SINPHAR GROUP

SynCoreBio

SynCore Biotechnology Co., Ltd.

杏國新藥股份有限公司

2017 6th APAC DA Session

"Dawning Era in Drug Discovery with Natural Resources in Asia"

Drug Discovery Using Natural Compounds in Taiwan

Muh-Hwan Su, Ph. D.

General Manager

04/05/2017

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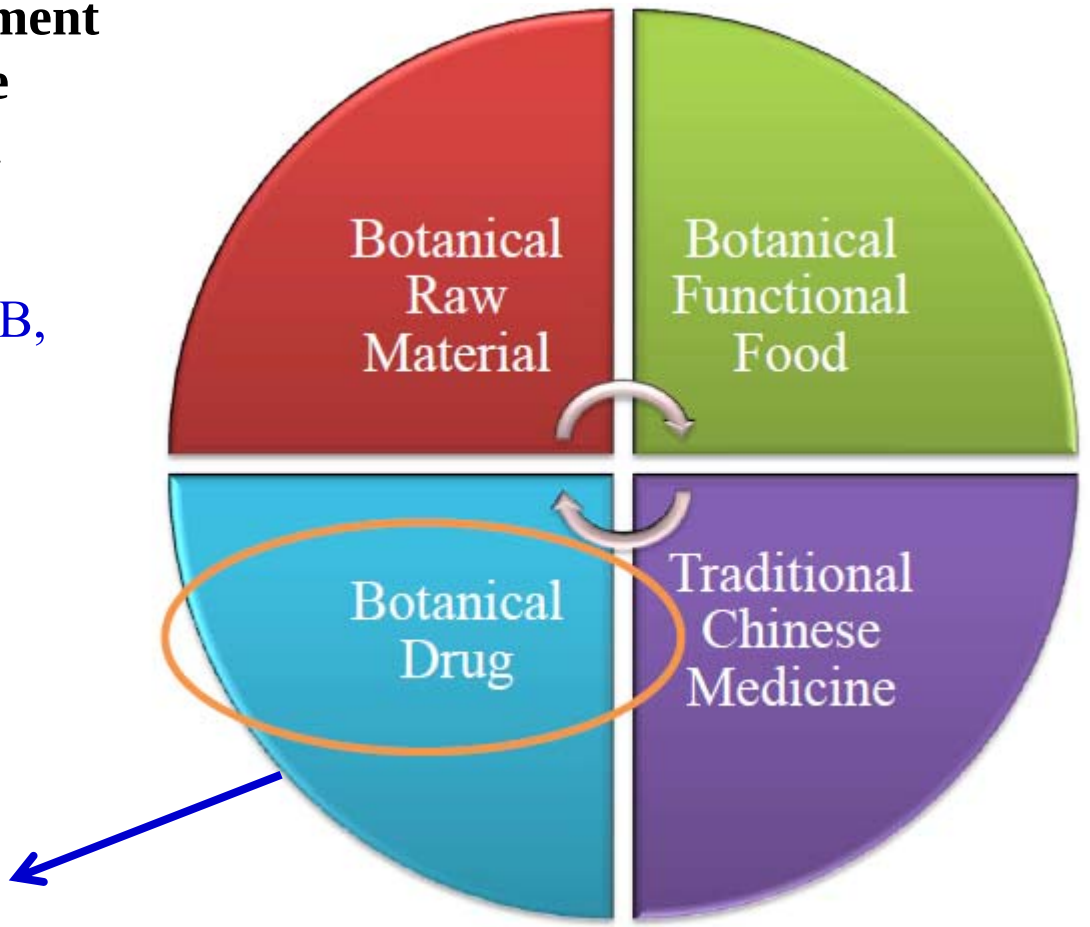
Natural Product Classification in Taiwan

Botanical new drug develoment has been encouraged by the Taiwanese government and focused in

1. Research Institutions : DCB, ITRI, PITDC
2. Universities
3. Biotech Companies

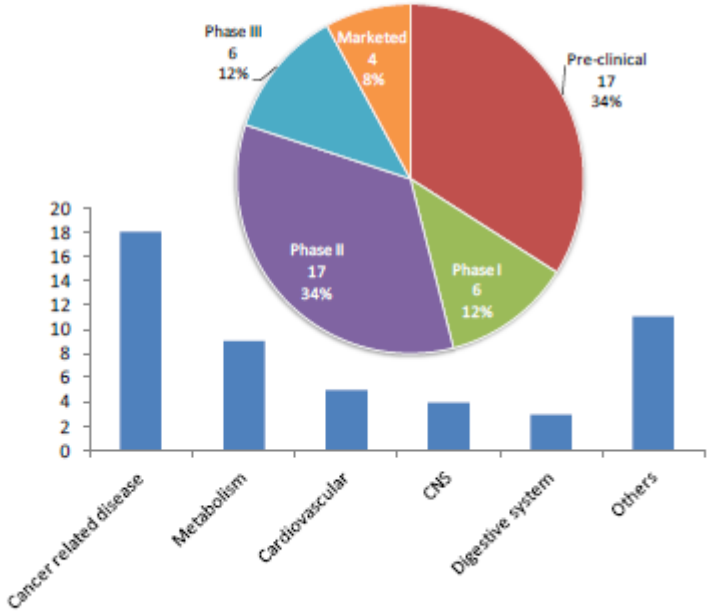


Pure Compound/ Derivatives

Source: Dept. of Industrial Information, DCB

Botanical Drug Pipelines in Taiwan

Preclinical	Phase I	Phase II	Phase III	NDA
OB412 (diabetes)	*VN-B101(diabetes)*	*PHN013（purpura (FDA orphan drug)）*	*ON101 (diabetic foot ulcer)*	LipoCol Forte capsules (hypolipidemic)
KGbi01 (diabetes wound healing)	*BEL-X (liver disease)*	*PHN031 (osteoporosis)*	*MB-6 (Adjuvant therapy for colorectal cancer)*	PG2 (cancer adjuvant)
GHP110 (stroke)	*OB318 (liver cancer)*	*PHN033 (diabetes)*	*SR-T100 (skin squamous cell carcinoma)*	Chemo Young (cancer adjuvant)
BLI-1401 (cancer adjuvant)	*BLI-1301 (leukemia)*	*SR-T100 (condyloma acuminata)*	*MCS-2 (prostate hypertrophy)*	Herbiron (iron deficiency anemia)
BLI-1006 (enteritis)	ACA (cancer adjuvant)	*STA-1 (dementia)*	BNG-1 (stroke)	
DCB-AD1 (dementia)	TSB-9-W1 (cancer)	*STA-2 (angina pectoris)*	Uni-TongXin patch (Analgesic anti-inflammatory)	
ZC008 (liver fibrosis)		*CSTC1 (diabetes wound healing)*		
ITRI-AGT (gout)		*JBM-TC4 (cancer adjuvant)*		
PDC-2363(intestinal mania)		*BLI-1005 (depression)*		
DCB-CA1 (cancer adjuvant)		*BLI-1008 (hyperactivity disorder)*		
PDC-1427 (cough)		Onepower-01 (nephritis)		
Onepower-02 (breast cancer postoperative metastasis)		GHP219 (myocardial infarction)		
LEAC102 (cancer adjuvant)		TCM-606F (nonalcoholic fatty liver disease)		
MA-SNC-1 (cancer adjuvant)		TCM-800B (HBV)		
YB109 (cancer adjuvant)		PHN015 (stroke)		
DS1370 (cancer adjuvant)		MCS-5(male unexplained infertility)		
ZG5236(cancer)		MCS-8(prostate cancer prevention)		



- Currently 50 of botanical drugs are under development, 17 preclinical , 4 NDA approval, 29 in clinical trial.
- 19 (38%) apply for US FDA clinical trials (red letters)
- 36% are cancer related disease
- 14 (28%) are supported by gov. funding (pink boxes)

Source: company websites, news; Dept. of Industrial Information, DCB (2016.04)

Achievements of Professors

The achievements done by the professors present in this conference are examples. They are not all of the professors in the Universities in Taiwan who are interested in natural product drug discovery. However, they are very productive. The achievements list here are also not all of the achievements done by these professors.

Chair Professor **Yueh-Hsiung Kuo**

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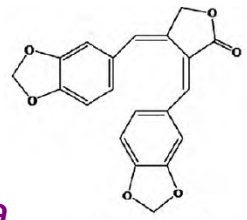
Graduate Institute of Pharmaceutical Chemistry, China Medical University.

1. Corrigendum to "Osteoporosis Recovery by *Antrodia camphorata* Alcohol Extracts through Bone Regeneration in SAMP8 Mice". (Evid Based Complement Alternat Med. 2017;2017:6297946)
2. Antcin K, a Triterpenoid Compound from *Antrodia camphorata*, Displays Antidiabetic and Antihyperlipidemic Effects via Glucose Transporter 4 and AMP-Activated Protein Kinase Phosphorylation in Muscles. (Evid Based Complement Alternat Med. 2016;2016:4867092)
3. Taiwanin E Inhibits cell Migration in Human LoVo Colon Cancer Cells by suppressing MMP-2/9 Expression via p38 MAPK Pathway. (Environment Toxicology，2016 Nov，1(1))
4. Taiwanin A Inhibits MCF-7 Cancer Cell Activity through Induction of Oxidative Stress, Upregulation of DNA Damage Checkpoint Kinases, and Activation of p53 and FasL/Fas Signaling Pathways. (Phytomedicine, 2010, 50892)
5. Dual Inhibition of Key Proliferation Signaling Pathways in Triple-Negative Breast Cancer Cells by a Novel Derivative of Taiwanin A. (Mol Cancer Ther. 2017 Mar;16(3):480-493)

Taiwania cryptomerioides



Taiwanin A

Professor Guo has isolated > 200 compounds from *Antrodia camphorata*

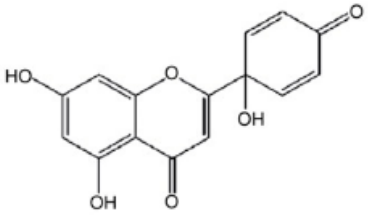
http://webap.cmu.edu.tw/TchEportfolio/journal_1/kuoyh

Chair Professor **Yang-Chang Wu**

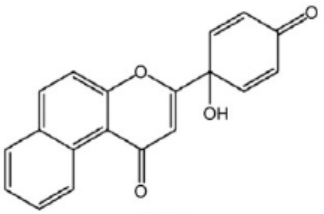
College of Chinese Medicine, China Medical University.

SynCoreBio

1. Total synthetic protoapigenone WYC02 inhibits cervical cancer cell proliferation and tumour growth through PIK3 signalling pathway. (Basic & Clinical Pharmacology & Toxicology, 2013, 113,8–18).
2. Inhibition of ATR-dependent signaling by protoapigenone and its derivative sensitizes cancer cells to interstrand cross-link-generating agents *in vitro* and *in vivo*. (Mol Cancer Ther. 2012 Jul;11(7):1443-53.)
3. Synthesis and evaluation of cytotoxic effects of novel α-methylenelactone tetracyclic diterpenoids. (Bioorg Med Chem Lett. 2012 Mar 1;22(5):1922-5)
4. Chemical Constituents from *Flueggea virosa* and the Structural Revision of Dehydrochebulic Acid Trimethyl Ester. (Molecules，2016 Sep，21(9):1239)
5. New eunicellins from the Formosan octocoral *Cladiella tuberculosa* (Tetrahedron letters，2016 Sep，57:4239-4242)



WYC02



WYC0209

http://webap.cmu.edu.tw/TchEportfolio/index_1/yachwu

Distinguished Professor **Tian-Shung Wu,**

Department of Chemistry, National Cheng-Kung University

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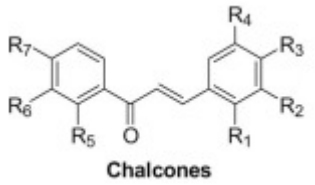
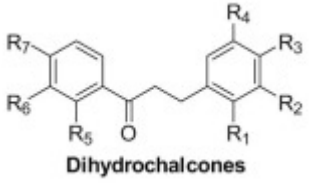
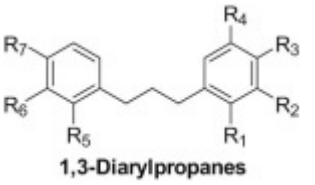
1. Synthesis and biological evaluation of chalcone, dihydrochalcone, and 1,3-diarylpropane analogs as anti-inflammatory agents. (Bioorg Med Chem Lett. 2017 Apr 1;27(7):1547-1550)
2. Chemical constituents and anti-inflammatory principles from the fruits of *Forsythia suspensa*.(J Nat Prod. 2017 Feb 20)
3. Immunosuppressive effect of zhankuic acid C from Taiwanofungus *camphoratus* on dendritic cell activation and the contact hypersensitivity response.(Bioorg Med Chem Lett. 2015 Oct 15;25(20):4637-41)
4. Anti-inflammatory principles from the stem and root of *Citrus medica*. (Chemical & Pharmaceutical Bulletin，2010 Jan，58(1):61-65)
5. Potent α-glucosidase inhibitors from the roots of *Panax japonicus* C. A, Meyer var. major. (Phytochemistry，2010 Apr，71(2010):1360-1364)



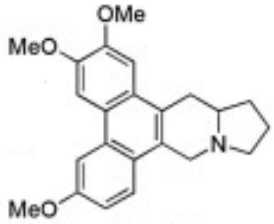
Chalcones



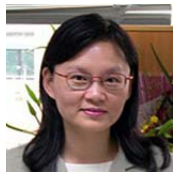
Dihydrochalcones



1,3-Diarylpropanes



(±)-antofine



Professor **Lie-Fen Shyur**

Agricultural Biotechnology Research Center, Academia Sinica

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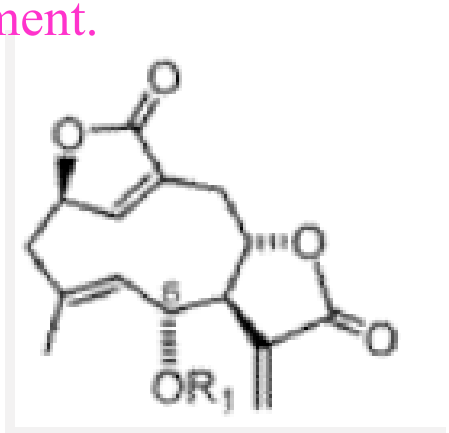
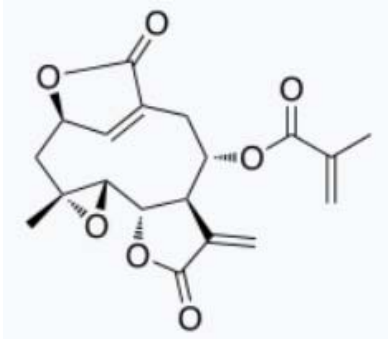
Novel sesquiterpene derivatives and their use in inflammation or cancer treatment.



Deoxyelephentopin



Elephentopin

***Elephantopus scaber* L. ssp. *oblanceolata* Kitam.**,

wherein R_1 is selected from the group consisting of hydrogen, -carbonyl(C_1-C_8)alkyl(C_1-C_8)alkylene, -carbony C_1-CgJalkylCd-CgJalkyleneCC_1-Cgialkyl, -carbonyl(C_1-C_8)alkylene(C_6-C_{20})aryl, -carbonyl(C_1-C_8)alkylene(C_1-Cg)alkoxy(C_6-C_{20})aryl, -carbonyl(C_1-C_8)alkylene, -carbonyl(C_1-Csjhaloalkyl, -carbonyl(C_1-C_8)alkyl, -carbonyl(C_1-C_8)alkylOCO(C_1-C_8)alkyl, -carbonyl(C_1-C_8)alkylene(C_1-C_8)alkyl(C_1-C_8)alkylene, -carbonyl(C_1-C_8)alkanol(CrC_8)alkyl, -carbonyl(C_1-C_8)alkylene(C_1-C_8)alkyl(C_6-C_{20})aryl, -carbonyl(C_1-C_8)alkylenehalo(C_6-C_{20})aryl, -carbonyl(C_1-C8)alkylene(C_3-C_8)heteroaryl, -carbonyl(C_6-C_{20})aryl, -carbonyl(CpC8)alkoxy(C_6-C_{20})aryl, -carbonyl(C_1-C_8)alkyl(C_6-C_{20})aryl, -carbonylhalo(C_6-C_{20})aryl, -carbonyl(C_3-C_8)cycloalkyl, (C_1-C8)alkylene(C_1-C_8)haloalkyl(C_6-C_{20})aryl, and -carbonyl(C_1-C_8)alkyl(C_1-C_8)alkoxy(C_6-C_{20})aryl

Professor **LEE, Kuo-Hsiung**

https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2015188169&recNum=10&docAn=US201503458 9&queryString=FP:(%22inflammatory%20diseases%22)%20AND%20EN_ALL:nmr&maxRec=5761

Professor **Pei-Wen Hsiao**

Agricultural Biotechnology Research Center, Academia Sinica

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Carcinogenesis vol.28 no.12 pp.2521–2529, 2007
doi:10.1093/carcin/bgm137
Advance Access publication October 17, 2007

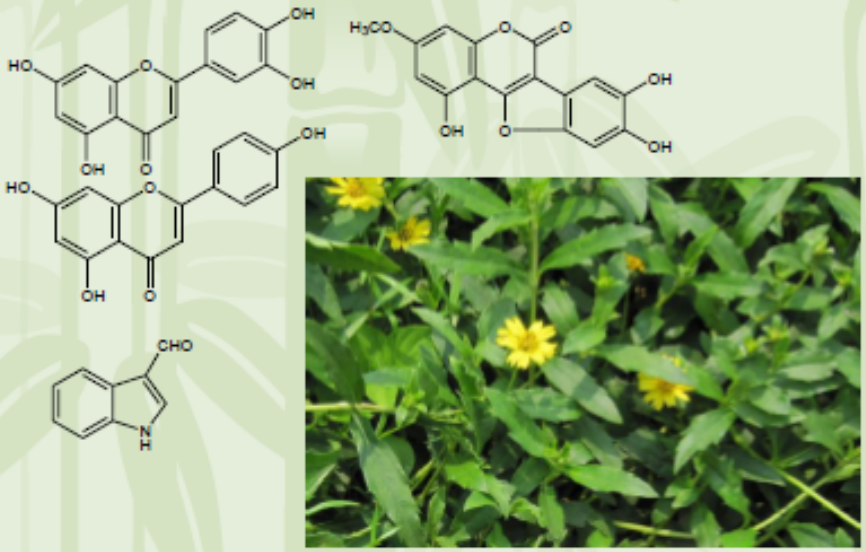
Compounds from *Wedelia chinensis* synergistically suppress androgen activity and growth in prostate cancer cells

Feng-Min Lin[1], Li-Ru Chen[1], En-Hau Lin[1,2], Ferng-Chun Ke[2], Hsin-Yi Chen[1], Meng-Jen Tsai[2] and Pei-Wen Hsiao[1,*]

[1]Agricultural Biotechnology Research Center, Academia Sinica, 128 Academia Road, Sec. 2, Nan-Kang, Taipei 11529, Taiwan and [2]Institute of Molecular and Cellular Biology, National Taiwan University, Taipei 10617, Taiwan

*To whom correspondence should be addressed. Tel: +886 2 2651 5747; Fax: +886 2 2785 9360;
Email: pwhsiao@gate.sinica.edu.tw

a supplement by PCa patients who also received orthodox medication, suggesting a need among PCa patients for therapeutic improvement (12,13). Chinese medicinal plant documentation states that *Wedelia chinensis* (Osbeck) Merr., also called hwang-hua-mih-tsay in Taiwan, has medicinal anti-inflammatory properties (14). This Asteraceae plant is a perennial herb with bright yellow flowers and a light, camphor-like odor and is used to relieve fever and to reduce cough and phlegm. It has also been studied for protection of the liver from toxicity (15,16). Here, we examined the bioactive phytocompounds in *W. chinensis* for



Wedelia chinesis (Osbeck) Merr

學名：*Wedelia chinensis* (Osbeck) Merr.
科名：菊科 Astreraceae
別稱：蟛蜞菊，黃花蜜菜，四季春，四季春仔，田烏草，蛇舌黃，黃花田路草，寒丹草，雞舌黃(以上為台灣民間習用名稱)；黃花蟛蜞菊，田黃菊，路邊菊，馬蘭草，蟛蜞花，水蘭，油地菊，黃花龍舌草，黃花曲草，鹿舌草，黃花墨菜，龍舌草。
分佈：生於田邊、路旁、溝邊、山谷或濕潤草地上。
用途：主治感冒發熱，咽喉炎，扁桃體炎，腮腺炎，白喉，百日咳，氣管炎，肺炎，肺結核咯血，鼻衄，尿血，傳染性肝炎，痢疾，痔瘡，瘰癧腫毒，前列腺肥大。
成分：蟛蜞菊含三十烷酸(melissic acid)，二十四烷酸(lignoceric acid)，豆甾醇(stigmasterol)，豆甾醇葡萄糖苷(stigmasterol glucoside)，參胚脂醇(sitosterol)，左旋-貝殼杉烯酸(kaur-16-en-19-oic acid)。葉含蟛蜞菊內酯(wedelolactone)，並含有異黃酮類化合物。

Experiences Sharing from Enterprise

1. *Poria cocos* Wolf

Origin

Sclerotium of eumycete Poria cocos (schw) Wolf of family Polyporaceae. The sclerotium mostly parasitizes on the root of Japanese red pine and pinus massoniana Lamb.

Uses

Poria is widely used in Asia, and approximately 10% of medicinal preparations in the 2000 Pharmacopoeia of the People's Republic of China contain poria (fu-ling). Animal studies suggest potential uses as an immunomodulator and anti-inflammatory agent, and in the management of cancer and diabetes; however, clinical studies are lacking.

Adjunct Professor **Han-Ching Lin**
Vice CSO, Sinphar Group

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Sinphar Lipucan®: Extract(s) with Lanostanes from Fuling (*Poria cocos* Wolf)

Patents	Countries	Active compounds
1. Immunity enhancement	R.O.C., China, European, Germany, Korea, Canada, Japan, U.S.A.	
2. Treatment for a disease induced from immune disorder	R.O.C., China, Singapore, Korea, Japan	
3. Enhancement for the uptake of nutrients	R.O.C., China, Japan, Australia, Korea, Singapore, Canada.	→ A
4. Treatment for cachxia	R.O.C., Canada, Japan, European, Korea, U.S.A.	
5. Treatment for diabetes	R.O.C., China, European, Singapore, Japan, U.S.A.	
6. Anti-lung cancer	U.S.A.	
7. Enhancement of human skin collagen and hyaluronic acid	Provisional Patent Application	→ A +B

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Active compounds

A

1. Dehydropachymic acid
2. Pachymic acid
3. Dehydrotumulosic acid
4. Tumulosic acid
5. Polyporenic acid C
6. 3-epi-Dehydrotumulosic acid

B

7. Dehydrotrametenolic acid
8. Trametenolic acid
9. Dehydroeburicoic acid
10. Eburicoic acid
11. Poricoic acid A
12. Poricoic acid B

* Pure compounds are available through negociation/corporation.

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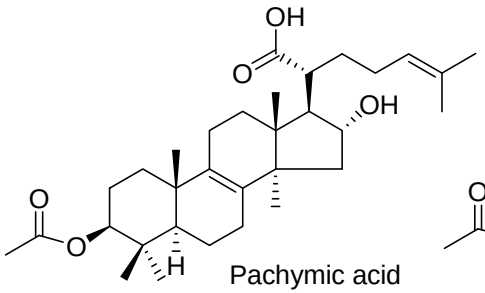
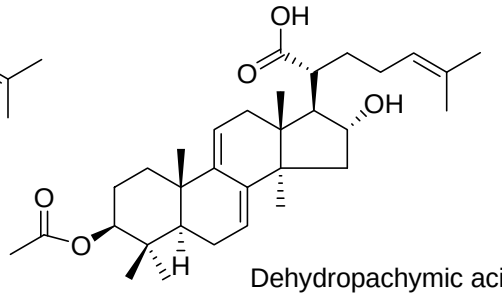
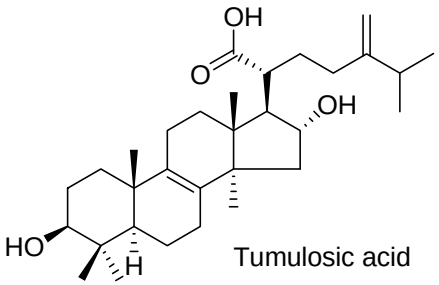
Active compounds available



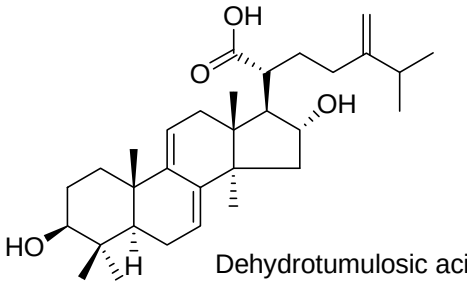
Pachymic acid



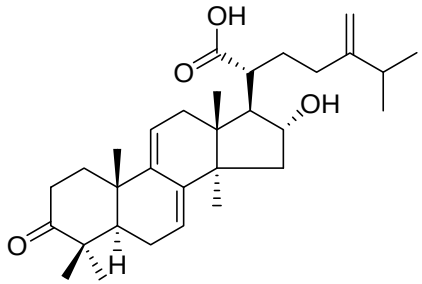
Dehydropachymic acid



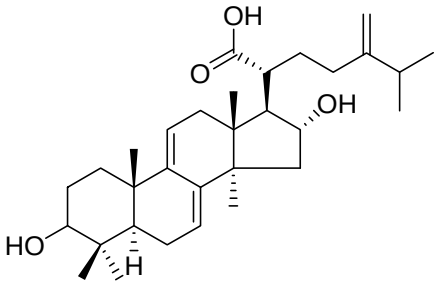
Tumulosic acid



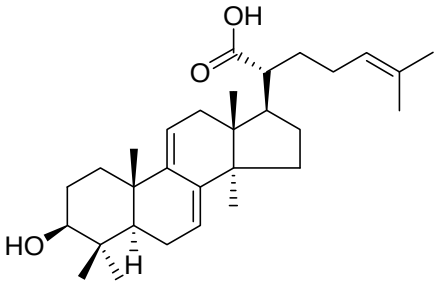
Dehydrotumulosic acid



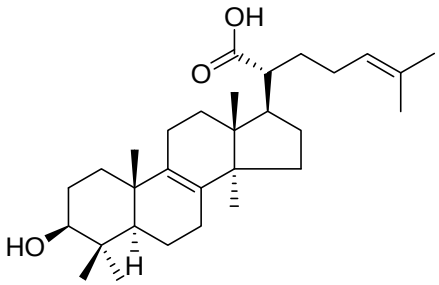
Polyporenic acid C



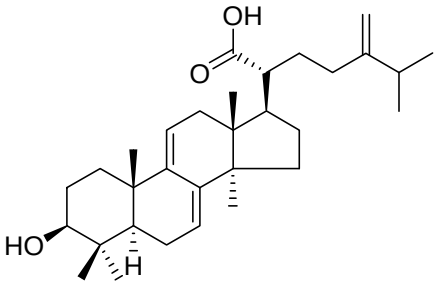
3-epi-Dehydrotumulosic acid



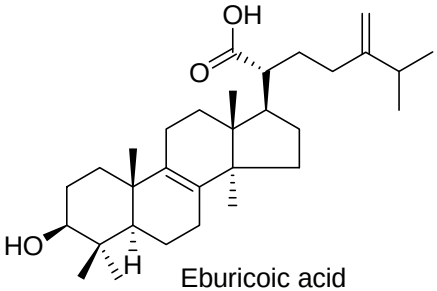
Dehydrotrametenolic acid



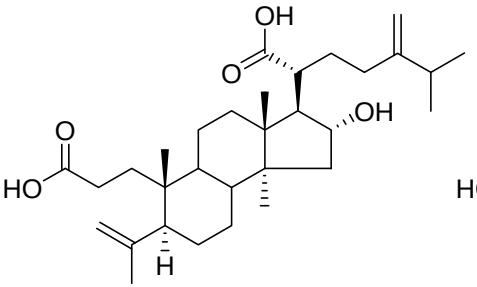
Trametenolic acid



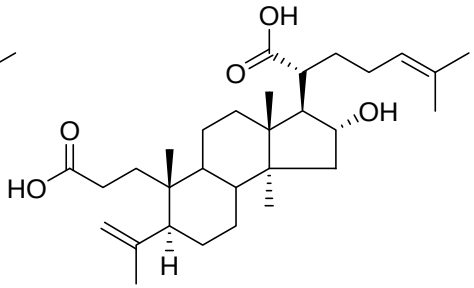
Dehydroeburicoic acid



Eburicoic acid



Poricoic acid A



Poricoic acid B

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2. *Psoralea corylifolia* L.

Origin and Uses

P. corylifolia L., or *Bu Gu Zhi* in traditional Chinese medicine (TCM) is an herb used to tonify the kidneys, particularly kidney yang and essence. It is used for helping the healing of bone fractures, for lower back and knee pain, impotence, bed wetting, hair loss, and vitiligo.

P. corylifolia extract contains a number of chemical compounds including flavonoids (neobavaisoflavone, isobavachalcone, bavachalcone, bavachinin, bavachin, corylin, corylifol, corylifolin and 6-prenylnaringenin), coumarins (psoralidin, psoralen, isopsoralen and angelicin) and meroterpenes (bakuchiol and 3-hydroxybakuchiol).

https://en.wikipedia.org/wiki/Psoralea_corylifolia

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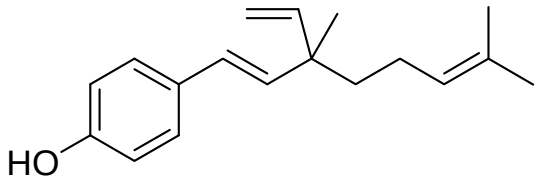
Bu Gu Zhi (*Psoralea corylifolia* L.)

Patents	Countries
Anti-breast cancer	**R.O.C.** **China** **Japan** **Korea** **Canada**
Anti-osteoporosis	**R.O.C.** **China** **Japan** **Korea** **U.S.A.** **Canada** **European**

Active compounds



Bakuchiol

*** Pure compounds are available through negociation/corporation.**

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3. *Cistanche Tubulosa* (Schenk) R. Wight

Origin

Cistanche tubulosa **(Schenk) R. Wight** is a holoparasitic desert plant species in the genus *Cistanche*. The plant lacks chlorophyll and obtains nutrients and water from the host plants (*Tamarix chinensis* Lour.) whose roots it parasitizes.

Uses

Food and cosmetic ingredients with tonics, memory improving, anti-aging, anti-fatigue, anti-sex dysfunction, immune boosting and fat metabolism accelerating properties .

http://www.oryza.co.jp/html/english/pdf/Cistanche%20tubulosa%20ver1.0.pdf

SynCoreBio

Sinphar Tianli Tianlife® : Extract(s) with Phenylethanoid glycosides from Rou Cong Rong (*Cistanche tubulosa*)

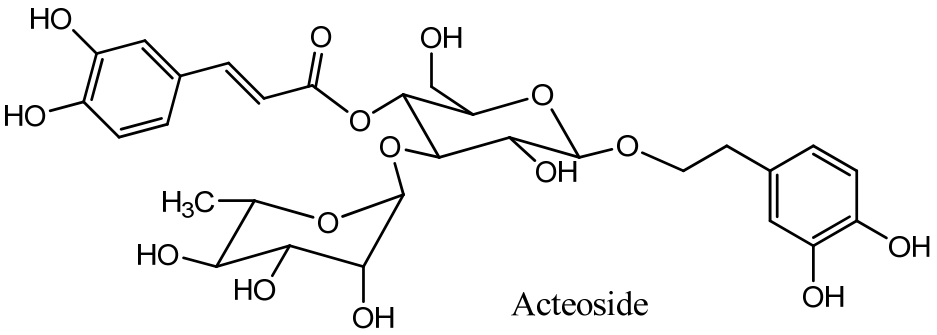
Patents	Countries
1. Preparation method	R.O.C. China Canada Japan European Spain Australia U.S.A
2. Neuroblast proliferation and nervous protuberance extend accelerant	R.O.C. China
3. Prevention of hyperlipidemia	China
4. Memory improvement	China
5. Prevention or treatment of beta amyloid peptide-associated diseases	Taiwan Singapore European
6. Regulating blood glucose level	Taiwan U.S.A.

Active compounds

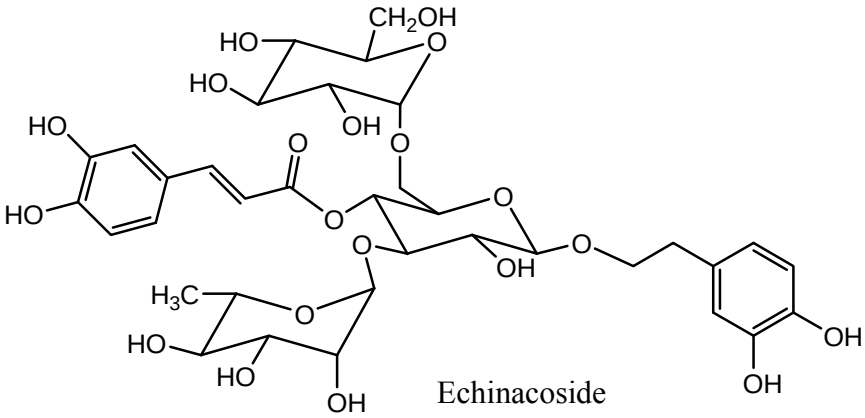
1. Echinacoside
2. Acteoside
3. Isoacteoside
4. Tubuloside A

SynCoreBio

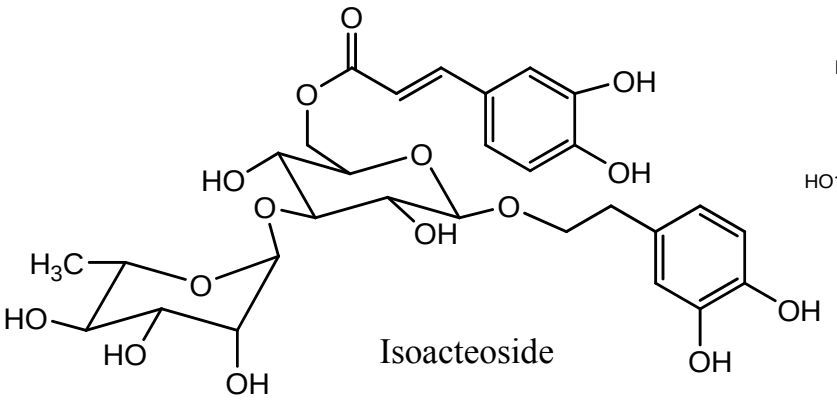
Active compounds



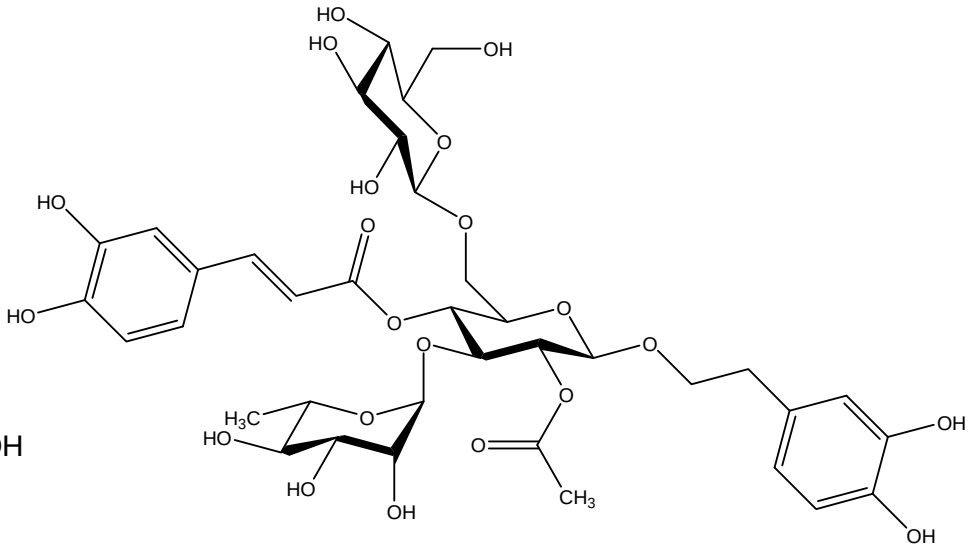
Acteoside



Echinacoside



Isoacteoside



Tubuloside A

*** Pure compounds are available through negociation/corporation.**

Kankanosides

Kinki University, Higashi Osaka: Acylated phenylethanoid oligoglycosides with hepatoprotective activity from the desert plant Cistanche tubulosa

Fresh data on life sciences are presented in the report 'Acylated phenylethanoid oligoglycosides with hepatoprotective activity from the desert plant Cistanche tubulosa.' "The methanolic extract from fresh stems of Cistanche tubulosa (Orobanchaceae) was found to show hepatoprotective effects against D-galactosamine (D-GalN)/lipopolysaccharide (LPS)-induced liver injury in mice. From the extract, three new phenylethanoid oligoglycosides, kankanosides H(1) (1), H(2) (2), and I (3), were isolated together with 16 phenylethanoid glycosides (4-19) and two acylated oligosugars (20, 21)," scientists in Higashi-osaka, Japan report.

For more information, contact T. Morikawa, Pharmaceutical Research and Technology Institute, Kinki University, 3-4-1 Kowakae, Higashi-osaka, Osaka 577-8502, Japan. *(2010 APR 12)*

https://books.google.com.tw/books?id=j3wr8bUoQSgC&pg=PA878&lpg=PA878&dq=cistanche+tubulosa+extract+japan+publication&source=bl&ots=GBxBNIfizQ&sig=MFbufCMBNHxQ30RdNRCZUMfoB84&hl=zh-TW&sa=X&ved=0ahUKEwjR9rqy8unSAhXILpQKHTBDAHAQ6AEIVDAH#v=onepage&q=cistanche%20tubulosa%20extract%20japan%20publication&f=false

Cistanche tubulosa was listed in 2005 Chinese Pharmacopoeia

SynCoreBio

The main sources of cistanche are *Cistanche salsa* and *Cistanche deserticola*, although it may also be obtained from *Cistanche tubulosa*, *Cistanche sinensis*, and *Cistanche ambigua*. *Cistanche deserticola* has been placed on CITES Appendix 2, a list of **endangered species** not banned from trade but requiring monitoring. Recently the major herb can be found in the market is *Cistanche tubulosa*. (https://en.wikipedia.org/wiki/Cistanche)

CITES (the Convention on International Trade in Endangered Species of Wild Fauna and Flora, also known as the Washington Convention)

Extract of *Cistanche tubulosa* had been approved as botanical new drug in mainland China in 2005.

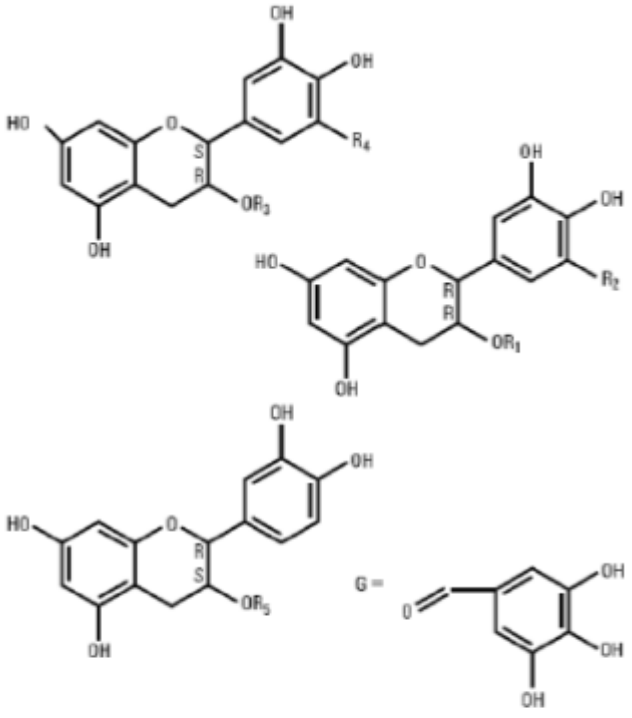





4. *Camellia sinensis (L.) O. Kuntze*

VEREGEN® (酚瑞淨)

First botanical drug approved by the US FDA in 2006



Component	Abbrev.	R1	R2	R3	R4	R5
(–)-Epigallocatechin Gallate	(–)-EGCg	G	OH		–	–
(–)-Epicatechin Gallate	(–)-ECg	G	H		–	–
(–)-Epigallocatechin	(–)-EGC	H	OH	–		–
(–)-Epicatechin	(–)-EC	H	H	–	–	
(–)-Gallocatechin Gallate	(–)-GCg	–	–	G	OH	–
(–)-Gallocatechin	(–)-GC	–	–	H	OH	–
(–)-Catechin Gallate	(–)-Cg	–	–	G	H	–
(+)-Catechin	(+)-C	–		–	–	H

Green tea extract

Tea polyphenol

Thank You for Your Attention!

Muh-Hwan Su, Ph.D.
SynCore Biotechnology Co., Ltd.
smh1027@syncorebio.com

bd@syncorebio.com

ZuniMed (Nantou, TW)

SynCore (Taipei, TW)

Tian-Li (HoTan, CN)

Tian-Li (HangZhou, CN)

Sinphar Pharma (I-Lan, TW)

RD Center (I-Lan, TW)

Training Center (I-Lan, TW)

CanCap (Canada)