Laboratory Investigation of Traditional Chinese Medicine Related Poisonings

Dr Tony MAK
Consultant Pathologist
Hospital Authority Toxicology Reference Lab
Hong Kong

The “Usual” Toxins

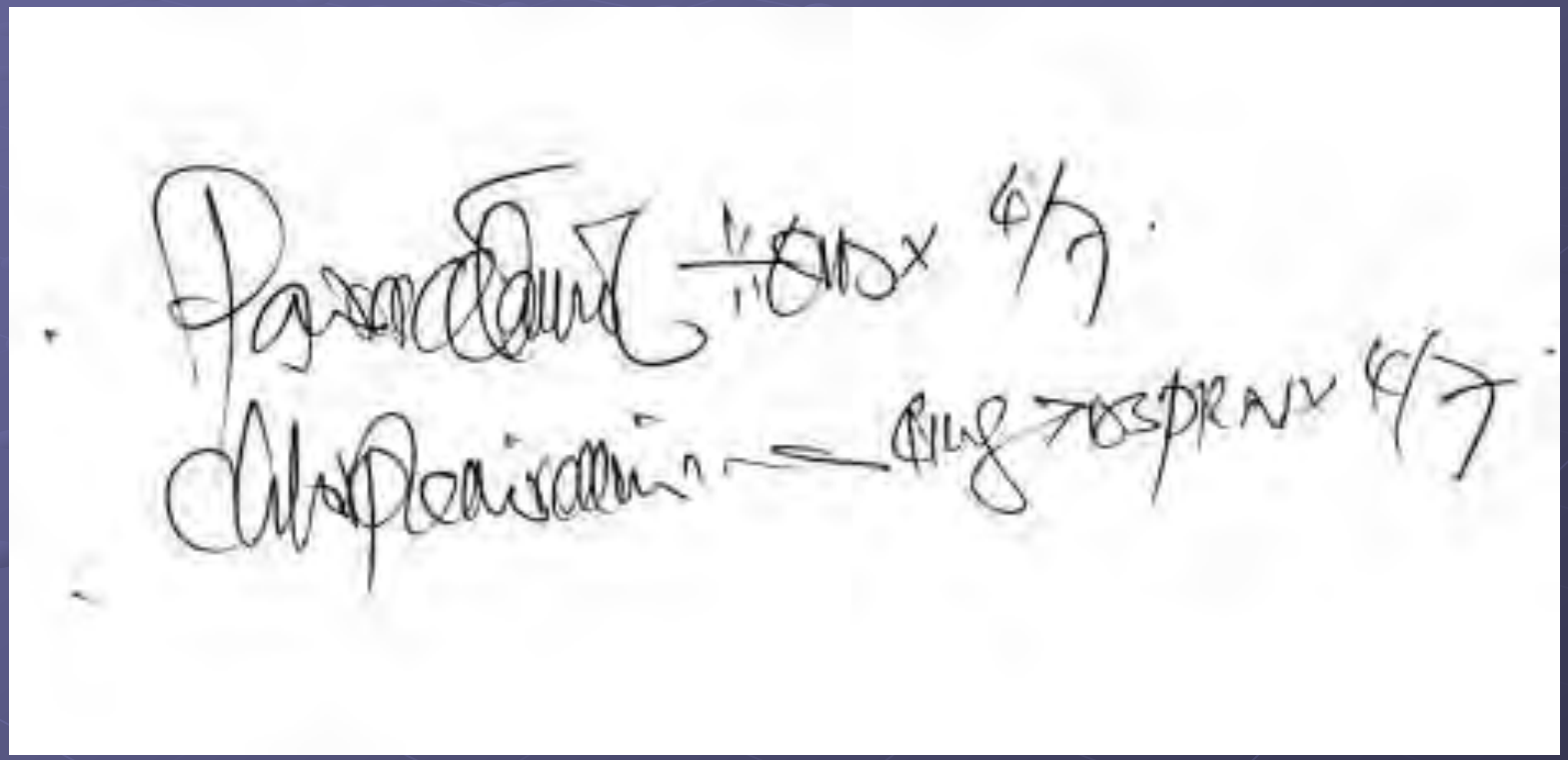
- More well defined
- Better studied
- Part of the medical school curri[illegible]m
- Assay commercially availab[illegible]

  - Western drugs: Paracetamol, glibenclamide…
  - Drugs of abuse: Morphine, amphetamines…
  - Heavy metals: Lead, mercury…

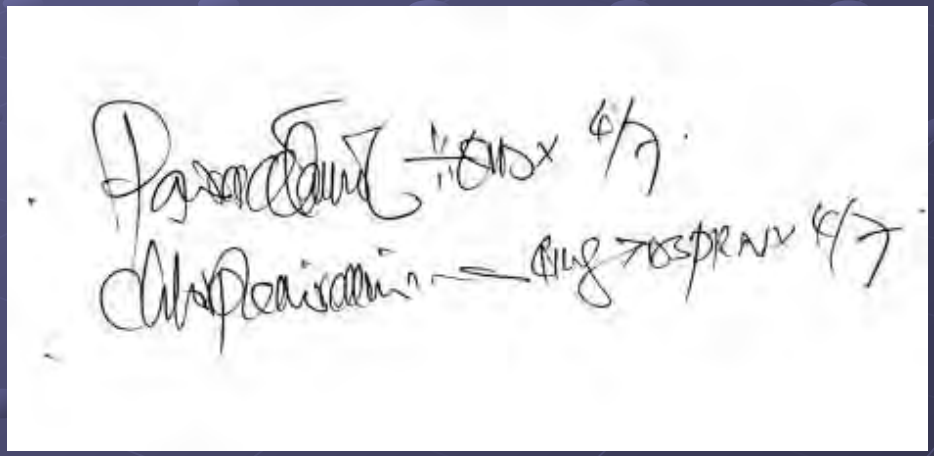
- Investigation of TCM-related poisoning…
- Need some new approaches
- My lab started this journey since 2004

Knowledge Gap

Knowledge Gap



Knowledge Gap



Knowledge Gap

雞血藤

川牛膝

甘草

威靈仙

五加皮

桂枝

川烏

白芍

製草烏

附子

川斷

Knowledge Gap

雞血藤

川牛膝

甘草

威靈仙

五加皮

桂枝

川烏

白芍

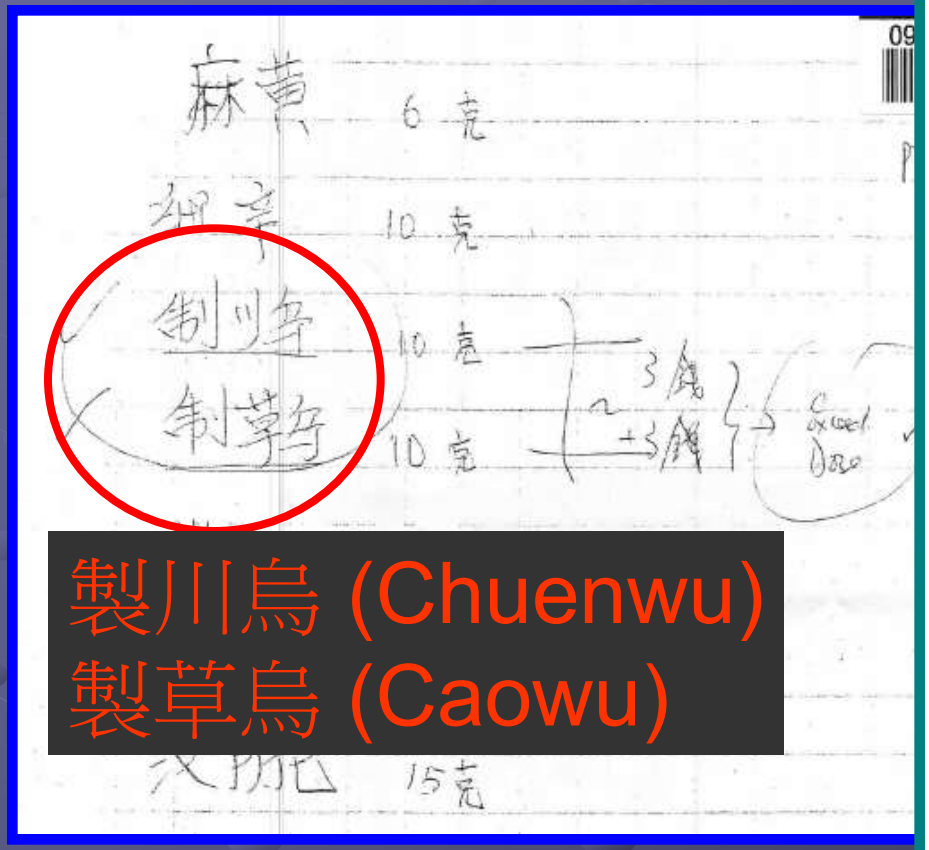
製草烏

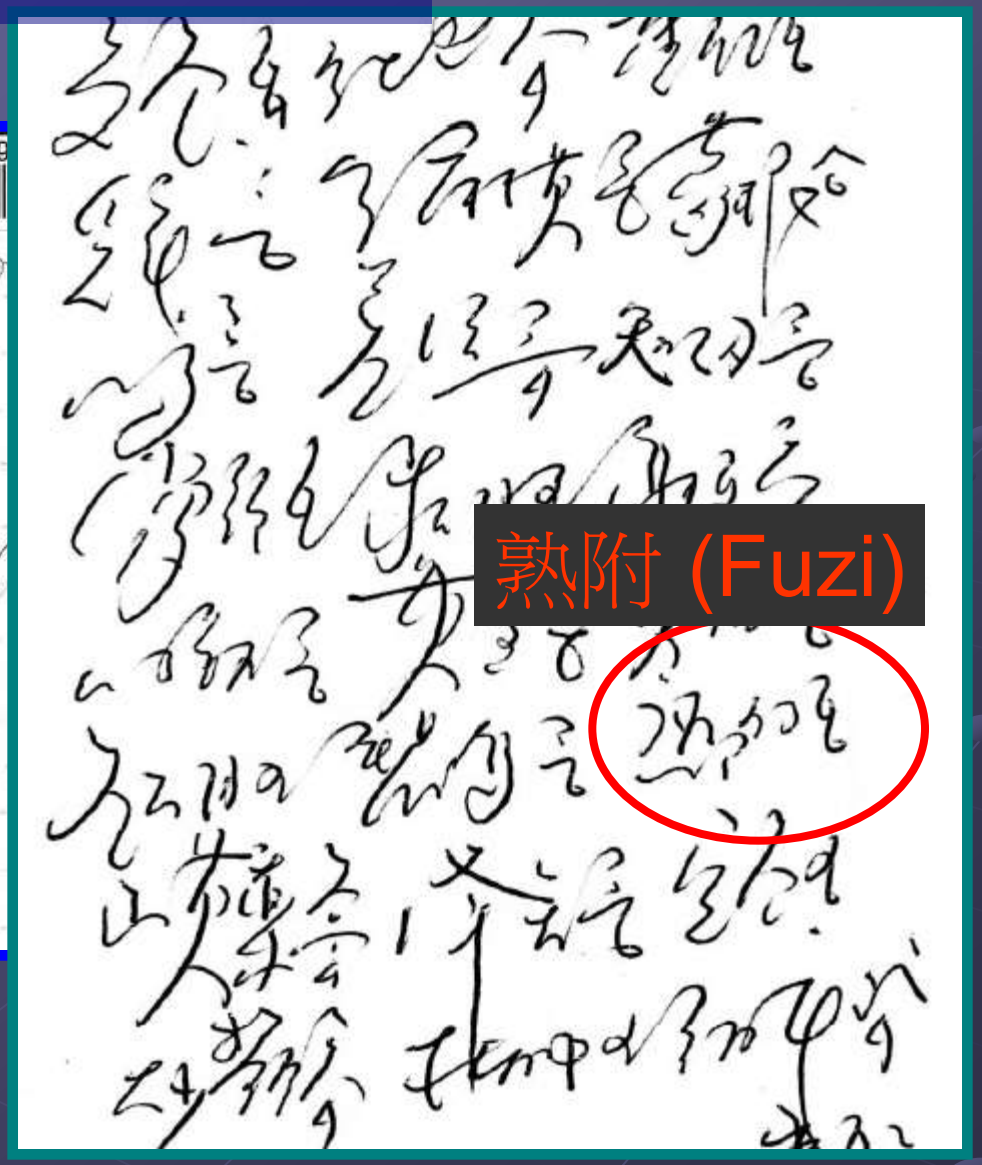
附子

川斷

✏ **Transcribe TCM formulae**

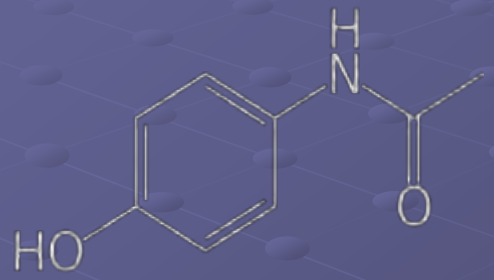
Transcribing TCM Formulae



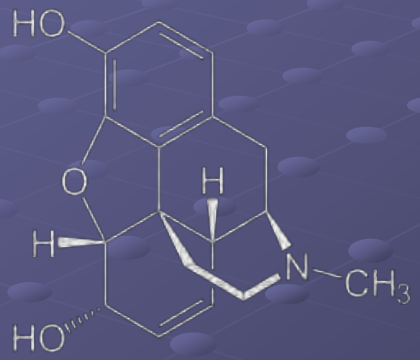


The complexity of herbs as a poison

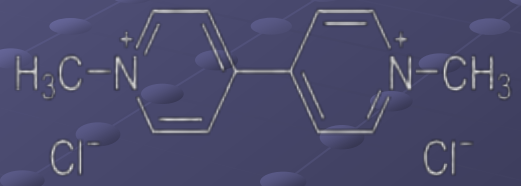
- The “usual” poisons:



Paracetamol



Morphine



Paraquat

- Relatively well-defined

The complexity of herbs as a poison

- Herbs:

- Not pure compounds, but
  - a complex mixture of compounds!
  - TCM: uses multiple herbs each time

→ Toxin: which compound in which herb?

✏ **Identify herbs morphologically**

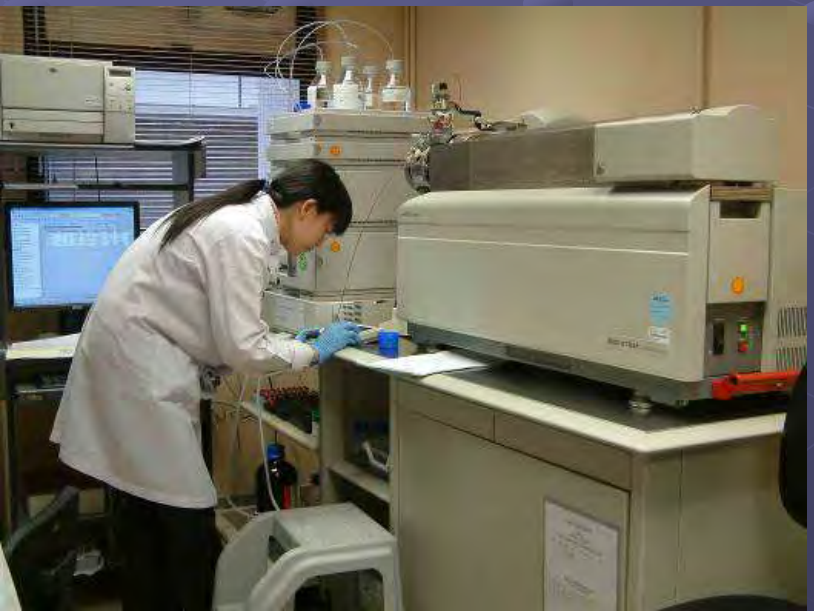
✏ **Develop assay in-house**

Herb Identification

Herbs Identification

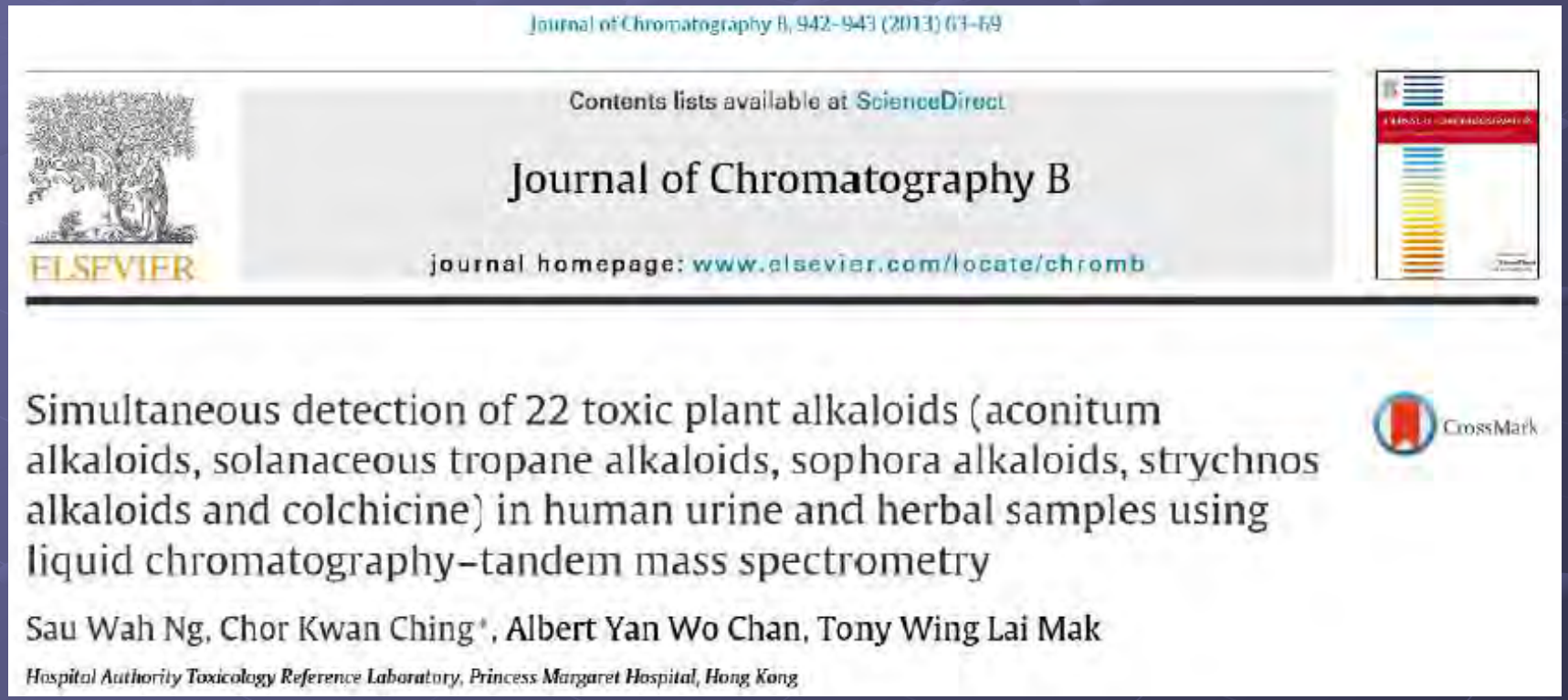
Biochemical Investigations

- ✦ No commercial assays
- ✦ Everything was developed in-house
- ✦ What to develop?
  →A big question!



Biochemical Investigations

- Detecting 22 toxic plant alkaloids at once



Journal of Chromatography B, 942-943 (2013) 63-69

Contents lists available at ScienceDirect

Journal of Chromatography B

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

Simultaneous detection of 22 toxic plant alkaloids (aconitum alkaloids, solanaceous tropane alkaloids, sophora alkaloids, strychnos alkaloids and colchicine) in human urine and herbal samples using liquid chromatography–tandem mass spectrometry

Sau Wah Ng, Chor Kwan Ching*, Albert Yan Wo Chan, Tony Wing Lai Mak

Hospital Authority Toxicology Reference Laboratory, Princess Margaret Hospital, Hong Kong

- Testing for other individual toxin as indicated
- Developing new assay for specific cases

Our Approach

- History
- Clinical features / toxidrome

- Specimens:
  - Biological samples
  - Herbs (raw / remnant)
  - Herbal broth
  - Herbal prescription
  - Proprietary CMs
  - Fresh plants

Better Worked up Problems

Aconite Poisoning

- As traditional Chinese medicine:
  - Caowu (草烏, *A. kusnezoffii*)
  - Chuenwu (川烏 *A. carmichaeli*)
  - Fuzi (附子 *A. carmichaeli*)
- Narrow therapeutic index
- Widely used by TCM practitioners
- Toxidrome:
  - GI
  - Neurological
  - Cardiovascular

Aconite Poisoning

- Most common in HK
- 70% of the severe TCM-poisoning cases*
- In-patient mortality rate: 5.5%*

*Chan TYK (1994, 2009)

Authors	No. of cases	Where
Lin CC	17 in 10 year	Taiwan
Tai YT	17 in 4 year	HK
Chan TY	22 in 8 year	

2 to 4 cases/year

TRL Since 2004

- ~~Hx of aconite herb used~~
- Compatible clinical features
- +/- Review of prescription
- + Idenfication of herbs
- + Analytical confirmation

~ 10 cases per year

Hidden aconite poisoning

- M/20
- Low back pain
- Took decoction of a composite formula:
  - 川牛膝, 杜仲, 杞子, 知母, 川斷, 白芥子,
  - 蒼術, 白術, 防風, 淫羊藿, 百花蛇, 枳殼,
  - 白芍, 威靈仙, 茯苓, 狗脊, 春砂仁
- No problem after the 1st dose

Hidden aconite poisoning

- 2 months later
- Same formula
- Immediately:
  - weakness, sweating, vomiting
- Attended Accident & Emergency Dept

Hidden aconite poisoning

- In A&E:
  - impaired consciousness
  - in shock, BP unmeasurable
  - ECG → ventricular tachycardia
  - cardioversion: unsuccessful
  - amiodaron given
  - intubated, ICU
  - → pulseless ventricular tachycardia
  - prolonged resuscitation
  - temporarily pacemarker
  - survived!

Hidden aconite poisoning

- Analysis:
  - Herbal broth remains & urine
  - Found yunaconitine
  - an aconitum alkaloid from caowu(草烏)

Hidden aconite poisoning

- Source of the aconite herb?
  - No problem 2/12 ago
  - No aconite herb in the formula

- A dose of unused herbs kept by the patient:
  - No aconite herb was identified

Hidden aconite poisoning

- Aconite herb was
  - NOT prescribed
  - NOT intentionally dispensed
  - but present by mistake

Hidden aconite poisoning

- Mistake: which stage?
  - harvest?
  - manufacturing?
  - herb processing?
  - transportation?
  - storage?
  - dispense?
  - ….

Hidden aconite poisoning

- ✦ "Hidden" aconite poisoning
- ✦ Isolated?
- ✦ 52 cases in 5 years
- ✦ 1/3 were "hidden"
- ➔ Quality of herbs: a BIG problem

5-Year Review

- How common?
- How severe?
- Why poisoning?

Why poisoning

Reason	No.	%
Overdose	17	98%
Hidden Aconite Poisoning	17	
Inadequately processed herbs	7	
Dispensing error	2	
Ingestion of externally used herb	1	2%

- Quality of prescribing
- Quality of herbs
- Quality of dispensing

J Anal Toxicol. 2006 Sep;30(7):426-33.

Hidden Aconite Poisoning: Identification of Yunaconitine and Related Aconitum Alkaloids in Urine

Hong Kong Med J. 2006 Dec;12(6):456-9.

MEDICAL PRACTI

WT Poon 潘永達
CK Lai 賴志剛
CK Ching 程楚君

Aconite poisoning in camouflage

Drug Safety 2012 Jul 1;35(7):575-87.

ORIGINAL RESEARCH ARTICLE

Aconite Poisoning over 5 Years

A Case Series in Hong Kong and Lessons Towards Herbal Safety

Sammy Pak Lam Chen,[1] *Sau Wah Ng,*[1] *Wing Tat Poon,*[1] *Chi Kong Lai,*[1] *Teresa Man Shan Ngan,*[2] *Man Li Tse,*[3] *Thomas Yan Keung Chan,*[4] *Albert Yan Wo Chan*[1] and *Tony Wing Lai Mak*[1]

Other Better Worked up Problems

Other better worked up problems

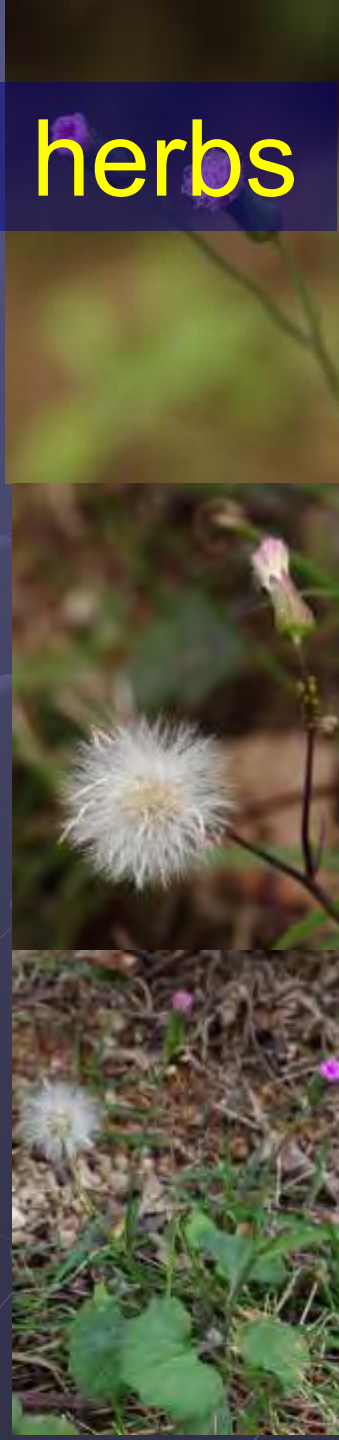
- Anticholinergic TCM herbs
  - Datura metel (洋金花);
  - Atractylodes lancea (蒼朮)
- Aristolochic acid nephropathy
  - Aristolochia mollissima Hance (尋骨風)
- TCM-related heavy metal poisonings
  - Lead
  - Mercury
  - Arsenic…
- Adulteration of proprietary CM
  - Many!

Emilia sonchifolia 一點紅

- M/10m, healthy all along
- Took herbal broth x 3 months
- Presented with:
  - Ascites, pleural effusion, hepatomegaly
  - Thrombosed right hepatic vein
  - ➔ Budd-Chiari syndrome
  - Recovered after stopping exposure
- The herb:
  - Identified to be *E. sonchifolia*
  - *Senkirkine* was detected in the plant
  - a pyrrolizidine alkaloid

Pyrrolizidine alkaloids containing herbs

- Present in many herbs, e.g.
  - *Senecio scandens* 千里光
  - *Farfugium japonicum* 蓮蓬草
  - *Gynura divaricata* 白背三七
  - *Heliotropium indicum* 大尾搖
  - ...
- Notoriously hepatotoxic
  - P-450: highly reactive metabolites
  - Binds to protein, DNA, RNA
  - Induce acute/chronic toxicities
  - Liver: principally affected
  - Budd-Chiari syndrome
- All can be found in HK



Emilia sonchifolia 一點紅

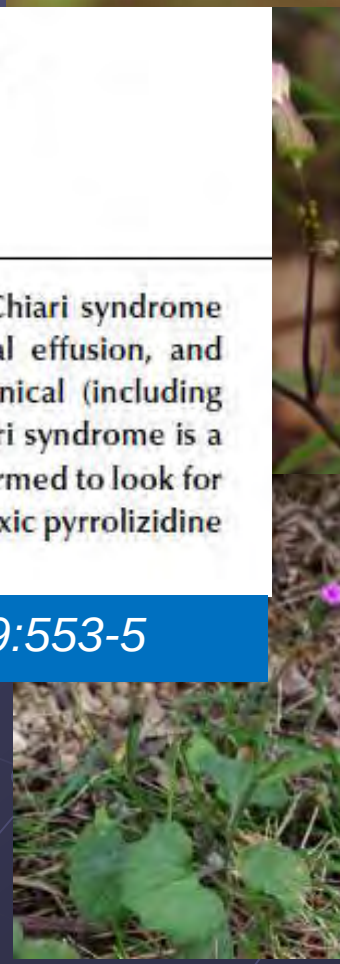
HONG KONG MEDICAL JOURNAL 香港醫學雜誌

Budd-Chiari syndrome secondary to toxic pyrrolizidine alkaloid exposure

Janet SW Wu 胡詩穎
WT Poon 潘永達
CK Ma 馬子軍
ML Chen 陳武龍
KS Pang 彭權森
Tony WL Mak 麥永禮
HB Chan 陳衍標

In this report, we describe a case of pyrrolizidine alkaloid–related Budd-Chiari syndrome in Hong Kong. A 10-month-old boy presented with ascites, right pleural effusion, and hepatomegaly after consumption of herbal drinks for 3 months. His clinical (including imaging) features were compatible with Budd-Chiari syndrome. Budd-Chiari syndrome is a rare disease entity in paediatric patients. In our case, extensive workup performed to look for the underlying cause of Budd-Chiari syndrome was unrevealing, except for toxic pyrrolizidine alkaloid exposure in his herbal drinks.

Hong Kong Med J 2013;19:553-5



Teucrium viscidum 山藿香

- F/51, back pain
  - Back pain, consulted a herbalist
  - prescribed “鬼見愁” x 3 days
  - Nausea, vomiting, tea-colour urine
  - Increased ALT
  - Typical acute hepatitis picture
  - Gradually recovered after 2 months
- The herb:
  - Identified to be *T visidum* 山藿香
  - Teucvin was detected → hepatotoxic

Teucrium viscidum 山藿香

Clinical Toxicology (2008) **46**, 819–822

ISSN: 1556-3650 print / 1556-9519 online
DOI: 10.1080/15563650701739590

CASE REPORT

Hepatitis induced by *Teucrium viscidum*

WING TAT POON[1], TAI LIN CHAU[2], CHI KONG LAI[1], KA YAN TSE[1], YIU CHEUNG CHAN[3], KING SUN LEUNG[2], and YAN WO CHAN[3]

[1]*Toxicology Reference Laboratory, Department of Pathology, Princess Margaret Hospital, Hong Kong, Hong Kong*
[2]*Department of Medicine and Geriatrics, United Christian Hospital, Kowloon, Hong Kong*
[3]*Hong Kong Poison Information Centre, United Christian Hospital, Hong Kong Special Administrative Region, Hong Kong*

Clin Tox 2008; 46: 819-822

Hepatotoxic Proprietary CM

- 火把花根片
  - Triptolide (雷公藤甲素)

- 驅白巴布期片
  - Psoralen (補骨脂素)

- **Jianmeisu (健美素)**
  - Ingredient?

Jianmeisu (健美素)

04C0309660
N-nitroso-fenfluramine

沖劑藥丸竟達數十種

少女濫服保健品換肝保命

醫院每月都收到一至兩宗服用中成藥導致肝
至肝衰竭的個案。

近年市面中成藥保健食品

星報衛生署
中藥不良反應個案

(2000年至2004年6月)

數　目：40宗證實個案（另22宗懷疑
人　數：49人（20男、29女）
年　齡：6-87歲
入院人數：38人（6人需深切治療）
個案類別：34宗服用中草藥、
6宗服用中成藥

資料來源：衛

中藥中毒案
今年大幅飆升

衛生署由二〇〇〇年至今年六月期
共接獲六十二宗懷疑中藥不良反應的呈

Jianmeisu (健美素)

- 2004
- F/33
- Weight reduction
- Took Jianmeisu x 6 weeks
- Sold >100 boxes/month in HK
- Claimed: 12 benign TCM herbs

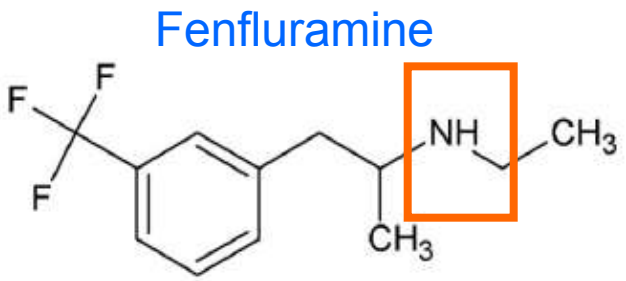
Jianmeisu (健美素)

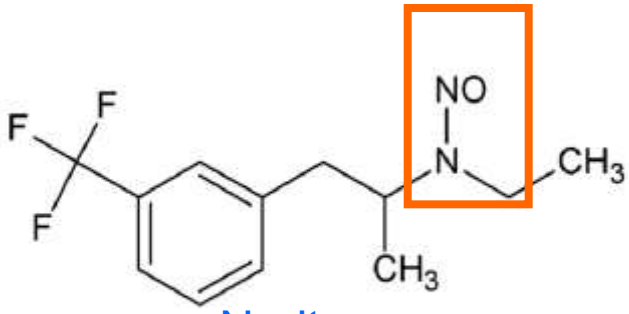
- ✦ Fulminant hepatic failure!
- ✦ Saved by liver transplantation
- ✦ Cause of liver failure??
- ✦ Idiosyncratic reaction to a herb?
- ✦ TRL found N-nitroso-fenfluramine (NNF)
- ✦ NNF – an analogue of fenfluramine
- ✦ Department of Health:
  → banned the product

Jianmeisu (健美素)

- ✦ Fenfluramine
- ✦ Banned slimming agent
- ✦ NNF – an analogue
- ✦ Singapore, UK
- ✦ Japan >800 cases

Fenfluramine

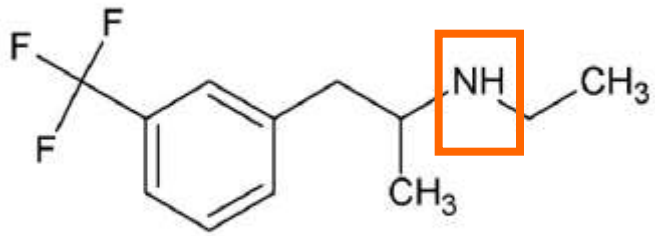




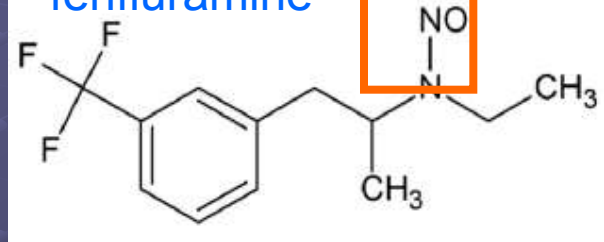
N-nitroso-fenfluramine

Jianmeisu (健美素)

Fenfluramine



N-nitroso-fenfluramine



Heart valve defects	??
Pulmonary HT	??
No liver toxicity	Liver toxicity ++++
Appetite suppressant	Appetite suppressant x

Poorly Worked up Problems

→ Many!

Herb → Hepatotoxic?

- Herbs with "known" hepatotoxins
  - Some are known
- Herbs without known hepatotoxin
  - Far more
  - Causally related?

Clinical Toxicology (2011) **49**, 34–39
© 2011 Informa Healthcare USA, Inc.
ISSN 1556-3650 print/ISSN 1556-9519 online
DOI: 10.3109/15563650.2010.537662

Clin Tox 2011; 49: 34-39

ARTICLE

Causality assessment of herb-induced liver injury using multidisciplinary approach and Roussel Uclaf Causality Assessment Method (RUCAM)

TAI NIN CHAU[1], WING I. CHEUNG[1], TERESA NGAN[2], JIERU LIN[2], KEN WING SAN LEE[2], WING TAT POON[3], VINCENT KING SUN LEUNG[1], TONY MAK[3], MAN LI TSE[4], and the Hong Kong Herb-Induced Liver Injury Network (HK-HILIN)

Conclusions

- TCM-related poisonings
- A very difficult problem
- Need some new approaches
- Cracked some hard nuts
- Lab investigation: infancy
- Collaboration is most welcome!

Thank you!