



香港大學

THE UNIVERSITY OF HONG KONG

CCM 文件 03/2015



# Research on Oncology of TCM in HKU

香港大學與中醫藥有關的癌症  
研究工作

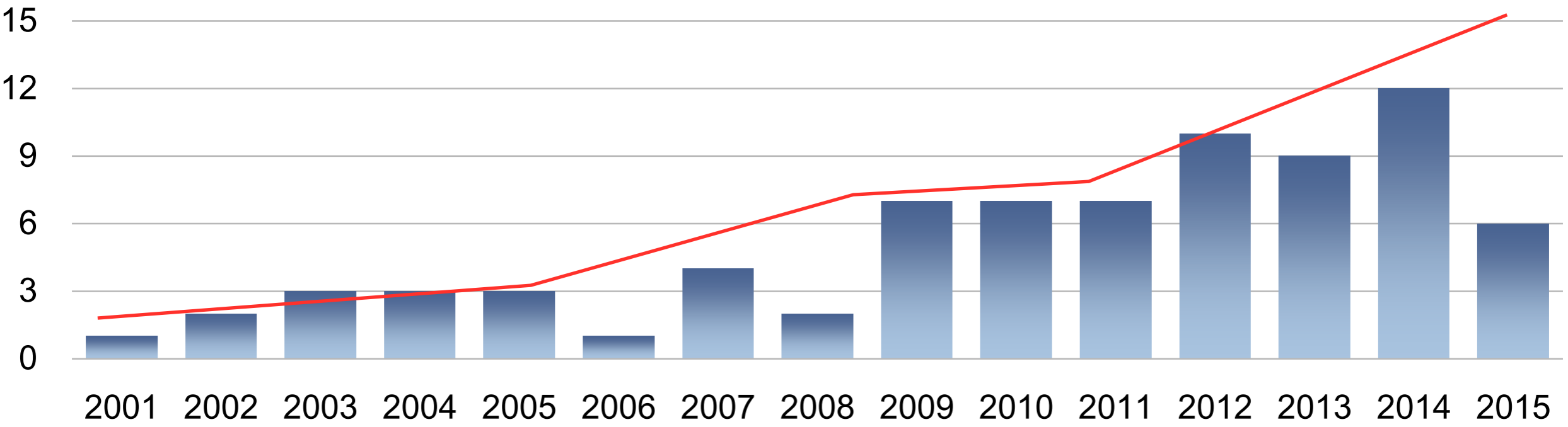
**馮奕斌 Dr. Feng Yibin**

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Director School of Chinese Medicine  
The University of Hong Kong  
香港大學中醫藥學院，副教授，副院長

# Research on Oncology of TCM in HKU

## 香港大学中医药治疗肿瘤的研究

Publication/Yr 发表文章数/年



Increased by year (数量逐年增长)

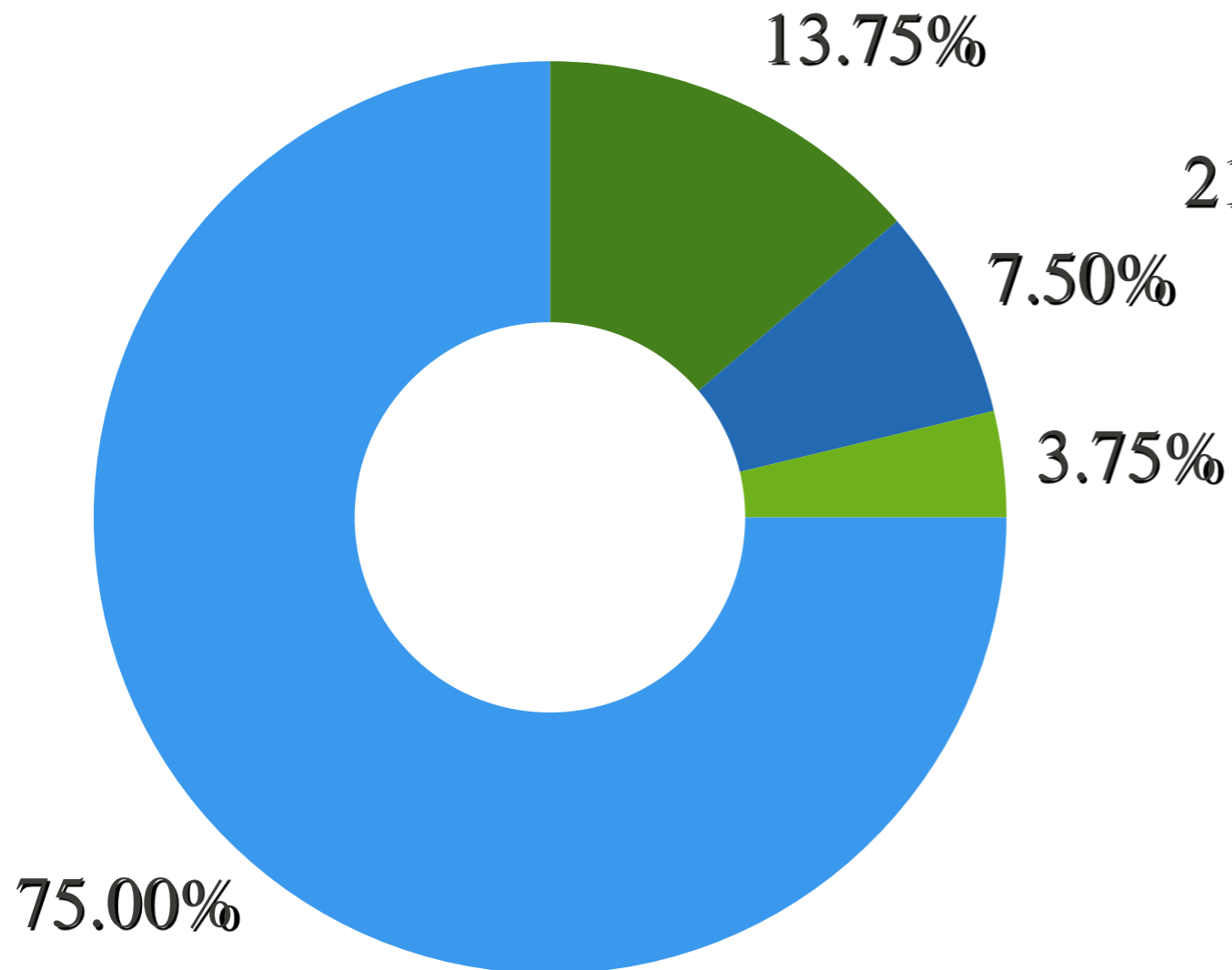
Improved quality (质量有所提高)





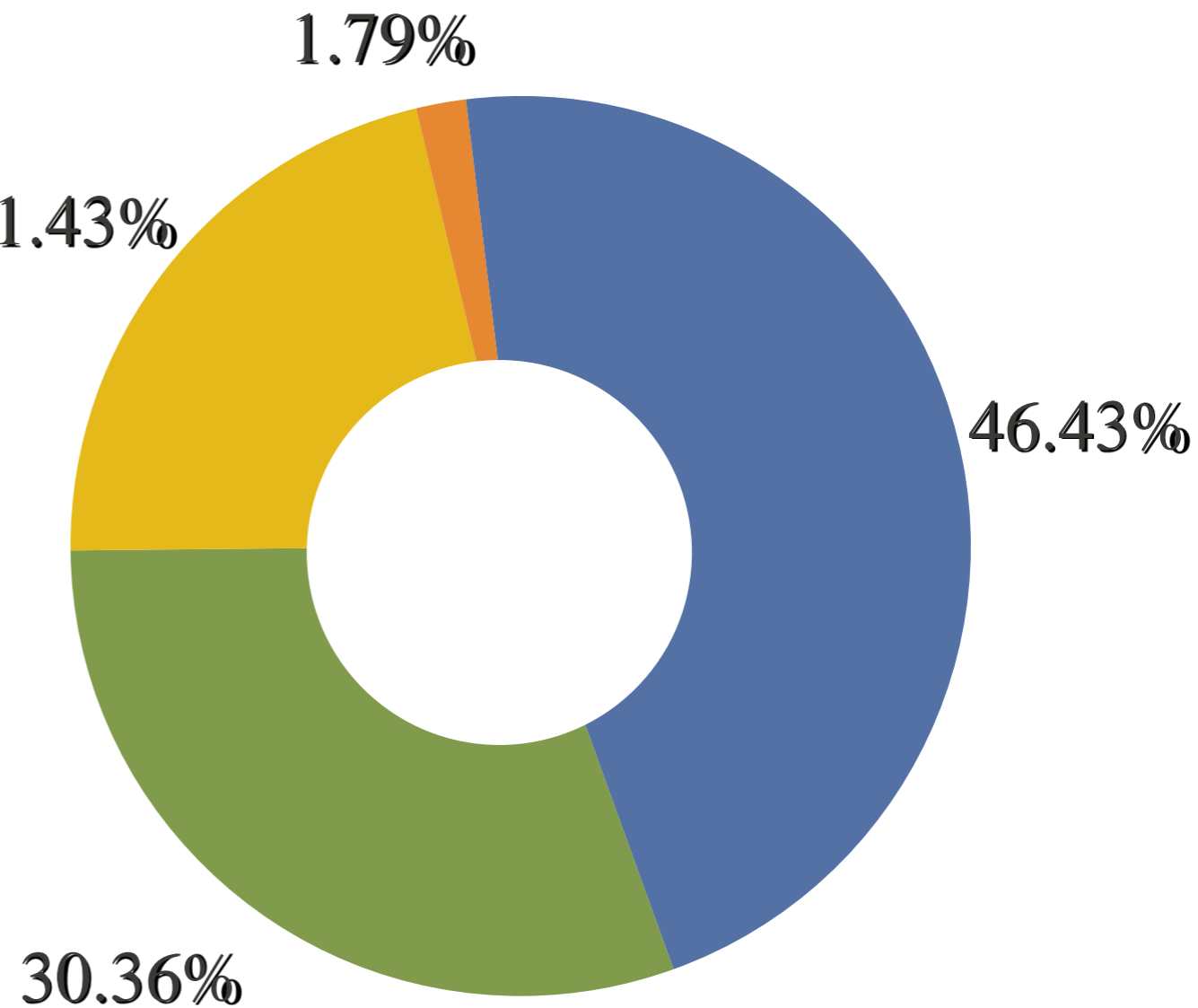
# Facts 基礎資料

## Type of Study 研究类型



- Review (綜述)
- Systematic review metanalysis (薈萃分析)
- Dermatological study (調查分析)
- Original study (原創性研究)

## Study Subjects 研究对象



- Single Compound (單體)
- Single Herbal Extracts (單味中藥提取物)
- Formula (複方)
- Qigong (氣功)

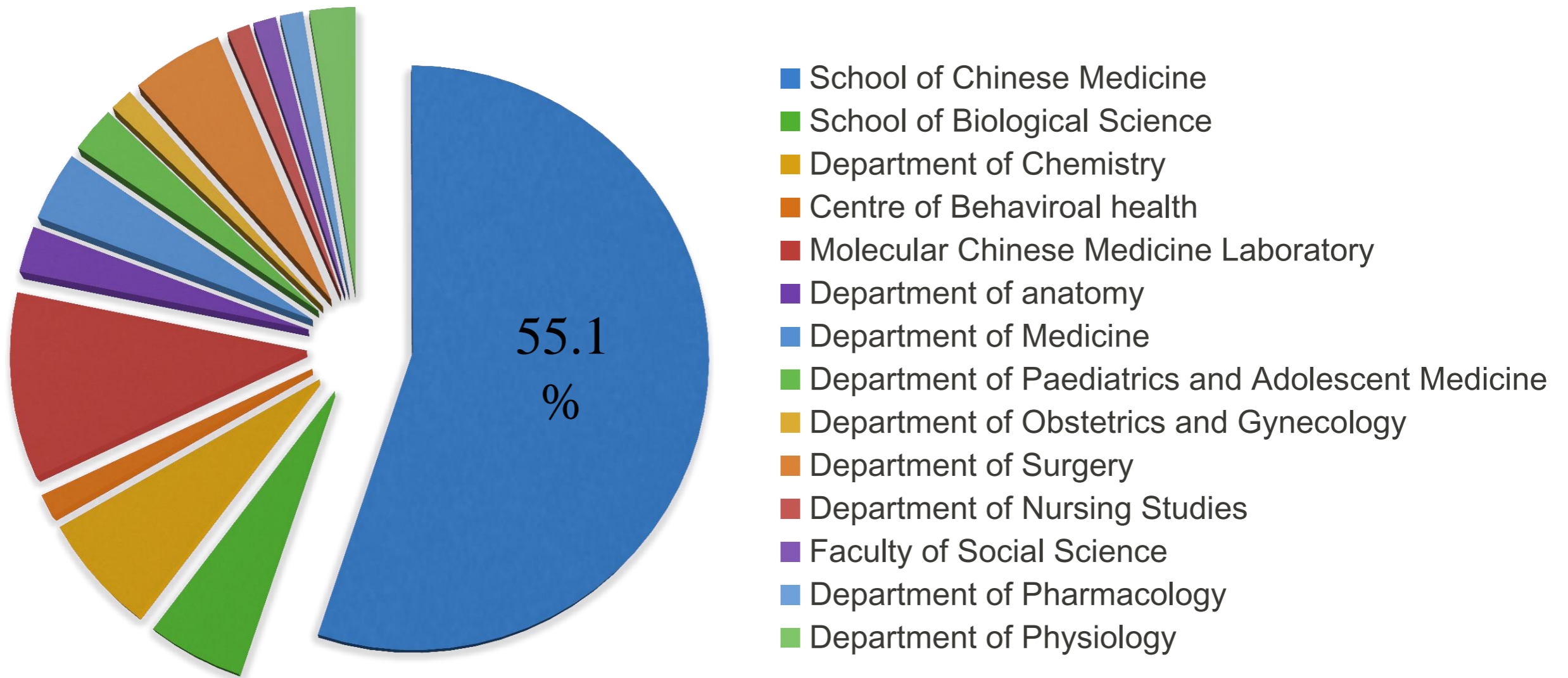


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# Department Contribution

## 各部门发表研究工作比例

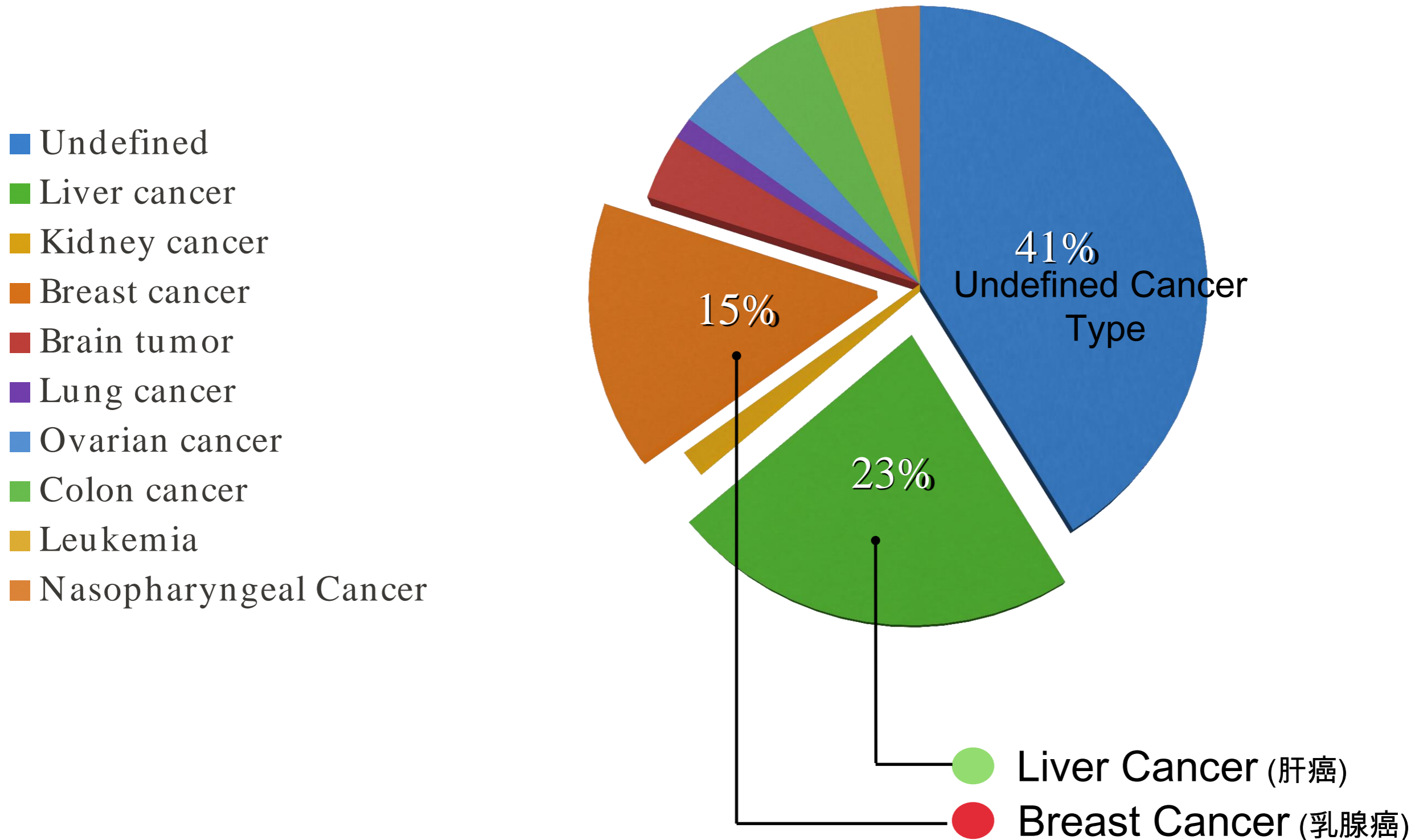


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# Cancer Type Distribution

## 研究涉及的腫瘤類型分佈



# 香港大學中醫藥的腫瘤研究的類型：

- 1) Research on new drug derived from Chinese medicines for new treatment.  
從中醫藥中開發抗腫瘤新藥.
- 2) Research on complementary and alternative treatments to WM.  
從中醫藥中開發抗腫瘤補充和替代新療法.
- 3) Research on Science and art of CM.  
研究中醫藥自身抗腫瘤的科學和藝術.

# Three types of Anticancer CMs

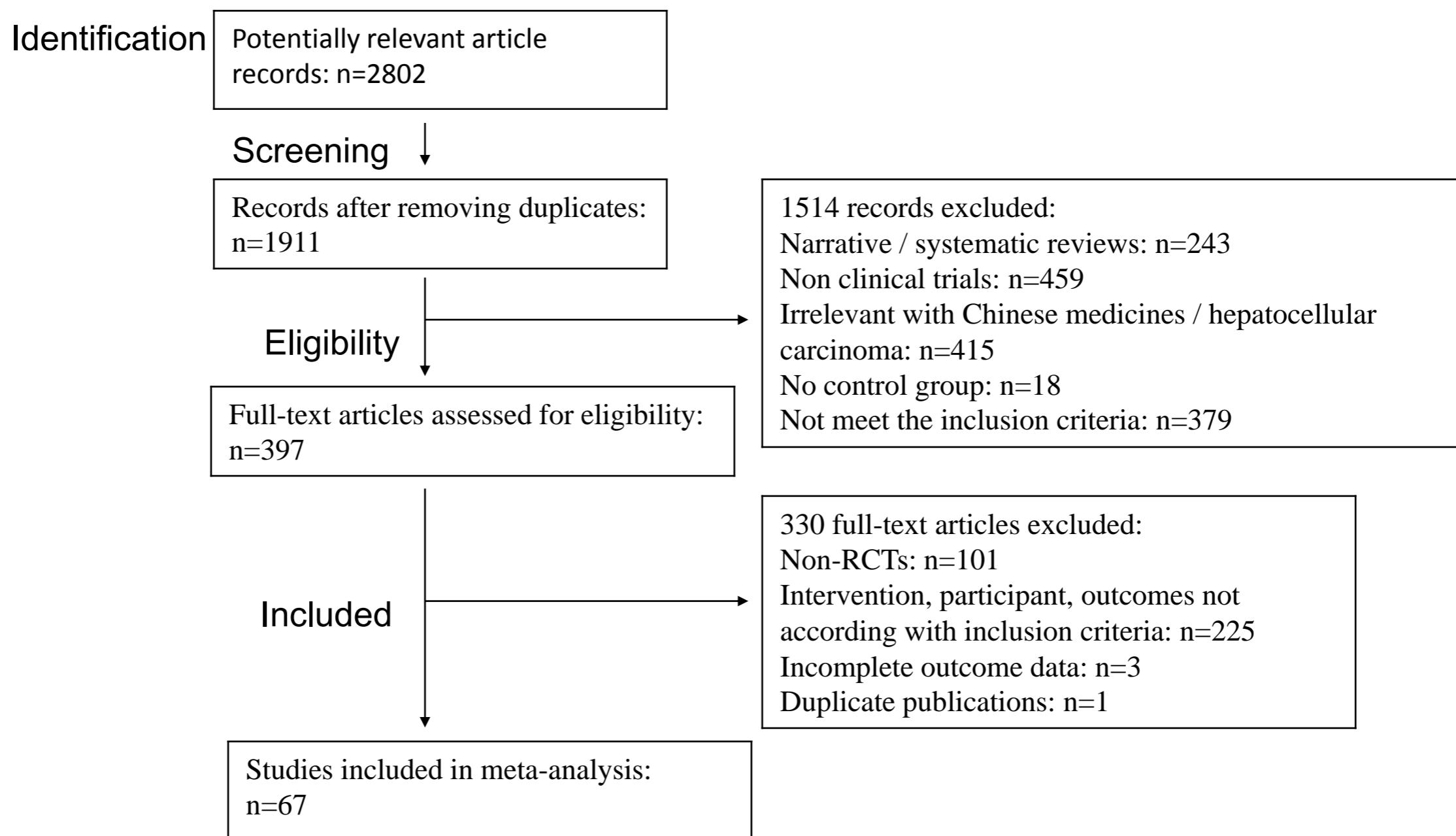
## 三大類抗癌中藥

- Anticancer candidates in patents of herbal medicinal products 各國來自於中藥及其他草藥的抗癌專利
  1. 15 single compounds and 42 extracts derived from single herbs 15個單體和42個單個植物提取物
  2. 8 combinations of single compound or formulae 8個單體或複方的組合
  3. 17 single compounds, extracts or formulae in phase 1 or II studies 17個單體，提取物或複方在進行一期或二期的臨床試驗

(Feng Y\*, Wang N, Zhu M, Feng Y, Li H, Tsao S. Recent progress on anticancer candidates in patents of herbal medicinal products. Recent Pat Food Nutr Agric. 2011; 3(1):30-48)

# Chinese medicines as an adjuvant therapy for unresectable hepatocellular carcinoma during transarterial chemoembolization: a meta-analysis of randomized controlled trials

## 中醫藥在肝癌動脈栓塞化療中作為輔助治療的薈萃分析

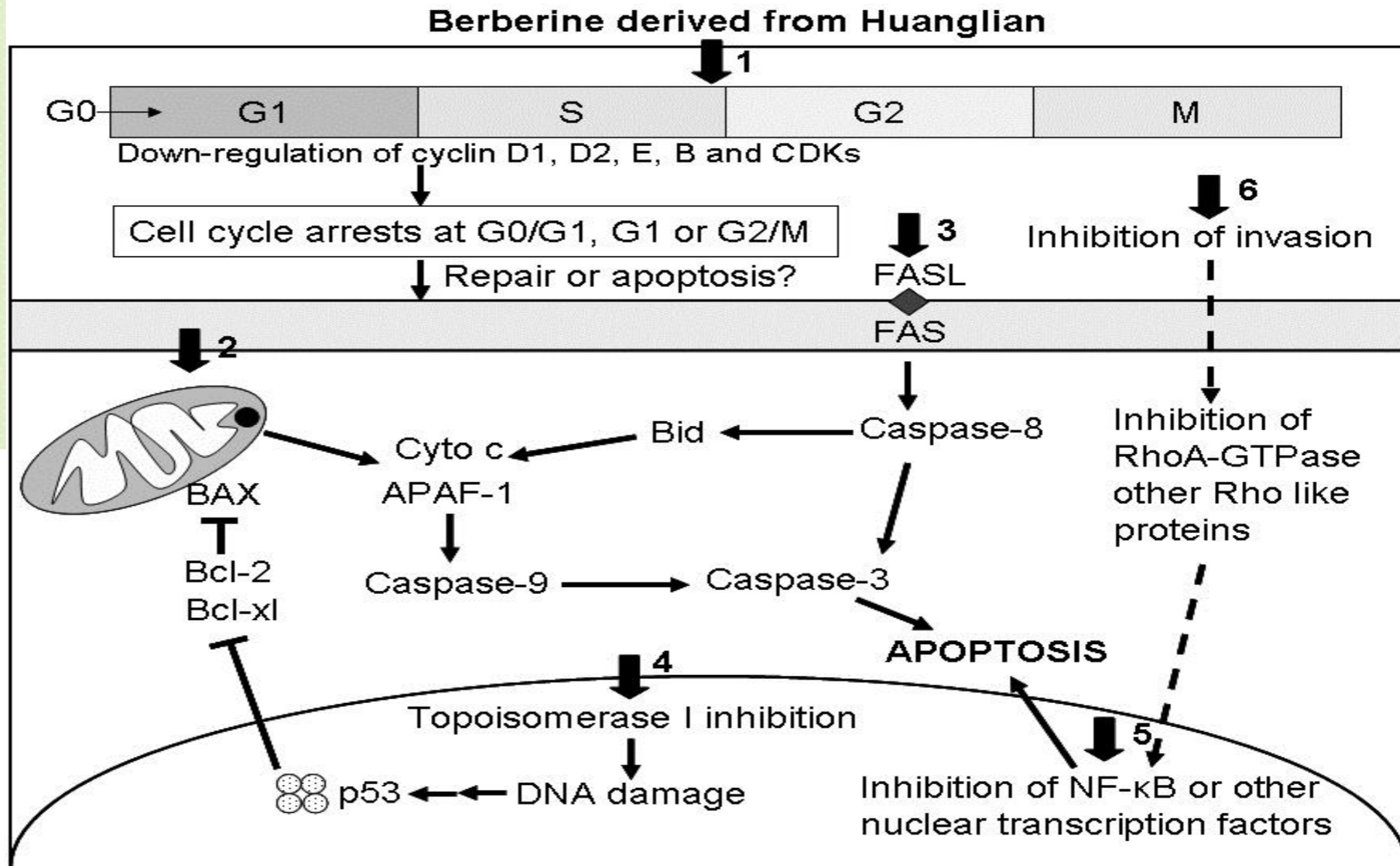




## Appendix C. The Top 10 most frequently used CMs of the included studies. eCAM 20130718

CM Herb Latin Name (Chinese Pinyin)	No.	TCM Diagnosis	Pharmacological Properties
Radix Astragali (黄芪)	35	Qi deficiency	<ol style="list-style-type: none"> <li>1. Suppresses the oncogenic transformation of cancer cells<sup>1</sup>;</li> <li>2. Induces apoptosis<sup>2</sup>;</li> <li>3. Induces macrophage, LAK and NK cell activity<sup>3, 4</sup>;</li> <li>4. Inhibits T-helper cell type 2 cytokines<sup>4</sup>.</li> </ol>
Poria Cocos (茯苓)	25	Dampness accumulation	<ol style="list-style-type: none"> <li>1. Induces apoptosis<sup>5, 6</sup>;</li> <li>2. Cytotoxicity against cancer cell lines<sup>5</sup>;</li> <li>3. Inhibits tumor angiogenesis <sup>7</sup>.</li> </ol>
Rhizoma Atractylodis Macrocephalae (白朮)	23	Qi deficiency	<ol style="list-style-type: none"> <li>1. Induces apoptosis <sup>8, 9</sup></li> </ol>
Radix Ginseng (人參)	19	Qi deficiency	<ol style="list-style-type: none"> <li>1. Induces apoptosis <sup>10, 11</sup>;</li> <li>2. Inhibits tumor cell proliferation <sup>11</sup>;</li> <li>3. Cytotoxicity against cancer cell lines <sup>12, 13</sup>;</li> <li>4. Inhibits tumor angiogenesis <sup>14</sup>.</li> </ol>
Radix Bupleuri (柴胡)	19	Qi stagnation	<ol style="list-style-type: none"> <li>1. Induces apoptosis <sup>15</sup>;</li> <li>2. Activates macrophages, NK and LAK cells <sup>16</sup>;</li> <li>3. Down-regulates TNF-<math>\alpha</math>, IL-6 and NF-kB p65 expression <sup>17</sup>.</li> </ol>
Radix Codonopsis (丹參)	18	Qi deficiency	<ol style="list-style-type: none"> <li>1. Inhibit cancer cells invasion and migration <sup>18</sup>;</li> <li>2. Enhances T cell, B cell and macrophage production, and activates macrophages <sup>19</sup>.</li> </ol>
Semen Coicis (薏苡仁)	15	Dampness accumulation	<ol style="list-style-type: none"> <li>1. Induces apoptosis <sup>20</sup>;</li> <li>2. Inhibits NF-kB signaling and protein kinase C activity <sup>21</sup>;</li> <li>3. Stimulates T cell proliferation<sup>22</sup>.</li> </ol>
Herba Oldenlandia Diffusa (白花蛇舌草)	14	Fire toxin	<ol style="list-style-type: none"> <li>1. Inhibits cancer cell proliferation and induces apoptosis<sup>23, 24</sup>.</li> </ol>
Radix Paeoniae Alba (白芍)	13	Blood deficiency	<ol style="list-style-type: none"> <li>1. Inhibits angiogenesis and induces apoptosis<sup>25, 26</sup>.</li> </ol>
Rhizoma Curcumae (莪朮)	12	Blood stagnation	<ol style="list-style-type: none"> <li>1. Inhibits cancer cell proliferation and angiogenesis, induces cell cycle arrest and apoptosis <sup>27</sup>;</li> <li>2. Inhibits platelet aggregation<sup>28</sup>.</li> </ol>

# 黃連及其黃連素作為新的抗癌藥：傳統應用和現代研究



Tang J, Feng Y\*, Tsao S, Wang N, Curtain R, Wang Y. Berberine and Coptidis Rhizoma as novel antineoplastic agents: A review of traditional use and biomedical investigations. *Journal of Ethnopharmacology* 2009; 126:5-17.

# Case Study: Coptis and its formulae

## 實例:黃連及其複方

- under the category of clearing heat
- 属于清热解毒药

- detoxify, purify liver, improve eyesight, as well as treating eclampsia, epilepsy, tic caused by fire, carbuncle of heat type, pyocutaneous diseases
- 解毒,清肝,明目,用于治疗热毒引起的目赤,口疮等

- Huang Lian Jie Du Tang, Ge Gen Qin Lian Tang, Zuo Jin Wan etc.
- 常用方剂有100多個, 諸如黄连解毒汤,葛根芩连汤,左金丸等

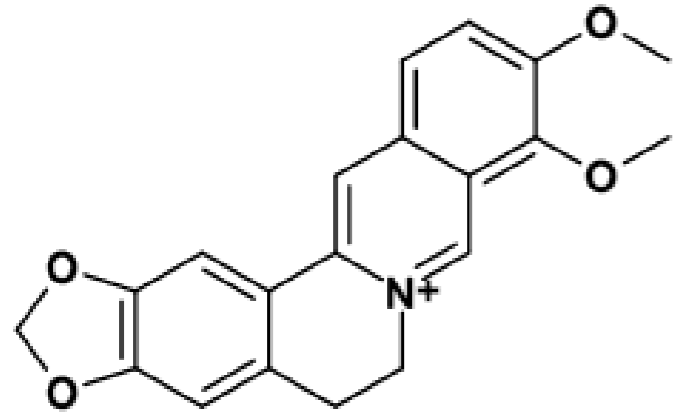


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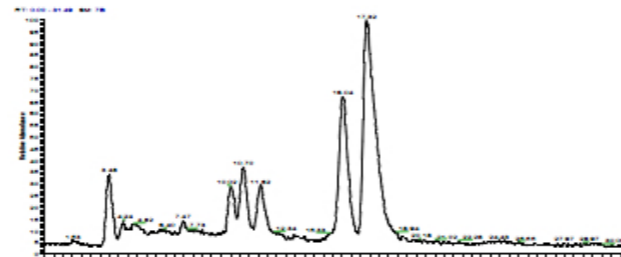
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# Research Strategies (研究策略)



Berberine



Huanglian Extract  
黃連提取物



Huanglian



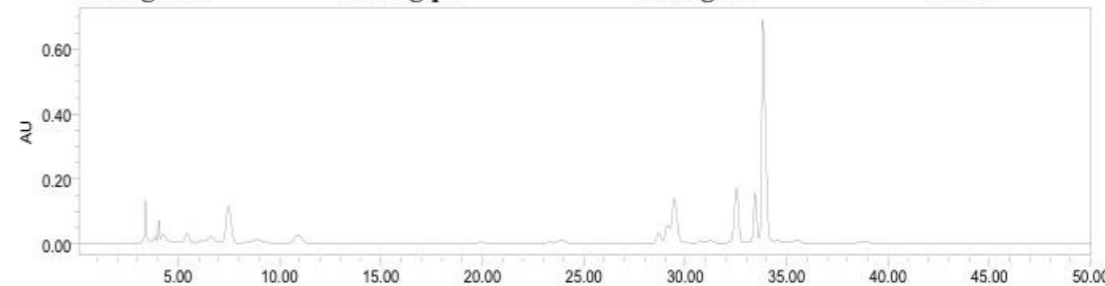
Huangqin



Huangbai



Zhizi



Huanglian Formula  
黃連複方

Traditional use  
傳統用法

Biomedical investigations  
現代生物醫學研究

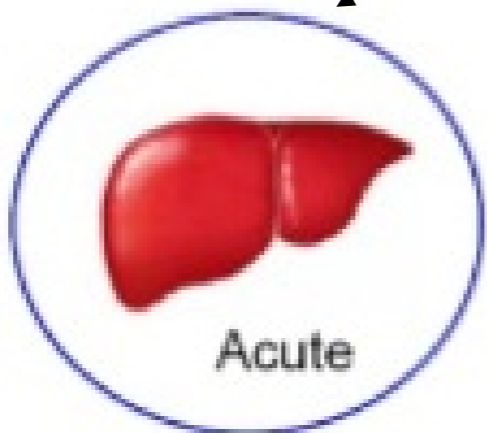
Novel protection  
and antineoplastic  
agents for liver  
治療肝病新型藥物

Removing damp-  
heat, fire and  
counteracting  
toxicity

清熱解毒



Normal liver



Acute

Acute  
Hepatitis  
急性肝炎



Chronic liver  
inflammation

Chronic  
Hepatitis  
慢性肝炎



Liver  
Cirrhosis

Fibrosis 15-40 yrs  
纖維化15-40年



HCC

HCC  
肝癌

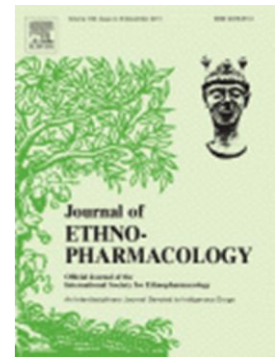
Sustained injury  
長期慢性損傷

Time (min)



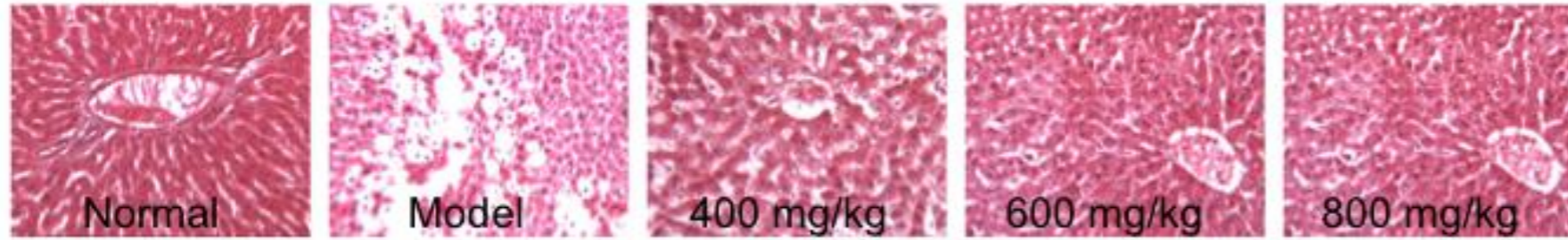
# Huanglian in treating Acute Hepatic Injury

## 黃連用於治療急性肝損傷



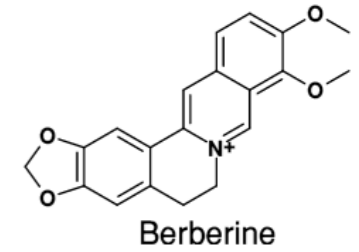
Effect of CRAE and berberine on CCl<sub>4</sub>-induced liver damage in rat (mean ± S.D., n=8).

Group	ALT (U, in serum)	AST (U, in serum)	SOD (%, in serum)	SOD (%, in tissue)
Normal	19.877 ± 7.34	61.759 ± 30.62	77.26 ± 0.11	72.42 ± 5.89
Control	133.27 ± 32.11**	342.11 ± 55.27**	10.80 ± 0.21**	9.32 ± 5.31**
CRAE 400 mg/kg	66.26 ± 11.24**	366.22 ± 52.16**	26.70 ± 0.23*	21.61 ± 4.97*
CRAE 600 mg/kg	41.17 ± 10.66**	155.39 ± 30.24*	40.30 ± 0.15*	46.22 ± 4.46*
CRAE 800 mg/kg	23.29 ± 12.76**	20.78 ± 10.77**	73.70 ± 0.20**	70.63 ± 6.54**



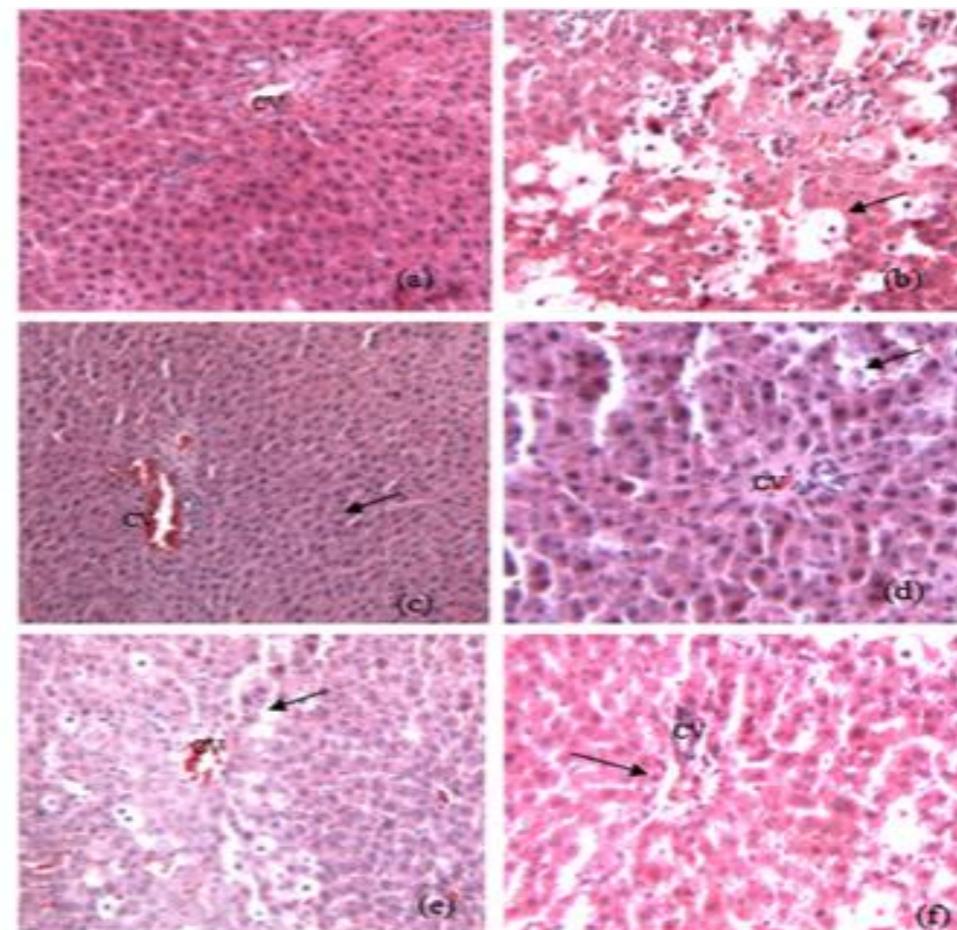
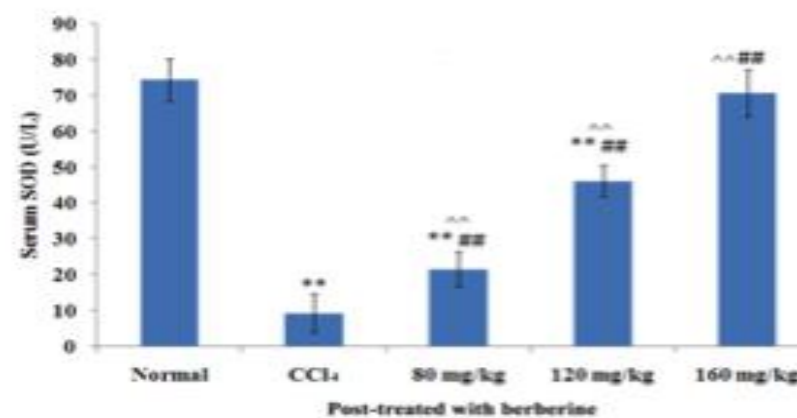
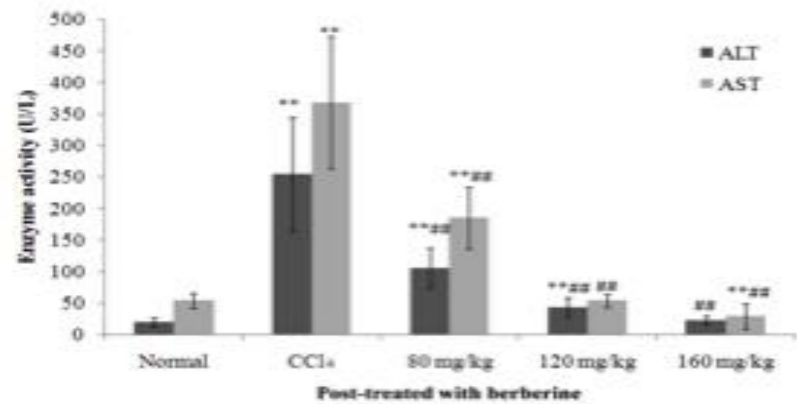
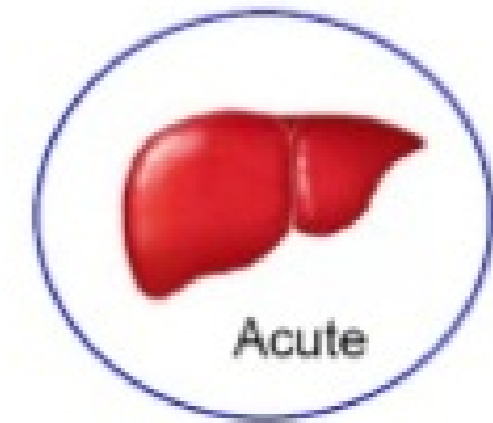
Microscopic observation on CRAE and berberine against CCl<sub>4</sub>-induced acute liver damage (mean ± S.D., n=8).

Group	Vacuolation	Nuclei	Hepatocyte necrosis	Inflammatory cell infiltration	Central vein and portal triad	Combined score
Normal	0.4 ± 0.3	1.0 ± 0.7	0.5 ± 0.2	0.6 ± 0.3	1.1 ± 0.6	0.5 ± 0.3
Control	5.0 ± 0.6**	0.7 ± 0.2	4.2 ± 0.8**	3.9 ± 1.6**	0.5 ± 0.3*	4.9 ± 0.5**
CRAE 400 mg/kg	4.2 ± 1.1*	0.8 ± 0.6	2.2 ± 1.7*	2.8 ± 1.3*	1.3 ± 0.8*	3.6 ± 1.4*
CRAE 600 mg/kg	3.0 ± 1.0**	1.1 ± 0.3	2.1 ± 1.5**	2.1 ± 1.3**	1.1 ± 0.6*	2.7 ± 0.9**
CRAE 800 mg/kg	1.9 ± 0.7**	1.2 ± 0.6	1.5 ± 1.2**	1.3 ± 0.9**	0.9 ± 0.5	1.7 ± 0.6**



Anti-oxidant  
抗氧化因數

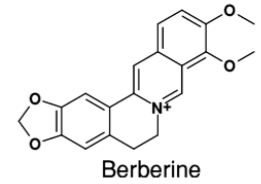
Pathogens  
致病因數





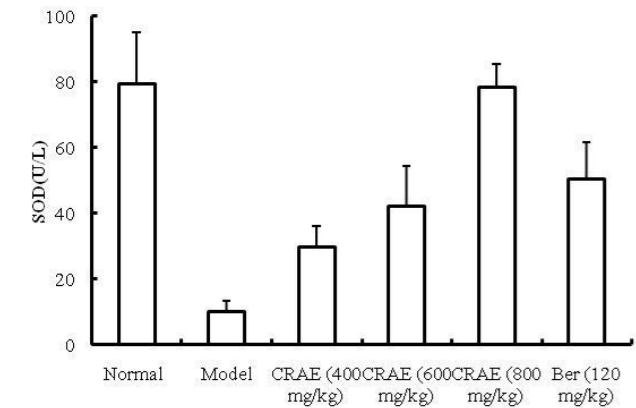
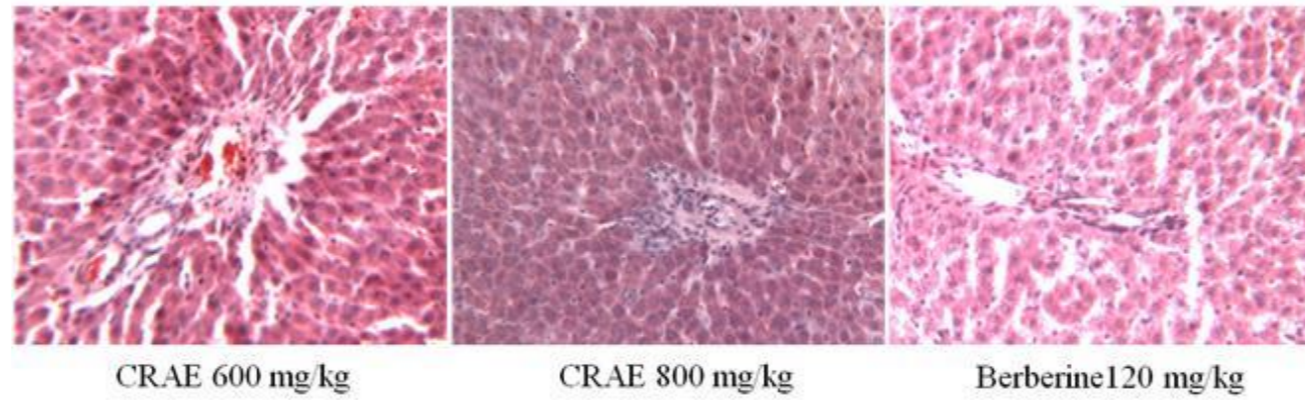
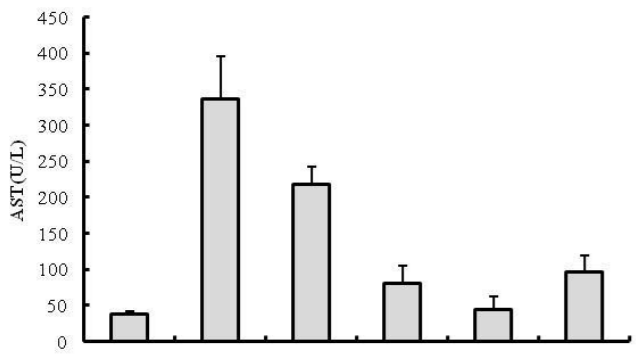
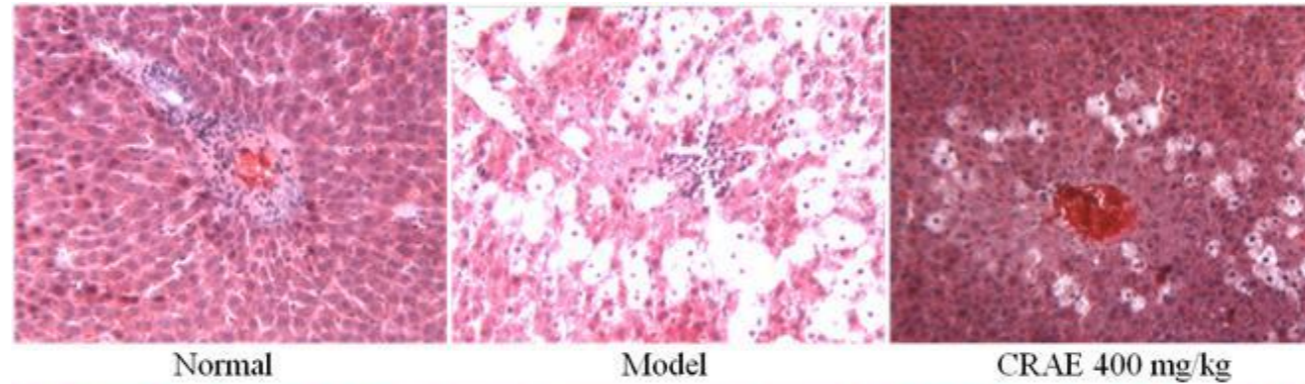
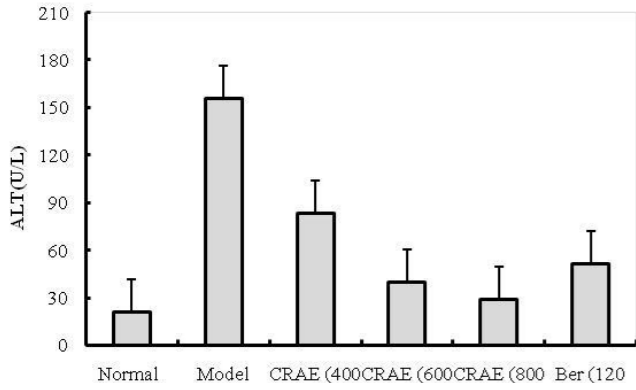
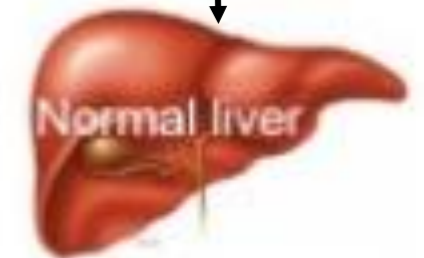
# Huanglian in treating Chronic Hepatic Injury

## 黃連用於治療慢性肝損傷

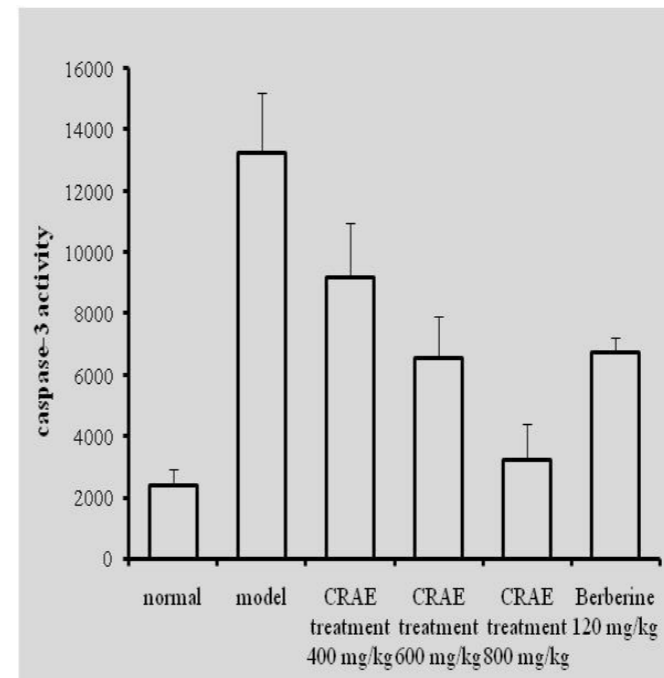
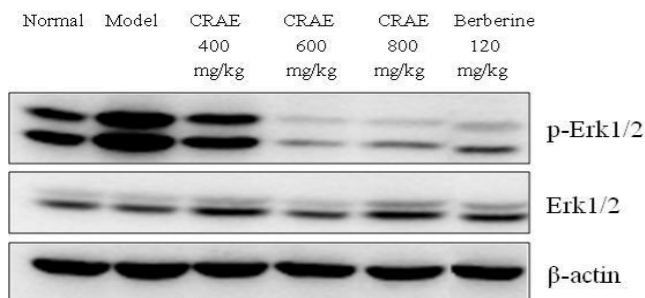
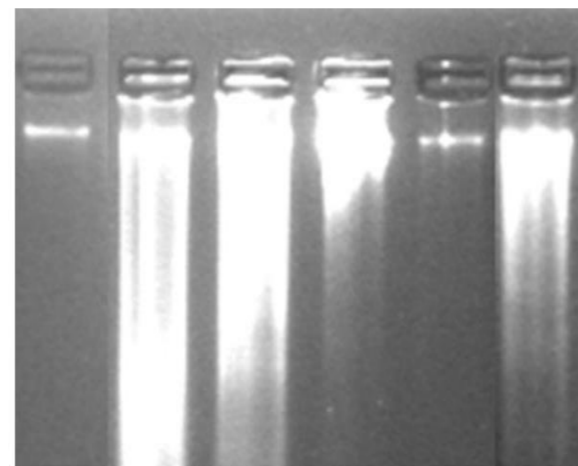


Anti-oxidant  
抗氧化因數

Inflammation-related  
hepatocyte apoptosis  
炎症誘導的肝細胞凋亡



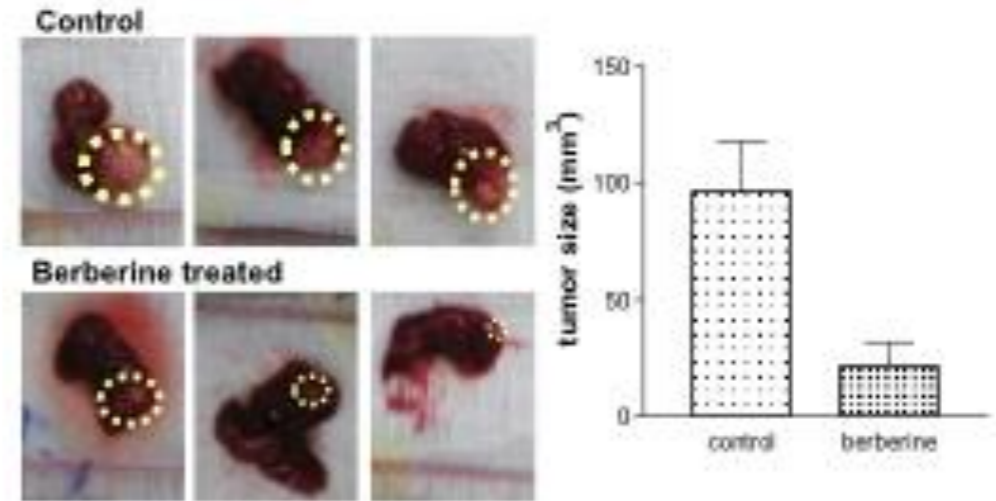
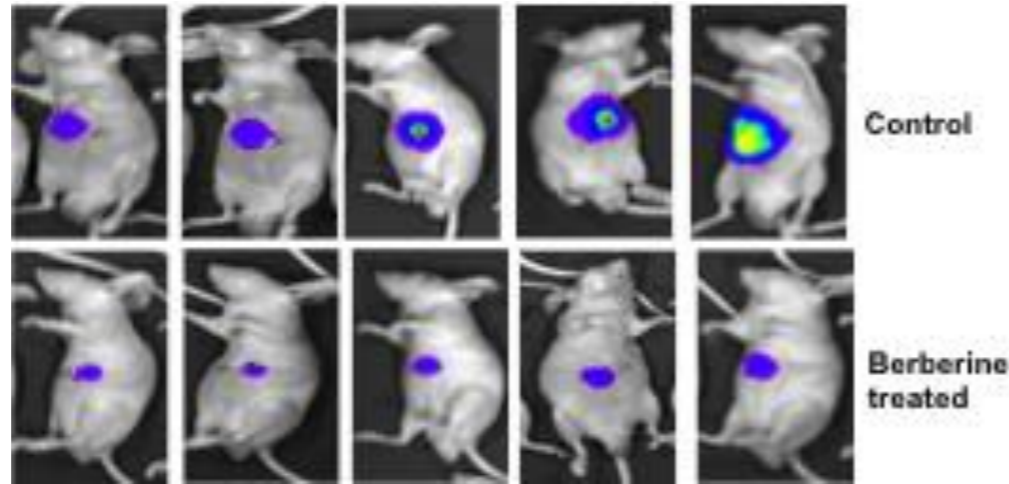
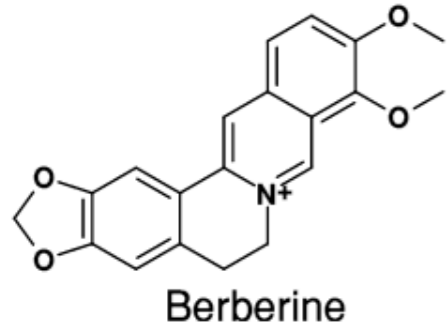
Normal	Model	CRAE 400 mg/kg	CRAE 600 mg/kg	CRAE 800 mg/kg	Berberine 120 mg/kg
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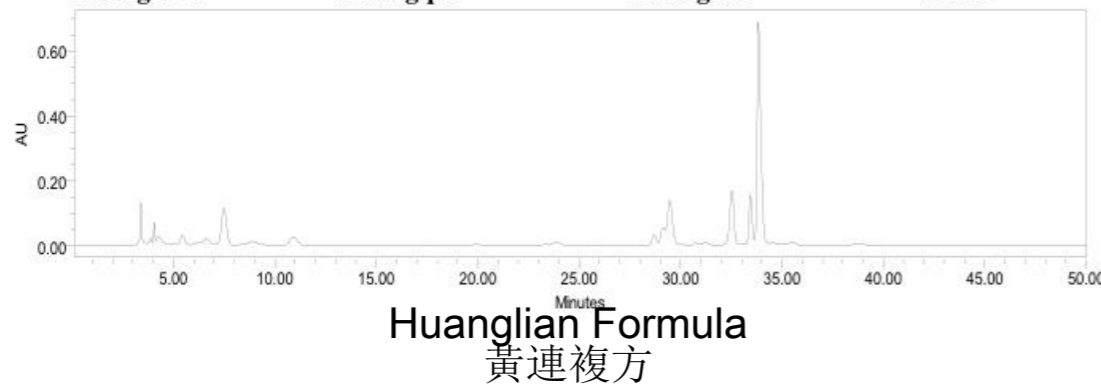
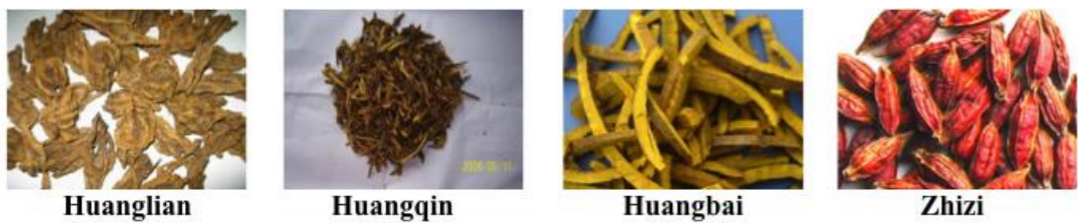
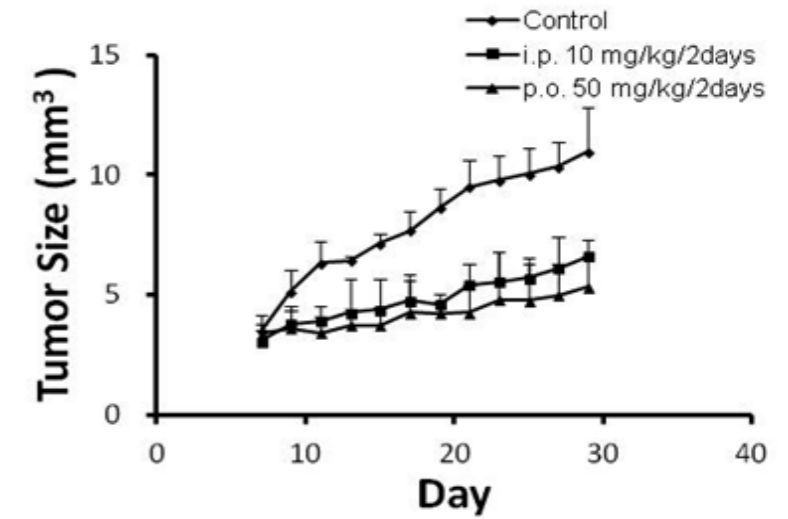
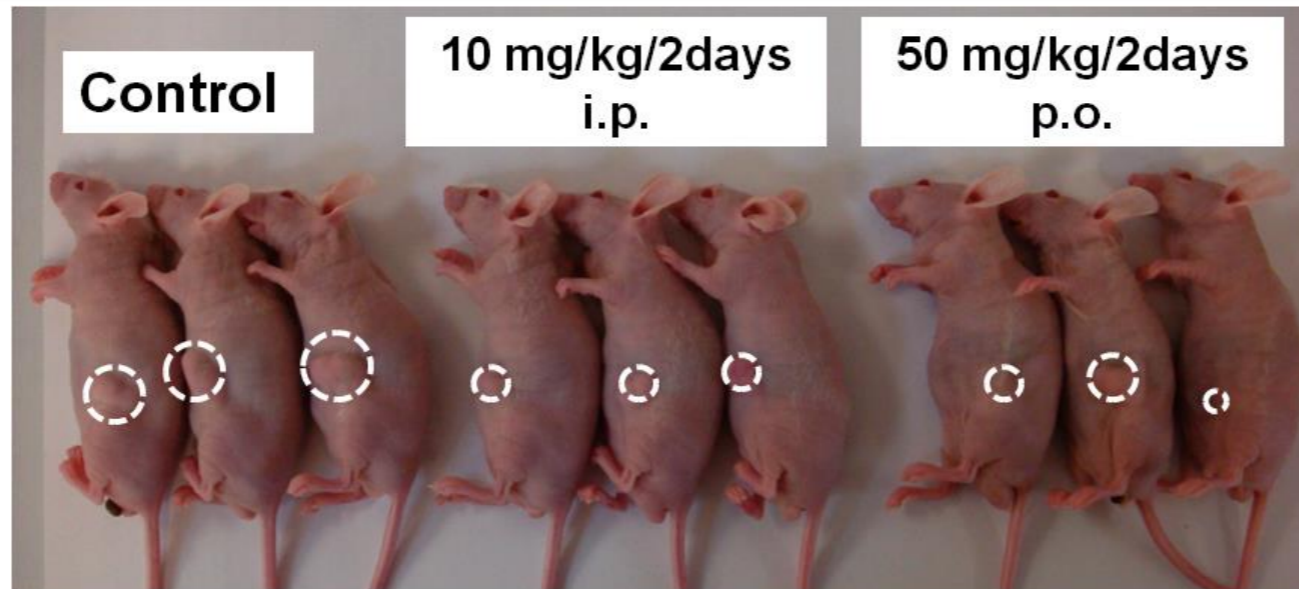


# Huanglian in treating Hepatocellular Carcinoma

## 黃連及其複方用於治療肝癌

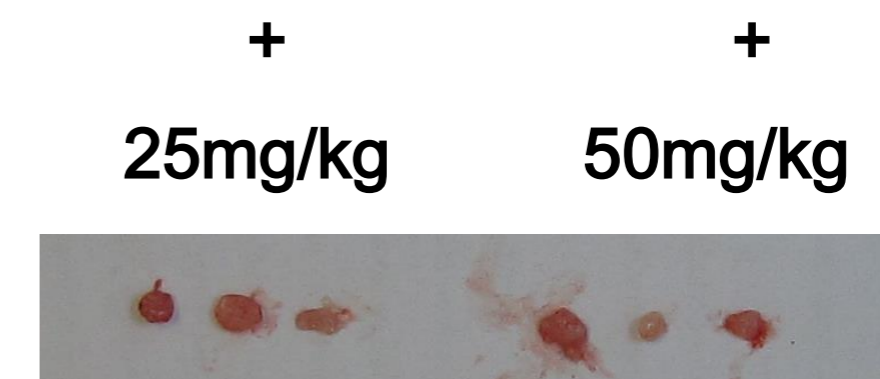


Huanglian Extract  
黃連提取物



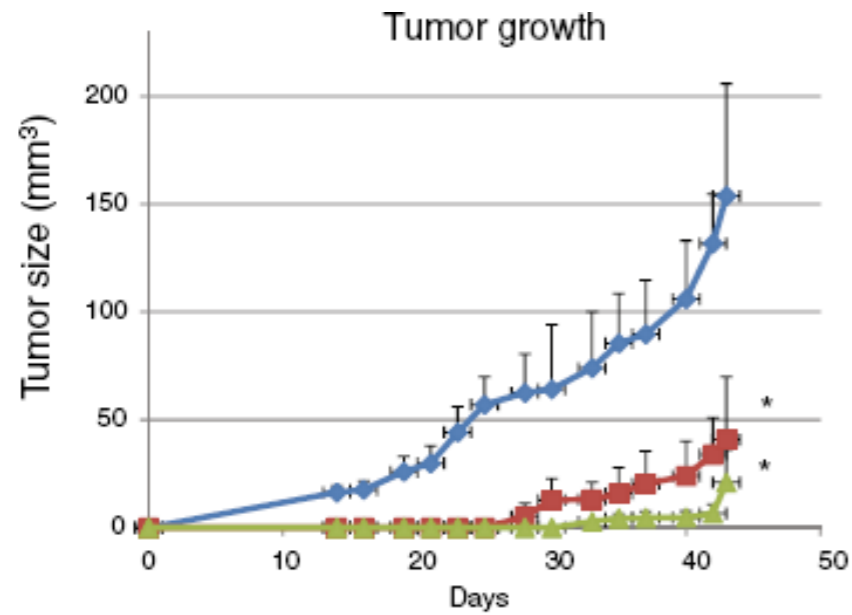
Doxorubicin  
多柔比星

Doxorubicin  
HLJDD  
多柔比星 +  
黃連複方

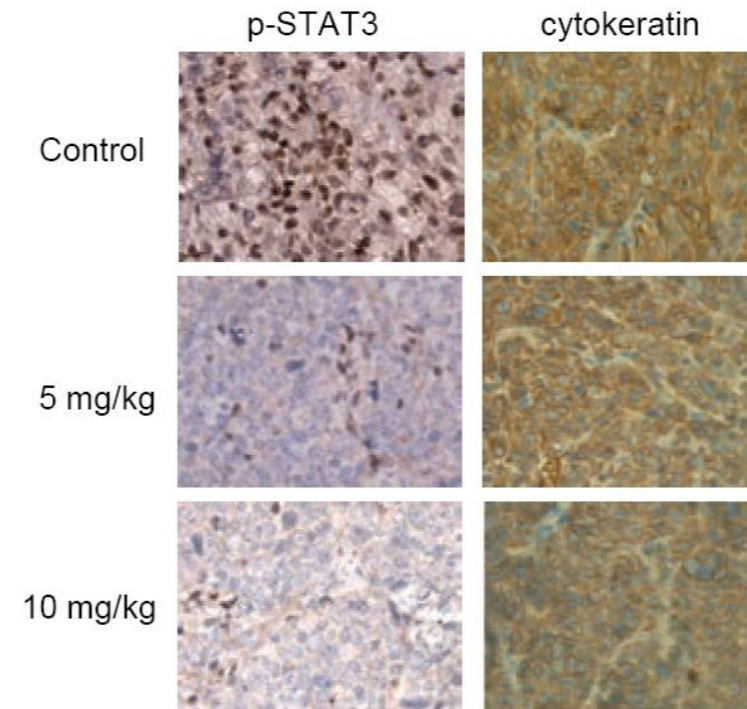


# Example: Huanglian for NPC Treatment

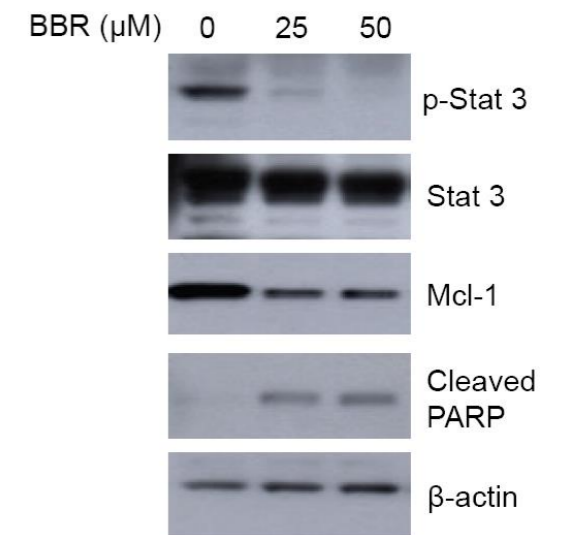
## 黃連用於鼻咽癌的治療



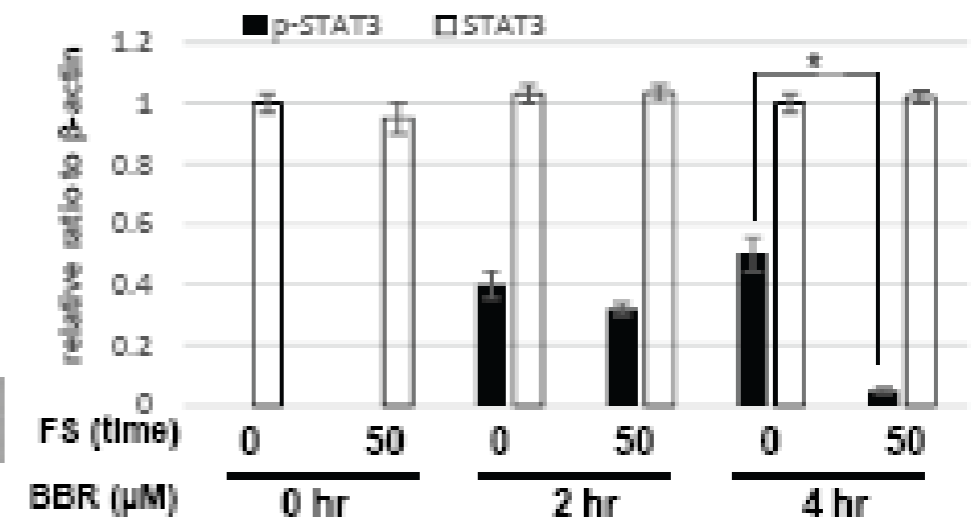
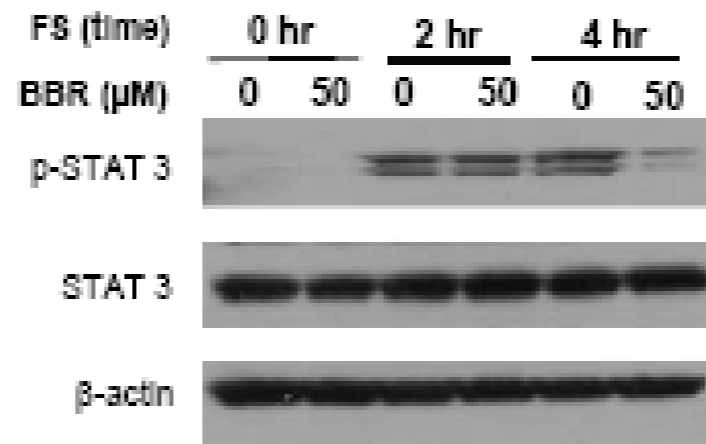
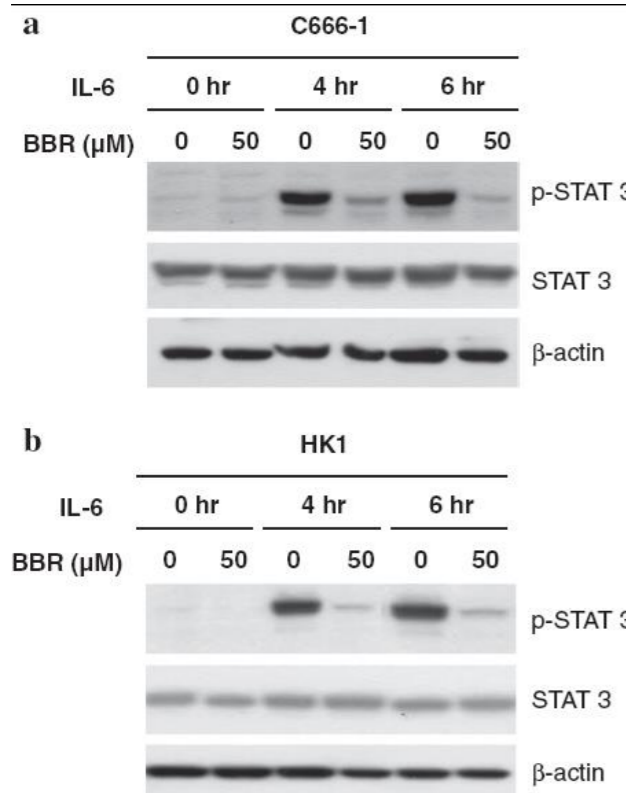
Suppression of tumorigenicity and growth of NPC cells by berberine *in vivo*.



Activation of STAT3 was inhibited by berberine *in vivo*.



Constitutive activation of STAT3 was downregulated by berberine in HONE1 cells



Berberine could inhibit the activation of STAT3 induced by IL6-containing Fibroblast Supernatant (FS). 50 μM of berberine could effectively suppress the FS-induced STAT3 activation at 4 hr time points.

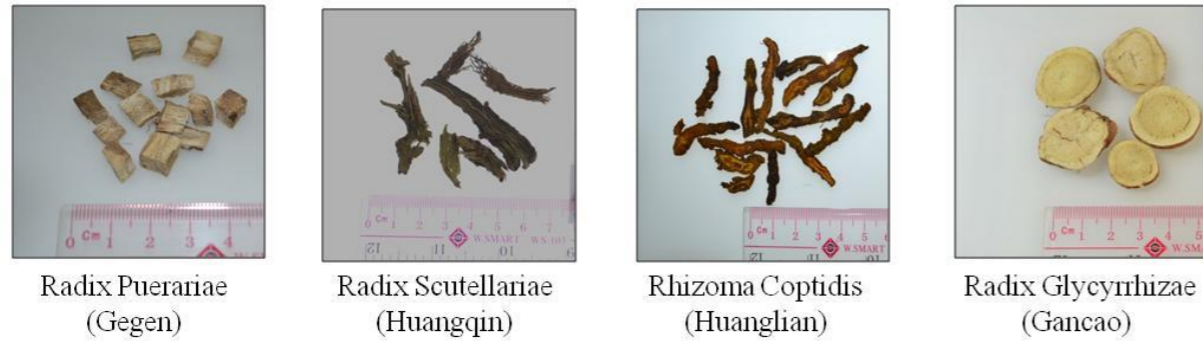
Berberine inhibited the IL-6-activated STAT3 in C666-1 and HK1 cells.



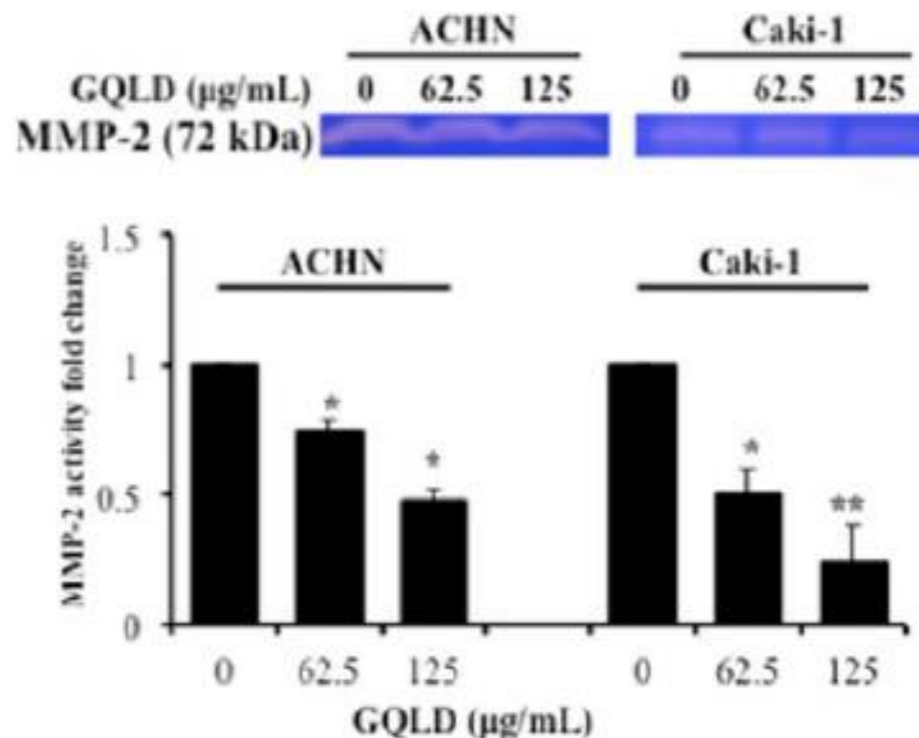
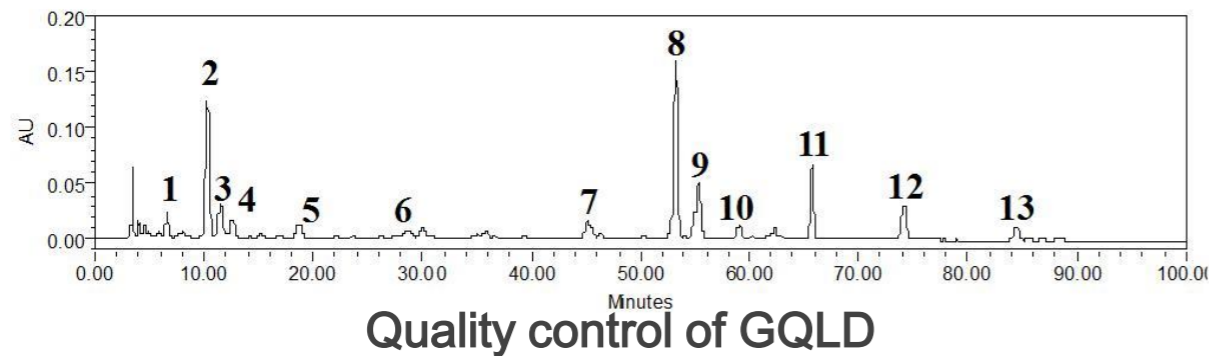
# Example: Renal Cancer Treatment

## 葛根芩連湯用於腎癌的治療

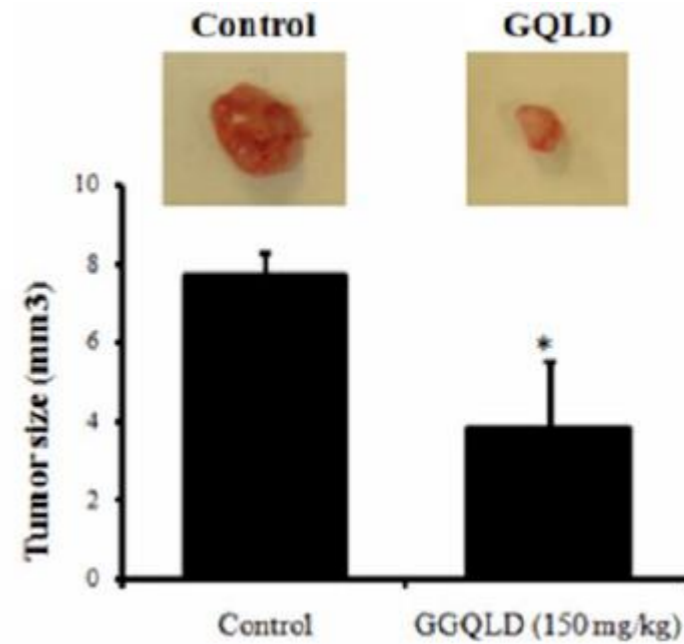
(A)



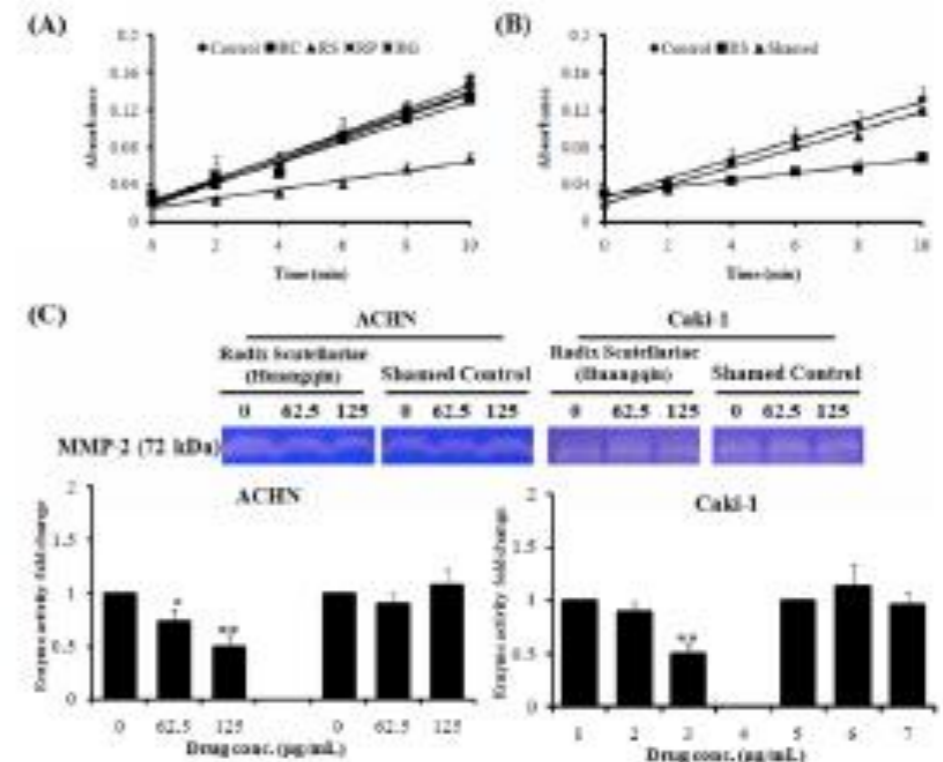
(B)



gelatinase activity of MMP-2 could be potently inhibited by 48-hour GQLD treatment in ACHN and Caki-1 cells.



GQLD has significant inhibition on the size of xenografted tumor

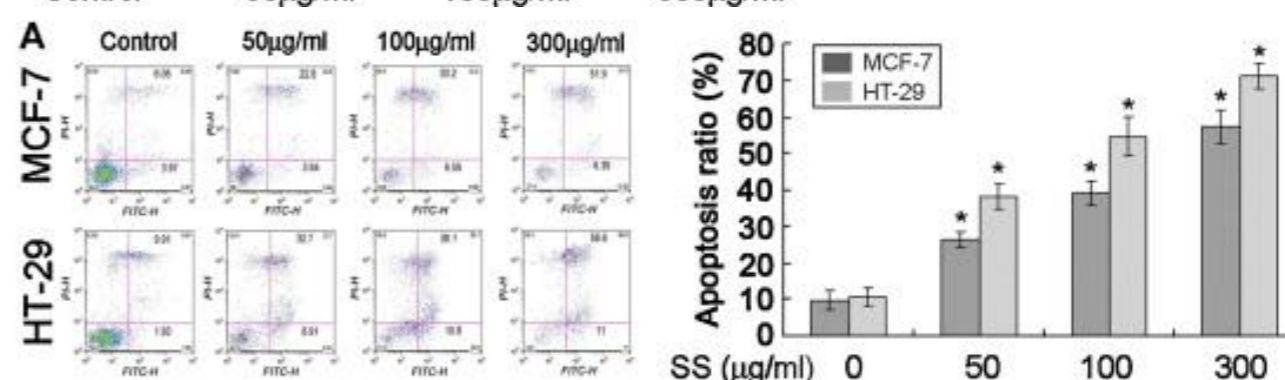
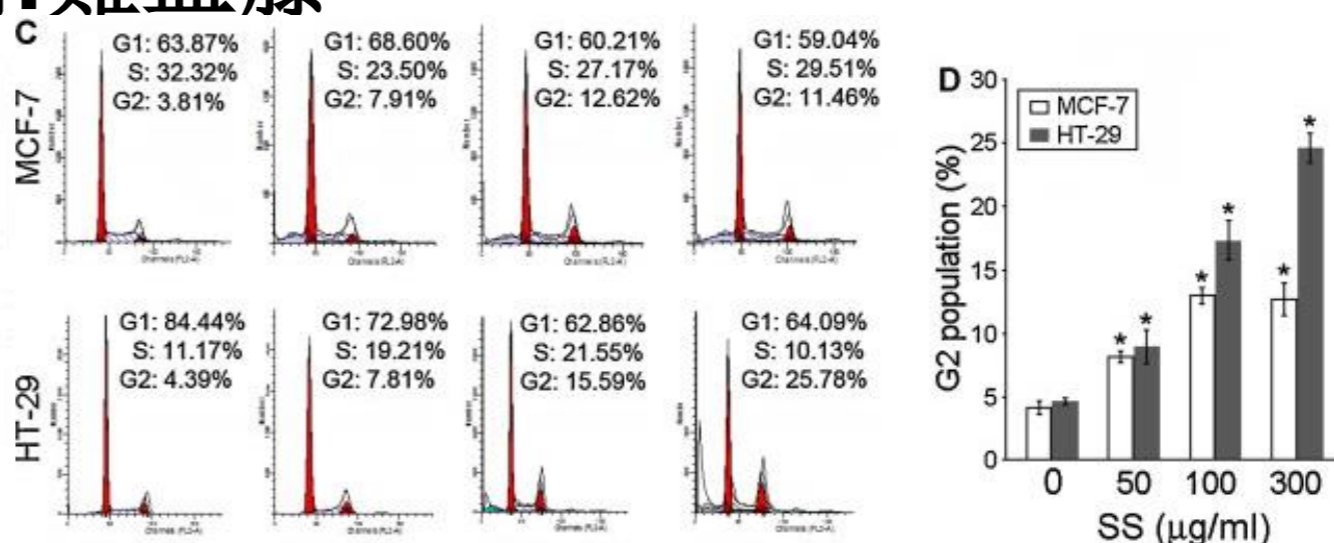
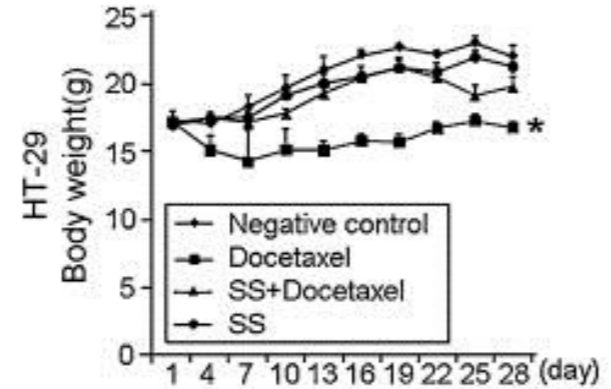
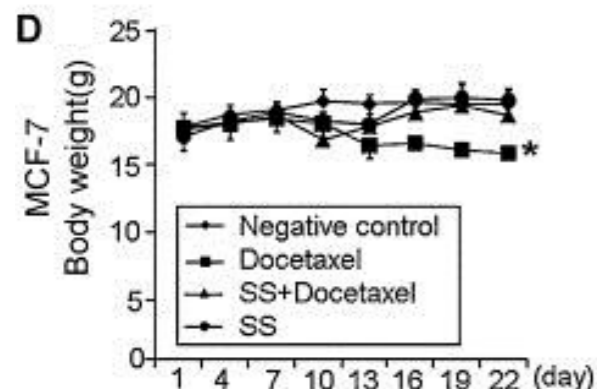
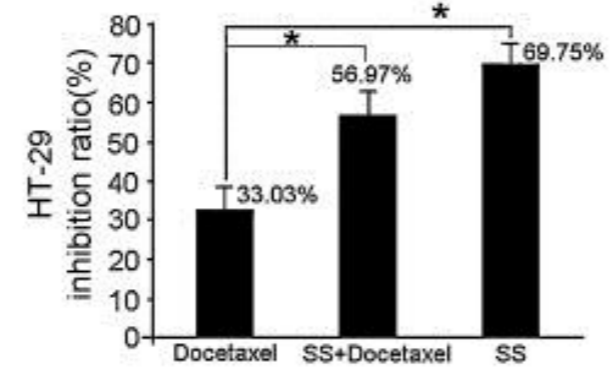
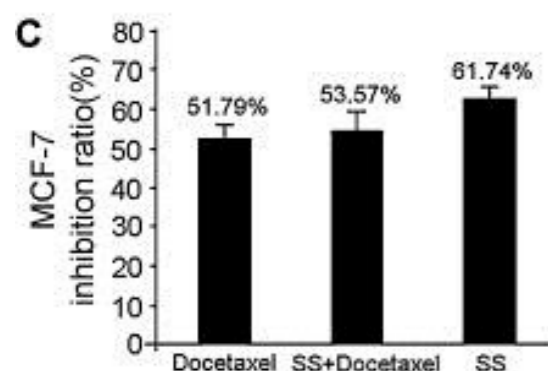
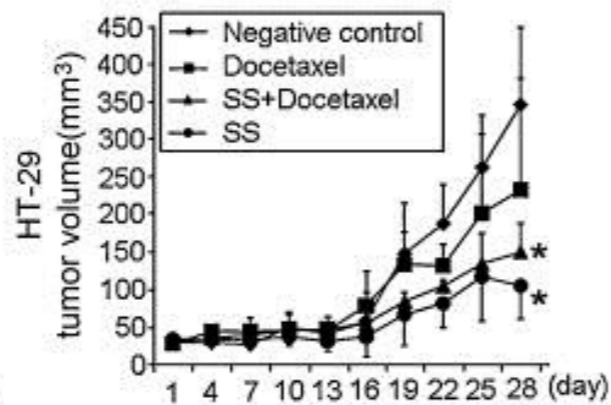
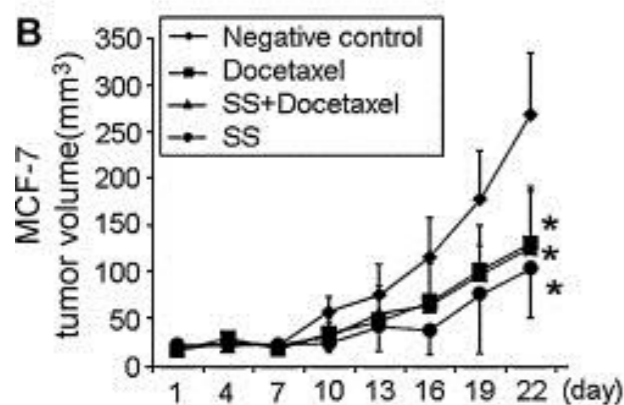
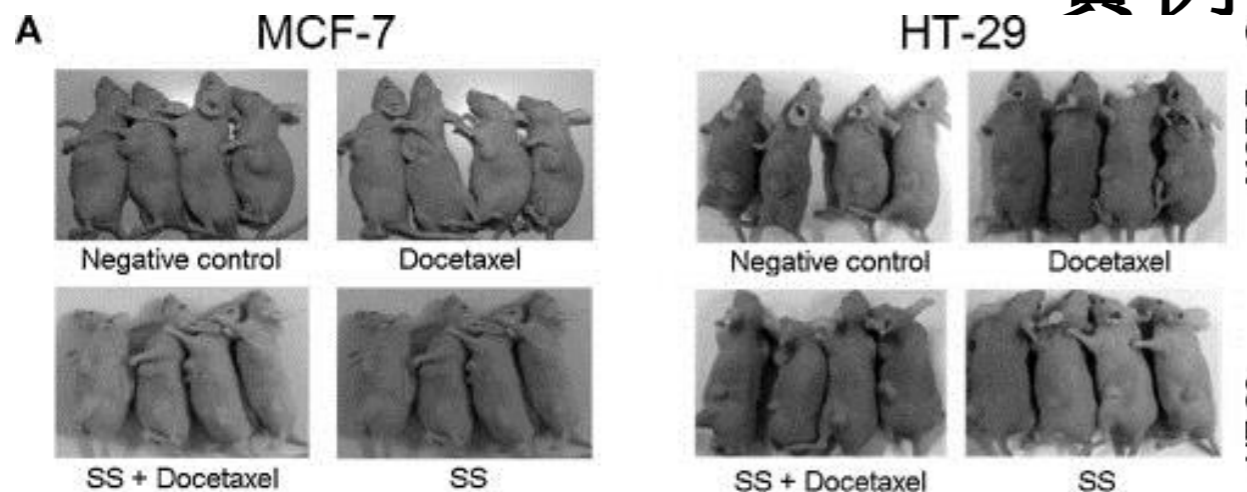


Radix Scutellariae (*Huangqin*) is the major active component herb in GQLD.

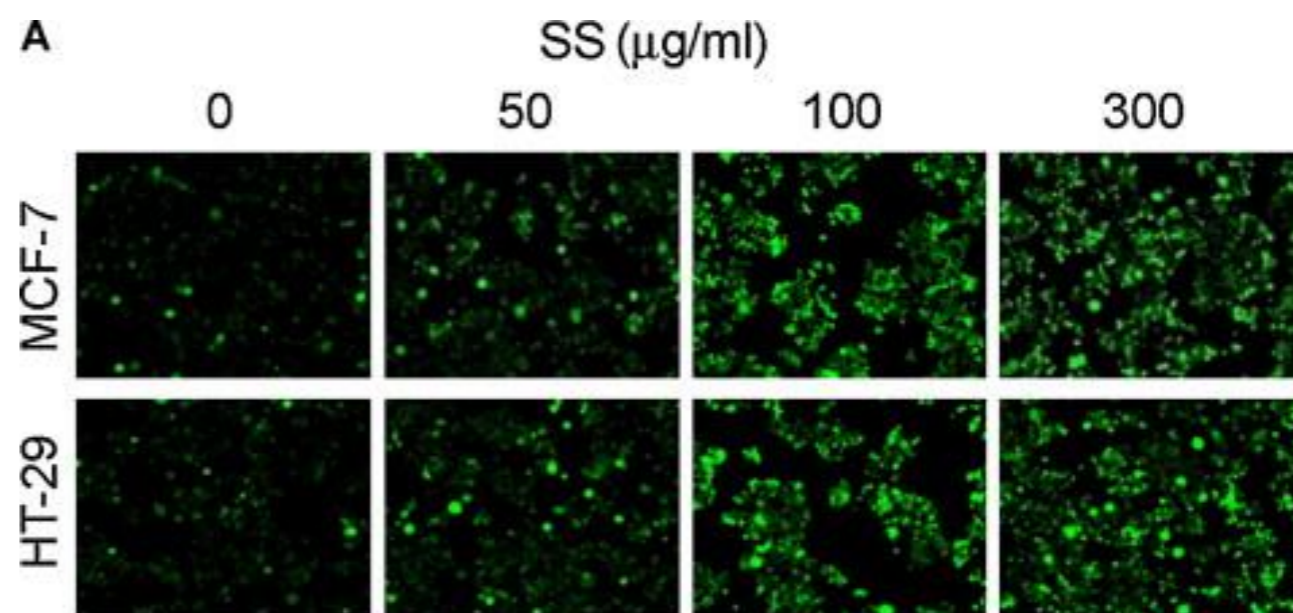


# Case Study: *Spatholobus suberectus* (Jixueteng)

## 實例: 雞血藤



SS induced G2/M arrest and apoptosis to cancer cells



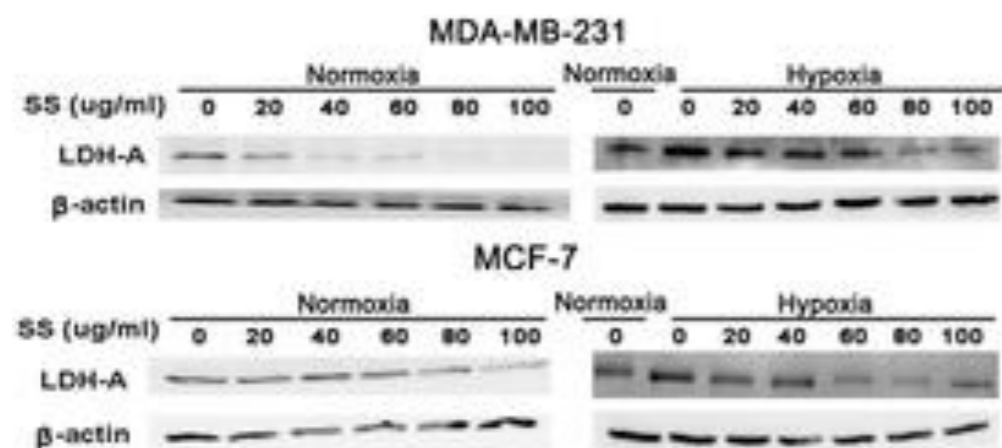
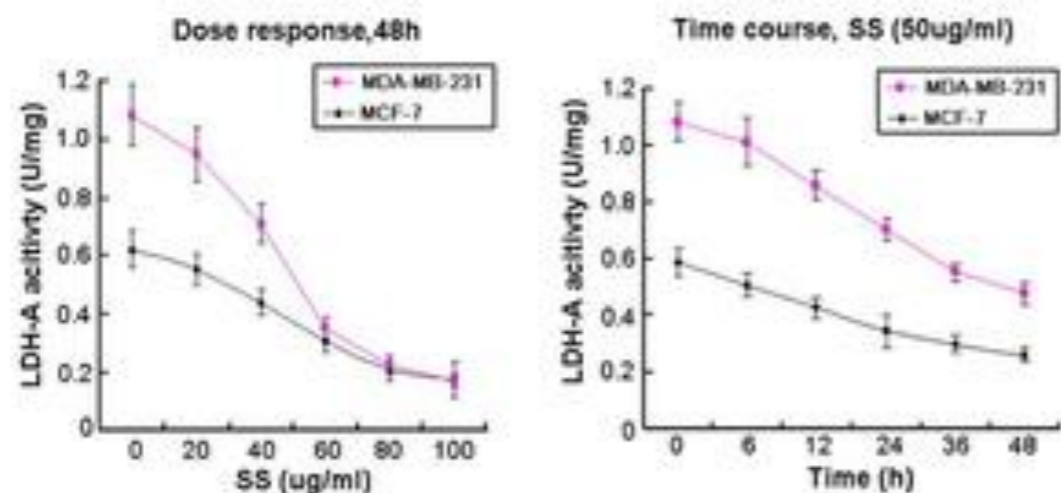
Elevated ROS level induced by SS

SS inhibits *in vivo* tumor growth.

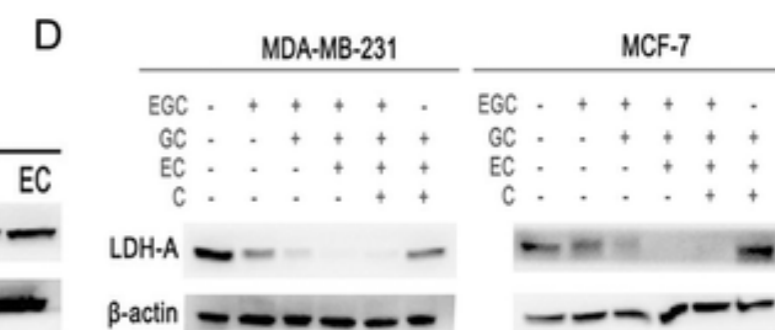
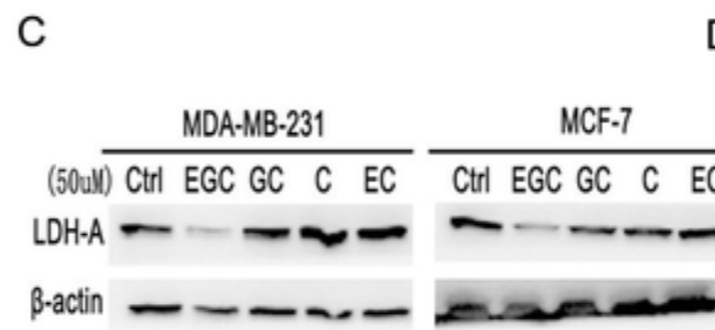
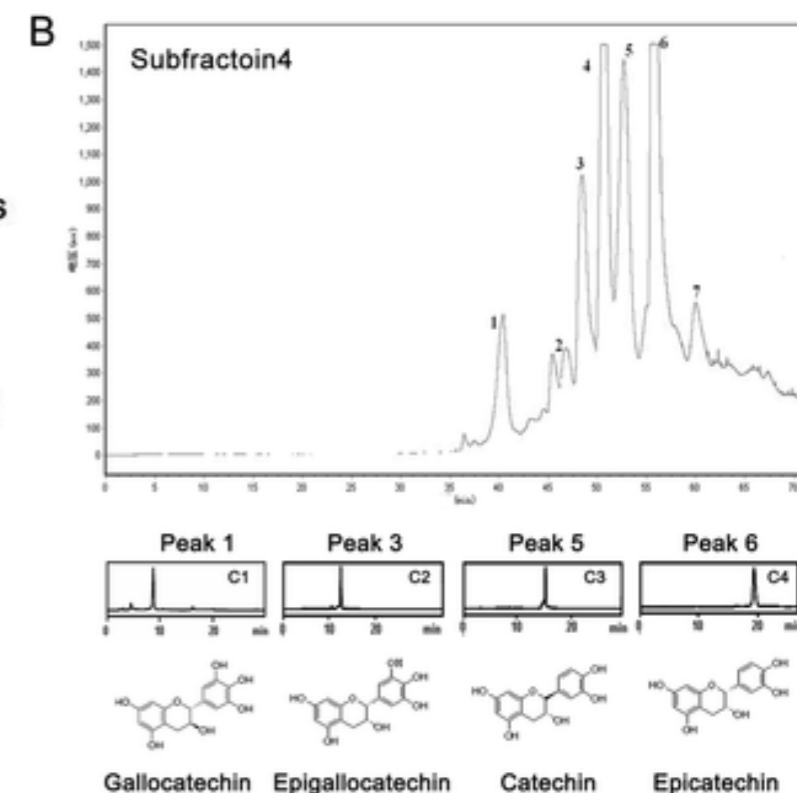
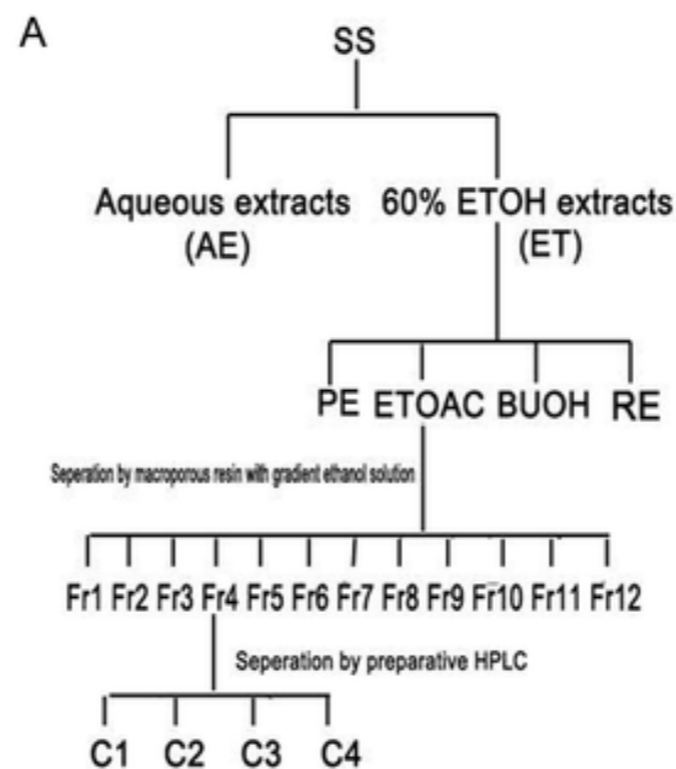


# Case Study: *Spatholobus suberectus* (Jixueteng)

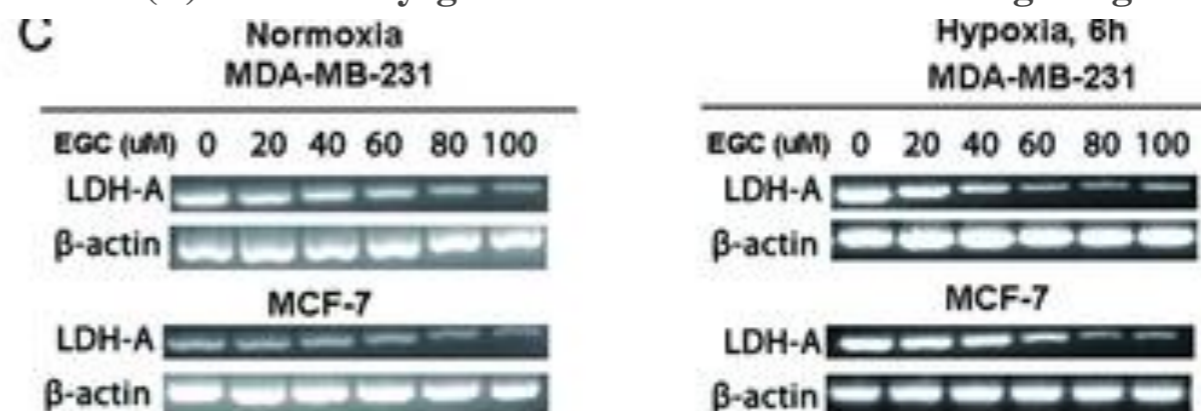
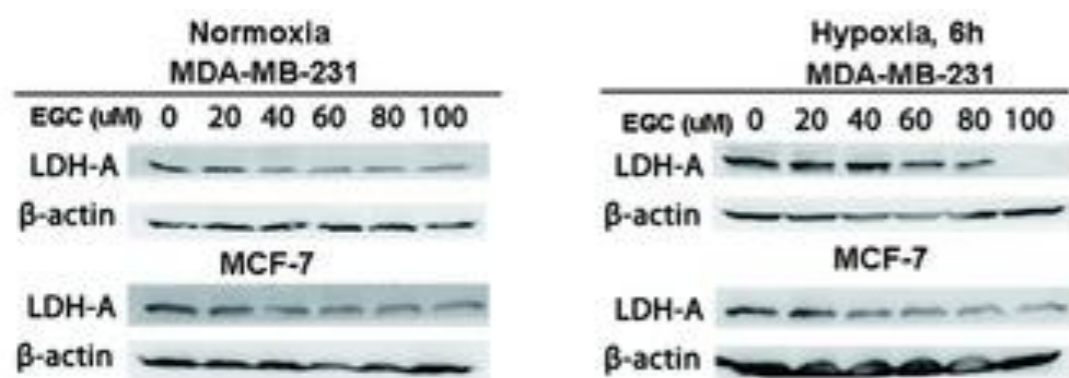
## 實例:雞血藤



(i) LDH-A is a direct target of SS



(ii) Bioactivity-guided fractionation of SS targeting on LDH-A.



(iii) EGC is the active compound in SS

# Perspectives 展望

Laboratory study on TCM in cancer treatment soars in recent years, and is expected to achieve greater outcome in future  
(基础研究仍将继续发展)

We noticed that high quality clinical trial is not yet available, which may require more attention and efforts in future  
(中醫藥抗腫瘤特點，臨床應用規範和臨床研究值得期待)

Collaborations with local, national and international pharmaceutical company is highly appreciated, which will make our ultimate goal of curing cancer achievable.  
(产学研合作是推广中医药肿瘤治疗的关键)



香港大學

THE UNIVERSITY OF HONG KONG



# 參考文獻

- 論文發表資料根據PubMed統計而來

- 中文文獻(\*通訊作者)

- 1 馮奕斌\*, 羅偉權, 朱世清. 從黃連及其複方古今臨床應用, 發掘現代臨床新應用. 中國中藥雜誌. 2008, 33(10):1221-1225
- 2 林小珊, 馮奕斌\*. 香砂六君湯合葛根芩連湯治療大腸癌經驗探析. 香港中醫雜誌. 2011, 6(3):35-38.
- 3 林蓓茵, 馮奕斌\*. 糖尿病合併膽管癌關係探討及病案分析一例. 香港中醫雜誌. 2013, 8(1):26-29.
- 4 林蓓茵, 馮奕斌\*. 糖尿病合併結直腸癌關係探討及中藥免煎顆粒治療驗案一例. 香港中醫雜誌. 2014, 9(1):31-36
- 5 馮奕斌\*, 朱世清, 羅偉權. 中醫藥抗癌研究及其思考. 中國中藥雜誌. 2015, 接受發表.

- 英文文獻 (\*通訊作者)

- 1 Tsang CM, Cheung KC, Cheung YC, Man K, Lui VW, Tsao SW, **Feng Y\***. Berberine suppresses Id-1 expression and inhibits the growth and development of lung metastases in hepatocellular carcinoma. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease* 2015 Mar;1852(3):541-51.
- 2 Wang N, **Feng Y\***, Tan HY, Cheung F, Hong M, Lao L, Nagamatsu T. Inhibition of Eukaryotic Elongation Factor-2 Confers to Tumor Suppression by a Herbal Formulation Huanglian-Jiedu Decoction in Human Hepatocellular Carcinoma. *Journal of Ethnopharmacology*, 2015 Feb 17. pii: S0378-8741(15)00103-8.
- 3 Wang N, Feng Y, Cheung F, Wang X, Zhang ZJ, **Feng Y\***. A Chinese Medicine Formula Gegen Qilian Decoction Suppresses Expansion of Human Renal Carcinoma with Inhibition of Matrix Metalloproteinase-2. *Integrated Cancer therapy* 2015 Jan; 14(1):75-85.
- 4 Wang N, Zhu M, Wang X, Tan HY, Tsao SW, **Feng Y\***. Berberine-induced tumor suppressor p53 up-regulation gets involved in the regulatory network of MIR-23a in hepatocellular carcinoma. *Biochim Biophys Acta*. 2014 Jun 3. pii: S1874-9399(14)00141-2.
- 5 Tsang CM, Cheung YC, Lui VW, Yip YL, Zhang G, Lin VW, Cheung K, **Feng Y\***, Tsao SW\*. Berberine suppresses tumorigenicity and growth of nasopharyngeal carcinoma cells by inhibiting STAT3 activation induced by tumor associated fibroblasts. *BMC Cancer*. 2013 Dec 31; 13(1):619.
- 6 Tan HY, Wang N, Tsao SW, Zhang Z, **Feng Y\***. Suppression of Vascular Endothelial Growth Factor via Inactivation of Eukaryotic Elongation Factor-2 by Alkaloids in *Coptidis rhizoma* in Hepatocellular Carcinoma. *Integrated Cancer therapy* 2014 Sep;13(5):425-34.
- 7 Wang N, Zhu M, Tsao SW, Man K, Zhang Z, **Feng Y\***. MiR-23a-mediated inhibition of topoisomerase 1 expression potentiates cell response to etoposide in human hepatocellular carcinoma. *Mol Cancer*. 2013 Oct 8;12(1):119.
- 8 Wang N, Feng Y\*, Zhu M, Siu FM, Ng KM, Che CM\*. A Novel Mechanism of XIAP Degradation Induced by Timosaponin AIII in Hepatocellular Carcinoma. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research* 2013; 1833(12):2890-2899.
- 9 Cheung F, Wang XB, Wang N, Yuen MF, Ziea Eric TC, Tong Y, Wong VT, **Feng Y\***. Chinese medicines as an adjuvant therapy for unresectable hepatocellular carcinoma during transarterial chemoembolization: a meta-analysis of randomized controlled trials. *Evidence-Based Complementary and Alternative Medicine* 2013:487919.
- 10 Wang N, **Feng Y\***, Zhu M, Chow O, Wang XB, Su W, Tong Yao. A Comparative Study on the Hepatoprotective Action of *Coptidis Rhizoma* Aqueous Extract and Bear Bile on Carbon Tetrachloride induced Liver Fibrosis in Rats. *BMC Complement Altern Med*. 2012;12(1):239.
- 11 Wang N, Zhu M, Tsao SW, Man K, Zhang ZJ, **Feng Y\***. Up-regulation of TIMP-1 by Genipin Inhibits MMP-2 activities and Suppresses the Metastatic Potential of Human Hepatocellular Carcinoma. *PLoS One* 2012;7(9):e46318.
- 12 **Feng Y\***, Wang N, Ye X, Li H, Feng Y, Cheung F, Nagamatsu T. Hepatoprotective effect and its possible mechanism of *Coptidis rhizoma* aqueous extract on carbon tetrachloride-induced chronic liver hepatotoxicity in rats. *Journal of Ethnopharmacology* 2011 Dec 8;138(3):683-90.
- 13 Wang N, Pan W, Zhu M, Zhanf M, Hao X, Liang G, **Feng Y\***. Fangchinoline induces autophagic cell death via p53/sestrin2/AMPK signaling in human hepatocellular carcinoma cells. *British Journal of Pharmacology*. 2011;164(2b):731-742.
- 14 **Feng Y\***, Wang N, Zhu M, Feng YG, Li HY, Tsao SW. Recent progress on anticancer candidates in herbal medicinal products. *Recent patent in Food, Nutrition & Agriculture*. 2011, 3(1):30-48.
- 15 Zhu M, Wang N, Tsao S, Yuen M, Feng YG, Wan Thomas SK, Man K, **Feng Y\***. Up-regulation of microRNAs, miR21 and miR23a, in human liver cancer cells treated with *Coptidis Rhizome* aqueous extract. *Experimental and Therapeutic Medicine* 2011, 2: 27-32.
- 16 Wang N, **Feng Y\***, Lau EP, Tsang C, Ching Y, Man K, Tong Y, Nagamatsu T, Su W, Tsao S. F-actin reorganization and inactivation of rho signaling pathway involved in the inhibitory effect of *Coptidis Rhizoma* on hepatoma cell migration. *Integrate Cancer Therapy*. 2010, 9(4):354-64.

# 參考文獻

- 16 Wang N, Feng Y\*, Zhu M, Tsang CM, Man K, Tong Y, Tsao SW. Berberine induces autophagic cell death and mitochondrial apoptosis in liver cancer cells: the cellular mechanism. *Journal of cellular biochemistry* 2010, 111(6):1426-36.
- 17 Tang J, Feng Y\*, Tsao S, Wang N, Curtain R, Wang Y. Berberine and Coptidis Rhizoma as novel antineoplastic agents: A review of traditional use and biomedical investigations. *Journal of Ethnopharmacology* 2009; 126:5-17.
- 18 Tsang CM, Lau Echo PW, Di K, Cheung PY, Hau PM, Ching YP, Wong YW, Cheung Annie LM, Wan Thomas SK, Tong Y, Tsao SW\* and Feng Y\*. Berberine inhibits RhoGTPases and cell migration at low doses but induces G2 arrest and apoptosis at high doses in human cancer cells. *International Journal of Molecular Medicine* 2009; 24:131-138.
- 19 Ye XS, Feng Y\*, Tong Y, Ng KM, Tsao SW, Lau George KK, Sze CW, Zhang YB, Tang J, Shen JG, Kobayashi S. Hepatoprotective effects of Coptidis Rhizoma aqueous extract on carbon tetrachloride-induced acute liver hepatotoxicity in rats. *Journal of Ethnopharmacology* 2009; 124:130–136.
- 20 Wang Z, Wang D, Han S, Wang N, Mo F, Loo TY, Shen J, Huang H, Chen J\*. Bioactivity-guided identification and cell signaling technology to delineate the lactate dehydrogenase A inhibition effects of *Spatholobus suberectus* on breast cancer. *PLoS One*. 2013;8(2):e56631. doi: 10.1371/journal.pone.0056631.
- 21 Wang N, Wang Z, Peng C, You J, Shen J, Han S, Chen J\*. Dietary compound isoliquiritigenin targets GRP78 to chemosensitize breast cancer stem cells via  $\beta$ -catenin/ABCG2 signaling. *Carcinogenesis*. 2014 Nov;35(11):2544-54. doi: 10.1093/carcin/bgu187.

謝謝!

