# Chinese Medicine (CM) Safety - From Scientific Evidence to Clinical Practice

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# Integrative Chinese-Western Medicine

* Pilot project of using CM in inpatient settings

中西合醫 3醫院今起試行
中風癌症腰痛病人先受惠

特稿

政府銳意推動本港中醫發展，今年施政報告宣布將預留一幅將軍澳土地以興建中醫院，醫管局亦於今日起試行中西醫協作先導計劃，在3間醫院安排中醫上病房與西醫一起治療中風、癌症及腰痛病人，住院病人需額外支付中醫診費200元。計劃將試行兩年，預計首階段有600至800名病人受惠。

自願參加 需付額外診費

第一階段「中西醫協作項目」先導計劃下，東華

中西醫協作項目先導計劃

| 醫院 | 提供中西合醫的環節及內容 | 提供的中醫治療方法 |
|---|---|---|
| 東華醫院 | 病發少於1個月而需接受中風治療的病人（神經外科中風除外） | 針灸及中藥 |
| 屯門醫院 | 癌症舒緩治療方面，任何癌症患者，並有疼痛、便秘、失眠、局部性水腫、食慾不振、急倦嗜眠等其中一項或以上徵狀人士 | 針灸及中藥 |
| 東區醫院 | 因扭傷、跌傷等引起急性下腰痛的病人 | 針灸 |

三公院今推中西合璧治療

【本報訊】醫管局今日起推出中西醫治療項目先導計劃，首階段由屯門、東區和東華醫院，分別為癌症舒緩治療、急性下腰痛和中風的住院病人，提供特定的針灸或中藥療程，料可服務600至800人，明年3月會進行計劃中期評估，再擬定第二階段的實施時間。

上述計劃由醫管局與非政府機構合作，東華醫院和東區醫院均與香港三院香港大學中醫藥臨床教研中心合作，屯門醫院則與仁愛堂綜合診所暨中大中醫臨床教研中心合作。

醫管局中醫部主管謝達之表示，獲先導計劃的醫院，各有最少有四年經驗的中醫負責，並由一名資深中醫監督。

整個計劃由西醫主導，中醫為輔。以癌症病人為例，西醫會聯同中醫巡房，共同揀選適合參與計劃的個案，例如因癌症出現失眠、疼痛、食慾不振及便秘等症狀的病人。自願參與計劃的病人，會由西醫提供常規治療以控制病情或減輕症狀，中醫則負責按病人的體質及證型，處理西醫未能控制的症狀或治療產生的副作用。



■張偉麟（左）稱西醫會聯同中醫巡房，共同揀選適合病人接受治療。右為謝達之。

醫管局聯網服務總監張偉麟表示，中、西醫都會將病歷寫在住院病人的「牌板」上，雙方所屬機構均有購買保險，如發生醫療事故，會按事故起因決定由哪方負責，「有灰色地帶嘅就各分擔一半」。先導計劃的評估報告需提交政府，日後發展中醫院時作為參考。

中醫診療費每日200元

參與計劃的病人，除每日100元的住院費外，需另付每日200元的中醫診療費，出院後可由門診跟進，每次定額收費120元。每宗個案最長可參與計劃半年；如參與計劃期間病人病情有變，計劃特定的治療方案已不適用便需退出。第二階段計劃將擴展至廣華、瑪嘉烈、威爾斯親王和沙田醫院，料服務對象可提升至逾1,000人。

# Integrative Chinese-Western Medicine

* Major concerns:
  * CM Toxicity
  * Interactions between CM and WM
    → Herb-Drug Interaction (HDI)
  * Inpatient setting
    * Severe clinical conditions
    * Complex drug regimens

# Use of CM with WM?

" You should not take CM while on WM therapy ! "

# Use of CM with WM?

" Please separate the intake of CM and WM by at least two hours ! "


* Possible outcomes:
  * Improved/ Worsened?
  * Toxic effect?
  * Herb-drug interaction?

# Mission

* **Evidence-based medicine**
  * Need scientific evidence to support clinical practice

# Challenges of evaluating CM safety

**Use of Herbs**

- Complex nature of herbs (e.g. multiple components, multi-pharmacological targets)
- Evolving pharmacopeia standards
- Traditional practice in prescribing (e.g. composite formula)

**Scientific evidence**

- Limited scientific data on safety (mainly on beneficial effects)
- Mostly in-vitro / animal studies
- Case reports (n=1)
- Human studies subject to challenge
- Reproducibility of testing samples of the study

# HA Drug-herb Interactions Database

*Drug(s), as single entity or in regimen(s)*

*Chinese / herbal medicine (s), as single entity or in formulae or compound*

*Assigned level of significance*

*Description of Interaction*

*Brief summary on content of the reference(s)*

*Legends for additional information*

## Interaction of CM / Herbal Medicine(s) with Anticancer Drug(s)

| Drug(s) | CM / Herbal Medicine(s) / (Compound) |
|---|---|
| Irinotecan | *Hypericum perforatum*, St. John's wort† |

**Level of Significance: 1**

| Severity of Adverse DHI | Level of Evidence |
|---|---|
| ☐ High | ☐ A |
| ☑ Moderate | ☑ B |
| ☐ Mild | ☐ C |
| ☐ Insignificant /Uncertain | ☐ D |
| ☐ Not known | ☐ E |

Effects: The combination of St. John's wort† with irinotecan may decrease the drug efficacy of irinotecan in various cells and animal models as well as cancer patients.

Mechanism: The combination of St. John's wort† with irinotecan may affect the pharmacokinetics of irinotecan.

Management: Concomitant administration of irinotecan and St. John's wort† should be avoided.

Summary:
The combined treatment of irinotecan and St. John's wort† was investigated in several animal and human studies. Results showed that irinotecan-induced intestinal damage, pro-inflammatory cytokine production and intestinal epithelial apoptosis were attenuated by the pretreatment of St. John's wort (SJW). These inhibitions of pro-inflammatory cytokines and intestinal epithelium apoptosis partly explained the protective effect of SJW against irinotecan-induced diarrhea (1). However, other recent studies reported that although the co-administration of SJW with irinotecan resulted in lesser toxicity induced by irinotecan, the maximum plasma concentration ($C_{max}$) of irinotecan and SN-38 (active metabolite of irinotecan) had significantly decreased after a long term exposure to SJW for consecutive 14 days (2, 3). Similar results were obtained from another low quality RCT, in which two patients had colorectal cancer, two had lung cancer and one had sarcoma, that the plasma levels of SN-38 in patients were significantly reduced by 42% following co-treatment of irinotecan and SJW (4).

Reference(s):


1. Hu ZP, Yang XX, Chan SY, Xu AL, Duan W, Zhu YZ, et al. St. John's wort attenuates irinotecan-induced diarrhea via down-regulation of intestinal pro-inflammatory cytokines and inhibition of intestinal epithelial apoptosis. Toxicology & Applied Pharmacology. 2006;216(2):225-37.
2. Hu Z, Yang X, Ho P-L, Chan E, Sui YC, Xu C, et al. St. John's wort modulates the toxicities and pharmacokinetics of CPT-11 (Irinotecan) in rats. Pharmaceutical Research. 2005;22(6):902-14.
3. Hu ZP, Yang XX, Chen X, Cao J, Chan E, Duan W, et al. A mechanistic study on altered pharmacokinetics of irinotecan by St. John's wort. Current Drug Metabolism. 2007;8(2):157-71.
4. Mathijssen RH, Verweij J, de Bruijn P, Loos WJ, Sparreboom A. Effects of St. John's wort on irinotecan metabolism. J Natl Cancer Inst. 2002 Aug 21;94(16):1247-9. (Jadad Score: 1)


† St John's wort: Hyperici Perforati Herba (貫葉金絲桃)

Data extraction: May 08
Updated: Jan 11 (v.1)

## Table 1. Level of Significance

| Severity of Adverse DHI \ Level of Evidence | A | B | C | D | E |
|---|---|---|---|---|---|
| High | 1 | 1 | 1 | 2 | 2 |
| Moderate | 1 | 1 | 2 | 2 | 3 |
| Mild | 2 | 2 | 2 | 2 | 3 |
| Insignificant / Uncertain | 3 | 3 | 3 | 3 | 3 |
| Not known | * | * | * | * | * |

# How to interpret data ?
# - Example (Irinotecan & St John's Wort)

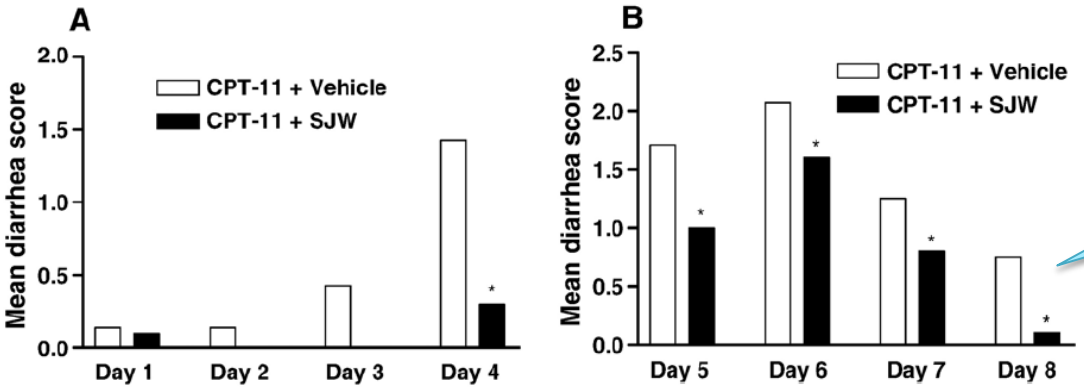



Fig. 1. Effects of coadministered St. John's wort on the early- (A) and late-onset (B) diarrhea induced by irinotecan (CPT-11) in rats.

**Assay such as mean diarrhea score lower in combination group**

**Author: "…combined SJW markedly reduced CPT-11-induced diarrhea and intestinal lesions."**

*SJW attenuated irinotecan-in… diarrhea*

including IL-1β, IL-2, IL-6, IFN-γ and TNF-α and intestinal epithelial apoptosis were monitored over 11 days. Our studies demonstrated that combined SJW markedly reduced CPT-11-induced diarrhea and intestinal lesions. The production of pro-inflammatory cytokines such as IL-1β, IFN-γ and TNF-α was significantly up-regulated in intestine. In the mean time, combined SJW significantly suppressed the intestinal epithelial

## *Also mentioned in the article:*

induced diarrhea. Our preliminary study in the rat clearly demonstrated that pretreatment with SJW significantly reduced the diarrhea induced by use of irinotecan (Hu et al., 2005). Interestingly, a recent pilot study in 5 cancer patients found that oral treatment of SJW at 900 mg/day for 18 days alleviated irinotecan-induced diarrhea (Mathijssen et al., 2002). However, the mechanism for this is unknown. In the

**Herb + Drug = reduce toxicity?**

Hu, ZP et al. St. John's wort attenuates irinotecan-induced diarrhea via down-regulation of intestinal pro-inflammatory cytokines and inhibition of intestinal epithelial apoptosis. *Toxicol. Appl. Pharmacol*. 2006, 216, 225-237

# How to interpret HDI data ?
# - Example (Irinotecan & St John's Wort)

***Results.*** Rats treated with CPT-11 alone experienced rapid decrease in body weight, whereas co-administration of SJW with CPT-11 resulted in lesser body weight loss. The gastrointestinal and hematological toxicities following CPT-11 injection were both alleviated in the presence of SJW. The rat pharmacokinetics of both CPT-11 and its metabolite SN-38 were significantly altered in presence of SJW. ***Conclusions.*** In conclusion, co-administered SJW significantly ameliorated the toxicities induced by CPT-11. The protective effect of SJW may be partially due to pharmacokinetic interaction between CPT-11 and SJW.

**Table II.** Comparison of Pharmacokinetic Parameters Between Two Groups of Rats Receiving CPT-11 Alone or Pretreated with St. John's Wort for 14 Days

| Parameters | Treatment groups: CPT-11 + SJW | CPT-11 + vehicle | Change (%) | *p* value[a] |
|---|---|---|---|---|
| CPT-11 | | | | |
| $C_0$ (ng/ml)[b] | 9358.4 ± 1971.4 | 15469.9 ± 6206.0 | −65.3 | **0.031** |
| $t_{1/2\beta}$ (h) | 2.01 ± 0.31 | 1.73 ± 0.15 | 16.2 | **0.043** |
| $AUC_{0-10\ hr}$ (ng·h/ml) | 23227.6 ± 4847.1 | 28678.5 ± 9284.8 | −19.0 | 0.140 |
| $AUC_{0-\infty}$ (ng·h/ml) | 23967.5 ± 5389.2 | 29104.7 ± 9368.2 | −17.7 | 0.160 |
| $V_d$ (ml/kg) | 7393.9 ± 1077.5 | 5541.5 ± 1636.8 | 33.4 | **0.033** |
| CL (ml/h/kg) | 2597.1 ± 509.3 | 2242.4 ± 723.5 | 15.8 | 0.194 |
| SN-38 | | | | |
| $C_0$ (ng/ml) | 639.4 ± 200.3 | 1046.9 ± 232.2 | −38.9 | **0.004** |
| $AUC_{0-10\ hr}$ (ng·hr/ml) | 4342.7 ± 1250.0 | 5895.3 ± 1372.7 | −26.3 | **0.034** |
| $t_{1/2\beta}$ (h) | 4.25 ± 1.63 | 4.82 ± 3.81 | −11.8 | 0.374 |
| $AUC_{0-\infty}$ (ng·h/ml) | 5688.7 ± 1409.9 | 8644.4 ± 5543.2 | −34.2 | 0.128 |
| SN-38G | | | | |
| $C_0$ (ng/ml) | 2681.8 ± 963.1 | 2320.8 ± 544.8 | 15.6 | 0.224 |
| $AUC_{0-10\ hr}$ (ng·h/ml) | 7038.2 ± 1837.7 | 6523.4 ± 1577.1 | 7.9 | 0.307 |
| $t_{1/2\beta}$ (h) | 2.61 ± 0.50 | 2.79 ± 0.56 | −6.5 | 0.277 |
| $AUC_{0-\infty}$ (ng·h/ml) | 7649.9 ± 2293.1 | 7073.1 ± 1688.3 | 8.2 | 0.316 |

[a] Compared with the controls using Students' unpaired *t* test.
[b] Obtained by back-extrapolation to the zero time using WinNonlin program.

**Decrease GI toxicity**

**But also:**
**Cmax, AUC0-10hr of SN-38 (major active metabolite) were significantly reduced!**

**↓ Plasma level** → **↓ diarrhea?**

**↓ efficacy?** → **Dose adjustment?**

***Letter to Editor:***
**"The article… ignores the well-known CYP450 and P-glycoprotein effects of St. John's wort on drug metabolism."**

irinotecan-induced diarrhea ignores the well-known CYP450 and P-glycoprotein effects of St. John's wort on drug metabolism. It is also troubling that the authors appear to misrepresent the study by Mathijssen et al. (2002) when they state: "Interestingly, a recent pilot study in 5 cancer patients found that oral treatment of SJW at 900 mg/day for 18 days alleviated irinotecan-induced diarrhea (Mathijssen et al., 2002). However, the mechanism for this is unknown."

Mathijssen *et al.* actually did NOT report less diarrhea (although they did show a decrease in SN-38, the irinotecan metabolite associated with diarrhea): "Clinically, irinotecan-

Hu, ZP et al. St. John's wort modulates the toxicities and pharmacokinetics of CPT-11 (Irinotecan) in rats. Pharm Res. 2005 Jun; 22 (6) :902-14

Birdsall TC. St. John's wort and irinotecan-induced diarrhea. *Toxicol Appl Pharmacol.* 2007 Apr 1;220(1):108

# POSITE FORMULA

## Interaction of CM / Herbal Medicine(s) with Cardiovascular Drug(s)

| Drug(s) | CM / Herbal Medicine(s) / (Compound) |
|---|---|
| Atenolol, Diltiazem, Glyceryl trinitrate, Isosorbide dinitrate | Aurantii Fructus + Bupleuri Radix + Carthami Flos + Chuanxiong Rhizoma + Paeoniae Radix Rubra + Persicae Semen |

**Level of Significance**

**3**

| Severity of Adverse DHI | Level of Evidence |
|---|---|
| ☐ High | ☐ A |
| ☐ Moderate | ☑ B |
| ☐ Mild | ☐ C |
| ☑ Insignificant/ Uncertain | ☐ D |
| ☐ Not known | ☐ E |

Effects: The combination of atenolol and isosorbide dinitrate or diltiazem and isosorbide dinitrate, with or without glyceryl trinitrate, along with purified Xuefu Capsule (PXFC)† may improve the overall treatment effective rate in patients with angina pectoris. However, the use of this combination may be associated with adverse effects.

Mechanism: Unknown

Management: Nil


Summary:
The combined effects of atenolol and isosorbide dinitrate or diltiazem and isosorbide dinitrate, with or without glyceryl trinitrate, together with purified Xuefu Capsule (PXFC)† in the treatment of angina pectoris (AP) were investigated in a low quality RCT. A total of 57 patients were randomly divided into two groups. In group A, 30 patients were treated with western drugs (isosorbide dinitrate with diltiazem or isosorbide dinitrate with atenolol) and PXFC† whereas 27 patients in group B were treated with western drugs only. In addition, glyceryl trinitrate was given when necessary to relieve angina symptoms. The treatment duration for this study was 4 weeks. Adverse effects such as headache following isosorbide dinitrate administration were reported in both groups (8 and 3 cases in group A and B, respectively), of which 4 cases from group A had discontinued isosorbide dinitrate. There were several reports of gastrointestinal discomfort following the intake of PXFC† capsules, which resolved with administering PXFC† after meals. Results showed that the overall treatment effective rates (93.3% vs 66.7%) and ECG ST-T changes of AP (63.3% vs 37%) were significantly higher in group A than in group B ($p$ <0.05). Besides, the plasma level of endothelin in group A was significantly lower than group B ($p$ <0.01) and the calcitonin gene related peptide of group A was significantly higher than group B ($p$ <0.01). The present study suggested that the addition of PXFC† with western drugs might have beneficial effects in treating angina pectoris over western drugs alone (1).



Reference(s):

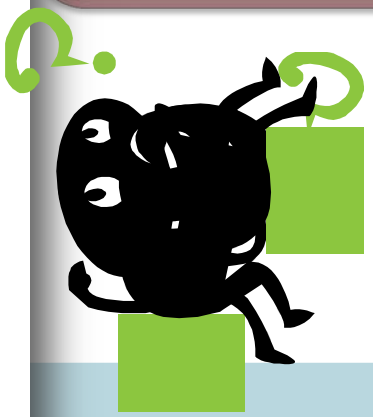
1. 汪曉芳, 陳可遠, 王偉, 史大卓, 周佩雲, 陳可冀. 精製血府膠囊治療冠心病心絞痛的臨床研究.中國中西醫結合雜誌. 1998年，18 (7): 399-401. (Jadad Score: 1)


† Purified Xuefu Capsule (精製血府膠囊): Aurantii Fructus (枳殼) + Bupleuri Radix (柴胡) + Carthami Flos (紅花) + Chuanxiong Rhizoma (川芎) + Paeoniae Radix Rubra (赤芍) + Persicae Semen (桃仁)

Data extraction: May 09

A drug regimen vs a CM composite formula

identify the causative agent



# Scope in this pilot project

**232** CMs

to be used in

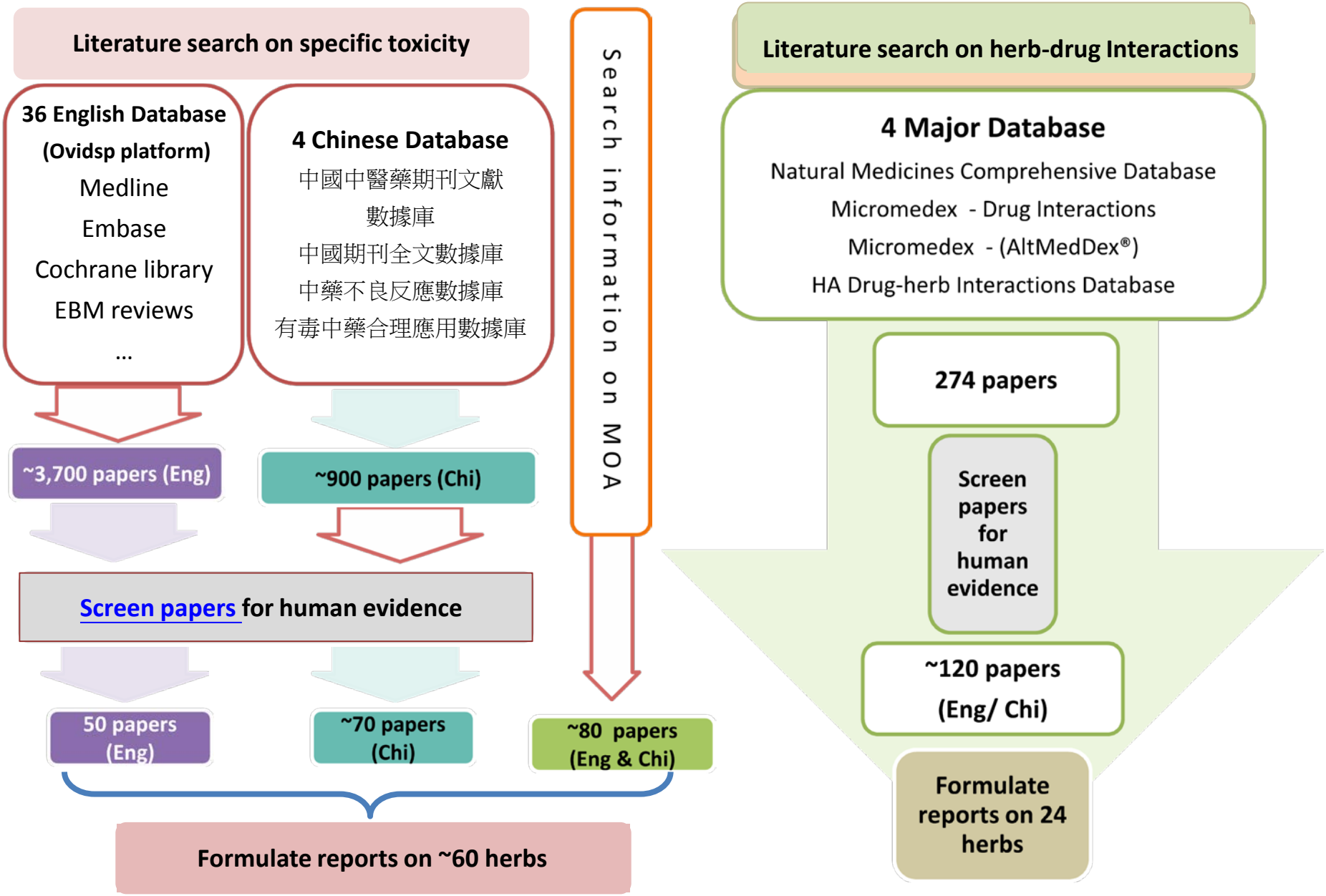
**Stroke** and **Cancer** treatment protocols

**Reports**

**~ 60 herbs on CM Toxicity**

**~ 24 herbs on HDI**

# Perform pragmatic search….



# What we are looking for?

* Human evidence
* RCT, non-RCT, case reports
* Toxicities on specific organ systems
  * Cardiovascular
  * Liver
  * Renal

# Formation of Expert Panel

* Clinicians specialized in toxicology, clinical pharmacology, oncology, cardiology, hepatology and nephrology
* Pharmacists
* CM experts

# NOVEL APPROACH FOR CLINICAL PRACTICE

**Modified** risk stratification matrix

| Quality of studies \ Level of Evidence | I | II | III | IV |
|---|---|---|---|---|
| Good | 1 | 2 | 2 | 2 |
| Fair | 2 | 2 | 3 | 3 |
| Poor | 2 | 3 | 3 | 3 |

1= high risk 2= moderate risk 3= low risk

**Expert opinion –**

local experience &

clinical management

**Risk Rating – Level of Evidence vs Quality of Evidence (as assessed by Expert Panel)**

**High Risk**

- Significant impact on clinical effects likely
- Use is prohibited in at-risk patient group(s)
- Concurrent use with certain drug(s) is prohibited or specific monitoring (e.g. TDM, INR) is requried if use is deemed necessary

**Moderate Risk**

- Significant impact on clinical effects possible
- Avoid / not recommend in at-risk patient group(s) or specific clinical monitoring is required if used
- Concurrent use with certain drug(s) should be avoided / is not recommended or specific monitoring (e.g. TDM, INR) is requried

**Low Risk**

- Significant impact on clinical effects less likely
- Specific clinical monitoring as recommneded

**No Reported Risk**

- Significant impact on clinical effects unlikely
- Routine clinical monitoring

# Risk Assessment and Recommendations

- Risk ratings of CM Toxicity (on specific organ systems) and potential HDIs (against individual drug or drug classes)
- Practical recommendations (e.g. avoid, not recommend, use with close monitoring)


**Risk Assessments and Recommendations on Use of Chinese Medicines In the Integrated Chinese-Western Medicine (ICWM) Pilot Project**

**Risk Assessments by Expert Panel**

All Chinese medicines (CMs) listed in the IM protocols are assessed by an Expert Panel (EP) on CM Safety for ICWM Pilot Project. The EP performed systematic review of scientific literatures relating to their intrinsic toxicities and herb-drug interactions. Agreement among experts was made on the likelihoods of adverse effect and herb-drug interactions associated with the use of CMs at doses within the recommended ranges by official references. Based on these consensuses, the CMs were classified into four different risk ratings: (1) High Risk; (2) Moderate Risk; (3) Low Risk; and (4) No Reported Risk. Specific warning of the possible toxicities or potential herb-drug interactions together with recommendations of use from the EP are formulated and tabulated for the "High, Moderate and Low" Risk CMs (see annexes). CMs listed in the IM Protocol but not listed in the annexes are considered "No Reported Risk".

**Risk Rating – Level of Evidence vs Quality of Evidence (as assessed by Expert Panel)**

| | |
|---|---|
| High Risk | •Significant impact on clinical effects likely<br>•Use is prohibited in at-risk patient group(s)<br>•Concurrent use with certain drug(s) is prohibited or specific monitoring (e.g. TDM, INR) is requried if use is deemed necessary |
| Moderate Risk | •Significant impact on clinical effects possible<br>•Avoid / not recommend in at-risk patient group(s) or specific clinical monitoring is required if used<br>•Concurrent use with certain drug(s) should be avoided / is not recommended or specific monitoring (e.g. TDM, INR) is requried |
| Low Risk | •Significant impact on clinical effects less likely<br>•Specific clinical monitoring as recommneded |
| No Reported Risk | •Significant impact on clinical effects unlikely<br>•Routine clinical monitoring |

**Special Recommendation(s):**

1. Contraindication in G6PD: 黃連 and 金銀花 are contraindicated in patients with known G6PD deficiency.

Annexes

*Annex I: CM Safety for ICWM Pilot Project - Risk Rating on CM Toxicity vs Specific Organ Systems*
*Annex II: CM Safety for ICWM Pilot Project - Risk Rating on Herb-drug Interactions (by CM)*
*Annex III: CM Safety for ICWM Pilot Project -Risk Rating on Herb-drug Interactions (by drug / drug class)*

Disclaimer

Medical science is constantly evolving. Basing upon the best available evidence, the expert panel has made every effort to ensure the information in this protocol is accurate and up-to-date at the time of the assessment. However, clinicians should not solely rely on the risk assessments and recommendations provided and must exercise due diligence in obtaining all relevant clinical data prior to critical decision making.

# POTENTIAL TOXIC HERB-DRUG INTERACTIONS (HDI)

## Ephedrine-like alkaloids :

1. Bitter orange（枳實，枳殼)
2. Ephedra (麻黃)

# 1. Bitter orange（枳實，枳殼）

* For treatment of interior retention of accumulation and stagnation, stuffiness and fullness, distention pain, constipation, phlegm stagnation and qi obstruction

枳實（young）
破氣消積，化痰散痞．用於積滯內停，痞滿脹痛，瀉痢後重

枳殼（immature）
理氣寬中，行滯消脹．用於胸脇氣滯，脹滿疼痛，食積不化

# BITTER ORANGE (SEVILLE ORANGE) - 枳實 (YOUNG) & 枳殼 (IMMATURE)

## 枳實 (young)

dried, young fruit collected in May and June

biologically active cpd

[CP] synephrine not <3 mg/g (4.5 mg/g[1])

marker cpd

*6',7'-dihydroxybergamottin*, a CYP3A4 inhibitor (20μg/g in peel[2])

## 枳殼 (immature)

dried, immature fruit collected in July

biologically active cpd

[CP] synephrine not listed (1.3 mg/g[1])

marker cpd

*6',7'-dihydroxybergamottin*, a CYP3A4 inhibitor (336μg/g in peel[2])

**Synephrine**

- Natural occurring alkaloid in some plants
- Adrenergic agent with chemical structure similar to ephedrine
- Sympathomimetics effects, cardiac stimulant

**CP2010 recommendation:**

- 3-10g for both

**% of aqueous extraction of synephrine:**

- 枳實 (young): 69.1 – 86.17% [3, 4]
- 枳殼 (immature): no information

[1] 趙宇, 謝培山, 盧平華,等.枳實、枳殼、青皮和陳皮等藥材中辛弗林含量測定研究.世界科學技術, 2006(04)
[2] Saita, T., Screening of furanocoumarin derivatives in foods and crude drugs by enzyme-linked immunosorbent assay. Jpn. J. Pharm. Health Care Sci, 2006. 32: p. 693-699.
[3] 蘇子仁, 呂雪斌, 梁遠園, 徐暉, 枳實提取工藝優化研究. 中國實驗方劑學雜志, 1999(05).
[4] 廖茂梁等, 正交試驗優選枳實中辛弗林提取工藝. 中國實驗方劑學雜志, 2011(13).

# POTENTIAL ADVERSE / TOXIC EFFECTS

## RCTs, self-controlled studies (SCS), case reports *[total papers:10; sample size of RCT/SCS:7-15]*

**Synephrine extract** ♥ ♥

- ♥ **[cross over RCT]** young healthy subjects & **[case report]** female with hypothyroidism on thyroxine x ~10yr
  - ⊙ taken synephrine cap (30mg & 54 mg synephrine) x 1 day → ↑ **blood pressure & tachycardia**
  - ⊙ calculated based on CP standard: ~eqv to 10g & 18g 枳實 (young) respectively
- ♥ **[case report]** Positive rechallenge: tachyarrhythmia appeared after resuming synephrine extract x 1 day

**Weight loss supplements** 🚹 🚹

Effects described based on proprietary product containing bitter orange (standardized for synephrine, N-methyltyramine, hordenine, octopamine, & tyramine) & caffeine

- 🚹 **[RCT]** healthy non-smokers → ↑ **HR & BP**

| Product | (1) Single dose of ~5.5mg synephrine (multi-component containing caffeine) | (2) Single dose of ~46.9mg synephrine (synephrine-containing product) |
|---|---|---|
| ~Eqv. dose | 1.8g 枳實 (young) | 15.6g 枳實 (young) |
| 6hr-post dose | significant ↑ in HR (by ~16.7 beats/min) | significant ↑ in HR (by ~11.4 beats/min) |
| | Significant ↑ in SBP & DBP | no change observed with SBP & DBP |

  - ⊙ Effects more pronounced with low dose synephrine-containing multi-component product
- 🚹 **[Case report]** healthy female; taken (1) x 1 year (dosage unk; overdose cannot be excluded)→ stopped x 3 months → restarted i bid
  - ⊙ exercise-induced syncope occurred 1 hr after the 2nd dose; ECG showed sinus tachycardia 100 beats/min with QT interval of 400ms (QTc 516ms); borderline prolonged QTc (466ms) still noted 4 hr after

# INTERACTIONS WITH CYTOCHROME P450 3A4 (CYP3A4) SUBSTRATE

**RCTs, self -controlled studies (SCS)** – healthy subjects, non-smokers

**Seville orange juice (SOJ) and Grapefruit juice -** 6',7'-dihydroxybergamottin (a mechanism-based inactivator → accelerated degradation of the enzyme CYP3A4)

| Level of evidence | Drugs | Seville orange juice (SOJ) | Grapefruit juice |
|---|---|---|---|
| Randomized 3-way crossover study | Felodipine (10mg) | Significant ↑ in AUC (by ~76%) and $C_{max}$ (by ~61%)<br>No significant change in $T_{max}$ and terminal $T_{1/2}$ | Significant ↑ in AUC (by ~93%) and $C_{max}$ (by ~88%)<br>No significant change in $T_{max}$ and terminal $T_{1/2}$ |
| SCS | Cyclosporin | No significant effect on cyclosporin disposition & ↓ enterocyte concentrations of CYP3A4 by ~40% | Significant ↑ in AUC (by 55%) and $C_{max}$ (by 35%) |
| Open-label 3-period crossover study | Indinavir | Significant ↑ in $T_{max}$<br>No significant change in $AUC_{0-8}$, $C_{max}$, $T_{1/2}$, CL/F or $C_{min}$ | No significant change in PK parameters |
| SCS | Dextro-methorphan (DM) | Significant ↑ in BA; only returned to half the baseline value after 3 days of washout<br>Suspect inhibition of CYP3A activity and P-glycoprotein | Results similar to SOJ |

**SOJ (8 ounces) ~** eqv. to 13-14 mg of synephrine (57μg/ml to 240ml of juice)

- ~ 4.6g 枳實 (young)

# GRAPE FRUIT JUICE (GFJ) WARNING ON CALCIUM CHANNEL BLOCKERS

dihydropyridines ← → benzothiazepines

| Ref. | Felodipine (F) ✓ | Amlodipine (A) | Nifedipine (N) ✓ | Diltiazem (D) |
|---|---|---|---|---|
| BNF 67 | ↑plasma conc (F) | possibly ↑plasma conc (A) | ↑plasma conc (N) | NIL |
| | Do not usually have serious consequences | Do not usually have serious consequences | Do not usually have serious consequences | |
| Micromedex DRUGDEX Evaluations | Concurrent use may result in severe hypotension, myocardial ischemia, ↑vasodilator side effects | NIL | Concurrent use may result in severe hypotension, myocardial ischemia, ↑vasodilator side effects ; another study demonstrated no significant differences | Concurrent use may result in ↑ serum (D) concentrations |
| | Severity: Moderate<br>Documentation: Excellent | | Severity: Moderate<br>Documentation: Excellent | Severity: Minor<br>Documentation: Good |
| | Avoid GFJ during (F) therapy; GFJ should be d/c x 2-3 days before (F) therapy is initiated | | Avoid GFJ while taking (N); GFJ should be d/c at least 3 days prior to initiating (N) therapy | Advise patients taking (D) to avoid GFJ |
| Dynamed | ↑oral BA | Altered BA possible; no clinically important changes in another study | ↑oral BA | NIL |
| | Avoid concomitant use | | Avoid concomitant use; d/c GFJ at least 3 days prior to initiating nifedipine therapy | |
| Lexi-Drugs | May ↑$C_{max}$ (F) by twofold | May modestly ↑(A) levels | May ↑serum conc (N) resulting in therapeutic and vasodilator ADRs | Serum conc (D) not altered by GFJ in small clinical trials |
| | Severity: Major<br>Reliability: Good | Severity: Moderate<br>Reliability: Good | Severity: Major<br>Reliability: Good | Severity: Moderate<br>Reliability: Good |
| | Avoid GFJ during therapy | Monitor closely with concurrent use | Avoid concurrent use | - Monitor response to (D) (i.e., BP, HR) when patients are using with GFJ<br>- Impact likely to be minor for most of the patients |
| Package Insert | Co-administration resulted in ~2x ↑of the Cmax and the AUC of (F)<br><br>Combination with GFJ should be avoided | No significant effect on the pharmacokinetics of (A) in co-administration in a single oral dose study | Should not be taken with GFJ<br><br>After regular intake of GFJ, this effect may last for at least 3 days after the last ingestion of grapefruit juice | NIL |

# RISK ASSESSMENTS AND RECOMMENDATIONS

| | 枳實 (young)  | 枳殼 (immature)  |
|---|---|---|
| **Effects** | • May increase risk of hypertension and adverse CVS effects<br>• May increase blood concentration of felodipine | |
| **Adverse events** | Hypertension, tachycardia, may prolong QTc if taken with QT interval-prolonging drugs | |
| **Recommendations** | Contraindicated in patients with uncontrolled hypertension and/or tachyarrhythmia | Not recommended in patients with uncontrolled hypertension and/or tachyarrhythmia |
| | • **Close monitoring of BP and pulse**<br>• **If taken with QT interval-prolonging drugs:**<br>1) Measure ECG 3-5 hours after 1st dose<br>2) Avoid this herb if QTc ≥480ms | |
| | • **Avoid dihydropyridine calcium channel blockers with exception of amlodipine**<br>• Close monitoring of BP is required if amlodipine is used<br>• Not recommended to use with cough preparations containing DM<br>• Consider using alternative<br>• Caution if patient is on CNS stimulant or MAOI | |
| **Remarks** | Contains ephedrine-like alkaloids | |

# 2. 麻黃 (EPHEDRA, MA HUANG)

Perspiration for dispelling cold, relieving asthma and causing diuresis

For cold, edema in acute nephritis, bronchial asthma

- Total alkaloid can exceed 2% depending on the species, in which 40 – 90% are (-)-ephedrine, accompanied by (+)-pseudoephedrine
- CP 2010: not less than 0.80 % (~16mg to 80mg) of the total amount of ephedrine HCl and pseudoephedrine HCL calculated with the reference to the dried drug
- Drugs: Promethazine compound linctus (each 5ml contains DM 10mg, ephedrine HCl 8mg, promethazine HCL 4mg); and pseudoephedrine alone (60mg) or in c/b (30-240mg) with antihistamine / cough and cold preparations are available

CP 2010 recommended dose: 2-10g

% of aqueous extraction:

- ephedrine (16%) → 3-13mg
- pseudoephedrine (28.7%)

劉昌美等, 中藥麻黃浸提方法的比較研究. 上海中醫藥雜志, 2000(04).

| Health Canada | US FDA | HK |
|---|---|---|
| 2002 - a voluntary recall of<br>• all ephedrine products containing >8 mg per dose;<br>• all c/b of ephedrine with other stimulants; and<br>• all ephedrine products marketed for weight-loss or bodybuilding<br><br>Ephedrine is only sold as an oral nasal decongestant in 8 mg pills | Since 2004 - prohibited the sale of dietary supplements containing ephedrine alkaloids<br><br>Not apply to TCM remedies, or products such as herbal teas that are regulated as conventional foods | Ephedrine and pseudoephedrine - Part I Poisons, shall be sold at premises of an authorized seller of poisons by a registered pharmacist or in his presence and under his supervision<br>• Rx required - aerosol dispenser<br><br>Products containing ephedra should be registered as pCM unless it is registered under western medicine<br>• Specific labeling requirement stating that the product is not suitable for long term use or the product should be used in accordance with doctor's instruction<br><br>Ephedra (麻黃) should be prescribed by CM practitioners, and in accordance with the proposed dosage of the pharmacopoeia |

# SUSPECTED ADVERSE / TOXIC EFFECTS

*[total papers:22; sample size of RCT/CCS:3-702]*

| Evidence | Subjects | Dosage | Outcome |
|---|---|---|---|
| Case-control study (CCS) / case series / case reports | Healthy & some with underlying conditions (asthma, ht condition, drug addict etc) ± smoker | Mostly taken as dietary supplement in c/b product (some containing caffeine) from a single dose or for up to 4 yrs<br>Ephedra alkaloids ranged from 20mg-72mg; some doses unknown or markedly overdose<br>~8mg-64.8mg ephedrine | • Haemorrhagic stroke / ischaemic stroke / cardiomyopathy / MI / ventricular arrhythmia / cardiac arrest / death<br>• CCS (702 subjects): ephedra-containing products at higher dose (>32mg/day) consumption might have higher risk of stroke<br>assuming ephedra alkaloids were used ~12.8-28.8mg ephedrine |
| Randomized crossover study | Healthy volunteers | Single dose of dietary supplement (DS) containing 12mg ephedra alkaloids & caffeine etc or matching placebo (7 days wash-out period)<br>~4.8mg-10.8mg ephedrine | **ADRs reported with DS**<br>• Sinus tachycardia, palpitations & premature ventricular complexes<br>**QTc**<br>• Mean max QTc interval was 5.9% higher with DS (419.4ms) compared to placebo (396.1ms, $p<0.001$);<br>• QTc interval was prolonged by avg 27ms vs baseline (392.2ms) in DS group; and<br>• Postdosing levels were ~23ms higher with DS than placebo gp<br>**SBP**<br>• Max SBP 5hr post dose was 4.8% greater with DS compared to placebo |

# RISK ASSESSMENTS AND RECOMMENDATIONS

| | 麻黃 (Ephedra, Ma huang) |
|---|---|
| **Effects** | May increase risk of adverse CVS effects e.g. hypertension<br>May potentiate cardiovascular stimulatory effect of pseudoephedrine / phenylpropanolamine |
| **Adverse events** | Hypertension, tachycardia, may prolong QTc if taken with QT interval-prolonging drugs |
| **Recommendations** | **Avoid** in hemorrhagic stroke, uncontrolled hypertension and tachyarrhythmia |
| | • Monitor BP and pulse<br>• For short term use only<br>• If taken with QT interval-prolonging drugs:<br>1) Measure ECG 3-5 hours after 1st dose<br>2) Avoid this herb if QTc ≥480ms |
| | Caution if patient is on CNS stimulant or MAOI |
| **Remarks** | Contains ephedrine-like alkaloids |

# POTENTIAL TOXIC HERB-DRUG INTERACTIONS (HDI)

## Anticoagulation / Anti-platelet effects:

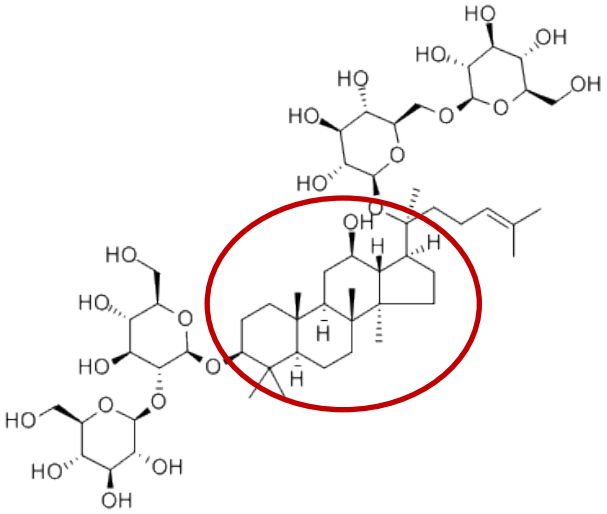
Ginseng (人參) / American ginseng (西洋參)

Other CM: Danshen (丹參), Dong Quai (當歸)

# GINSENG（人參）

Ginseng or Radix ginseng - dried root of ***Panax ginseng***

1. Asia ginseng, Chinese ginseng, Korean ginseng
   - Red ginseng 紅參 (steamed and dried Ginseng) - commonly used form
2. American ginseng (*Panax quinquefolius*, 西洋參)
3. Panax notoginseng (Sanchi / 三七)

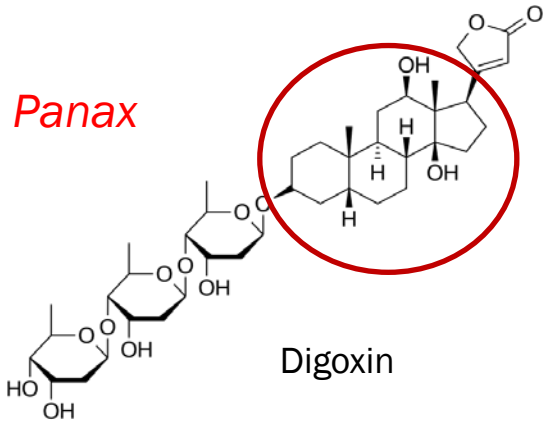


ginsenoside Rb1

## Ginsenosides

- active compounds found exclusively in the plant genus *Panax*
- Panax ginseng, American ginseng and sanchi contains 3.8%, 4.05% and 6.24% ginsenosides respectively [1]

[1] 董曉強, 董文天, 洪霞,等.三七、人參和西洋參化學成分與藥效學之間的關系.*承德醫學院學報*, 2011(03).



Digoxin

**Case reports on CV** [total papers:12]

- Ginseng & American ginseng - hypertension, bradyarrhythmia, tachyarrhythmia, AF
- Sanchi - arrhythmia (especially AV block)
  - Recommendations for Sanchi: (1) Not recommended in patients with AV heart block; (2) ECG monitoring for at risk patient groups

# INTERACTION WITH ANTICOAGULATION (WARFARIN) / ANTI-PLATELET (AP) DRUGS

RCTs, Clinical trial simulation (CTS), Case reports (Crpt) *[total papers:11; sample size of RCT:12-25]*

| CM - drug | Outcomes | Effects | Recommendations |
|---|---|---|---|
|  Ginseng (人參) / American ginseng (西洋參) | **[RCT]:** healthy subjects and ischemic stroke pts (warfarin-naïve); warfarin (W) vs c/b (W) & ginseng fr 2-4 wks<br>• (conflicting results) – (i) sign. ↓ peak INR; sign. ↓ INR, AUC, peak plasma warfarin after 2 wks; (ii) No stat. diff in INR, AUC, peak, and pK or pD of S- or R-warfarin<br>**[CTS]:** 100 trials simulated; population PK-PD based on data (e.g. conc of S-warfarin, INR) pooled from 2 RCT<br>• ↑CL/F of S-warfarin by 14% (not likely clinical sign.)<br>**[C Rpt]:** mechanical ht valve, HT, angina, DM; previously stable on (W); unk dosage of pCM ginseng x 5 wks to months<br>• ↓INR; INR returned fr 1.5 to 3.3 upon d/c of ginseng; Naranjo score –probable | May ↓ INR | Use alternative CM if possible.<br>If the concurrent use cannot be avoided, routine monitoring & weekly monitoring of INR until 2 weeks after stopping the CM |
|  | [Animal study]: *suggested ginseng does not affect pK of warfarin due to low BA and rapid elimination of ginsenoside*<br>[In vitro]:– *Panaxynol (main active antiplatelet components), inhibited the aggregation, release reaction, and thromboxane formation in rabbit platelets; and ginsenosides (not the main antiplatelet components) suppressed the release reaction only* | | |

# OTHER CM - INTERACTION WITH ANTICOAGULATION (WARFARIN) / ANTI-PLATELET (AP) DRUGS

## Case reports (C Rpt) *[total papers:13]*

| CM - drug | Outcomes | Effects | Recommendations |
|---|---|---|---|
| Danshen (丹參) | **[C Rpt]:** - rheumatic ht dis., AF, mitral valve repl.; previously stable on warfarin; taken decoction (unk dosage) fr 2 days to 1 month<br>• ↑↑↑ PT (>60s), ↑↑↑ INR (>5.62, >5.5, >8.4) and bleeding complications; INR returned to target (2-3) after given FFP + RBC & d/c CM<br>[Animal study]: ↑↑ BA and AUC of warfarin; ↑ Ka, ↑ elimination t ½; ↓ clearance and Vd of both isomers of warfarin<br>[In vitro]: inhibition of cAMP phosphodiesterase by danshen may result in additive antiplatelet effects | May ↑ INR and risk of bleeding |  <br>Not recommended with warfarin<br>If the concurrent use cannot be avoided, monitor INR 2-3 times / week |
| Dong Quai (當歸) | **[C Rpt]:** rheumatic ht dis., stroke, AF, mitral valve repl; previously stable on warfarin; taken DQ tab (unk dosage) x ~1 month<br>• ↑ PT (27s) and ↑↑↑ INR (4.9) asymptomatic; or widespread bruising ↑↑↑ INR (10)<br>[Animal study]: ↓ or slightly ↑ PT but no effect in other PK parameters of warfarin<br>[In vitro]: Dong quai contains coumarin derivatives and components that may inhibit platelet aggregation | May ↑ INR and risk of bleeding |  |

# Conclusion

* Use of herbs and drugs together is NOT without risk
* Pertinent evidence on HDI is scarce and requires careful data interpretation
* Predefined risk stratification matrix is pivotal in risk assessment
* Multidisciplinary input (i.e. an expert panel) is imperative in achieving clinical needs
* A novel approach is adopted in predicting, interpreting and preventing potential toxic HDI in the local setting
* Close monitoring is still required in clinical practice
* Close collaboration between clinicians and CM practitioners is needed

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