



R&D Laboratory for Testing of Chinese Medicines 中藥研發實驗室

Prof. Chi-Ming Che 支志明教授 Department of Chemistry, HKU 香港大學化學系



香港賽馬會慈善信託基金 The Hong Kong Jockey Club Charities Trust

Objectives 目標

Modernization of Chinese medicines via evidence-based research 通過循証 研究中藥之現代化

To improve the efficacy of current drug leads such as timosaponins, berberine and artemisinin 提高現有中藥的藥效, 如知母皂苷、黃連素以及青蒿素

To strengthen the public confidence in using Chinese medicines 加強公眾對使用中藥的信心



To explore the potential medicinal uses of Chinese medicines such as Anemarrhena asphodeloides 發掘中藥的潛在功用如知母

To act as a bridge linking both academia and industry and leverage the intellectual and financial resources 作為連接學術界和產業的橋樑、撬動高學歷人才和財富的杠杆

To explore new analytical methods for testing Chinese medicines in particular precious herbs such as Cordyceps (冬蟲夏草) and Cervi Cornu Pantotrichum (鹿茸) and solve problems of adulteration, counterfeits and etc. 開發新的分析方法以檢測中藥,特別是珍貴藥物如冬蟲夏草、鹿茸,以解決摻假、仿品等問題

Core members 重要研究人員

Dr. Kwan-Ming Ng (Analytical chemistry)

Prof. Chi-Ming Che (Chemistry)



Dr. Yibin Feng (Chinese medicine)

Prof. Alice Wong (Anticancer)

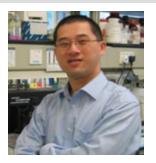
中藥研發

Prof. Mingfu Wang (Function of food)



Dr. Yungen Liu
Organic synthesis)

Dr. Raymond Chang (Alzheimer's disease)





Dr. Ning Wang (Chinese medicine)

Dr. Chun-Nam Lok (Chemical biology)

Dr. Chang Xiaoyong (X-ray diffractometry)

Dr. Eva Fung (Mass spectrometry)



Other research personnel

其他參與中藥之研究人員



Established Collaborations 合作伙伴



FACULTY OF SCIENCE
THE UNIVERSITY OF HONG KONG
香港大學 理學院

- ◆ Department of Chemistry 香港大學化學系
- ◆ School of Biological Science 香港大學生物科學學院

Li Ka Shing Faculty of Medicine HKU



香港大學醫學院

- ◆ School of Chinese Medicine 香港大學中醫藥學院
- ◆ Department of Anatomy 香港大學解剖學系

National Research

Institutes/Centers: 國際科研機構

- Professor John R. Yates III, Scripps Research Institute, California
- ◆ Prof Tommy Cheng, Department of Pharmacology, Yale. School of Medicine
- ◆ Centre for Drug Safety Evaluation and Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences 中國科學學院上海藥物研究所
- ◆ Prof. G.-Q Lin, Shanghai Institute of Organic Chemistry上海有機所
- Dr. Z.-J. Xu, Shanghai-HK Joint Laboratory in Chemical synthesis and State key Laboratory of Synthetic Chemistry

中藥研發



Local stakeholders: 本地合作機構

 Chinese medicines information and research section of Department of Health, HKSAR

衞生署中藥信息及研究組衞生署

- ◆ SGS Hong Kong Ltd. 香港通用公證行有限公司
- ◆ Healthy Pharmaceutical Ltd. 康怡藥業



SERVIER (France)

Research Infrastructures and Facilities at HKU for R&D of Chinese Medicines 香港大學中藥研究基礎設施與設備

R&D Laboratory for Testing of Chinese Medicines 中藥研發實驗室

Chemical Biology Centre at The HKJC Building for Interdisciplinary Research 化學生物中心

Open Laboratory of Chemical Biology of the Institute of Molecular Technology for Drug Discovery and Synthesis 分子科技研究院及化學生物學開放實驗室

State Key Laboratory of Synthetic Chemistry 合成化學國家重點實驗室









Chinese medicines and targeting disease investigated at HKU

香港大學研究的中藥及其針對疾病

Targeted diseases	Chinese medicines compounds	Experimental model	HKU team members
Anti-cancer 抗癌症 Anti-Alzheimer's disease 阿茲海默 氏症	Steroidal saponins 甾體皂苷	Different cancer nude mice xenograft Transgenic mice	Prof. Chi-Ming Che Chemistry (化學系 支志明)
Neuroprotection against Parkinson's disease 抗柏金遜症	Chrysin and derivatives 白楊素及其衍生物	Dopaminergic neurons in mice receiving MPTP	Dr. Raymond Chang, Anatomy (解剖學 鄭傳忠)
Anti-metastasis 抗癌症轉移	Ginsenosides 人参皂苷	Ovarian cancer model with metastatic phenotypes	Dr. Alice Wong, Biological Sciences (生命科學 黃思齊)
Anti- hepatocarcinoma 抗肝癌	Coptis rhizoma 黃連 Berberine 黃連素	Hepatoma cell lines and nude mice xenograft	Dr. Yibin Feng, Chinese Medicine (中醫藥 馮奕斌)
Anti-obesity 抗痴肥	Saponins, phenolics 皂苷, 酚	3T3-L1 adipocyte and Sprague-Dawley rat models	Dr. Mingfu Wang, Biological Scienses (生命科學 王明福)

Multidisciplinary projects - industrial

跨學科研究 - 產業







RESEARCH COLLABORATION AND LICT AGREEMENT IN OSTEOGENESI:

Made this June 7th, 2010 (hereinafter the "Effective Date")

BY AND BETWEEN:

THE UNIVERSITY OF HONG-KONG

A Hong Kong Special Administration Region entity duly establishe The laws of Hong Kong Special Administrative Region, China, hav Pokfulam Road Hong Kong

VERSITECH LIMITED

A wholly owned subsidiary and the technology transfer compan Kong incorporated in Hong Kong, having its business address at: RM 405A, Cyberport 4, 100 Cyberport Road, Hong Kong

(The UNIVERSITY OF HONG KONG and VERSITECH LIMIT referred to as "HKU")

AND

LES LABORATOIRES SERVIER

A corporation duly organized and existing under the laws of France Having its registered office at 22 Rue Garnier 92200 Neuilly Sur Seine

France

ORIGINAL MEMORANDUM OF UNDERSTANDING

THIS MEMORANDUM OF UNDERSTANDING is made this 12th of March, ("Effective Date ").

BY AND BETWEEN:

LES LABORATOIRES SERVIER

A corporation duly organized and existing under the laws of France Having its registered office at: 22 Rue Garnier

92200 Neuilly Sur Seine

INSTITUT de RECHERCHES SERVIER (IdRS)

A corporation duly organized and existing under the laws of France Having its registered office at: 3 Rue de la République

92150 Suresnes

ON THE France

(LES LABORATOIRES SERVIER and INSTITUT de RECHERCHES SERVIER hereinafter referred to as "SERVIER")

on the first part

AND

THE UNIVERSITY OF HONG-KONG

A Hong Kong Special Administration Region entity duly established and validly ex under the laws of Hong Kong Special Administrative Region, China Having its registered address at :

Pokfulam Road Hong Kong

台灣葛迪夫生物科技股份有限公司台北市中山區敬業一路 162 號 6 櫻 6F, No 162, Jing-Yeh 1st Road

06 May, 2010

Prof Chi-Ming Che.

Department of Chemistry, The University of Hong Kong

Dear Prof Che.

It is with delight that we, the Goldeby Biotech Ltd, Taiwan, are able to offer sponsorship for your ITF project entitled "Discovery and Pre-Clinical Evaluation of Promising Metal-Based Anti-Cancer Drug Leads". We envision that this project would make great impact in the medical field including the discovery of new metal-based anti-cancer agents. We are willing to provide cash sponsorship amounting SHKD 200,000 to support this project.

We are looking forward for the success of your project.

Yours sincerely





于"通往临床应用之路:对金属类抗癌先导药物的开发与 预临床评估"项目研究经费赞助

本公司愿意为香港大学的创新科技基金研究项目 "通往临床应 之路:对金属类抗癌先导药物的开发与预临床评估"提供现金赞 本次支持经费共港币二十万五千元,给与香港大学支志明教授领 的研究小组, 祈望这项目能得到丰盛的成果。

司名称: 北京阿格蕾雅科技发展有限公司



期: 2010年1月21日

R&D of Chinese medicines 中藥研發





New analytical testing methods 新分析測試方法



Synthesis and chemical modification of Chinese medicines drug leads 藥物合成與修飾



中藥研發 之 五大元素

Phytochemical analysis of Chinese medicines 中藥的植物化學分析



Bioinformatics of Chinese medicines 中藥的生物信息學 (collaborating with HKUST) Chemical biology and product development 化學生物學與產品研發

QSTAR XL ™ LC/MALDI/MS/MS

Highlighted and Significant Projects 重要科研項目

I. Imaging mass spectrometry (IMS) for authentication of precious Chinese medicines 成像質譜於鑒定珍貴中藥的使用

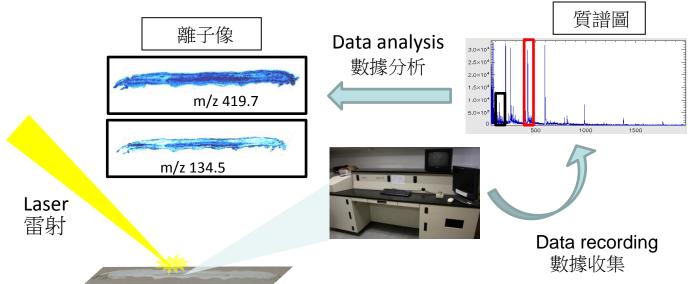
To visualize the special distribution of chemical compositions

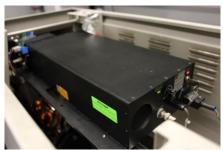
原理

- ◆利用 MALDI-TOF MS 質譜儀於樣本 一些特定的點上施加 激光直至完全掃描整個樣本表面並於個定點收集質譜
- ◆在這些收集得來的質譜中提取離子信號,根據其信號強度及 空間分佈用顏色通過軟件建立離子圖像
- ◆在離子圖像中,離子於樣本某個位置的信號越強,會用越深 的顏色顯示



Voyager-DE STR MALDI Time-of-Flight Mass Spectrometer

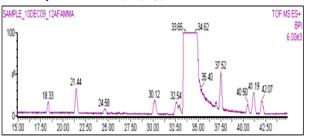




Nitrogen laser system

我們對IMS的新應用

MS spectrum 質譜



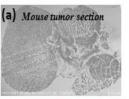
掺假 仿品 偽品 不確定性 安全性

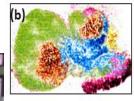


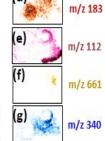
ABI 4000QTRAP LC/MS/MS System



LTQ Orbitrap Velos LC/MS/MS system







m/z 357

成像質譜



品質管制



現時質量控制的方法 — 形態學研究 限制:

無化學信息可得到 難以分辨類似形態的中草藥 需要相關專業知識



IMS 的質量控制 好處:

可提供形態及化學信息提供可靠和可重複的結果



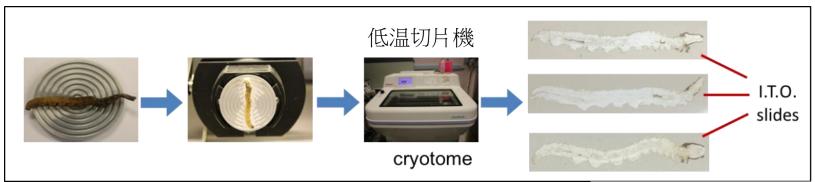
發展成像質譜 (IMS) 作珍貴的中國藥品認證

IMS的應用 1 - 冬蟲夏草



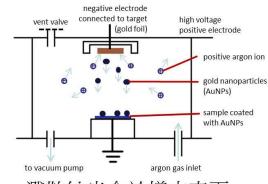
步驟:

- ◆ 利用低温切片機縱切冬蟲夏草(12 µm 厚)
- ◆ 把冬蟲夏草片附在膠片上 (on the conductive side of a indium-tin-oxide slide)



塗加基質

- ◆ 利用濺散機把納米金散於樣本表面
- ◆ 利用導電膠紙把塗了納米金的樣本貼於質譜儀的目標上

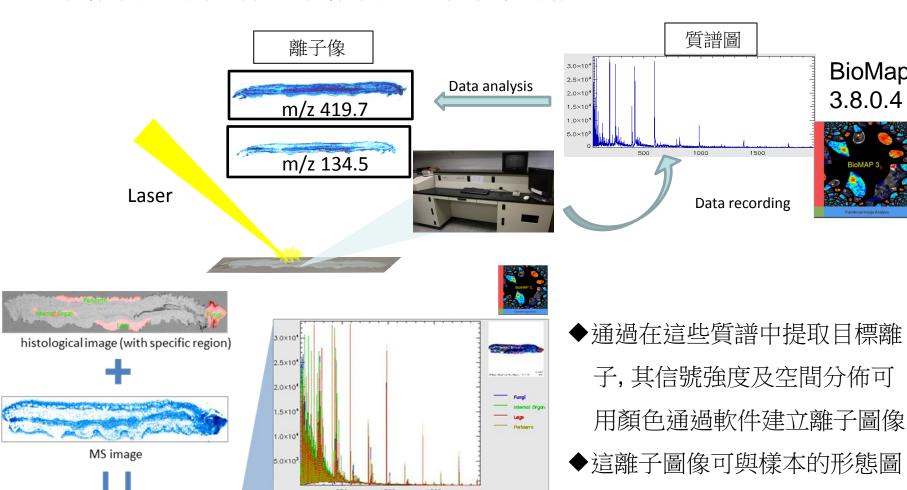


濺散納米金於樣本表面

建立成像質譜

MS image (with specific region)

◆在樣本表面施加激光及在樣本表面各處收集質譜



mass range = 50 - 2000 Da

◆幫助尋找生物標記

像對應

14

BioMap

3.8.0.4

質量控制結果

◆通過比對真及假的冬蟲夏草的生物標記,可識別標誌性的生物標記作真假冬蟲夏草的區分

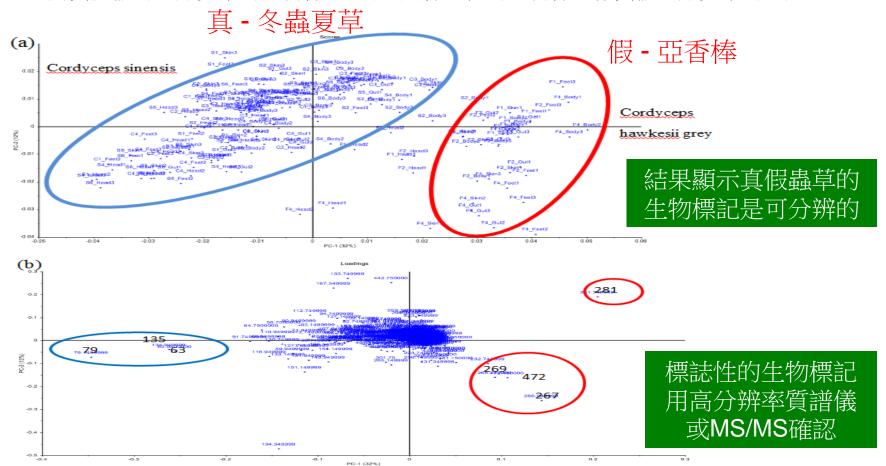


Figure 1. PCA (主成分分析) of the mass spectrometric data sets of Cordyceps sinensis and Cordyceps hawkesii grey obtained using IMS analysis. (a) Score plot result of the analysis revealed that the ion intensities of characteristic ions of the two herbs were distinguishable along the PC1. (b) Loading plot results of the analysis revealed that the characteristic ions being responsible for the differentiation were the ions at m/z 63, 79, 135, 267, 269, 281 and 472. Ions at m/z 135 was confirmed to be a deprotor hypoxanthine and with higher abundance in Cordyceps sinensis.

優勢

- 1. 省卻複雜及費時的樣本提取過程
- 2. 不需要標籤便可研究樣本中的生物分子
- 3. 可於同一時間內研究多個生物分子
- 4. 得到的生物分子離子圖像可以與樣品的形態學圖像重疊,從而提供 化學和形態學的資料
- 5. 尋找新的生物標記
- 6. 研究標記在樣本表面的空間分佈

參考:

Analytical Chem. **2010**, *8*2, 1589-1593 Rapid Commun. Mass Spectrom. **2011**, *25*, 3690-3696 Analytical Chem. **2011**, *8*3, 453-458

SALDI-TOF/MS



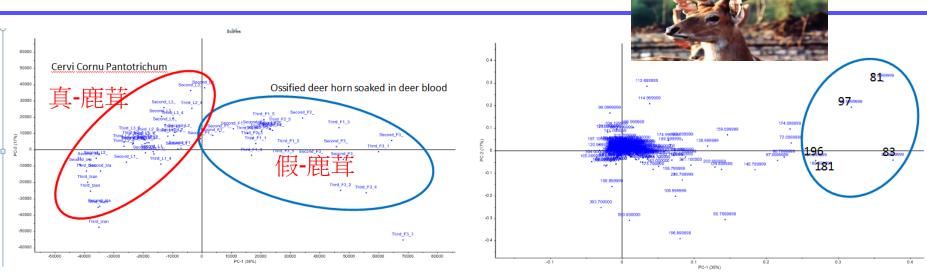
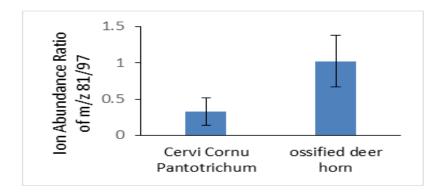


Figure 1: PCA (主成分分析) of the mass spectrometric data sets of Cervi Cornu Pantotrichum and Cervi Cornu soaked with deer blood obtained using MALDI-TOF mass spectrometric analysis. (a) Score plot results of the analysis revealed that the ion intensities of characteristic ions of the two herbs were distinguishable along the PC1. (b) Loading plot results of the analysis revealed that the characteristic ions being responsible for the differentiation were the ions of *m/z* at 81, 83, 97, 181 and 196.



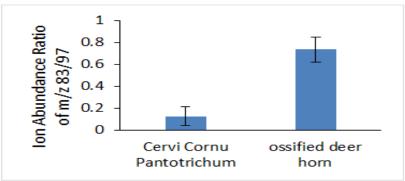


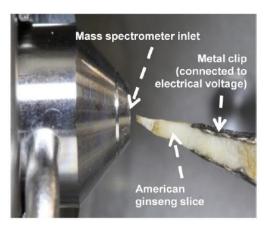
Figure 2. The differentiation of Cervi Cornu Pantotrichum and fake Cervi Cornu Pantotrichum on the ion abundance ratios of m/z 81/97 and m/z 83/97.

II. Tissue spray ionization mass spectrometric method for direct and rapid analysis of raw herbs

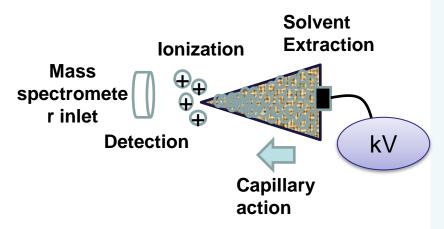
組織噴霧電離質譜法 -直接快速分析應用於未加工中藥材

-原理-

- ◆把固態狀的中藥材放近質譜儀的入口,加入少量 提取溶劑並進行通電
- ◆直接對樣本內的組織物進行化學分析

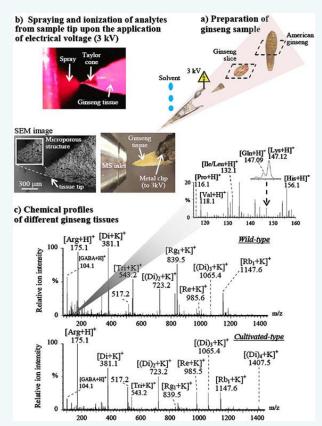


The herbal samples are placed in front of the ion inlet of a mass spectrometer, and analyte molecules can be directly sprayed and ionized from the solvent-wetted tissues upon the application of a high electrical voltage.



Tissue-spray ionization MS 的應用:

分辨真假美國蔘



參考:

Rapid Commun. Mass Spectrom. 18 **2011**, 25, 2837-2843.

組織噴霧電離質譜法的應用1-洋金花及鬧羊花





組織噴霧電離質譜法的應用2-威靈仙, 龍膽草及鬼臼



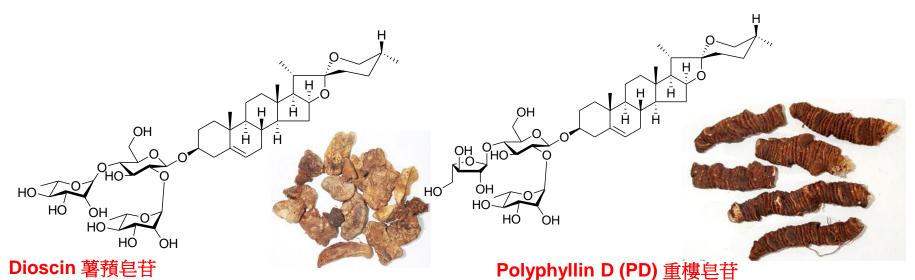




Advantages 優勢

- ◆ Rapid differentiation of morphologically similar herbs 快速區分形態相似之中藥材
- ◆ In situ analysis of sample, no sample treatment and separation 樣品原生態分析,不需進行處理與分離

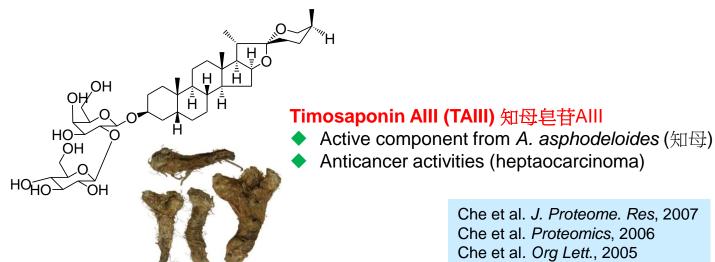
III. Discovery of steroidal saponins from Chinese medicines for treatment of cancer 中藥中甾體皂苷的發現及其對癌症治療



- Active component from Polygonatum zanlanscianense
- Anticancer activities

(湖北黃精)

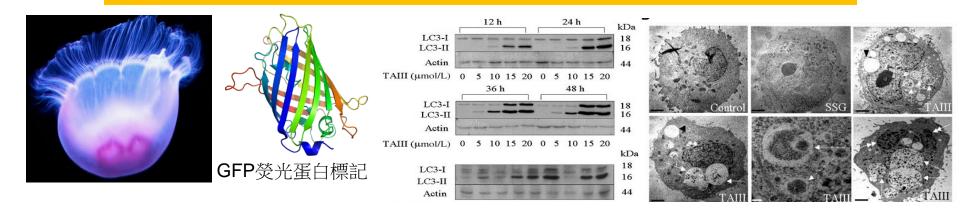
- ◆ Active component from Paris Polyphylla (重樓)
- Anticancer activities



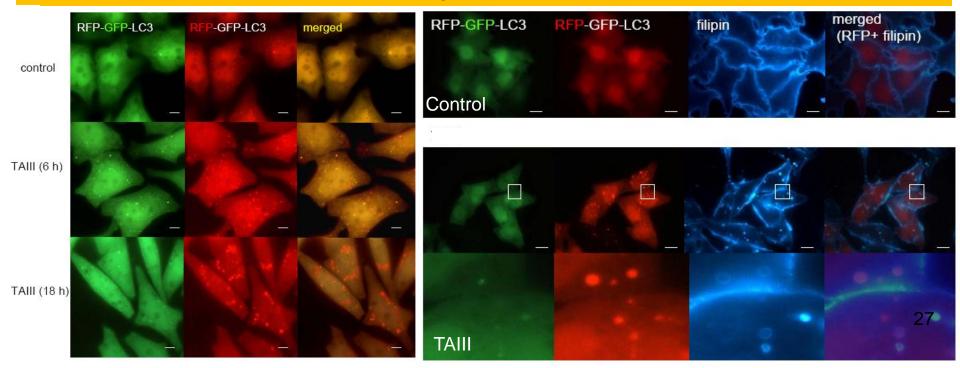


Saponin TAIII enhances autophagy 知母皂苷TAIII促進細胞自噬作用

TAIII引起的細胞自噬作用 (利用綠色熒光蛋白和活細胞染色技術研究)

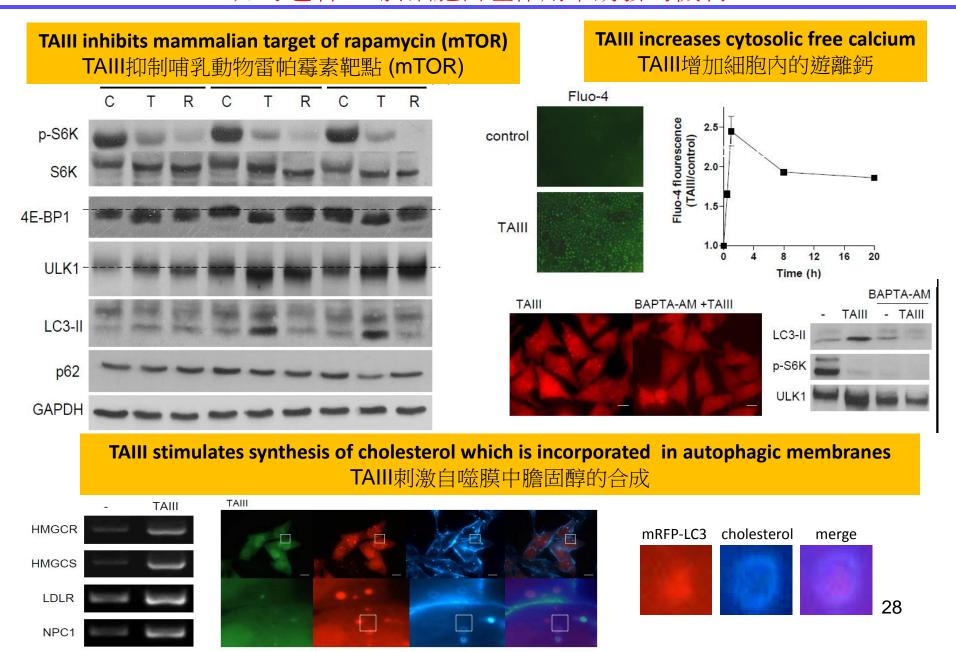


TAIII induces LC3-associated autophagic structures (TAIII誘導LC3關聯的自噬性結構)

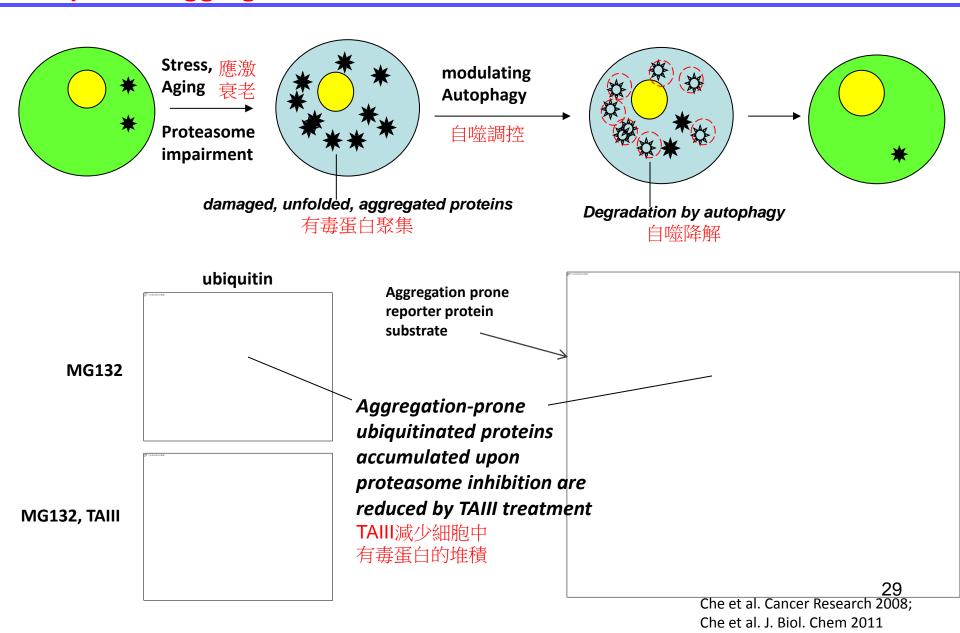


Mechanism of saponin TAIII-induced autophagy

知母皂苷AIII於細胞自噬作用下誘發的機制



Saponin TAIII activates autophagic clearance of disease-associated protein aggregates 知母皂苷AIII的細胞自噬作用有助於清除蛋白質的聚集



Saponin TAIII as an autophagy enhancers with potential for treatment of cancer 知母皂苷AIII之細胞自噬作具備抗癌性質

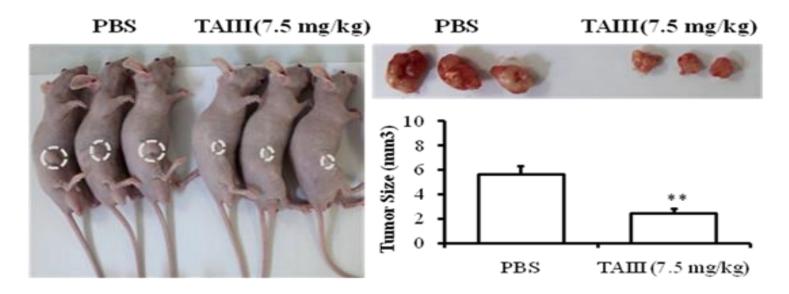
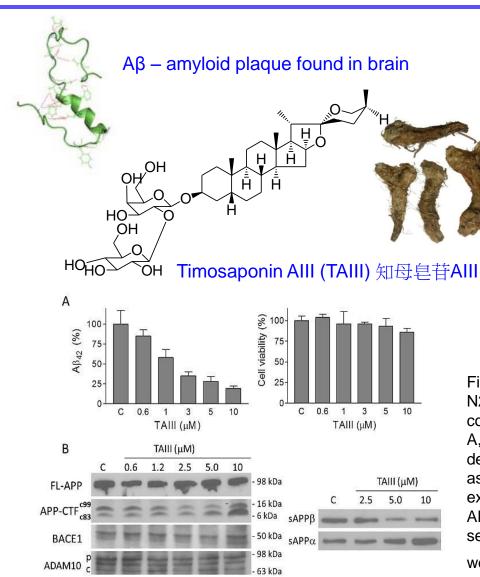


Figure 1: TAIII exhibit anti-tumor activities in nude mice xenograft model. The *in vivo* anti-tumor activity of TAIII was examined by xenograft model of HCC. In tumor bearing nude mice generated by subcutaneous injection of MHCC97L HCC cells, no remarkable body weight loss could be observed in mice treated with TAIII (7.5 mg/kg/2 days) while the tumor growth was significantly restricted. 知母皂苷TAIII有效抑制老鼠肝腫瘤

Project IV: Discovery of steroidal saponins from Chinese medicines for treatment of neurodegeneration diseases

中藥中甾體皂苷的發現及其對神經退行性變疾病的治療



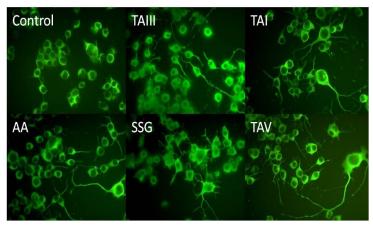


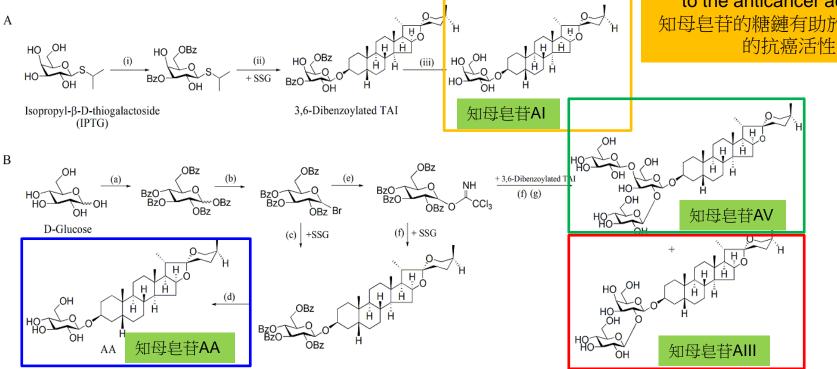
Fig. 1 Effects of timosaponins and SSG on neurite outgrowth of Neuro-2A cells. Cells were treated with DMSO (Control), TAIII (5 μ M), TAI (10 μ M), AA (10 μ M), SSG (25 μ M) and TAV (10 μ M) for 18 h, stained with a monoclonal antibody raised against type III β -tubulin and examined by fluorescence microscopy.

Fig. 2 Effects of TAIII on A β 42 production and APP processing in N2A-APPswe cells. Cells were treated with various concentrations of TAIII or DMSO vehicle as control (C) for 18 h. A, The A β 42 concentrations in the conditioned medium were determined by ELISA. The cell viability was determined by MTT assay. Data represents mean \pm standard deviation; n = 3. B, The expression of full length (FL), CTF (C99, C83), BACE1 and ADAM10 (p, precursor form; c, cleaved form) in cell lysates and secreted APP (sAPP α and sAPP β) in the conditioned medium

were examined by immunoblot.

Timosaponins derivatives are also effective

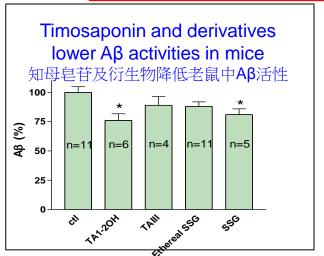
Synthesis of new timosaponin derivatives: confirmed that sugar chain is essential and beneficial to the anticancer activities 知母皂苷的糖鏈有助於提升細胞



The IC₅₀ of timosaponins and SSG in lowering Aβ₄₂ production in N2A-APPswe cells

知母皂苷及知母皂苷元降低N2A-APPswe細胞中Aβ42的生產

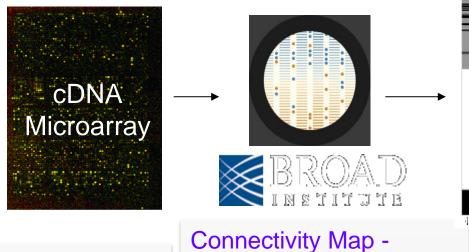
Compound	$IC_{50}(\mu M)$
SSG	50
TAIII	2
TAI	6
AA	6
TAV	4



V. Using chemo- and bio-informatics approach to study anticancer mechanism of steroidal saponins

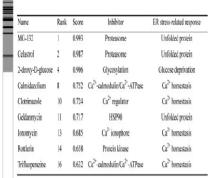
用化學、生物信息學方法研究甾體皂苷的抗癌機制

Identification of endoplasmic reticulum stress pathway as the anticancer mechanisms of polyphyllin D (PD) 重樓皂苷

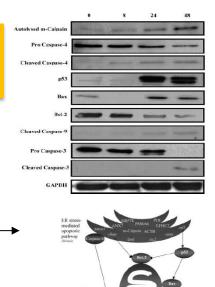


Genomic data obtained from PD treatment

Connectivity Map Computational pattern
mapping with existing
drug libraries
(Broad Institute, USA)



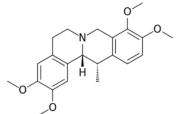
Identification of drugs with similar actions – prediction of the drug target



Experimental validation of hypothesis

VI. Potential Targets Mining of Active Component from Herbal Medicines using Quantitative Proteomics Pathway Analysis 量化蛋白組

By using proteomics expression data from lysate of drug-treated or untreated cells to deduce the potential drug targets with the help of bioinformatics databases.

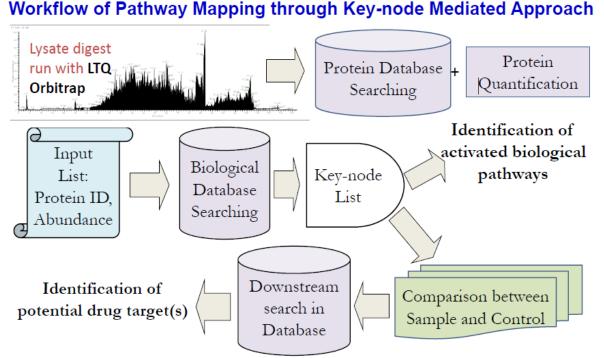


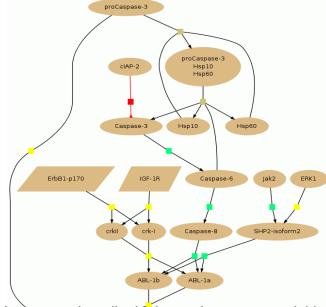
Corydaline 延胡索甲素

Camptothecin 喜樹鹼



Camptotheca喜樹





A network displaying the connectivities between the drug target and the top-scoring keynode molecules found in keynode analysis of proteomics data from camptothecine treated cell lysate

VII. Development of Coptidis Rhizoma for treatment of liver

cancer 黃連能有效抑制老鼠肝腫瘤

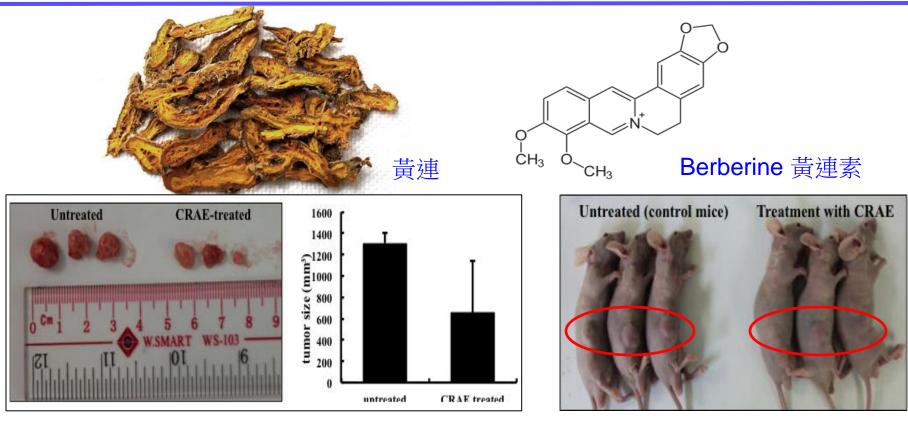


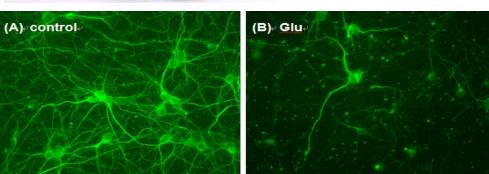
Fig. 2 The excised tumors were measured and established in average of mm³ ±SD. Significant reduction of tumor volume was observed in CRAE-treated mice

Fig.1 CRAE-treated mice have decreased tumor volume compared with the untreated mice. Two groups of mice were treated with or without CRAE for 3 weeks (n = 3).

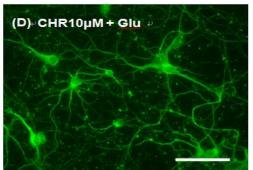
VIII. Neuroprotective effects of Chrysin against glutamate excitotoxicity by *in vitro* and in *vivo* models 白楊素的神經保護作用

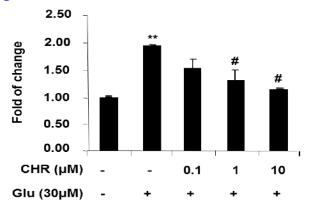
Excitotoxicity is the pathological process by which nerve cells are damaged or killed by excessive stimulation by neurotransmitters such as glutamate and similar substances.











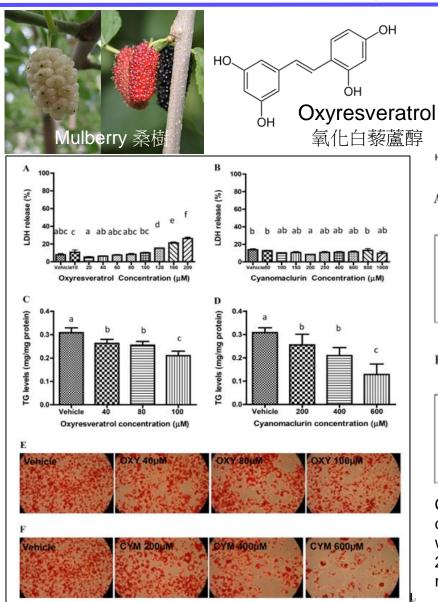
Chrysin attenuated the generation of intracellular ROS 活性氧類 induced by glutamate.

Chrysin preserved the fasciculation of neurites in glutamate-treated cultured neurons.

Immunocytochemical analysis of α -tubulin in neurons treated with chrysin. Neurons were treated with chrysin for 1 h, followed by exposure to 30 μ M glutamate for 24 h. (A) control, (B) glutamate stimulation for 24 h alone, (C) neurons treated with chrysin 1 μ M, and (D) 10 μ M for 24 h and then together with glutamate 30 μ M for 24 h. Scale bar represents 50 μ m.

IX. Development of anti-adipogenic agents from Chinese Medicines

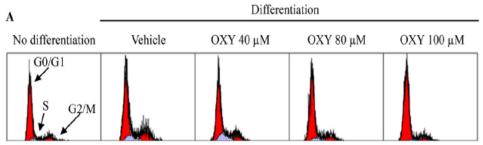
(抗脂肪積聚)

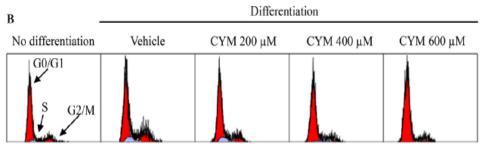


Oxyresveratrol and cyanomaclurin inhibit lipid accumulation in 3T3-L1 cells. 防脂質積聚









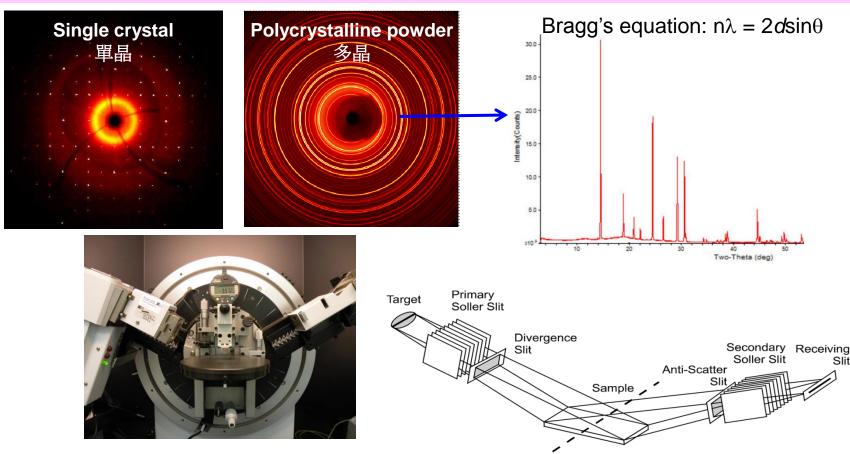
Cell cycle assay of oxyresveratrol and cyanomaclurin on 3T3-L1 cells. Postconfluent 3T3-L1 preadipocytes were differentiated with IDI plus (A) oxyresveratrol, (B) cyanomaclurin or vehicle for 24 hours. The harvested cells were stained with Vindelov's reagent and analysed by FACS.

41

X. X-ray Powder Diffraction (XRPD)

X-射線粉末衍射法

XRPD is a rapid and non-destructive analytical technique primarily used for phase identification of powder or a microcrystalline material and provides structural characterization. X-射線粉末衍射是一種快速、不具破壞性的分析技術,主要應用於粉末或微晶材料的物相鑒定和結構鑒定



Qualitative XRPD 粉末衍射定性分析 (Phase Identification 物相鑒定)

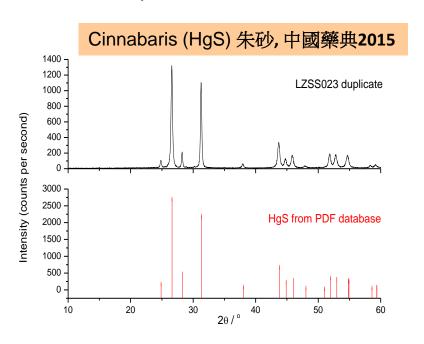
International Centre for Diffraction Data Powder Diffraction Files (ICDD PDF-2 or abbreviated as PDF

◆ The diffraction pattern of every phase is as unique as fingerprint (指紋圖譜)

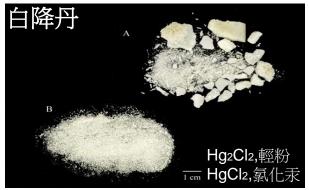
Phases with the same chemical composition can have different diffraction patterns

lacktriangle Identification: comparing the position (20) and relative intensity of sample peaks to

the reference patterns in the database.

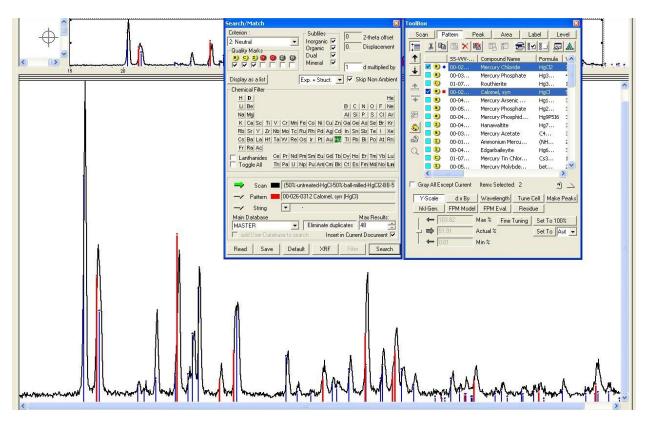






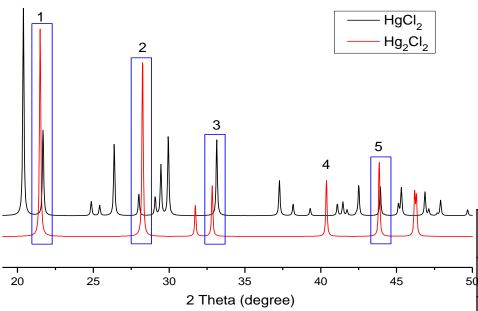
Quantitative XRPD (Q-XRPD) 粉末衍射定量分析

- ◆ Determine the content of each phase in a mixture混合物中各個物相的定量
- The ratio of peak intensities varies linearly as a function of weight of any two phases in a mixture.
- ◆ Relative Intensity Ratio (RIR,相對強度比) method is fast and gives semi-quantitative results.
- Whole pattern fitting/Rietveld refinement (擬合/Rietveld精修) is an accurate but complicated analysis



```
00-026-0312
               Calomel, syn
                HqCI
FWHM(30):
               0.209°
Crystallite Size (Scherrer):
                               388.8 A
I/Icor:
Space group: I4/mmm (139)
Cell param.: a=4.48010 c=10.90600
               Mercury Chloride
00-026-0315
             --- HgCl<sub>2</sub>
FWHM(30):
               0.233°
Crystallite Size (Scherrer):
                               348.8 A
               3.2
I/Icor:
Space group: Pmnb (62)
Cell param.: a=5.97560 b=12.76800
c=4.33470
Number of steps: 20
R/R0:
                3.42
RWP:
                22.7
Concentrations:
                               HgCl<sub>2</sub>
00-026-0315 56.8%
                Mercury Chloride
00-026-0312 43.2%
                               HgCl
```

Calomel, syn



- The severe peak overlaps coupled with the potential preferred orientation effect make the Reference Intensity Ratio (RIR) method unreliable in the QPA of HCC samples.
- Comparing with the single peak intensity strategy adopted in the RIR method, the whole pattern analysis method gives more accurate results.
- Refinement of crystallite size, strain, background and preferred orientation correction (March Dollase model) in Rietveld method can efficiently minimize the sample related effects and hence improve the accuracy.

Figure 1: Stack of simulated XRPD pattern of HgCl₂ (raised curve) and Hg₂Cl₂ (lowered curve) showing the peak overlaps in the 2θ range of 19 – 50°.

Quantified results

Sample	RHgCl2: RHg2Cl2 (from TOPAS)	$R_{\rm wp}$ [%]
BJDS001	99.54:0.46	10.9
BJDS003	0:100	1.7
BJDS004	100:0	10.1
BJDS005	99.74:0.26	10.6
BJDS006	99.69:0.31	10.4
BJDS007	99.86:0.14	9.73
LBJDS00166	99.20:0.8	10.6
LBJDS00170	99.79:0.21	10.4
LBJDS00172	99.28:0.72	10.6
LBJDS00174	99.55:0.45	10.1 ⁴⁶

Deliverables for R&D Laboratory for Testing of Chinese Medicines (項目成果)

Publications 已發表文章

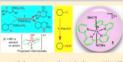


Nonheme Iron-Mediated Amination of C(sp3)-H Bonds. Quinquepyridine-Supported Iron-Imide/Nitrene Intermediates by **Experimental Studies and DFT Calculations**

Yungen Liu, Xiangguo Guan, Ella Lai-Ming Wong, Peng Liu, Jie-Sheng Huang, and Chi-Ming Che® Department of Chemistry and State Key Laboratory of Synthetic Chemistry, The University of Hong Kong, Pokfulam Road, Hong

Supporting Information

ABSTRACT: The 7-coordinate complex $[Fe(qpy)-(MeCN)_2](ClO_4)_2$ (1, qpy=2,2':6',2'':6',2'':6'',2''':quinquepyridine) is a highly active nonheme iron catalyst for intra- and intermolecular amination of C(sp³)—H bonds. This complex effectively catalyzes the amination of limiting amounts of not only benzylic and allylic C(sp³)=H bonds of hydrocarbons but also the C(sp³)=H bonds of cyclic alkanes and cycloalkane/linear alkane moieties in sulfamate esters, such as those derived from menthane and steroids cholane and



such as those derived from menthune and strends cholane and mandrostane, using $P^{\text{Theorem analysis}}$ in $P^{\text{Theorem analysis}}$ in $P^{\text{Theorem analysis}}$ in $P^{\text{Theorem analysis}}$, N_{t} (p-indiversellow)), N_{t} (p-indiversellow)), N_{t} (p-indiversellow)), N_{t} (p-indiversellow)), N_{t} (p-indiversellow)), N_{t} (p-indiversellow)), N_{t} (p-indiversellow)) as integer source, with the animation products isolated in up to 93% yield into middle-interior intermediates [Fe(qpy)(NR)(X)]). (C_{tot}) and P^{t} (p-indiversellow) and P^{t} (p-indiversellow) and P^{t} (p-indiversellow) P^{t} (p-indiversellow). Special consistent energies and with support P^{t} (p-indiversellow) P^{t} (p-indiverse

Ginseng and male reproductive function

Kar Wah Leung and Alice ST Wong*

School of Biological Sciences: University of Hono Kono: Hono Kono: PR China

Keywords: ginseng, ginsenosides, sexual behavior, sperm, spermatogenesis, steroid receptor Abbreviations: ACh, acetylcholine; AR, androgen receptor; cGMP, cyclic guanosine monophosphate; CREM, cAMP-responsive element modulator; CP, cyclophosphamide; DA, dopamine; ER, estrogen receptor; GABA, gamma-aminobutyric acid; GDNF, glial cell-derived neurotrophic factor; GR, gluco corticoid receptor; LH, luteinizing hormone; NO, nitric exide; NOS, nitric exide; synthuse: PR, propesterone receptor: ZEA, zearalenone

Ginseng is often referred to as the King of all herbs, and is found to be a promising agent to improve general well-being. Ginseng has also been reputed as an aphrodisiac, and is used to treat sexual dysfunction as well as to enhance sexual behavfor in traditional Chinese medical practices. Data from animal studies have shown a positive correlation among ginseng, libido, and copulatory performances, and these effects have been confirmed in case-control studies in human. In addition. ginseng is found to improve the sperm quality and count of healthy individuals as well as patients with treatment-related infertility. These actions are mostly attributed to ginsenosides. his review compiles the current knowledge about the mult faceted effects of ginseng on male reproductive function, and also focuses on its mechanisms of action that may represent novel therapeutic strategies for the treatment of male repro-

"Panax" is given to ginseng by the Russian botanist Carl AM eyer in 1843. "Panax" means "all-healing" in Greek, and Panax ginsong is conventionally referred to the Asian ginseng. Ginseng has been reported to have diverse physiological effects in multiple systems, including cardiovascular, immune, and neumnal. It has also been used to enhance sex performance and satisfaction. In this review, we will summarize the effects of ginseng on male sex performance and spermatogenesis. Recent evidences on its mechanisms of action that may represent novel therapeutic strategi for the treatment of male reproductive diseases or disorders will

Ginseng is commonly taken by itself or with an herbal for mula to enhance sexual performance in traditional Chinese

Sex Performance

Citation: Cell Death and Disease (2015) 6, e1942; doi:10.10 © 2015 Macmillan Publishers Limited All rights reserved 2041-4889

Autophagy-induced RelB/p52 activation mediates tumour-associated macrophage repolarisation and suppression of hepatocellular carcinoma by natural compound baicalin

DOI: 10.1002/asia.201402580

Amination

[Fe(F20TPP)CI]-Catalyzed Amination with Arylamines and {[Fe(F20TPP)(NAr)](Phl=NAr)}+ Intermediate Assessed by High-Resolution ESI-MS and DFT Calculations

Yungen Liu,[a] Guo-Qiang Chen,[a,b] Chun-Wai Tse,[a] Xianguo Guan,[a] Zheng-Jiang Xu,[b] Jie-Sheng Huang, [A] and Chi-Ming Che*[A, b]

Abstract: Amination of C-H bonds catalyzed by transition metal complexes via nitrene/imide insertion is an annealing strategy for C-N bond formation, and the use of imipolodinanes, or their in situ generated forms from Phi-(OAc)2+primary amides (such as sulfonamides, sulfamates, and carbamates)', as nitrogen sources for the ami nation reaction has been well documented. In this work, a 'metal catalyst+Phl(OAc)₂+primary arylamines' amination protocol has been developed using $[Fe(F_{20}TPP)CI]$ a catalyst. This catalytic method is applicable for both bonds (>27 examples), affording the amination products, including natural products such as rutaecarpine, in moder ate-to-good yields. ESI-MS analysis and DFT calculation lend support for the involvement of ([Fe(F₂₀TPP)(NC₀H_c-p-NO_J)(Phl=NC₀H₄-p-NO₂))* intermediate in the catalysis.

with examples of sulfonyl azides, Majakari phosphorazidates, Majakari and anyl azides Majakari (Figure 1). Primary amines without bearing strong electron-withdrawing group(s) (such a amides) could also be used as nitrogen source for oxidative C-N bond forming reactions. In the 1960s, Nagata and co-work-ers reported the intramolecular aziridination reaction of unsaturated primary amines to give bridged aziridines using stoidant.⁵⁰ Hydrazine compounds are also known to act as nitro gen source for C–N bond forming reactions⁽²⁾ (Figure 1). Our interest in the use of primary arylamines (ArNH₂) as nitrogen source for nitrene/imide transfer or insertion stemmed from the in situ generation of iminoiodinanes from 'Phi(OR)₂+NH₂Y (Y=sulfonyl, acyl)' in metal-catalyzed intermolecular C-H ami-









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Received 4th June 2014

DOI: 101039/c4no00080c

2.2

2.3

Brief history and current status

Anti-cancer activities

Ginsenosides: major therapeutic constituent

NPR

Recent advances in ginseng as cancer therapeutics: a functional and mechanistic overview

Alice S. T. Wong, *a Chi-Ming Cheb and Kar-Wah Leung

Covering: 2000 to 2014

Cancer is one of the leading causes of death worldwide. Ginseng, a key ingredient in traditional Chinese medicine, shows great promise as a new treatment option. As listed by the U.S. National Institutes of Health as a complementary and alternative medicine, its anti-cancer functions are being increasingly recognized. This review covers the mechanisms of action of ginsenosides and their metabolites, which can modulate signaling pathways associated with inflammation, oxidative stress, angiogenesis, metastasis, and stem/progenitor-like properties of cancer cells. The emerging use of structurally modified ginsenosides and recent clinical studies on the use of ginseng either alone or in co with other herbs or Western medicines which are exploited as novel therapeutic strategies will also be

of AD therapeutics.

Cite this: DOI: 10.1039/c0xx00000x

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journal homepage: www.elsevier.com/locate/bbamo

A novel mechanism of XIAP degradation induced by timosaponin AIII in hepatocellular carcinoma

Ning Wang a, Yibin Feng a,*, Meifen Zhu a, Fung-Ming Siu b, Kwan-Ming Ng b, Chi-Ming Che b,** * School of Chinese Medicine, U.Ka Shing Faculty of Medicine, The University of Nong Kong, 10 Sassoon Road, Polyfulaw, Nong Kong, China * Department of Chemistry, Open Laboratory of Chemical Sindays of the Institute of Molostor Technology for Drug Disovery and Synthesia and State Key Laboratory of Synthesis Chemistry, The University of Hosp Kong, Publisher Nock, Hong Kong, China and State Key Laboratory of Synthesis Chemistry, But Visionship of Hosp Kong, China

ARTICLE INFO

Article history: Received 15 March 2013

Indian's graner oil death is one of the major therapoint: catagins in monting cancer. The aim of this study is to investigate the mechanism underlying the insolvement of analysis on oil locals induced by incomposition All investigates the mechanism underlying the insolvement of analysis or oil locals induced by incomposition All investigations was detected by your desired by read-some of the analysis of the ana protessional-driven procedynis, instruct, Tull-induced AMPlika, mUTM-departed autophagy was responsible from TXMP requestions in the heading placeman for TXMP requestion for TXMP requestion for the autophagy degradation indexed by TXMI Blockade of autophagy turns on the wintch of necroic cold don'th TXMI resultant of TXMI TXMI Blockade of autophagy turns on the wintch of necroic cold don'th TXMI resultant of TXMI for TXMI Blockade of autophagy turns on the wintch of necroic cold don'th TXMI resultant of TXMI for the TXMI Blockade of autophagy turns on the wintch of necroic cold don'th TXMI resultant of TXMI for the TXMI Blockade of autophagy turns on the wintch of necroic cold don'th TXMI resultant of the TXMI for the TXMI

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Inhibitory effects of oxyresveratrol and cyanomaclurin on adipogenesis of 3T3-L1 cells



Hui-Yuan Tan, Iris M.Y. Tse, Edmund T.S. Li, Mingfu Wang * School of Biological Sciences, The University of Hong Kong, Pokfulam Road, Hong Kong, China

ARTICLE INFO ARSTRACT

Received 23 September 2014 Received in revised form 19 January Accepted 5 March 2015 Available online 31 March 2015

Many phenolics are known to possess anti-obesity properties through mechanisms that inhibit adipogenesis, stimulate lipolysis or induce apoptosis. This study aimed to examine the antiexposure of oxyresveratrol (0-100 µM) or cyanomadurin (0-600 µM) in the first three days of differentiation led to a dose-dependent decrease of triacylglycerol accumulation on day 9 post-confluent. Results of cell proliferation and cell cycle study demonstrated that both

ARTICLE TYPE 8 Identification of "sarsasapogenin-aglyconed" timosaponins as novel Aβ lowering modulators of amyloid precursor protein (APP) processing

Lai-King Sy¹, Chun-Nam Lok¹, Juan-Yu Wang¹, Yungen Liu¹, Lu Cheng¹, Pui-Ki Wan¹, Chi-Ting Leung¹, Bei Cao, ¹ Wai-Lun Kwong¹, Raymond Chuen-Chung Chang², and Chi-Ming Che¹

s Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXX 20XX

The inhibition of amyloid β peptide (A β) production is a key approach in the development of therapeutics for the treatment of Alzheimer's disease (AD). We have identified that timosaponins consisting of sarsasapogenin (SSG) as the aglycone can effectively lower the production of AB peptides and stimulate neurite outgrowth in neuronal cell cultures. Structure-activity relationship studies revealed 10 that the cls-fused AB ring, 3β-configuration, spiroketal F-ring and 25S-configuration of SSG are the essential structural features responsible for the Aß lowering effects and neurite-stimulatory activities. New synthetic derivatives which retain the SSG scaffold also exhibited an Aß lowering effect. Treatment of cells with timosaponins led to modulation of amyloid precursor protein (APP) processing through suppression of β -cleavage and preferential lowering of the production of the 42-amino acid A β species (A β_{42}) without affecting another γ -secretase substrate. The SSG and "SSG-aglyconed" timosaponins also penetrated brain tissue and lowered brain $A\beta_{42}$ levels in 15 mice. Our studies demonstrate that timosaponins represent a unique class of steroidal saponins which may be useful for the development

OPEN

Patent 已發表專利



US 20150050367A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2015/0050367 A1 Che et al.

Feb. 19, 2015 (43) **Pub. Date:**

TIMOSAPONIN COMPOUNDS

- Applicants: Chiming Che, Hong Kong (CN); Laiking Sv., Hong Kong (CN); Chunnam Lok, Hong Kong (CN)
- Inventors: Chiming Che, Hong Kong (CN); Laiking Sy, Hong Kong (CN); Chunnam Lok, Hong Kong (CN)
- 14/390,400 Appl. No.:
- PCT Filed: Apr. 2, 2013
- PCT No.: PCT/CN2013/073666 (86)

§ 371 (c)(1),

Oct. 3, 2014 (2) Date:

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Provisional application No. 61/619,439, filed on Apr. 3, 2012.

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- (52) U.S. Cl.

CPC C07J 71/0031 (2013.01); A61K 31/7048 (2013.01); A61K 45/06 (2013.01); A61K 31/58 (2013.01)

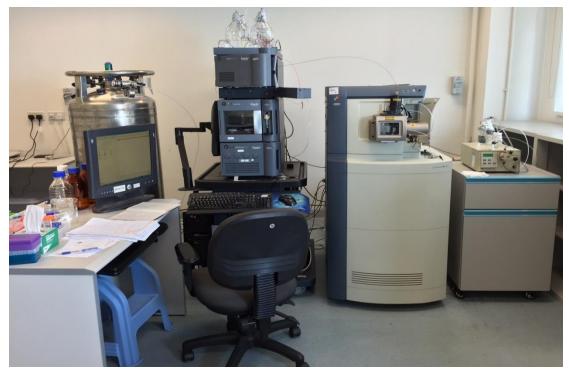
USPC . **424/752**; 536/6.1; 514/26; 540/48; 514/172; 514/171; 540/17; 514/173

ABSTRACT (57)

Provided herein are timosaponin compounds of Formula I, II, III, I', II' and III', pharmaceutical compositions comprising the compounds, and processes of preparation thereof. Also provided are uses of said timosaponin compounds for preparing medicament for the treatment of diseases associated with beta-amyloid in hosts or subjects in need thereof.

Waters UPLC-QTOF Donated by HKJCCT

馬會捐贈之液相色譜法-質譜聯用



- (a) Chemical profiling comparison of easily-confused Chinese medicine 易混淆中藥之化學分析
- (b) Metabolite analysis 代謝物分析
- (c) Pharmacokinetics 藥物代謝動力學
- (d) Bio-distribution study of intriguing drug leads and 前體藥物體內分佈
- (e) A teaching tool for promoting collaborative research 教育工具鼓勵合作性科研

Chemical markers are available from the following website

中藥對照品可循下述網站查詢



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香港創新科技署



The Hong Kong University of Science and Technology 香港科技大學