



Seminar on Research & Development of Chinese Medicines 2015

Measures to Ensure the Quality and Safety of Chinese Medicines in Hospital Authority **醫院管理局中藥質量及安全管理策略**

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10 Sept 2015



Background

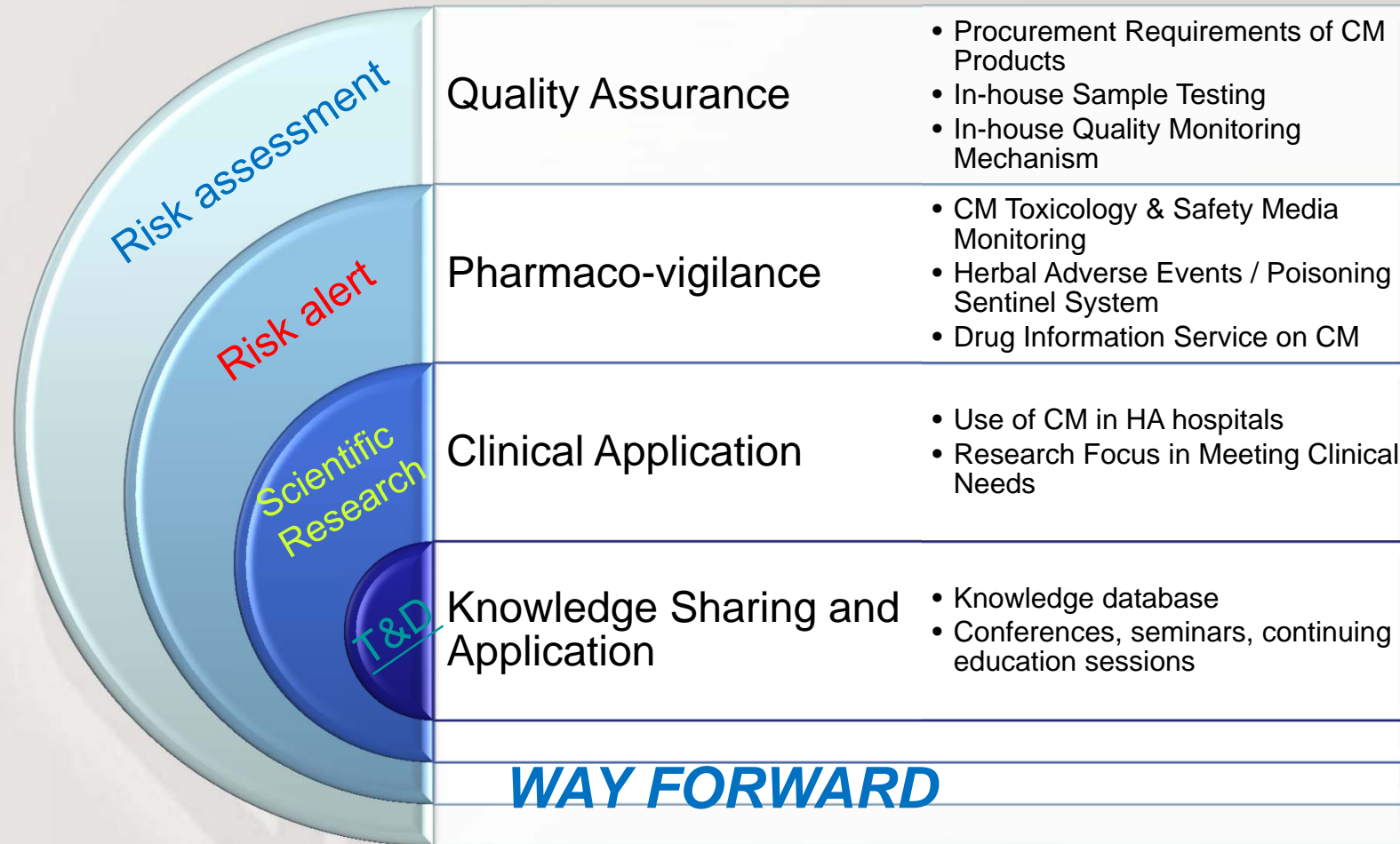
2003

- Toxicology Reference Laboratory
- 3 CM Clinics in operation
(Tripartite approach: NGO-HA-U)

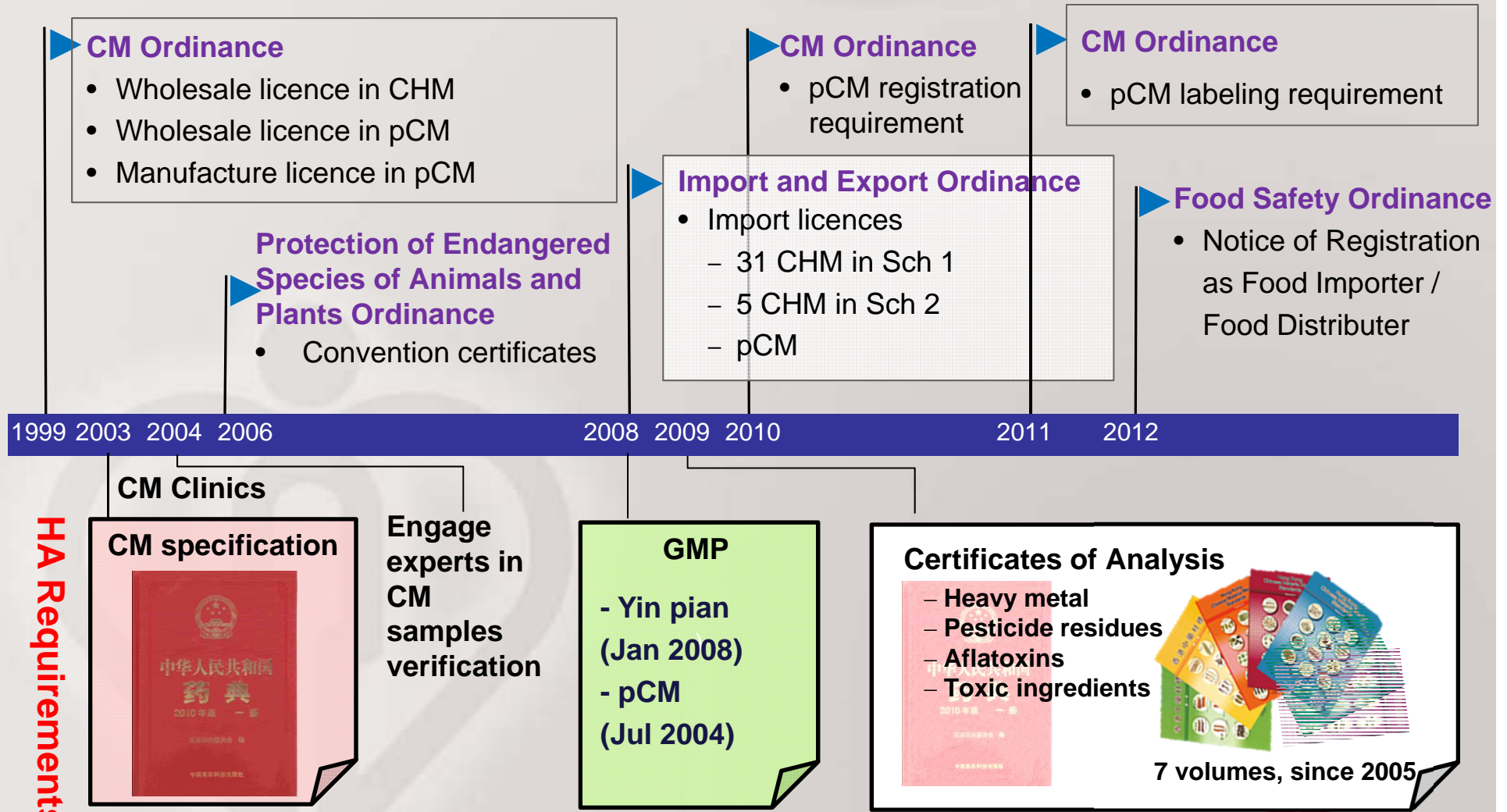
2014

- 18 CM clinics
- No. of attendance: ~1M
- 50% Yin pian (YP 飲片) : 50% CM granules
- Decoction service (14%)

Measures to Ensure the Quality and Safety of CM in HA

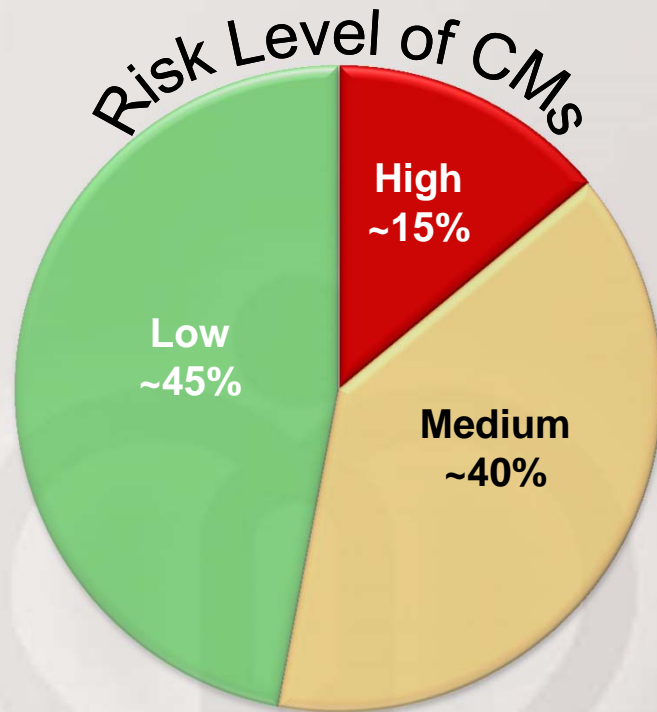


Procurement Requirements of CM Products



HA Requirements

In-house Sample Testing



Factors for Risk Stratification

1. Toxicity e.g Sch 1 CM in CM Ordinance
2. Specific CM in Chinese Pharmacopoeia (CP) with safety concern e.g. herbal markers for authentication
3. Local surveillance data e.g. reported poisonings / ADRs in HK
4. Volume of use

Specific Tests

1. Authentication and quality
2. Safety
 - a) Heavy metals, pesticide, microbial limits
 - b) Aflatoxins
 - c) Intrinsic toxic ingredient(s) in CM
 - d) Others requirements by HA, e.g.
 - Toxic contaminants: aconitine, atropine, aristolochic acid...
 - Dyes and foreign matters (e.g auramine O)

Standards and Methods

Laboratories involved:-

1. Laboratory accredited through HOKLAS
2. Institutions involved in the establishment of the HKCMMS

Standards

HKCMMS / CP

Not Detected

Methods

HKCMMS / CP

HOKLAS

HKCMMS / CP

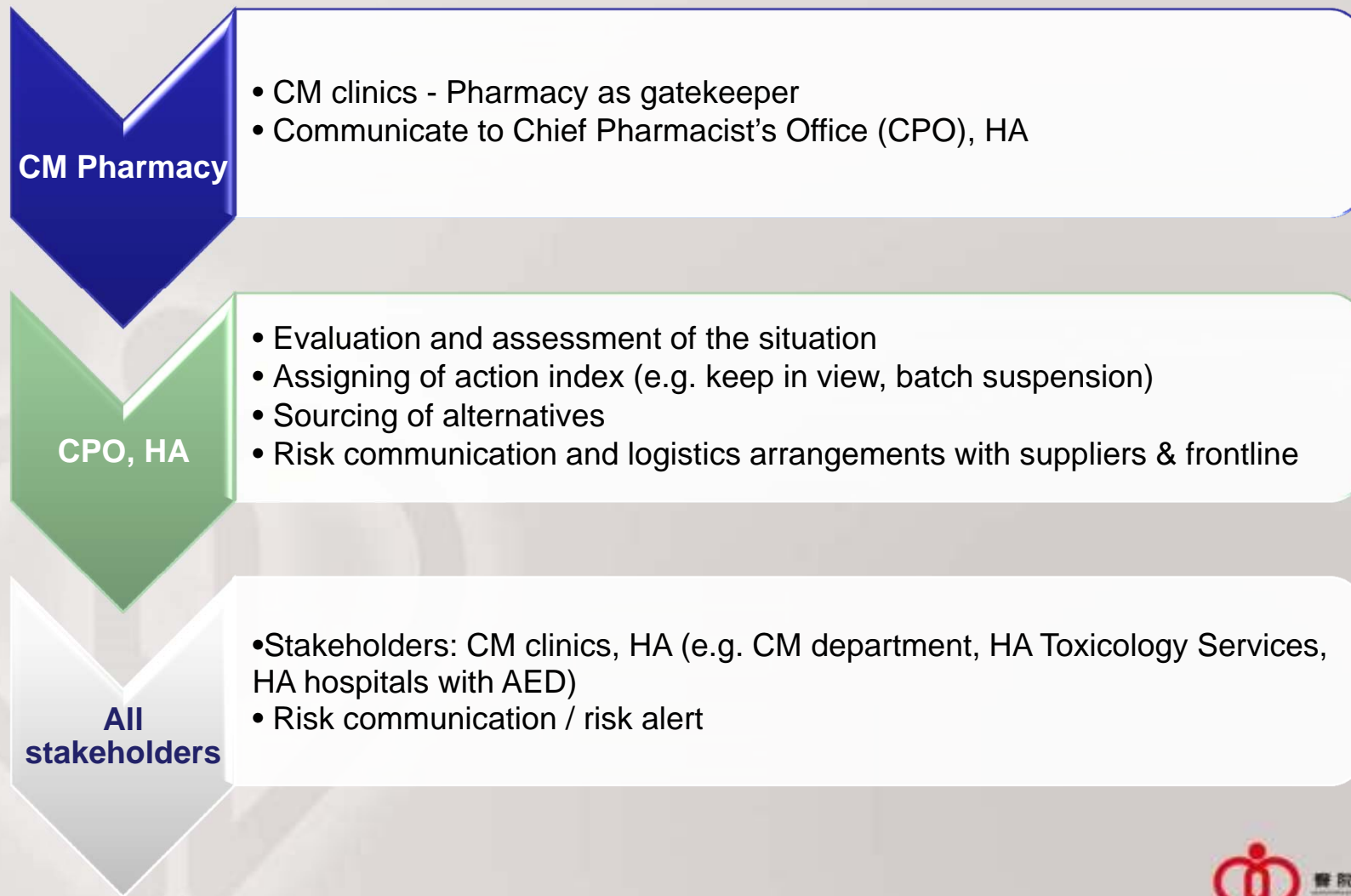
In-house methods

Tests

1. Authentication and quality
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* HOKLAS: Hong Kong Laboratory Accreditation Scheme
 CP: Chinese Pharmacopeia
 HKCMMS: Hong Kong Chinese Herbal Medicine standards

In-House Quality Monitoring Mechanism



CM Toxicology and Safety Media Monitoring

- Daily monitoring via global & local news / websites



WHO



HK



China



UK



USA

.....

- Risk communication with stakeholders, e.g.
 - CM Toxicology & Safety Media Monitoring (中藥毒理及安全媒體監聽)
 - [香港中藥中毒及不良反應資料匯總](#)
- Early signal detection for local hazard identification & risk assessment
 - HA Toxicology Services (HA Toxicology-intelligence Team)

Herbal Adverse Events / Poisoning Sentinel System

- Established in Aug 2004
- CM-related adverse events / poisoning notification in HA
- Work closely with the HK Department of Health on important public issues (Hong Kong Poison Control Network -HKPCN)
- Adverse events reported provide valuable information and signal clinical significance areas
- Identify herbs with potential toxicity for literature review, database development and research

Drug Information Service on CM

- Enquires from western and Chinese medicines professionals in HA, mainly clinicians
- Enquiries mainly involve:
 - Adverse reactions and toxicities of CM
 - Interpretation of CM prescriptions
 - Identification of processed herbs
 - Herb-drug interactions
 - Legislations and regulations on CM



Novel Approach for Risk Assessments on Use of CM in HA Hospitals

Expert Panel

- Toxicologist,
- Clinicians from various specialties (e.g. oncologist cardiovascular, liver, renal)
- Clinical pharmacologist
- Pharmacists
- CM experts (e.g. practitioners)
- Academia

Well-defined Risk Stratification Matrix

Level of Evidence \ Quality of studies	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

Local Experience & Clinical Management

Risk Rating:

High, Moderate, Low, No Reported Risk

Recommendations:

- Impact on clinical effects
- Use in at-risk patient group(s)
- Concurrent use with certain drug(s) or specific monitoring (e.g. TDM, INR)

Research Focus in Meeting Clinical Needs

(1) *Herb-induced Liver Injury (HILI) Network*

Objectives

- Create a registry of carefully documented HILI cases in patients under HA
- Identify risk factors and clinical outcomes of HILI

Process

1. Pilot study in 08/09 -- identified culprit hepatotoxic herbs by ruling out underlying causes and through literature review
2. Herb-induced Liver Injury Network (HILIN) formed in 2009 -- to conduct a prospective study (paper published in 2011*)

Consists of:-

- Hepatologist
 - Toxicology expertise (clinicians from Poison Centre and Toxicology Reference Lab)
 - Pharmacist (western medicines & Chinese medicine)
3. Use of scientific scoring system in clinical setting
 - RUCAM - Roussel Uclaf Causality Assessment Method

* Nin, C. T., Cheung, W. I., Ngan, T., et al., Causality assessment of herb-induced liver injury using multidisciplinary approach and Roussel Uclaf Causality Assessment Method (RUCAM). *Clin Toxicol (Phila)*, 2011. 49(1): p. 34-9.

Research Focus in Meeting Clinical Needs

(2) Systematic Reviews of Herb-drug Interactions (HDI)

- **Objectives of the Study**

- To identify any clinical and theoretical interactions of commonly used herbal medicines with drug groups of paramount concern in the HA
- To determine the interactions identified in terms of the mechanisms of action, degrees of severity and levels of evidence

- **Evidence-based Process**

- Blind parallel evaluation by University group and HA group
- Refer to expert panel if consensus cannot be reached

Evaluate the level of evidence and degree of severity of each interaction, and accordingly compile the level of significance



- Drug groups: anti-cancer drugs, drugs for CVS, metabolic syndromes, CNS etc.



Specialties / Focus Areas

Diseases

e-Resources

One Click Search

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Useful Links

HA Drug-herb Interactions Database

Introduction

Drug List

Search

eKG

Background

The HA Drug-herb Interactions Database is developed through joint collaboration by the Hospital Authority and academic institution(s) with strong background in western medicines and Chinese medicines (CM) education and research.

The HA Drug-herb Interactions Database is aimed to provide information on adverse drug-herb interactions (DHI) to healthcare professionals on specific drug groups, based on the latest published information from both English and Chinese databases at the time of data extraction and with a level of significance (LOS) rating assigned (Refer to Table 1. Level of Significance). The rating 1, 2, or 3 denotes the LOS from highest to lowest, whereas an asterisk would be indicated for which adverse drug-herb interaction was not known or studied (e.g. toxicity of the drug-herb combination was not studied despite a beneficial effect on its efficacy might have been demonstrated).

With the information retrieved, only primary data was assessed; therefore, reviews that describe an interaction but cited the original sources were excluded; however, the original source referred to was included. Jadad scores would be assigned to randomized controlled trials (RCT) as a determinant of the quality of RCT. While a set of criteria was developed for the evaluation of the relevant drug-herb interaction information and its level of significance, critical appraisal examining the articles was not performed. As the focus of the database is primarily on Chinese medicines that are commonly used by the people in Hong Kong, information relating to health food or supplement may not be found in this database.

DHI reports

Reviewed information would be reported as a unique pair of drug(s) and herb(s) with a LOS rating assigned on the potential interaction, brief summary, and the reference(s) used.

Sample of HDI report

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

Drug name

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

Chinese medicine / herbal medicines

Level of Significance

Level of Significance	Severity of Adverse HDI	Level of Evidence
1	<input type="checkbox"/> High	<input type="checkbox"/> A
	<input checked="" type="checkbox"/> Moderate	<input checked="" type="checkbox"/> B
	<input type="checkbox"/> Mild	<input type="checkbox"/> C
	<input type="checkbox"/> Insignificant / Uncertain	<input type="checkbox"/> D
	<input type="checkbox"/> Not known	<input type="checkbox"/> E

Effects

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

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

Management

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

Discussion

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).

References

- Reference(s):
- 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.
 - 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.
 - 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.
 - 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)

Prepared by Dept. of Pharmacology & Pharmacy, HKU

Severity of Adverse HDI \ 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	*	*	*	*	*

Herbal Toxicology Database

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中醫藥
Chinese
Medicine

HOSPITAL AUTHORITY TOXICOLOGY SERVICES

HATS | Hospital Authority Toxicology Services

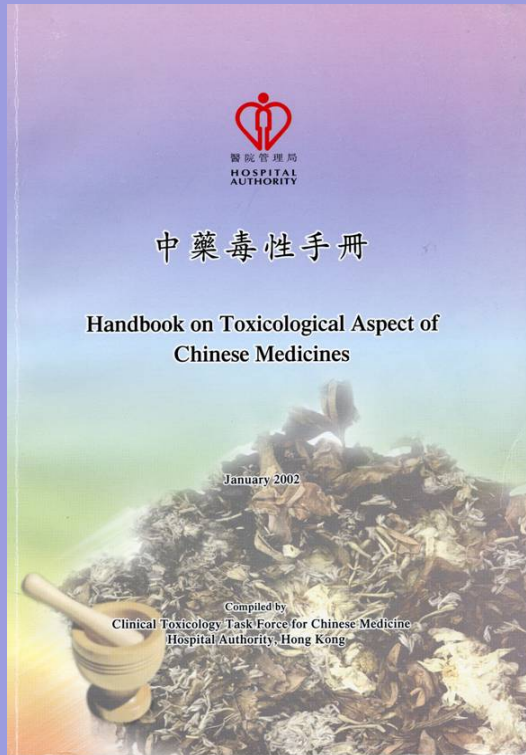
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SERVICE DIRECTORY TOXICOLOGY MONOGRAPHS TOXICOLOGY CASE SHARING EDUCATION PUBLICATIONS HERBAL TOXICOLOGY POISONING STATISTICS TOXICO-INTELLIGENCE

Home > Herbal Toxicology > Chinese Herbal Medicine

Handbook Published in Jan 2002



Database Established in Aug 2004

HA Herbal Toxicology Database

Home	About This Database	Task Force	Links	Site
Monograph Search	By Names	By Ingredients	By Products	By We Med
Table Search	System	Action/Symptoms	Ingredient	Prop Prod
	CM	Reference		
Management	General Treatment	GI Decontamination	Antidotes	
Traditional Use	Traditional Use			
Help	Glossary			

HA Herbal Toxicology Database

Home - About this Database

Background

Chinese Medicines have been used for thousands of years and have long been regarded by the Chinese as a relatively safe modality of therapy. With increased utilization in the community, there is an increase in awareness of reported poisoning in local hospitals. In addition, the recent development in Chinese Medicine opens up a new sphere of interest in Chinese Medicine, in particular herbal toxicology.

Front-line clinical staff of the Hospital Authority are trained to practice Western Medicines and have little experience in handling the toxicology issues of Chinese Medicines. Furthermore, there is a lack of suitable references on this subject in the practice of Western Medicine. The paucity of published information on the subject is particularly true with pharmacology, treatment and antidoting of Chinese Medicine poisoning in the context of modern medicine practice.

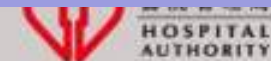
Structure of Database

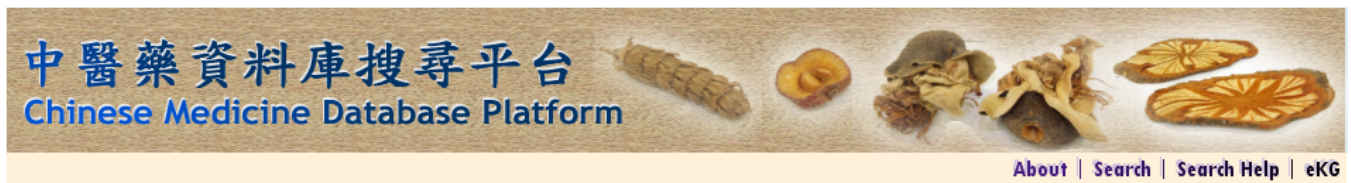
596 monographs on herb

- Pharmacology
- Toxicology
- Herb-drug interaction
- Photos

example, Radix Salviae Miltiorrhizae (丹参, Dan shen), according to Traditional Chinese Medicine theory, invigorate blood flow and eliminates stasis of blood (活血祛瘀). Animal studies show Dan shen to have anticoagulation effect, thus

Task Force on Clinical Toxicology (HA)
[Members : clinicians, pathologists, toxicologists and pharmacists]





Search Tips		
Phrases	Examples: or	"當歸", "dang gui", "blood pressure" 當歸 (with no space in between the words)
Keywords (AND)	Examples:	經絡 (with a space in between the words) scalp acupuncture, scalp AND acupuncture, scalp +acupuncture
Keywords (OR)	Examples:	脾 OR 胃 spleen OR stomach
Keywords (NOT)	Examples:	膽 NOT 痛, 膽 - 痛 cholesterol NOT high, cholesterol - high

Synonyms Table of CMs

中國藥典2010版及其附錄(869種); 中華本草(9,012種)

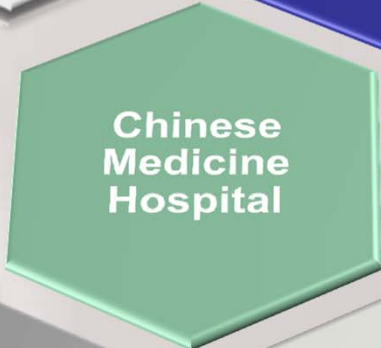


Chinese name	Latin name	Chinese plant name	Latin plant name	Pinyin
人參	RADIX ET RHIZOMA GINSENG	人參	Panax ginseng C. A. Mey.	Renshen
人參葉	FOLIUM GINSENG	人參	Panax ginseng C. A. Mey.	Renshenye
兒茶	CATECHU	兒茶	Acacia catechu (L. f.) Wild.	ErCha
九里香	FOLIUM ET CACUMEN MURRAYAE	九里香 千里香	Murraya exotica L. Murraya paniculata (L.) Jack	JiuliXiang
九香蟲	ASPONGOPUS	九香蟲	Aspongopus chinensis Dallas	Jiuxiangchong
刀豆	SEMEN CANAVALIAE	刀豆	Canavalia gladiata (Jacq.) DC.	Daodou
三七	RADIX ET RHIZOMA NOTOGINSENG	三七	Panax notoginseng (Burk.) F. H. Chen	Sanqi
三白草	HERBA SAURURI	三白草	Saururus chinensis (Lour.) Baill.	Sanbaicao

Way Forward



To be launched in 2016



Policy Address 2014



2014



END



醫院管理局
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