mice with SK-Hep-1 tumor xenograft. Taken together, our results provide new insights into the pivotal role of PT in ER stress induced autophagy and eIF2α in autophagy-induced apoptosis in HCC cells.

Key words：pterostilbene, ER-stress, autophagy, ATF4, LC3

Hepatoprotective Mechanism of Taxifolin on Carbon Tetrachloride-Induced Acute Liver Injury in Mice

翁錦魁(Jin-Kuei Wong)[1,#],楊兆霖(Chao-Lin Yang)[2],劉耿帆(Keng-Fan Liu)[1],邱傳淞(Chuan-sung Chiu)[3],林穎志(Ying-Chih Lin)[4],鄭皓元(Hao-Yuan Cheng)[5],彭文煌(Wen-Huang Peng)[1,*],許志明(Chih-Ming Hsu)[6,*]

1. *Department of Chinese Pharmaceutical Sciences and Chinese Medicine Resources, College of Chinese Medicine, China Medical University, Taichung 40402, Taiwan.*
2. *Ph.D. Program for Biotechnology Industry, College of Biopharmaceutical and Food Sciences, China Medical University, Taichung 40402, Taiwan.*
3. *Department of Nursing, Hsin Sheng Junior College of Medical Care and Management, No.418, Gaoping Sec., Zhongfeng Rd., Longtan Township, Taoyuan County 32544, Taiwan.*
4. *Department of Optometry, Jen-Teh Junior College of Medicine, Nursing and Management No. 79-9, Sha-Luen-Hu, Xi Zhou Li, Hou-Loung Town, Miaoli County 35664, Taiwan.*
5. *Department of Nursing, Chung-Jen Junior College of Nursing, Health Sciences and Management, Chia-Yi, Taiwan.*
6. *Department of Medical Education, Chang Gung Memorial Hospital, Chiayi, Taiwan.*

The aim of this study was intended to investigate the effects of taxifolin on carbon tetrachloride (CCl_4)induced acute liver injury in mice. The indexes evaluated included liver pathological changes, the activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), glutathione reductase (GSH-Rd) and the level of malondialdehyde (MDA) in the serum and expressions of Bcl-2 and Caspase 3. Compared with the model group, the results indicated that the activities of ALT, AST, and MDA level in the serum, and the protein expressions of Caspase 3 were significantly decreased, and the degree of pathologic damage were significantly reduced after taxifolin treatment. Additionally, the activities of SOD and GSH-Px, GSH-Rd in the serum, the expression of Bcl-2 was significantly increased after taxifolin treatment. These results indicated that Taxifolin possessed hepatoprotective effect on CCl4-induced acute liver injury via increasing in the activities of anti-oxidases and expression of Bcl-2. Taxifolin should play an important role in liver disease.

Key words：Liver injury、Taxifolin、Superoxide dismutase、Bcl-2、Caspase 3

Intraocular pressure-lowering effect of *Cordyceps cicadae* mycelia extract in a glaucoma rat model

Ya-Lan Yang[1], Chi-Ting Horng[2], Chin-Chu Chen[3], Yu-Syuan Huang[1], Fu-An Chen[1,*]

[1] Department of Pharmacy and Master Program, Tajen University, Pingtung, Taiwan
[2] Department of Ophthalmology, Fooyin University Hospital, Pingtung, Taiwan
[3] Grape King Bio Ltd, Zhong-Li Dist., Taoyuan City 320, Taiwan

Abstract

Glaucoma is one of the world's leading causes of blindness. *Cordyceps cicadae* is a well-known and most valued traditional Chinese herbal medicine. The aim of this study is to evaluate the intraocular pressure (IOP)-lowering effect of *C. cicadae* mycelia extract in steroid-induced glaucoma rat model. The *C. cicadae* mycelium was cultured by liquid fermentation technique. The lyophilized samples were further extracted using solvents as water and 95% ethanol. The obtained *C. cicadae* mycelia extracts (CCME) were obtained after lyophilization. The SD rats used in the study were divided into five groups (n=6): sham group, control group, positive control group (topical brimonidine instillation therapy), and two groups treated with CCME (aqueous and alcoholic extracts, 50 mg/kg,bw). Rats in experimental groups received daily administration of CCME via oral gavage for 28 days. The ability to lower intraocular pressure (IOP) signified the efficiency of treating glaucoma. The results revealed that IOP significantly decreased after treatment with CCME (p<0.05). The IOP-lowering effect of CCME was comparable to those of brimonidine instillation. The increase of glutathione peroxidase (GPx) and superoxide dismutase (SOD) level were found after administration of CCME for 28 days. CCME is a relatively safe Chinese herbal medicine with no significant changes through hepatic and renal serum biological and optical pathological observations. In conclusion, *Cordyceps cicadae* mycelia may be safe and beneficial for treating glaucoma due to its significant IOP-lowering and antioxidant activities.

Key words：*Cordyceps cicadae* mycelium, Glaucoma, intraocular pressure (IOP)

Effect of *Plectranthus amboinicus* (Lour.) Spreng on tyrosinase and elastase activity

Hsuan-Yu Lin[1], Ya-Lan Yang[1], Chen Chun[1,2], Fu-An Chen[1,*]

[1] Department of Pharmacy and Master Program, Tajen University, Pingtung, Taiwan
[2] School of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan

Abstract

Reactive oxygen species (ROS) caused by ultraviolet (UV) radiation are clinically associated with specific markers of photoaging, including increased skin wrinkling and darkening. *Plectranthus amboinicus* (Lour.) Spreng is a perennial herb belonging to the family Lamiaceae which has been widely distributed in Taiwan. The present study is to investigate the optimal methods for producing *P. amboinicus* (Lour.) Spreng leaf extract (PASLE) with high antioxidant carvacrol content, and tyrosinase and elastase inhibitory activity. *P. amboinicus* (Lour.) Spreng leaves were dried and then extracted with different solvents including aqueous and ethanolic aqueous solvents. The obtained PASLE was then subjected to total polyphenol and carvacrol content analysis. The 1,1-diphenyl-2-pycrylhydrazyl scavenging (DPPH), antielastase and antityrosinase activity of the PASLE were determined to evaluate the antioxidant and skin aging-associated enzyme inhibitory activities of PASLE. The results revealed that PASLE yielded a higher polyphenol and carvacrol content, and stronger antioxidant activity as the ratio of the ethanolic content of the extraction solvent used increased. PASLE possesses potent tyrosinase and elastase inhibitory activities. These results indicate that the concentration of the extraction solvent was associated with the antioxidant component and skin aging-associated enzyme inhibitory activity of PASLE. The reactive oxygen species scavenging theory of skin aging may explain the tyrosinase and elastase inhibitory activity of PASLE. The antielastase and antityrosinase activities of the PASLE produced may be aid in the development of skincare products with skin-whitening and antiwrinkle activities. In addition, cultivation method may affect the content of phytochemical components resulting in affecting its pharmacological activities. The effect of cultivation method on variations of phytochemical component content such as carvacrol is currently under investigation.

Key words: *Plectranthus amboinicus* (Lour.) Spreng, antioxidant, carvacrol, antityrosinase, antielastase

Fistein suppresses human osteosarcoma U-2 OS cell migration and invasion via affecting FAK, uPA and NF-κB signaling pathway *in vitro*

陳志鎧 (Jr-Kai Chen)[#]，彭淑芬(Shu-Fen Peng)，賴光啟 (Kuang Chi Lai)，劉馨中 (Hsin-Chung Liu)，吳世銓(Rick Sai-Chuen Wu)，黃安正(An-Cheng Huang)，闕甫心 (Fu-Shin Chueh) *,‡，鍾景光 (Jing-Gung Chung) *,†

#Attending Physician of Orthopaedadics, Department of Chang Bing Show-Chwan Memorial Hospital, Changhua, Taiwan

‡Department of Food Nutrition and Health Biotechnology, Asia University, Wufeng, Taichung, Taiwan

†Department of Biological Science and Technology, China Medical University, Taichung, Taiwan

†Department of Biotechnology, Asia University, Wufeng, Taichung, Taiwan

Numerous evidences have indicated that fisetin induced cytotoxic effects including the inhibition of cell migration and invasion in human cancer cell lines, however, the exact molecular mechanism of fisetin suppresses cell migration and invasion of human osteosarcoma cells remains unclear. In this study, we investigated anti-metastasis mechanisms of fisetin in human osteosarcoma U-2 OS cells in vitro. Fisetin reduced viable cell number at the different concentrations (2.5, 5, and 10 μM) which were measured by flow cytometric assay. Fisetin suppressed cell mobility, migration and invasion of U-2 OS cells that were assayed by wound healing and transwell filter chambers, respectively. The gelatin zymography assay showed that fisetin inhibited MMP-2 activity in U-2 OS cells. Results from western blotting indicated that fisetin reduced the levels of pEGFR, SOS-1, GRB2, Ras, PKC, p-ERK1/2, p-JNK, p-p-38, VEGF, FAK, RhoA, PI3K, p-AKT, NF-κB, uPA, MMP-7, MMP-9, and MMP-13 at 48 h treatment, but increased GSK3β and E-cadherin in U-2 OS cells at 48 h treatment. Based on these observations, we suggest that fisetin can be used in anti-metastasis of human osteosarcoma cells in the future.

Key words：Fisetin, human osteosarcoma U-2 OS cell, migration, invasion, NF-κB

Asiatic acid, a consitutent of *Centellae*, inhibits glutamate release from rat cerebral cortex nerve terminals through suppressing Ca^{2+} influx and protein kinase C activity

Cheng Wei Lu [a], Tzu Yu Lin[a], Shu Kuei Huang[a], Su Jane Wang[b*]

[a]Department of Anesthesiology, Far-Eastern Memorial Hospital, Pan-Chiao District, New Taipei City, Taiwan 22060

[b]School of Medicine, Fu Jen Catholic University, No.510, Zhongzheng Rd., Xinzhuang Dist., New Taipei City, Taiwan, 24205

Asiatic acid is a major component of *Centellae* which was reported to exhibit antiepileptic profile. Considering that excitotoxicity induced by glutamate is involved in the pathogenesis of epilepsy, the effect of asiatic acid on glutamate release in rat cerebrocortical nerve terminals and the possible mechanism involved in such effect was investigated. We observed that asiatic acid inhibited the release of glutamate evoked by the K^+ channel blocker 4-aminopyridine (4-AP). The effects of asiatic acid on the evoked glutamate release were prevented by the chelation of extracellular Ca^{2+} ions and the vesicular transporter inhibitor bafilomycin A1. However, the glutamate transporter inhibitor DL-threo-beta-benzyl-oxyaspartate did not have any effect on asiatic acid action. Asiatic acid reduced the depolarization-induced increase in cytosolic free Ca^{2+} concentration ($[Ca^{2+}]_C$), but did not alter 4-AP-mediated depolarization. In addition, the inhibitory effect of asiatic acid on 4-AP-evoked glutamate release was markedly reduced in the presence of the $Ca_v2.2$ (N-type) and $Ca_v2.1$ (P/Q-type) channel blocker ω-conotoxin MVIIC, but was insensitive to the intracellular Ca^{2+}-release inhibitors dantrolene and CGP37157. Furthermore, in the presence of the PKC inhibitor GF109203X, the action of asiatic acid on evoked glutamate release was prevented. Western blot analyses also showed that asiatic acid decreased the 4-AP-induced phosphorylation of PKC. These results are the first to suggest that asiatic acid inhibits glutamate release from rat cortical synaptosomes by suppressing presynaptic Ca^{2+} entry and PKC activity.

Hypoglycemic and hypolipidemic effect of *Ophiocordyceps sinensis* in high-fat diet fed-induced diabetic rats

林高有(Gao-You Lin)[#],黃苡庭(I-Ting Huang),陳瑛宜(Ying-I Chen),
徐泰浩(Tai-Hao Hsu),張世良(Shih-Liang Chang)[*]

[#]*Department of Medicinal Botanicals and Health Applications, DaYeh University, Changhua 515, Taiwan.*

In recent years Taiwan citizens' physical inactivity and diet had gradually become westernized. Therefore, it is easy to result in insulin resistance, increase plasma glucose finally caused three-hypers series (hyperglycemia, hyperlipidemia, hypertension) and other related problems. According to studies revealed, *Ophiocordyceps sinensis* (OS) has the effects of enhancing insulin sensitivity and stabilizing plasma glucose. Therefore, the present study has applied OS to rats which had been induced to high fat diet (HFD), in order to investigate its effects on plasma glucose and plasma lipids.

We've been using with male Wistar (n=8), continued to fed with HFD for eight weeks. Induced it to HFD induced rats model. Observation and recording daily to physiological response, water and food intake, measured weekly body weight gain. During the HFD, feeding in the first and the eighth week respectively collecting a blood from a femoral vein to measured plasma glucose and plasma lipids gain. Afterwards, continuous feeding with 500 mg/kg of OS for two weeks treatment, has been observed its effect of hypoglycemic and hypolipidemic.

After feeding HFD eight week, plasma glucose in the eighth week : first week= 144 ± 9.77 : 113.83 ± 6.36 mg/dl, significantly increased ($p<0.01$); On the other hand about triglyceride, the eighth week : the first week = 84 ± 14.92 : 40.63 ± 9.82 mg/dl, a significant increased ($p<0.001$). Continue to feed OS for two weeks, the plasma glucose has decreased from 144±9.77 to 120.67±6.94 mg/dl, significant decline ($p<0.01$), but there was no significant improvement in triglyceride and total cholesterol.

Successfully, the continuous HFD induction rat model for 8 weeks, and later 500 mg/ kg OS application can effectively reduced to hyperglycemia in HFD animals, but it did not improved blood lipids. Non significant improvement in plasma lipids probable related to the time of feeding OS for only two weeks, further experiments are needed to confirm.

Key words:
Diabetes mellitus, *Ophiocordyceps sinensis*, high fat diet, triglyceride, cholesterol

Exploring the effect of *Antrodia cinnamomea* mycelium on plasma lipids in ob/ob mice.

劉安喬(An-Qiao Liu)[#]，陳瑛宜(Yin-I Chen)，何偉真(Wai-Jane Ho)，張世良(Shih-Liang Chang)[*]

[#]*Department of Medicinal Botanicals and Health Applications*
Email:slchang@mail.dyu.edu.tw

Background and Aim:
Antrodia cinnamomea(AC), a Taiwanese unique fungus consider as a traditional medicine which has hepatoprotective, anti-oxidant, anti-inflammatory and prevent cardiovascular diseases. Previous studies have shown that *Antrodia cinnamomea* have the potential for anti-obesity. In this research, we used ob/ob leptin defective mice to explore the effect of AC on plasma lipid of this kind of autologous obese animal and the possible mechanism of body action.

Materials and Method:
We used 12 female leptin deficiency type(B6.V-*Lep*^{ob}, ' *ob / ob* ')mice of four-week-old, randomly divided into two groups of 6 animal each one being fed with: AC (oral AC 500 mg/kg every day), Control(Saline 1 ml/kg). About 4 weeks, record their weight, food and water intake every day. Fasting for 12 hours on the week 2 and week 4 testing results by taking blood through facial veins to detect total cholesterol and triglycerides.

Result and Conclusion:
After oral AC 500 mg/kg during a 4 weeks interval, it could be observed that the weight of AC group decreased significantly compared to the control group in the third week and the fourth week. Food intake: There was also a significant decrease in the AC group compared to the control group at the third and fourth weeks. Plasma lipids: AC group compared with control group, total cholesterol and triglycerides also decreased significantly in the fourth week. Feeding with AC mycelium 500 mg/kg will effectively lower the food intake on ob/ob mice improving their overweight problem. In this kind of animal model of autologous obesity, total cholesterol increase between week 2 and week 4, and AC inhibits this phenomenon, so that total cholesterol is no longer elevated and triglycerides also decrease, It was confirmed that AC may have the potential to treat the dyslipidemia in ob/ob mice.The mechanism of its action is worth further exploration.

Keyword:
Antrodia cinnamomea 、obesity、plasma lipids、*ob/ob* mice、food intake

Anti-cancer activity of three bufadienolides in CL1-5 highly metastatic human lung cancer cells

黃慧琪 (Hui-Chi Huang)[1,#], 李孟修 (Meng-Shiou Lee)[1], 張文德 (Wen-Te Chang)[1], 陳欣俞 (Hsing-Yu Chen)[1], 陳玉華 (Yu-Hua Chen)[1], 林季千 (Chi-Chen Lin)[2], 林民昆 (Ming-Kuem Lin)[1,*]

[1]Department of Chinese Pharmaceutical Sciences and Chinese Medicine Resources, College of Chinese Medicine, China Medical University, Taichung, Taiwan.
[2]Institute of Medical Technology, College of Life Science, National Chung Hsing University, Taichung, Taiwan.

Lung cancer is the second leading cause of cancer death worldwide. Clinically, chemotherapy is the conventional therapy applied to eradicate cancer cells; however, a more effective drug remains to be developed. In this study, the effects of 3 bufadienolides, namely kalantuboside B, kalantuboside A, and bryotoxin C, isolated from *Kalanchoe tubiflora* (Harvey) were evaluated in CL1-5 highly metastatic human lung cancer cells. We found that these 3 compounds dramatically reduced the number of live cells and indeed increased trypan blue-stained cells which are identified as dead cells at nanomolar concentrations. In contrast to their apoptosis-promoting activity in other cancer cells, these bufadienolides only slight or did not induce apoptosis in CL1-5 cancer cells. Instead, they activated an autophagy pathway, as indicated by increased autophagosome formation and the relative signaling pathway. Autophagy induced by these bufadienolides was demonstrated to be linked to the down-regulation of p-mTOR and the up-regulation of LC3-II, ATG5, ATG7, and Beclin-1. Moreover, among these 3 compounds, kalantuboside B, in which a monosaccharide is attached at the bufadienolide aglycon, exhibited higher autophagy induction. Our findings revealed an autophagy as the alternative mechanism of drug action by bufadienolides in CL1-5 lung cancer cells and provided evidence that bufadienolides are a potential therapeutic strategy for highly metastatic human lung cancer.

Key words: *Kalanchoe tubiflora*, bufadienolides, CL1-5 human lung cancer cells, autophagy

The Protective Effect of The Extracts of *Glehnia littoralis* on A549 Cells Induced by Dust Mite

宋依玲(Yi-Ling, Sung)[†,#]，吳佩芝(Pei- chih, Wu)[‡]，梁珊瑗(Shan-Yuan, Liang)[†]，劉沛均(Pei-Chun, Liu)[†]，蔡仁傑(Jen-Chieh, Tsai)[†,*]

[†]*Department of Medicinal Botanicals and Health Care, Da Yeh University, Chunghua, Taiwan*

[‡]*Cheng Ching Hospital, Taichung, Taiwan*

Glehnia littoralis (Apiaceae) is a perennial herb and the medicinal section is root. It's used for the treatment with lung and respiratory diseases traditionally and pharmacological researches indicated its anti-inflammatory, antitussive, expectorant and other effects. In this study, we investigated the effects of the extract of *G. littoralis* on the expressions of IL-6, PI3K, and NF-κB in human lung epithelial cells A549 induced by dust mites. The effects of different concentrations of *G. littoralis* extract on the survival rate of A549 cells induced by dust mites were studied by MTT assay, and then the expression of IL-6, PI3Kand NF-κB were analyzed by Western blotting. The results indicated that the extract of *G. littoralis* can alleviate the death of A549 cells induced by Der p and inhibit the expression of NF-κB by activating IL-6 and PI3K proteins. Therefore, it might be feasible to use the extract of *G. littoralis* in the prevention or treatment with lung or respiratory diseases, and it is worthy to be further explored in the future.

Key words: *Glehnia littoralis* (Apiaceae)、A549 cell, Dust Mite

Xanthine-derived KMUP-1 inhibits LPS-induced inflammatory activity in RAW 264.7 macrophages

黃上恩 (Shang-En Huang)[1,#], 徐仲豪 (Jong-Hau Hsu)[2], 傅偉銘 (Wei-Ming Fu)[3], 葉竹來 (Jwu-Lai Yeh)[3,*]

[1]Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
[2]Department of Paediatrics, School of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
[3]Department of Pharmacology, School of Medicine, College of Medicine, Kaohsiung Medical University,Kaohsiung, Taiwan

Objectives: Xanthine derivative KMUP-1 has been demonstrated to play a protective role in cardiovascular diseases, including pulmonary hypertension and cardiomyopathy via eNOS/cGMP-dependent pathway. However, the potential benefits of xanthine derivative against lipopolysaccharide (LPS) have not been addressed. The aim of this study was to investigate the anti-inflammatory activities and corrrelated molecular mechanisms of KMUP-1 on LPS-induced inflammation of RAW264.7 macrophages.
Methods: RAW264.7 macrophages pretreated KMUP-1, subsequently stimulated with LPS. Cell viability and inflammatory mediators were measured by MTT, ELISA assay and Western blot.
Results: We found that KMUP-1 attenuated LPS-induced cytotoxicity and production of NO, TNF-α and IL-6 in RAW264.7 cells. In addition, KMUP-1 preconditioning inhibited the activity and protein expression of matrix metalloproteinase-2 (MMP-2) and MMP-9. Finally, KMUP-1 inhibited the iNOS, COX-2 and phosphorylation of p38. In this study, the results of further experiment demonstrated that KMUP-1 inhibited expression levels of inflammatory mediators in a dose-dependent manner.
Conclusions: Xanthine-derived KMUP-1 can suppress LPS-induced cytotoxicity and inflammation in RAW264.7 cells. This study implies that KMUP-1 provide therapeutic benefits for inflammation-associated disorders.

Keywords: Xanthine-derived KMUP-1, LPS, RAW264.7, inflammation

1,2,3,4,6-Penta-*O*-galloyl-beta-D-glucopyranoside suppresses MYC expression and inhibits multiple myeloma cells proliferation

Duurenjargal Tseeleesuren [1,2], Rajni Kant [2], Chia-Hung Yen [2,3,4,5*], Hui-Hua Hsiao [1,6,7*], Yi-Ming Arthur Chen [1,2,8 *]

[1] Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
[2] Center for Infectious Disease and Cancer Research (CICAR), Kaohsiung Medical University, Kaohsiung, Taiwan
[3] Graduate Institute of Natural Products, College of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan
[4] Department of Medical Research, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan
[5] Research Center for Natural Products and Drug Development (CHY), Kaohsiung Medical University, Kaohsiung, Taiwan
[6] Division of Hematology-Oncology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan
[7] Faculty of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
[8] Institute of Biomedical Sciences, National Sun Yat-sen University, Kaohsiung, Taiwan

Abstract
Multiple myeloma (MM), is the second most common hematological malignancy. Despite the available treatment options, MM remains an incurable disease and the treatment outcome for patients has not been satisfactory. Therefore, the discovery of novel agents greatly boosts the potential therapeutics for MM. The natural compound 1,2,3,4,6-Penta-*O*-galloyl-beta-D-glucopyranoside (PGG) has been shown to exhibit antitumor activities against various cancer cells. Therefore, in this study we evaluated the antitumor effect of PGG on MM cell lines. PGG treatment inhibited the growth of three tested MM cell lines in a dose- and time-dependent manner. Cell cycle analysis revealed that PGG treatment caused cell cycle arrest in G1 phase. Annexin V positive cells, Caspase 3/7 activity, and protein expression level of cleaved caspase 3 was significantly increased by PGG treatment suggested that PGG induced apoptosis in MM cell. MYC hyperactivation was observed in more than half of MM patients. MYC inhibition leads to MM cell death, hence MYC is an attractive target for MM treatment. PGG decreased the protein and mRNA levels of MYC and reversed the mRNA expression of MYC target genes p21, p27 and cyclin D2. In addition, PGG treatment inhibited protein expression of DEPTOR which commonly overexpressed and have therapeutic potential in MM. Conversely, PGG antagonized the cytotoxic effect of bortezomib in combination treatment. However, PGG showed synergistic anti-myeloma effect with another proteasome inhibitor MG132. Moreover, MYC inhibitor JQ1 synergizes bortezomib effect against MM. These findings also provide a valuable information for the combination treatment of proteasome inhibitors with the particular type of chemicals for patients with MM. Altogether, our results demonstrated anti-myeloma effect of PGG and supported further development of this compound for the treatment of MM.

Identification of *Syzygium simile* leaves extract with anti-hepatic lipid accumulation activity by high-content screening of a Taiwanese indigenous plant extract library

Tsai-Hsun Yang[1], Hsun-Shuo Chang[1,2], Ho-Cheng Wu[1], Yu-Chang Chen[2], Kai-Jay Lin[1], Sheena Wang[1], Chia-Hung Yen[1,3,*]

[1] Graduate Institute of Natural Products, College of Pharmacy, Kaohsiung Medical University, Kaohsiung, 80708 Taiwan;
[2] School of Pharmacy, College of Pharmacy, Kaohsiung Medical University, Kaohsiung, 80708 Taiwan;
[3] Center for Infectious Disease and Cancer Research, Kaohsiung Medical University, Kaohsiung, 80708 Taiwan;

Abstract:

Non-alcoholic fatty liver disease (NAFLD) has become the most common liver disease during the past decades in developed and developing countries, and it is highly correlated with diseases such as metabolic syndrome, diabetes, and hyperlipidemia. Therefore, pharmacological strategies to treat NAFLD are urgently required. Natural products have been considered as the best source for drug discovery. By using an image-based high-throughput screening with a library containing 3,000 indigenous plant extracts from Taiwan, we identified the *Syzygium simile* leaves (SSLE) extract to have the effect of inhibiting lipid droplet (LD) accumulation in hepatic cell lines. The analyses of the genes expression involved in lipid metabolism revealed that SSLE suppressed the mRNA expression of CD36, the fatty acid translocase. In agreement with this observation, we further showed that SSLE inhibited CD36 protein expression, fatty acid uptake and has only limited effects on pre-formed LDs. In addition, SSLE reduced LD accumulation and CD36 expression in enterocyte and macrophage cell lines. In conclusion, our results indicated that SSLE could serve as a potential source for the developing of novel therapeutic modalities for NAFLD and that the suppression of CD36 expression and fatty acid uptake could contribute to the lipid-lowering effect of SSLE.

Sinularin Selectively Kills Breast Cancer Cells Showing G2/M Arrest, Apoptosis, and Oxidative DNA Damage

Hui-Ru Wang[#], Hurng-Wern Huang, Jen-Yang Tang, Pei-Ying Guan, Jyh-Horng Sheu*, Hsueh-Wei Chang*

Institute of Biomedical Science, National Sun Yat-Sen University, Kaohsiung, Taiwan.
Department of Biomedical Science and Environmental Biology, Kaohsiung Medical University, Kaohsiung, Taiwan.

The natural compound sinularin, isolated from marine soft corals, is antiproliferative against several cancers, but its possible selective killing effect has rarely been investigated. This study investigates the selective killing potential and mechanisms of sinularin-treated breast cancer cells. In MTS assay, sinularin dose-responsively decreased the cell viability of two breast cancer (SKBR3 and MDA-MB-231) cells, but showed less effect on breast normal (M10) cells after a 24 h treatment. According to 7-aminoactinomycin D (7AAD) flow cytometry, sinularin dose-responsively induced the G2/M cycle arrest of SKBR3 cells. Sinularin dose-responsively induced apoptosis on SKBR3 cells in terms of a flow cytometry-based annexin V/7AAD assay and pancaspase activity, as well as Western blotting for cleaved forms of poly(ADP-ribose) polymerase (PARP), caspases 3, 8, and 9. These caspases and PARP activations were suppressed by *N*-acetylcysteine (NAC) pretreatment. Moreover, sinularin dose-responsively induced oxidative stress and DNA damage according to flow cytometry analyses of reactive oxygen species (ROS), mitochondrial membrane potential (MitoMP), mitochondrial superoxide, and 8-oxo-2'-deoxyguanosine (8-oxodG)). In conclusion, sinularin induces selective killing, G2/M arrest, apoptosis, and oxidative DNA damage of breast cancer cells.

Key words : sinularin, selectively kills, G2/M arrest, apoptosis, oxidative DNA damage

Screening of a natural products library for anti-influenza virus neuraminidase activity

賴怡靜(Yi-Ching Lay)[1,2,#]，郭怡萍(Yi-Ping Kuo)[1]，余思穎(Szu-Yin Yu)[1]，趙裕展(Yu-Chan Chao)[3]，王聖帆 (Sheng-Fan Wang)[2,4]，鄭源斌(Yuan-Bin Cheng)[1]，顏嘉宏 (Chia-Hung Yen)[1,2,*]

1 Graduate Institute of Natural Products, College of Pharmacy, Kaohsiung Medical University, Kaohsiung, 80708 Taiwan
2 Center for Infectious Disease and Cancer Research, Kaohsiung Medical University, Kaohsiung, 80708 Taiwan
3 Institute of Molecular Biology, Academia Sinica, Taipei, 11529 Taiwan
4 Department of Medical Laboratory Science and Biotechnology, Kaohsiung Medical University, Kaohsiung, 80708 Taiwan

Influenza virus causes seasonal and pandemic infection. Currently, there are four FDA approved anti-influenza drugs: amantadine, rimantadine, oseltamivir, and zanamivir. However, drug resistance due to mutations of target proteins remains a critical issue for anti-influenza treatment. Therefore, development of new drugs against influenza virus are urgent. We utilized a baculovirus display neuraminidase on the surface (NA9-Bac) as a pseudotyped influenza virus for high-throughput drug screening. By collaborating with Dr. Cecilia Koo Botanic Conservation Center we established KBCC library, which containing 1248 plant extracts. By utilizing NA9-Bac platform and KBCC library we discovered that NPE extract has an anti-influenza activity. Bioactivity guided fractionation suggested that fractions eluted by 20% and 40% BuOH (N20 and N40) processed anti-neuraminidase activity. The IC_{50}s of N20 and N40 in NA9-Bac assay were 83 and 78 μg/ml, respectively. No significant cytotoxicity of both fractions was observed at concentration of 1000 μg/ml. Both fractions reduced neuraminidase activity of the influenza A/TW/2682/14 (H1N1) virus and the influenza B/TW/1868/14 virus dose-dependently. Treatment with N20 significantly reduced influenza virus-induced cytopathic effect in MDCK cells. Our results suggest that NPE extract is a promising source of novel anti-influenza drug candidates.

Hydrogen peroxide induces autophagy of oral cancer cells

沈堉憲(Yu-Hsian Shen)[#]，張學偉(Hsueh-Wei Chang) *

Department of Biomedical Science and Environmental Biology. Kaohsiung Medical University, Kaohsiung 807, Taiwan.

Hydrogen peroxide is a common byproduct of many oxidative stress-modulating drugs. Autophagy also plays an important role for regulating cancer cell survival. Hence, I am interested in hydrogen peroxide effect on autophagy for oral cancer cells. Using MTS, the cell viability of hydrogen peroxide-treated oral cancer cells was examined. Using Acridine Orange (AO) staining, the autophagy was detected by flow cytometry. Hydrogen peroxide decreased the cell viability of oral cancer cells in a dose-responsive manner. Moreover, the hydrogen peroxide increased the AO intensity of oral cancer cells in a dose-responsive manner, suggesting that hydrogen peroxide induced autophagy in oral cancer cells. In conclusion, autophagy may contribute to the hydrogen peroxide-induces cytotoxicity of oral cancer cells.

Key words: Hydrogen peroxide, autophagy, oral cancer cells

Antioxidant properties of ethyl ethanoate extraction from GTRA

郭蕙慈(Huei-Cih Guo)[#]，張芳榮(Fang-Rong Chang)[*]，張學偉(Hsueh-Wei Chang)[*]

Graduate Institute of Natural Products, Kaohsiung Medical University, Kaohsiung 807, Taiwan.
Department of Biomedical Science and Environmental Biology, Kaohsiung Medical University, Kaohsiung 807, Taiwan.

Background: GTRA is ethyl ethanoate extract from a red algae. Objective: However, the antioxidant properties for GRFA remain unclear. Method: The antioxidant properties were analyzed in terms of total phenol content (TPC), total flavonoid content (TFC), 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging. Results: All these antioxidant properties were dose-dependently increased. Conclusion: GTRA is a potential antioxidants resource.

Key words: Antioxidant properties, ethyl ethanoate extraction

Memory-enhancing effect of antioxidant oligopeptide from walnut (*Juglans regia* L.) protein hydrolysates

Ming-Chuan Liu[a], Sheng-Jie Yang[a], Da Hong[a], Jin-Ping Yang[a], Chien-Liang Chao[b], Yi-Ta Lee[b], Hang-Ching Lin[b,c] and Chao-Jin Wang[a,b]

[a] *R&D Center, Sinphar Tian-Li Pharmaceutical Co., Ltd., Sinphar Group, Hangzhou, China*
[b] *R&D Center, Sinphar Pharmaceutical Co., Ltd., Sinphar Group, Ilan (Taiwan), R.O.C.*
[c] *School of Pharmacy, National Defense Medical Center, Taipei (Taiwan) R.O.C.*

Abstract
Peptides have been reported to possess interesting biological properties. The present study was designed to evaluate the neuroprotective effect of walnut oligopeptide (WOP) against oxidative stress on PC12 cells and its effect on learning and memory of mice using the Morris water maze and the step-down passive avoidance tests. Moreover, the acute toxicity of WOP was carried out to assess their safety profile. It was found that WOP was able to suppress H_2O_2-induced cell death in PC12 cells. Besides, the treatment of mice with WOP shortened the escape latency and exhibited much longer target time and more crossing times significantly, compared with untreated control groups in the Morris water maze test. Similarly, the step-down passive avoidance test showed that the treatment of mice with WOP could ameliorate memory impairments. The admistrated dose (20.1 g/kg BW) did not produce mortality or treatment-related adverse effects with regard to body weight, general behavior, or relative organ weights of the tested males and females mice. The current results indicate that WOP could exert neuroprotective effect against oxidative damage, and attenuated learning and memory impairments. These ameliorating effects of WOP may be useful for treatment of memory impairment in Alzheimer's and its related diseases. Furthermore, we also found that WOP had anti-fatigue, immunomodulatory, and anti-hazing activities.

13-Acetoxysarcocrassolide, a Cytotoxic Cembranolide Derivative, Induced Apoptotic Activity on leukemia Cancer Cells through the Oxidative Stress

陳又瀅(You-Ying Chen) [1#],彭柏融(Bo-Rong Peng)[2,3],施守平(Shou-Ping Shih)[2,3], 溫志宏(Zhi-Hong Wen)[1], 呂美津(Mei-Chin Lu)[4,5*]

1. *[#]Department of Marine Biotechnology and Resources, National Sun Yat-sen University, Kaohsiung, Taiwan*
2. *Doctoral Degree Program in Marine Biotechnology, National Sun Yat-Sen University (NSYSU), Kaohsiung, Taiwan.*
3. *Doctoral Degree Program in Marine Biotechnology, Academia Sinica, Taipei, Taiwan*
4. *[*]Graduate Institute of Marine Biology, National Dong Hwa University, Pingtung, Taiwan*
5. *[*]National Museum of Marine Biology & Aquarium, Pingtung, Taiwan*

13-acetoxysarcocrassolide (13-AC), an active compound isolated from cultured Formosa soft coral *Lobophytum crassum*, was found to possess anti-proliferative and apoptosis-inducing activities against leukemia Molt 4 cells. In this study, we found that the marine cytotoxic product 13-AC, exhibited potent inhibitory activity on HSP90. 13-AC induced apoptosis in leukemia Molt 4 cells through the disruption of mitochondrial membrane potential (MMP) and the stimulation of reactive oxygen species (ROS) generation. Moreover, 13-AC exerted antitumor effect against leukemia Molt 4 cells as demonstrated by the in vivo xenograft animal model, It significantly reduced tumor volume (58.98%) . The molecular docking analysis demonstrated that 13-AC binds to N-terminal domain of HSP90 protein showing binding affinity more than 17-allylaminogeldanamycin (17-AAG), a HSP90 inhibitor of N-terminal ATP binding site and suppressed HSP90 client proteins including p-Akt, CDK4, HIF-1α, and MMP-2. On the proteins level, 13-AC increased the expression of apoptosis related proteins such as cleaved caspases-3 and -9 as well as cleaved PARP in a dose- and time-dependent manner. Moreover, the results suggested that 13-AC exerted its cytotoxic activity through the promotion of ROS generation and the suppression of antioxidant enzyme activities. Altogether, the apoptotic effect of 13-AC was found to be mediated through the inhibition of HSP90 suggesting its potential future application as an anticancer agent.

Keywords: Anticancer, 13-Acetoxysarcocrassolide, HSP90 inhibitor, Oxidative stress.

Antileukemia effect of Xestoquinone, induced apoptosis via oxidative stress combined with inhibition of Hsp90 and Topoisomerase II activities

施守平(Shou-Ping Shih)[1,2#]，陳又瀅(You-Ying Chen)[3],陳俊霖(Chun-Lin Chen)[2,4],
俞聖法(Steve Sheng-Fa Yu)[2]，呂美津(Mei-Chin Lu)[5,6*]

1. *[#]Doctoral Degree Program in Marine Biotechnology, National Sun Yat-Sen University (NSYSU), Kaohsiung, Taiwan.*
2. *[#]Doctoral Degree Program in Marine Biotechnology, Academia Sinica, Taipei, Taiwan*
3. *Department of Marine Biotechnology and Resources, National Sun Yat-sen University, Kaohsiung, Taiwan.*
4. *Department of Biological Sciences, National Sun Yat-sen University, Kaohsiung, Taiwan*
5. *[*]Graduate Institute of Marine Biology, National Dong Hwa University, Pingtung, Taiwan*
6. *[*]National Museum of Marine Biology & Aquarium, Pingtung, Taiwan*

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) exhibited the most potent activity against leukemia Molt 4 cells. We found that the use of XQ increased apoptosis and caused disruption of mitochondrial membrane potential (MMP) 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.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)

Antioxidant and antioral cancer cells properties of ethyl ethanoate extract from a tropical plant (EATP)

蔡宜璇(I-Hsuan Tsai)[#], 張學偉(Hsueh-Wei Chang)[*]

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Department of Biomedical Science and Environmental Biology, Kaohsiung Medical University, Kaohsiung 807, Taiwan.

The object of this study is to evaluate the antioxidant properties and cell viability of ethyl ethanoate extract from a tropical plant (EATP). I will meaure the total phenol content (TPC), total flavonoid content (TFC), 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging of EATP. The cell viability of EATP-treated oral cancer cells is determined by MTS assay. I found that EATP display a positive induction of these antioxidant properties. Moreover, EATP induces antiproliferation of several oral cancer cells and remains healthy to normal oral cells. Therefore, the antioxidant propterties may contribute to the antiproliferation against oral cancer cells.

Key words: Antioxidant properties, ethyl ethanoate extract

Heteronemin, a Marine Sesterterpenoid-Type Metabolite, Induces Apoptosis in Prostate LNcap Cells via Oxidative and ER Stress Combined with the Inhibition of Topoisomerase Ⅱ and Hsp90

施守平(Shou-Ping Shih)[1,2#], 劉益昌(Yi-Chang Liu)[3,4], 洪明昌(Ming-Chang Hong)[5], 杜英齊(Ying-Chi Du)[6,7], 宋秉鈞 Ping-Jyun Sung[9,10], 呂美津 Mei-Chin Lu[9,10*]

[1] #Doctoral Degree Program in Marine Biotechnology, National Sun Yat-Sen University, 70 Lien-Hai Road, Kaohsiung 80424, Taiwan
[2] #Doctoral Degree Program in Marine Biotechnology, Academia Sinica, 128 Academia Road, Section 2, Nankang, Taipei 11529, Taiwan
[3] Division of Hematology-Oncology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, 807, Taiwan
[4] Department of Internal Medicine, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, 807, Taiwan
[5] Department and Graduate Institute of Aquaculture, National Kaohsiung Marine University, Kaohsiung 811, Taiwan
[6] *Graduate Institute of Marine Biology, National Dong Hwa University, Pingtung 944, Taiwan
[7] *National Museum of Marine Biology & Aquarium, Pingtung 944, Taiwan

Heteronemin, a marine sesterterpenoid-type natural product, possesses diverse bioactivities, especially antitumor effect. To understand the antitumor mechanism of heteronemin, we further explored the precise molecular targets in prostate cancer cells. Initially, the growth inhibition effect of heteronemin was determined using MTT and colony formation assays. It exhibited the most potent activity against prostate cancer LNcap. With the xenograft animal model, the tumor size was significantly suppressed in the heteronemin-treated group about 51.88% as compared to the control group with no significant difference in the mice body weights. In addition, the results of a cell-free system assay demonstrated the inhibitory activity of heteronemin on Topoisomerase II (topo II). We found that the use of heteronemin induced apoptosis and disruption of mitochondrial membrane potential (MMP) and elevated the calcium release compared with the control group in a dose-dependent manner, as demonstrated by annexin-V/PI, Rhodamin 123 and Fluo-3 staining assays, respectively. Moreover, our findings indicated that the pretreatment of LNcap cells with an inhibitor of protein tyrosine phosphatase (PTPi) diminished ROS generation and apoptosis induced by heteronemin, suggesting that PTP activation plays a crucial rule in the cytotoxic activity of heteronemin.The expression of Hsp90 client proteins, phosphorylation of Akt (Ser473), STAT 3 (Ser 727 and Tyr705), PCNA, Rb2, as well as XIAP were suppressed by the use of heteronemin. However, the expression of p-HSF1, Hsp70 and acetylated tubulin were induced after heteronemin treatment. Thus, heteronemin significantly induced apoptotic and autophagic on LNcap cells by modulating ER and oxidative stress combined with the inhibition of topo II catalytic activity and Hsp 90 function.

Keywords: Antitumor; Apoptosis; Autophagy; ER stress; Heteronemin; Hsp90; Topoisomerase II catalytic inhibitor

Studies on the anti-metastatic effect of acridone alkaloids from *Severinia buxifolia* in NSCLC

黃聖凱 (Sheng-Kai Huang)[#]，郭靜穎(Ching-Ying Kuo)[#]，鄭源斌 (Yuan-Bin Cheng)[#]，李佩銜 (Pei-Shian Li)，王惠君 (Hui-Chun Wang)[#,*]

#Graduate Institute of Natural Products, Kaohsiung Medical University, Kaohsiung 807, Taiwan.

Lung cancer is the most common cancer globally and is one of the deadliest cancer due to the rapid metastasis. HIF-1 transactive genes have been linked to cancer metastasis; thence, inhibition of HIF-1 would be effective to limit lung cancer metastatic progression. In the present study, the acridone alkaloids isolated from *Serverinia buxifolia* were examined in the A549 NSCLC cell line for their anti-metastatic activity. Among 7 compounds, atalaphyllidine (Sbs-A), atalaphyllinine, and 5-hydroxy-N-methylseverifoline have a better inhibitory effect on cancer survival and metastasis. The reporter assay revealed Sbs-A compound significantly inhibits HIF-1 transactive activity. The Western blot and real-time PCR assays validated which was mainly resulted from decreasing of HIF-1α protein and minor from decreasing of HIF-1α mRNA. Using inhibitors of protein synthesis and degradation, we found Sbs-A inhibits HIF-1α protein synthesis accounts for it decreases HIF-1α protein levels. Probe into the mechanism we found that Sbs-A inhibit protein synthesis via inhibition of 5'UTR of HIF-1α, this leader sequence controls the translation efficiency of HIF-1α. Sbs-A also downregulated the putative HIF-1α target gene c-Myc, twist, Sox2, and CA9 expression and epitopic HIF-1α expression promoted HEK293T cell invasion which was inhibited by Sbs-A treatment. The study suggests that Sbs-A may have development potential to inhibit lung cancer metastasis via inhibition of HIF-1α protein synthesis.

Key words: NSCLC, acridone alkaloids, HIF-1, metastasis

Compare the water and ethanol extracts of Coptidis Rhizoma on adipogenesis inhibition in 3T3-L1 cells

楊婷伊(Ting-Yi Yang)[#]，郭靜穎(Ching-Ying Kuo)[#]，王惠君 (Hui-Chun Wang)[#,*]

#Graduate Institute of Natural Products, Kaohsiung Medical University, Kaohsiung 807, Taiwan.

Obesity is defined as a complex metabolic disorder that directly increases the risk of serious human diseases, such as type 2 diabetes mellitus, cardiovascular diseases, hypertension, and hyperlipidemia. It is a reason why we need to fight against obesity now. Previously, the methanol extract of the rhizome of Coptidis Rhizoma (CR) was fractionated by using different solvents, and the constituent berberine has been shown to exhibit anti-adipogenic activity. Given that the preparation of CR decoction is general by boiling water extraction, the present study is undertaken to compare the effect of water (CRW) and ethanol (CRE) extracts of Coptidis Rhizoma on 3T3-L1 adipogenesis. Our results showed CRE exhibited higher cytotoxicity than CRW. Both CRW and CRE displayed similar potency on inhibition of triglyceride accumulation and adipogenic gene expressions, such as CCAAT/enhancer-binding protein alpha (C/EBPα), peroxisome proliferator-activated receptor gamma (PPARγ), and fatty acid synthase in 3T3-L1 adipocytes. In addition, using HPLC analysis showed CR extraction by water has a higher yield of berberine than ethanol. Considering safety, preparation, and berberine yield, the CRW is more suggested than CRE in the treatment of obesity.

Key words: Coptidis Rhizoma, obesity, adipogenesis, berberine

Resveratrol protects against *Staphylococcus aureus*-induced lung inflammation through reduction of VCAM-1 expression

李宜達 (I-Ta Lee)#*

Department of Medical Research, Taichung Veterans General Hospital, Taichung, Taiwan
Department of Nursing, College of Nursing, Hungkuang University, Taichung, Taiwan

Staphylococcus aureus (*S. aureus*) is the most commonly found Gram-positive bacterium in patients admitted in intensive-care units, causing septicaemia or pneumonia. *S. aureus* is considered to play an important role in the induction of cell adhesion molecules. Resveratrol, a compound found in the skins of red fruits, may inhibit the inflammatory process involved in the lung diseases. Human lung epithelial cells (HPAEpiCs) were used in this study. The effect of *S. aureus* on vascular cell adhesion molecule-1 (VCAM-1) expression was determined by Western blot and real-time PCR. The involvement of signaling pathways in these responses was investigated by using the selective pharmacological inhibitors and transfection with siRNAs. We report that resveratrol protected against *S. aureus*-mediated lung inflammation by down-regulation of VCAM-1 expression and monocyte adhesion in HPAEpiCs and the lungs of mice. Resveratrol inhibited *S. aureus*-induced pulmonary hematoma and leukocyte count in BAL fluid in mice. Resveratrol also attenuated *S. aureus*-induced TLR2, MyD88, and PI3K complex formation. *S. aureus* stimulated Akt, JNK1/2, and p42/p44 MAPK phosphorylation, which were inhibited by resveratrol. *S. aureus* induced IκBα and NF-κB p65 phosphorylation and NF-κB p65 translocation, which were reduced by resveratrol. We found that *S. aureus* induced NF-κB and p300 complex formation and p300 phosphorylation, which were inhibited by resveratrol. Thus, resveratrol functions as a suppressor of *S. aureus* signaling, not only by inhibiting VCAM-1 expression but also by diminishing TLR2/MyD88/PI3K complex formation and Akt, JNK1/2, p42/p44 MAPK, p300, and NF-κB activation in HPAEpiCs.

Keywords: *Staphylococcus aureus*, Vascular cell adhesion molecule-1, Lung diseases, Inflammation

Breaking down Leukemia Walls: Heteronemin, a Sesterterpene Derivative, Induces Apoptosis in Leukemia Molt4 Cells through Oxidative Stress, Mitochondrial Dysfunction and Induction of Talin Expression

Yu-Cheng Chen[1], Mohamed El-Shazly[2,3], Kuei-Hung Lai[4], Tung-Ying Wu[5], Mei-Chin Lu[4,6]*

1 The Ph.D. Program for Cancer Biology and Drug Discovery, China Medical University and Academia Sinica,Taichung 404, Taiwan
2 Department of Pharmacognosy, Faculty of Pharmacy, Ain-Shams University, Organization of African Unity Street, Abassia, Cairo 11566, Egypt
3 Department of Pharmaceutical Biology, Faculty of Pharmacy and Biotechnology, German University in Cairo, Cairo 11432, Egypt
4 National Museum of Marine Biology & Aquarium, Pingtung 944, Taiwan
5 Graduate Institute of Natural Products, College of Pharmacy, Kaohsiung Medical University, Kaohsiung 807, Taiwan
6 Graduate Institute of Marine Biotechnology, National Dong Hwa University, Pingtung 944, Taiwan

Abstract:

Heteronemin, the most abundant secondary metabolite in the sponge Hippospongia sp., exhibited potent cytotoxic activity against several cancer cell lines. It increased the percentage of apoptotic cells and reactive oxygen species (ROS) in Molt4 cells. The use of ROS scavenger, N-acetyl cysteine (NAC), suppressed both the production of ROS from mitochondria and cell apoptosis that were induced by heteronemin treatment. Heteronemin upregulated talin and phosphorylated talin expression in Molt4 cells but it only upregulated the expression of phosphorylated talin in HEK293 cells. However, pretreatment with NAC reversed these effects. Talin siRNA reversed the activation of pro-apoptotic cleaved caspases 3 and 9. On the other hand, the downstream proteins including FAK and NF-_B (p65) were not affected. In addition, we confirmed that heteronemin directly modulated phosphorylated talin expression through ROS generation resulting in cell apoptosis, but it did not affect talin/FAK complex. Furthermore, heteronemin interfered with actin microfilament and caused morphology changes. Taken together, these findings suggest that the cytotoxic effect of heteronemin is associated with oxidative stress and induction of phosphorylated talin expression. Our results suggest that heteronemin represents an interesting candidate which can be further developed as a drug lead against leukemia.

Keywords: heteronemin; reactive oxygen species; mitochondrial; talin; phosphorylated talin

EANA exerts ROS-mediated antiproliferation, apoptosis and DNA damage against oral cancer cells

彭聖堯 (Sheng-Yao Peng)[1,#]，余姿蓉 (Tzu-Jung Yu)[1]，湯人仰 (Jen-Yang Tang)[2,*]，張學偉 (Hsueh-Wei Chang)[3,*]

[1]Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan.
[2]Department of Radiation Oncology, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan.
[3]Department of Biomedical Science and Environmental Biology, Kaohsiung Medical University, Kaohsiung, Taiwan.

The anticancer activity of ethyl acetate extract of certain plants (EANA) remains unclear. The aim of this study is to examine the effects on cell viability of oral cancer cells by EANA. MTS assay was used to analyze cell viability. The possible mechanism such as cell cycle, apoptosis, oxidative stress, and DNA damage were investigated by flow cytometry or western blotting. For the cell viability after 24 h EANA treatment, IC_{50} values of oral cancer cells (CAL 27, Ca9-22, OECM-1, HSC-3, and SCC9) were ranging from 8 to 17 μg/ml but the normal oral cells (HGF-1) remains more healthy. CAL 27 and Ca9-22 cells were selected for examining the possible mechanism. EANA induced time- and concentration-dependent apoptosis based on subG1 and annexin V analyses and cleaved poly (ADP-ribose) polymerase (c-PARP)) expression. Moreover, EANA also induced oxidative stress and DNA damage in oral cancer cells with the evidence of reactive oxygen species (ROS), mitochondrial superoxide (MitoSOX) generations, mitochondrial membrane potential (MMP) disruption, and γH2AX expression. All these EANA-induced changes were recovered by the free radical scavenger *N*-acetylcysteine (NAC) pretreatment. Therefore, EANA exerts oxidative stress-mediated preferential killing, apoptosis and DNA damage against oral cancer cells.

Key words：Oral cancer cell, oxidation stress, apoptosis, DNA damage

Bioactivity assays of soft coral-derived compound SS9

林育聖(Yu-Sheng Lin)[#], 張學偉(Hsueh-Wei Chang) *

[#]**Department of Biomedical Science and Environmental Biology, Kaohsiung Medical University, Kaohsiung 807, Taiwan.*

Soft coral is able to be cultivated. Many marine compounds are identified. In this study, the bioactivity assays of soft coral-derived compound SS9 were evaluated. Using MTS assay, the cell viability of SS9-treated oral cancer cells was determined. Moreover, the oral normal cells (HGF-1) were also chosen to test its side effect for cytotoxicity. Using several oral cancer cells, soft coral-derived compound SS9 were able to decrease their cell viability. In contrast, SS9 remains more healthy to normal oral cells than oral cancer cells. Therefore, soft coral-derived compound SS9 displays a selective killing effect against oral cancer cells but shows healthy to normal oral cells.

Key words: Soft coral, oral cancer

Ethyl acetate extract of the herbal plants (EAHP) induces autophagy and mitochondrial dysfunction of oral cancer cells

曹立儀(Li-Yi Tsao)[#], 張學偉(Hsueh-Wei Chang)[*]

Department of Biomedical Science and Environmental Biology, Kaohsiung Medical University, Kaohsiung 807, Taiwan.

Autophagy and mitochondria are important for regulating cancer cell survival. Hence, I am interested in autophagy and mitochondrial effects of ethyl acetate extract of the herbal plants (EAHP)-treated oral cancer cells. Using MTS assay, the cell viability of EAHP-treated oral cancer cells was examined. Using acridine orange (AO) staining, the autophagy was detected by flow cytometry. Using mitochondrial inner membrane dye, the mitochondrial membrane potential (MMP) was detected by flow cytometry. EAHP decreased the cell viability of oral cancer cells in a dose-responsive manner. Moreover, the EAHP increased the AO intensity and decreased the MMP of oral cancer cells in a dose-responsive manner, suggesting that EAHP induced autophagy and mitochondrial dysfunction in oral cancer cells. Moreover, a free radical scavenger *N*-acetyl cysteine (NAC) was able to revert the EAHP-induced cell death, autophagy, and MMP changes in oral cancer cells. In conclusion, oxidative stress may contribute to the EAHP-induced cytotoxicity of oral cancer cells associated with autophagy and mitochondrial dysfunction.

Key words: autophagy, mitochondrial dysfunction, cell viability

Chemical X9 selectively targets oral cancer cells showing apoptosis, oxidative stress, and DNA damage

王聖傑(Sheng-Chieh Wang)[#], 張學偉(Hsueh-Wei Chang)[*]

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Department of Biomedical Science and Environmental Biology, Kaohsiung Medical University, Kaohsiung 807, Taiwan.

In this study, we evaluate antioral cancer effect of chemical X9 in terms of cell viability, cell cycle, apoptosis, oxidative stress, and DNA damage. In cell viability assay, chemical X9 selectively kills two oral cancer cells (Ca9-22 and CAL 27) with less affecting normal oral cells (HGF-1). Although chemical X9 does not change the cell cycle distribution significantly, chemical X9 induces apoptosis validated by flow cytometry for annexin V and western blotting for cleaved poly(ADP-ribose) polymerase (PARP) and caspases 3/8/9. Furthermore, chemical X9 induces oxidative stress validated by flow cytometry for the generations of reactive oxygen species (ROS) and mitochondrial superoxide (MitoSOX), and the suppression of mitochondrial membrane potential (MMP). Chemical X9 also induces DNA damage validated by flow cytometry for the increases of DNA double strand break marker γH2AX and oxidative DNA damage marker 8-oxo-2'-deoxyguanosine (8-oxodG). Therefore, chemical X9 induces apoptosis, oxidative stress, and DNA damage, which may lead to selectively killing of oral cancer cells.

Key words: Apoptosis, Oral Cancer, Reactive Oxygen Species

Ethyl acetate extract of Traditional Chinese Plants (EATC) induces apoptosis and DNA damage of oral cancer cells

吳光涵 (Kuang-Han Wu)[#], 張學偉(Hsueh-Wei Chang)[*]

[#*]*Department of Biomedical Science and Environmental Biology, Kaohsiung Medical University, Kaohsiung 807, Taiwan.*

Ethyl acetate extract of Traditional Chinese Plants (EATC) is rarely reported. Hence, I am interested in the proliferation effect on EATC-treated oral cancer cells. Using MTS assay, the cell viability of EATC-treated oral cancer cells was performed. Using annexin V/7-amino-actinomycin D (7AAD) staining, the apoptosis was detected by flow cytometry. Using γH2AX and 8-hydroxy-2'-deoxyguanosine (8-oxodG) antibodies, the DNA damage was detected by flow cytometry. EATC dose-dependently decreased the cell viability of oral cancer cells. Moreover, the EATC increased the annexin V, H2AX, and 8-oxodG intensities of oral cancer cells in a dose-responsive manner. Moreover, a reactive oxygen species (ROS) scavenger *N*-acetyl cysteine (NAC) was able to recover the EATC-induced cell death, apoptosis, and DNA damage in oral cancer cells. In conclusion, oxidative stress may contribute to the EATC-induces cytotoxicity of oral cancer cells associated with apoptosis, and DNA damage.

Key words：Oral cancer cell, oxidation stress, apoptosis, DNA damage

Herbal medicine comb inhibit metastasis in Breast cancer

戴昀皓 Yun-Hao Dai[1#]，楊顓丞 Juan-Cheng Yang[2]，吳永昌 Yang-Chang Wu[3,4,5*]

[1]School of Pharmacy, China Medical University, Taichung 40402, Taiwan,
[2]Chinese Medicine Research and Development Center, China Medical University Hospital, Taichung 40447, Taiwan
[3]Research Center for Natural Products & Drug Development, Kaohsiung Medical University, Kaohsiung 807, Taiwan
[4]Graduate Institute of Natural Products, Kaohsiung Medical University, Kaohsiung 807, Taiwan
[5]Department of Medical Research, Chung-Ho Memorial Hospital, Kaohsiung Medical University, Kaohsiung 807, Taiwan

So far, cancer-related mortality rate was increased and ranked as the top cause of death in Taiwan. Although current available treatments for cancer disease were effective against tumor growth, the recurrence and distant metastasis still be a challenge for regimen. The survival rate of patients who suffer from metastatic cancer was dramatically decreased. Therefore, metastasis is a serious issue for cancer treatment. In this study, to explore the effective treatment for inhibiting cancer metastasis, we search for the traditional Chinese Medicine. Interestingly, we found two herbal medicine comb may act as a new therapeutic way for suppressing the metastasis of cancer. The migration and invasion assay showed that this comb inhibited the mobility of cancer cells. Furthermore, using 4T1-Luc tumor animal model, this comb also showed the significant inhibitory activity against tumor metastasis. Taken together, this new comb may provide a new therapeutic option for combination with current chemotherapy for treating with metastatic cancer disease.

Key words: metastasis, migration, herbal medicine, breast cancer

Water extract and ethanol extract of Coptidis Rhizoma affect the early stage of adipogenesis by different mechanisms

柯雅甄 [1#] (Ya-Chen Ko), 楊婷伊 [1] (Ting-Yi Yang), 王惠君 [1*] (Hui-Chun Wang)

[1]Graduate Institute of Natural Products, Kaohsiung Medical University, Kaohsiung, Taiwan.

The incidence of obesity increasing progressively worldwide becomes an unignorable risk of many diseases. In the *in vitro* study model, it is known that insulin, glucocorticoids, and cAMP activator IBMX are indispensable for 3T3-L1 adipogenesis, and the PI3K/AKT and PKA/CREB respectively activated by insulin and cAMP have roles at the early stage of adipogenesis, which are important to induce PPARs and C/EBPs gene expression. Our previous study found that the water (CRW) and ethanol (CRE) extracts from Coptidis Rhizoma inhibit 3T3-L1 adipogenesis at the early stage. Therefore, we investigated their effects on inducing medium consist of insulin, glucocorticoid, and IBMX (MDI)-induced AKT and CREB phosphorylation during 3T3-L1 adipogenesis. Our results showed that the phosphorylation of AKT and CREB was soon induced by MDI stimulation for 30 min in 3T3-L1 preadipocytes. The CREB phosphorylation was inhibited by pre-treatment of 4 μg/mL CRW, and which was stronger than 4 μg/mL CRE did. However, either 4 μg/mL CRW or CRE did not affect MDI-induced AKT phosphorylation. IBMX treated 3T3-L1 pre-adipocytes for 30 min were significantly induced cAMP/PKA mediated CREB phosphorylation and which was inhibited by CRW in a dose-dependent manner, but did not by CRE and the major constituent of Coptidis Rhizoma berberine. In this way, applying differentiation inducers individually we could clarify the mechanism of action for the compounds in Coptidis Rhizoma extracts on against 3T3-L1 adipogenesis.

Key words:Coptidis Rhizoma, anti-adipogenic, 3T3-L1 adipocyte

3,4-*seco*-4(23),20(29)-Lupadiene-3,28-dioic acid inhibits neutrophilic inflammation by blocking FPR1

汪依璿 (Yi-Hsuan Wang)[1,*], 蔡永豐 (Yung-Fong Tsai)[2], 張芳榮 (Fang-Rong Chang)[3], 吳永昌 (Yang-Chang Wu)[3], 黃聰龍 (Tsong-Long Hwang)[1,#]

[1]Graduate Institute of Natural Products, Chang Gung University, Taoyuan, Taiwan

[2]Department of Anesthesiology, Chang Gung Memorial Hospital, Taoyuan , Taiwan.

[3]Graduate Institute of Natural Products, Kaohsiung Medicine University, Kaohsiung , Taiwan

Neutrophils play significant pathogenic roles in inflammatory and autoimmune diseases, such as acute respiratory distress syndrome, chronic obstructive pulmonary disorder, rheumatoid arthritis, psoriasis, and systemic lupus erythematosus. Formyl peptide receptor 1 (FPR1) mediates bacterial and mitochondrial *N*-formyl peptides-induced neutrophil activation. Therefore, FPR1 can act as a therapeutic target for the treatment of neutrophilic inflammatory diseases. In this study, we found that 3,4-*seco*-4(23),20(29)-lupadiene-3,28-dioic acid (LS-PH), a lupine-type triterpene isolated from the leaves and branches of *Lithocarpus synbalanos* (Fagaceae), inhibited superoxide anion generation, reactive oxygen species production, elastase release, and adhesion in human neutrophils activated by bacterial or mitochondrial *N*-formyl peptides (fMLF or fMMYALF). In contrast, LS-PH did not have significant inhibitory effects in non-FPR1 agonists-activated human neutrophils. Importantly, LS-PH bound to FPR1 both in human neutrophils and FPR1-transfected HEK293 cells. LS-PH produced right shifts of the concentration-response curves of fMLF- and fMMYALF-induced superoxide anion generation and elastase release, suggesting that LS-PH acts as a competitive antagonist of FPR1. Furthermore, LS-PH competitively inhibited the FPR1-mediated intracellular signals, including Ca^{2+} mobilization as well as MAPKs and Akt phosphorylation. In addition, LS-PH showed therapeutic effects in lipopolysaccharide-induced acute lung injury and imiquimod-induced psoriasis in mice. Our results indicate that LS-PH is a novel FPR1 inhibitor and may have potential as an anti-inflammatory agent for the treatment of neutrophilic lung damage and skin diseases.

Keywords**:** acute lung injury, formyl peptide receptor, *Lithocarpus synbalanos*, neutrophils, psoriasis, 3,4-*seco*-4(23),20(29)-lupadiene-3,28-dioic acid

Anti-inflammatory effects of 1,9-Diallyl-9*H*-pyrido[3,4-*b*]indole in activated human neutrophils through inhibiting Src family kinases

Hsiang-Chih Ku[#], Tsong-Long Hwang*

Graduate Institute of Natural Products, Chang Gung University, Taiwan

Abstract

Neutrophils play an important role in innate immunity. However, recent evidences have suggested that neutrophils are involved in the pathogenesis of various inflammatory and autoimmune diseases. Therefore, suppression of neutrophil activation using drug has therapeutic potential in neutrophil-mediated diseases. In this study, we demonstrated that 1,9-Diallyl-9*H*-pyrido[3,4-b]indole (NCKU-S-4) significantly inhibited various stimulators-induced human neutrophil activations, including superoxide anion generation, reactive oxygen species, elastase release, CD11b expression, chemotactic migration, and neutrophil extracellular traps (NETs) formation. NCKU-S-4 did not directly scavenge superoxide anion and cause cytotoxicity. NCKU-S-4 significantly inhibited the phosphorylation of the Src family kinases (SFKs), Src (Tyr416), Lyn (Tyr396), HCK (Tyr410), but not p38 MAPK (Thr180/Tyr182), ERK (Thr202/Tyr204), and JNK (Thr183/Tyr185). Further study showed that NCKU-S-4 directly inhibited the enzymatic activities of Src and Fgr, suggesting that NCKU-S-4 acts as an inhibitor of SFKs. In addition, the downstream signals of SFKs, Vav (Tyr174) and Btk (Tyr223), were inhibited by NCKU-S-4. In conclusion, these data demonstrated that NCKU-S-4 inhibits oxidative burst, degranulation, migration and NETosis in activated human neutrophils through inhibition of SFKs activity. We suggest that NCKU-S-4 may has potential as an anti-inflammatory agent for treating neutrophilic inflammation.

Keywords: 1,9-Diallyl-9*H*-pyrido[3,4-*b*]indole, neutrophil, Src family kinases

FY01, an extraction from marine microorganism *Streptomyces sp*. induced prostate cancer cell apoptosis through mitochondrial dysfunction and induction of ROS generation

Chieh-Yu Lee (李婕瑜)[1#]; Shou-Ping Shih (施守平)[2]; Yu-Cheng Chen (陳又誠)[3]; You-Ying Chen (陳又瀅)[4]; Mei-Chin Lu (呂美津)[1,5*]

[1 #]Graduate Institute of Marine Biology, National Dong Hwa University, Pintung 944, Taiwan
[2] Doctoral Degree Program in Marine Biotechnology, National Sun Yat-Sen University, 70 Lien-Hai Road, Kaohsiung 80424, Taiwan
[3] Department of Marine Biotechnology and Resources, National Sun Yat-Sen University, 70 Lien-Hai Road, Kaohsiung 80424, Taiwan
[4] The PhD Program of Cancer Biology and Drug Discovery, China Medicine University, Taichung, Taiwan
[5 *]National Museum of Marine Biology & Aquarium, Pingting 944, Taiwan

Abstract

The marine microorganism were used as a valuable sources for drug development and it has been considered as an important treatment of diseases especially the secondary metabolites from marine actinomycetes. MTT assay were used to screened the marine secondary metabolite FY01, extracted by ethyl acetate from actinomycetes *Streptomyces sp*. This attracted component show an great anti-proliferation activity in prostate cancer cell line PC-3、Du145 and LNcap with the IC50 13.1±0.3、11.23±0.08 and 39.67±0.05, respectively. MTT result showed that LNcap were the most sensitive cell line and this result encouraged us to further investigated the molecular mechanism of FY01 using LNcap cells. The use of increasing doses of FY01 (0 to 25 μg/mL) increased the percentage of disruption of mitochondrial membrane potential, induced the reactive oxygen species, leading to decrease the cell viability. Taken together, these suggest that FY01 has a great potential in the development of anti-cancer drugs.

Keywords: marine natural products, marine actinomycetes, prostate cancer

ANTICANCER ACTIVITY OF VIETNAMESE *COCHINCHINA MOMORDICA* SEED

Nguyen Thi Dao[1], Ngo Thi Ngoc Yen[2], Nguyen Quang Vinh[3], Hoang Van Chuyen[1]

Faculty of Agriculture and Forestry, Tay Nguyen University, Vietnam

Faculty of Medicine and Pharmacy, Tay Nguyen University, Vietnam

Institute of Biotechnology and Environment, Tay Nguyen University, Vietnam

ABSTRACT

Cochinchina momordica seed is the dried ripe seed of *Momordica cochinchinensis* (Lour.) Spreng, which is a kind of fruit and consumed for dietary as well as medicinal uses. In this study, using the human D24 and MM418-C1 melanoma cancer cell lines, we explored the anticancer activity of water and ethanol seed extracts. Treatment with the *Momordica cochinchinensis* seed extracts at a dose of 2 mg/mL significantly reduced the cell viability of melanoma cells. The extracts caused up to 95% and 82% of cell lose for D24 and MM418-C1 melanoma cell lines, respectively. The melanoma cells treated with the extracts had distinct macroscopic and microscopic changes in cell's morphology. The plasma and nuclear membranes of the treated cells were fragmented caused a release all of cell's contents, while untreated cells had intact membranes. These results indicated that the seed extracts posse anticancer activity on the melanoma cells. The water seed extract was more effective against melanoma MM418-C1 cells than the ethanolic extracts did. Protein assay using SDS-PAGE revealed predominant proteins in the seed extracts include 3 to 37 kDa. This study suggested that *M. cochinchinensis* seeds possess anticancer activity on melanoma MM418C-1 and D24 cells. The benefits of this product were discussed for further applications of the discarded seeds and reduce waste footprint of *M. cochinchinensis* aril production.

Keywords: *Momordica cochinchinensis* (Lour.), human D24 and MM418-C1 melanoma cancer,

4-Acetylantroquinonol B suppresses tumor growth and angiogenesis via PI3K/ERK dependent signaling pathway

張倩馨 [1] Chien-Hsin Chang, 王士維 [2] Shih-Wei Wang, 鍾鏡湖 [2] Ching-Hu Chung*，

1.台灣大學醫學院 藥理學研究所 Institute of Pharmacology, College of Medicine, National Taiwan University, Taipei, Taiwan
2.馬偕醫學院 醫學系 Department of Medicine, Mackay Medical College, New Taipei City, Taiwan

Background: Prostate cancer is one of the major cause of cancer death for men in developed countries. A compound isolated from *Antrodia cinnamomea* (commonly known as Niu-chang-chih,) 4-acetylantroquinonol B (4AAQB), was shown to inhibit tumor growth. However, the prostate cancer inhibition and anti-angiogenic activity of 4AAQB has not been analyzed previously. This study aimed to investigate the anti-cancer and anti-angiogenic effect of 4AAQB and explored its mechanism of action.
Methods: Human prostate cancer cell (PC3) viability/migration/cell cycle and human umbilical vein endothelial cell (HUVEC) viability/migration/tube formation assays were used to evaluate the *in vitro* anti-tumor and anti-angiogenic efficacy of 4AAQB. The 4AAQB signaling transduction, xenograft model and vascular endothelial growth factor (VEGF)-induced angiogenesis were examined as well.
Results: We demonstrated that 4AAQB inhibits PC3 cell growth, migration and reduced *in vivo* tumor growth, as shown using the subcutaneous xenograft model. Furthermore, 4AAQB inhibits HUVEC migration, tube formation and aortic ring sprouting, and reduced neovascularization, as shown using the Matrigel implant angiogenesis assays *in vivo*. 4AAQB was also shown to decrease metastasis in the PC3 prostate cancer model *in vivo*. VEGF-induced phosphoinositide 3-kinase (PI3K) and extracellular signal-regulated kinase 1/2 (ERK 1/2) phosphorylation were attenuated by 4AAQB as well.
Conclusion: We demonstrated that 4AAQB may represent, due to its anti-angiogenic effects, a potential candidate for prostate cancer treatment.

Keyword: Prostate cancer, *Antrodia cinnamomea*, 4AAQB, metastasis, VEGF, angiogenesis

4β-hydroxywithanolide E inhibits tumor-associated procoagulant activity and promotes cell death in tumor necrosis factor α-treated human non-small cell lung cancers

Kan-Yen Hsieh 謝侃言#, Ya-Han Lin 林雅函, Fang-Rong Chang 張芳榮, Chin-Chung Wu 吳志中*

Graduate Institute of Natural Products, College of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan

The relation between cancer and inflammation has been widely discussed, and the onset of inflammation in tumor microenvironment promotes the progression of cancer is generally recognized. Tumor necrosis factor (TNF) α, a major inflammatory cytokine, which exists in tumor microenvironment and is constitutively produced by both stromal cells and malignant cells. TNFα causes tissue factor (TF) upregulation in several cell types, including monocyte, endothelial cells, and cancer cells that may contribute to tumor-associated coagulopathy and cancer metastasis. 4β-hydroxywithanolide E (4HW) is a natural compound isolated from an edible plant, *Physalis peruviana*. 4HW has been reported to exhibit promising anti-cancer and anti-inflammatory activities. In the present study, we examined the effect of 4HW on TNFα-induced TF expression and procoagulant activity in two non-small cell lung cancer (NSCLC) cell lines, A549 and H1299. 4HW potently prevented TNFα-induced TF expression at non-cytotoxic concentrations in both cell lines. In addition, the procoagulant activity of TNFα-induced TF was further studied by using plasma clotting assay and amidolytic assay. The plasma clotting time in the presence of TNFα-treated cancer cells was obviously shorter than that in the control group and was prevented by either 4HW or anti-TF antibody. Consistent with plasma clotting time assay, 4HW also inhibited cancer-associated TF activity in amidolytic assay. Interestingly, the combination of 4HW with TNFα significantly enhanced the cytotoxicity against NSCLC cells. Our results suggest that 4HW may be potential for treating NSCLC and tumor-associated thrombosis in tumor inflammatory microenvironment.

Key words：TNFα, inflammation, tissue factor, tumor-associated coagulation

Preventive Effects of *Dendrobium Officinale* Extracts on High Glucose-Induced Damage of Retinal Pigment Epithelial Cells

林鈺憲(Yu-Sian Lin) #，劉崇喜(Shorong-Shii Liou)，劉怡旻 (I-Min Liu)*

Tajen University

Diabetic retinopathy (DR) is a common and severe complication of diabetes mellitus (DM). High glucose is the important reason which causes retinal pigment epithelial (RPE) cells impairments. Emerging evidence suggests the potential of *Dendrobium officinale* (DO) in treating the complications of diabetes mellitus (DM). Therefore, we used extracts of DO to evaluate the effect against high glucose in cultured human RPE cells (ARPE-19). We separated stems and leaves of DO and extracted them with 95% alcohol and water. ARPE-19 cells were cultured in high glucose with and without DO extraction environment. The survival rates of the cells were measured using a 3-(4,5-dimethyl thiazol-2-yl)-2,5-diphenyl tetrazolium bromide reduction assay. The intracellular production of reactive oxygen species (ROS) was evaluated by fluorescent probe. The antioxidant capacity was analyzed by 1,1-diphenyl-2-picrylhydrazyl clearance and total flavonoids content. The present study showed the stems of DO extracted with alcohol improved ARPE-19 cells survival rate and reduced generation of ROS in high glucose environment. These results indicate that the stems of DO alcohol extracts protect ARPE-19 cells in high glucose environment. It is maybe a potential therapeutic alternative to treat DR.

Key words: High glucose, ARPE-19 cells, *Dendrobium officinale*

Discussion on quality management of Chinese medicine preparation in Taiwan - taking prepared slices of Chinese crude drug (PSCCD) as an example

翁順吉(Sun-Chi Weng)[1#], 江瑩真(Ying-Chen Chiang)[1], 謝伯舟(Po-Chow Hsieh)[1], 劉怡旻(Liu I-Min)[1*]

Department of Pharmacy and Master Program, College of Pharmacy and Health Care Tajen University, Pingtung 90741, Taiwan.[1]

Taiwan has started to implement the Good Manufacturing Practice (GMP) for Chinese Medicine manufacturers since September 30, 2005. In order to strengthen the quality management of prepared slices of Chinese crude drug (PSCCD), the former Department of Health, Executive Yuan announced on May 3, 2013. Accepting Chinese medicine manufacturers apply for the PSCCD GMP Voluntary certification. Encourage manufacturers to manage themselves. But no manufacturer has applied yet. On the contrary, Mainland China formally regulated the PSCCD GMP and conduct strict management. Ministry of Health and Welfare has announced cGMP for Chinese medicine drugs drafts on May 21, 2018. Hope the Chinese medicines will undergo a rigorous and effective operation evaluation from raw materials and processes to final products. Provide better Chinese medicine to safeguard public health.

For strengthening quality management, China National Market Supervision Administration Drafted a revised version of the "good processing practice for per-manufacturing traditional Chinese medicines" in 2018 and public consultation. Some Chinese medicinal herbs have been processed before imported to Taiwan. The source of Chinese herbal medicines is not mandatory to standardize. It increase the safety risk of Chinese medicine products.

Therefore, this study explores the regulations governing the consumption of Chinese herbal medicines in the mainland China, discussing the difference between the “good processing practice for per-manufacturing traditional Chinese medicines” and the regulations on PSCCD in Taiwan, drafting a GMP specification for PSCCD. According to the management of raw materials for western medicine, providing relevant advice on the management of PSCCD to ensure drug quality stability, safety and effectiveness. Strengthen the source management of Chinese herbal medicines to ensure the safety of the people.

Key words： prepared slices of Chinese crude drug(PSCCD), Processing, PSCCD GMP

Effects of processing on the free radical scavenging activity and total phenolic content in *Salvia miltiorrhiza*

劉怡旻(I-Min Liu), 陳雅莛 (Ya-Ting Chen), 洪毓岑 (Yu-Tsen Hung), 楊涴婷 (Wo-Ting Yang) , 劉崇喜(Shorong-Chii Liou)*

Department of Pharmacy & Graduate Institute of Pharmaceutical Technology, Tajen University

Salvia miltiorrhiza is the dry root and rhizome of Labiatae plant *Salvia miltiorrhizae* Bge.Its active ingredients are based on tanshinone which are lipophilic diterpenoids and hydrophilic depsides derivatives.Many scientific studies have proven that *Salvia miltiorrhiza* has pharmacological effects which are anti-inflammatory, anti-cancer, anti-thrombotic, organ protection and neuroprotection, etc. We used raw materials, vinegar steaming and ethanol steaming that three kinds of processing methods, then we extract them by RO water and 95% alcohol. After that, we can investigate the antioxidant capacity of *Salvia miltiorrhiza* by using the product extracted and processed from different ways.

Key words: *Salvia miltiorrhiza*, free radical scavenging activity, total phenolic content

The ethanol crude extraction of *Cyperus rotundus* regulates apoptosis-associated gene expression in HeLa human cervical carcinoma cells *in vitro*

林佳欣(CHIA-HSIN LIN)[1#]，彭淑芬(SHU-FEN PENG)[2]，劉育瑄(YU-HSUAN LIU)[1]，郭昭麟(CHAO-LIN KUO)[1*]，鍾景光(JING-GUNG CHUNG)[3,4*]

[1]Department of Chinese Pharmaceutical Sciences and Chinese Medicine Resources, China Medical University, Taichung 404, Taiwan; [2]Department of Medical Research, China Medical University Hospital, China Medical University, Taichung 404, Taiwan. [3]Department of Biological Science and Technology, China Medical University, Taichung 404, Taiwan; [3]Department of Biotechnology, Asia University, Taichung 413, Taiwan.

Cervical cancer has long been considered a poorly chemo-sensitive tumor within the woman population. However, the treatment of cervical cancer remains unsatisfactory. *Cyperus rotundus* has cured this disease as Chinese medicine. However, the effects and genetic mechanism of the ethanol extraction of *Cyperus rotundus* (CRE) on cervical cancer remain unclear. CRE was treated to HeLa human cervical cancer cells for different time periods and cell morphological change and total viable cells were examined by using contrast phase microscopy and flow cytometer, respectively. Results indicated that CRE induced cell morphological changes and cytotoxic effect in HeLa cells in dose-dependent manners. Cells were stained with DAPI and were photographed by using fluorescence microscopy and results indicated that CRE induced chromatin condensation in a dose-dependent manner. Furthermore, a complementary DNA microarray analysis demonstrated that CRE treatment led to ` 449 genes upregulation and 484 genes downregulation. For example, the DDIT 3 and GADD45A, DNA damage-associated gene, had a 17.22- and 7.15-fold upregulation, respectively and the CPA4, carboxypeptidase A4, had a 7.61-fold downregulation. The differential genes were classified according to the Gene Ontology and the key genes involved in the possible interaction pathways were analyzed. Those genes were affected by *Cyperus rotundus* will provided information for the understanding of the anti-cancer mechanism at the genetic level and provide additional targets for the treatments of human cervical cancer.

Keywords: *Cyperus rotundus*, cervical cancer, HeLa cell, apoptosis, gene expression.

The methanolic extract of *Indigofera suffruticosa* Mill. induces G2/M arrest by activation of ATR/CHK1 signaling pathway in Jurkat cell

Tran Thi Hong Loan[1,2#], Hsun-Shuo Chang[3], Ho-Cheng Wu[3], Hui-Hua Hsiao4, Chia-Hung Yen[1,2]*

[1]Graduate Institute of Natural Products, College of Pharmacy, Kaohsiung Medical University, Kaohsiung 80708, Taiwan;
[2]Center for Infectious Disease and Cancer Research, Kaohsiung Medical University, Kaohsiung 80708, Taiwan;
[3]School of Pharmacy, Kaohsiung Medical University, Kaohsiung 80708, Taiwan;
[4]Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung 80708, Taiwan.

Abstract
Indigofera suffruticosa Mill. is an herbaceous plant that has been used as a natural indigo dye in the textile industry. It belongs to the Fabaceae family. *I. suffruticosa* is a well-known folk medicine that has been used for treating adult leukemia patients in Tainan, Taiwan. However, no report regarding anti-leukemic effect of *I. suffruticosa* extract have been published. This study was aimed to evaluate bioactivities and its molecular mechanism of *I. suffruticosa* on leukemia cells. Cytotoxicity of *I. suffruticosa* extract (IS extract) in Jurkat cells were measured by Alarma blue staining assay and MultiTox-Glo multiplex cytotoxicity assay. Cell cycle distribution were determined by flow cytometry assay. The expression level of cell cycle regulator proteins was determined by West blot assay. The results indicated IS extract inhibited cell viability and promoted cell death in dose-dependent manners in Jurkat cells (T-cells acute lymphoblastic leukemia). IS extract inhibits cell growth through G2/M cell cycle arrest via activation of CHK1/ATR pathway in Jurkat cells. Accordingly, these data suggested that IS extract exerts anti-leukemic activity against T-cells acute lymphoblastic leukemia.

Key words: Leukemia, G2/M arrest, ATR/CHK1 signaling, *Indigofera suffruticosa*.

The active Compound Content Comparison from Different Sources of Chinese Herbs and Anti-osteoclastogenesis Research

Yu-Ting Wang, Chao-Tsen Lu, You-Shan Lin, Shou-Fang Wu

Natural Resource Development, Institute of Pharmaceutics, Development Center for Biotechnology, New Taipei City, 22180, Taiwan.

Magnolia bark is an important Traditional Chinese Medicine which has various pharmacological activities as anti-tumor, anti-bacterial, anti-ulcer and inhibition of autonomic nervous activity. However, the chemical constituents in herbs differ with seasons and cultivar environment. In this research, the active compound among of *Magnolia* bark from different sources was compared by HPLC analysis and to provide a reference for botanical new drug industry in the future. The result showed the different batch of MO-RM-Z which contained the active compound content more than others sources.

The Hot water extract of *Magnolia* sp. was separated by column chromatography to obtain the active compound. The anti-osteoclastogenesis of the separation fractions and pure compound were screened by Tartrate-resistant acid phosphatase (TRAP) activity exam in the RAW 264.7 macrophages model.

Key words: *Magnolia* sp., Tartrate-resistant acid phosphatase (TRAP) activity

Processing with vinegar steaming improves the cytotoxicity of *Rhinacanthus nasutus* against human hepatoma cells

劉崇喜 (Shorong-Chii Liou)[†], 李曄青 (Yeh-Ching Li)[†], 林靜嬋 (Jing-Chan Lin)[‡], 邱厚儒 (Hou-Ru Ciou)[†], 周偉凡 (Wei-Fan Chou)[†], 劉怡旻 (I-Min Liu)*[,†]

[†]*Department of Pharmacy and Master Program, College of Pharmacy and Health Care, Tajen University, Pingtung County 90741, Taiwan*

[‡]*Department of Food Science and Technology, College of Pharmacy and Health Care, Tajen University, Pingtung County 90741, Taiwan*

Rhinacanthus nasutus (Rhinacanthus nasutus L. Kurtz), the best known member of the family Acanthaceae, is tranditionally use to suppress hyperactive liver for calming endogenous wind. The plant is also the one of the traditional treatment used against cancer inThailand. The aim of the study was going to exploe whether process could elevate the benefit effect of *R. nasutus* on liver. In this experiment, whole plant of *R. nasutus* was used for wine extraction and water extraction, and human hepatoma cells (HepG2) was selected as the basis for cancer cells. According to Chinese Pharmacopoeia, the method uses white vinegar and yellow wine to cook and then extract with water and ethanol solvent to make uncooked raw water extract, raw wine extract, vinegar steamed water extract, vinegar steamed wine extract, wine steamed water extract and wine steamed wine. Then, the addition and multiplication effect of the extract on the cancer cell apoptosis were explored. The best extracts were screened by human hepatoma HepG2 cells. In addition, HepG2 cells were injected subcutaneously in nude mice to to establish the hepatocellular carcinoma model. The contents of β-sitosterol and stigmasterol were quantitatively by HPLC. From the results of the cell viability assay, it was found that the ethanol extracts of vinegar steamed *R. nasutus* significantly inhibited the growth of HepG2 cells compared to the unprocessed samples. From the tumor inhibition on tumor mice, it was found that when the ethanol extract of vinegar steamed *R. nasutus* was administered into tumor mice twice a day at a single oral dose of 500 mg/kg for 18 days, the inhibition rate on tumor growth is 73.5%. According to the quantitative analysis by HPLC, it was found that the contents of β-sitosterol and soybean sterol in the ethanol extract of vinegar steamed *R. nasutus* were the highest, 6.31 mg/g and 3.72 mg/g each. Through the above experimental results, it could be conclude that vinegar steaming could improve the inhibitory effect of *R. nasutus* on the growth of liver cancer cells.

Keywords: processing, vinegar steaming, *Rhinacanthus nasutus*, hepatoma

Hypoglycemic effect of fermented *Arctium lappa* extract on nicotinamide-streptozotocin induced type 2 model of diabetes in mice

蒙美津(Mei-Chin Mong)[1,2#], 喬長誠(Charng-Cherng Chyau)[3,4,5], 林怡君(Yi-Jun Lin)[3], 邱駿紘(Chun-Hung Chiu)[3,4,5*]

[1]Department of Food Nutrition and Health Biotechnology, Asia University, Taichung, Taiwan
[2]Department of Medical Research, China Medical University Hospital, China Medical University, Taichung, Taiwan
[3]Graduate Institute of Biotechnology, Hungkuang University, Taichung, Taiwan
[4]Department of Biotechnology, Hungkuang University, Taichung, Taiwan
[5]Bachelor Degree Program in Animal Healthcare, Hungkuang University, Taichung, Taiwan

Arctium lappa L. (Burdock) is commonly used in many foods as well as in traditional medicine. It is known to exert beneficial effects, such as antioxidant, anti-inflammatory and anticancer effects. The fermentation process for medicinal herbs is recognized to yield metabolites and has been used for improving the biological effects of the extracts. This study was conducted to evaluate the hypoglycemic properties of fermented burdock extract (FBE) on nicotinamide-streptozotocin (NA-STZ)-induced type2 diabetes in mice. In this investigation, 40 adult male ICR mice (25-30g) randomly divided into 4 groups (n=10) as follow: 1-control, 2-type 2 diabetic mice, 3 and 4-diabetic mice that received 3 and 6 ml/kg FALE, respectively, for 28 days. Diabetes has been induced by intraperitoneal injection of NA and STZ. Finally, the blood sample was taken and insulin, glucose, SGOT, SGPT, and leptin were evaluated.Induction of diabetes decreased the level of insulin, leptin and increased the level of glucose, and hepatic enzymes significantly ($p<0.05$). Administration of both doses of the extract significantly improved hyperglycemia. In addition, four weeks of FBE administration suppressed the mRNA expression of glucose-6-phosphatase (*G6Pase*), a key enzyme of gluconeogenesis, in the liver. Simultaneously, FBE administration induced adiponectin receptor-1 (*AdipoR1*) expression in the liver and phosphorylated AMP-activated protein kinase (pAMPK) expression, which suppressed G6Pase levels in the livers of diabetic mice. The improvement in hyperglycemia due to FBE administration may be associated with the suppression of G6Pase expression through the upregulation of *AdipoR1* mRNA and pAMPK protein expressions.

Key words：*Arctium lappa* L.; Burdock; Hypoglycemic

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