Common Toxic Ingredients in Traditional Chinese Medicines

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Introduction

- Traditional Chinese Medicine (TCM) Herbs
- Chinese Patent Medicines (CPM)
Traditional Chinese Medicine
Herbs Definition

- TCM Herbs
  - botanical
  - minerals
  - animal parts
Dosage Formulation of TCM herbs

- Herbs are prepared as slices or powder
- Decoction (medicinal tea) - usually involves boiling in water
- Medicated liquor - extraction of herbs with alcohol
- Tablets (herbal ball)
- Topical - plaster, ointment
Processed TCM herbs

- Heating
- Cooking with/without other additive (e.g. ginger, honey)
- Boiling
- Soaking - water, alcohol
- Distillation
Processed TCM herbs

- reduce toxicity
- altered chemical properties to enhance therapeutic effects
- increase shelf-life
- cleansing and odor removing
Processed TCM herbs

- 99% of herbs are processed (either by manufacturer or by consumer). Very few herbs are ingested raw!
- Most common method of processing are soaking or heating of herbs in water
- Processed herbs will generally look and smell different from naturally occurring herbs.
TCM Herbs Usage

- Medicinal use
  For treatment of diseases
- Tonic use
  Maintaining health
- Food use
  Taste, flavor and nutrient
Statistics of TCM herbs

- In 1999, China categorizes 8980 herbs.
- There are approximately 550 commonly used herbs in traditional Chinese medicine.
Problems with TCM herbs

- substitution
- misidentification/misbranded
- contamination
- toxic herbs
- use of endangered species
Toxic Unprocessed Chinese Herbs
(HK List of Schedule 1)

- Heavy metals
- *Flos Daturae Metelis*
- Mylabris
- Aconite species
- *Radix Podophylli emodis* or *Dysosmatidis*
- *Radix and Semen Euphorbiae*
- *Fructus Crotonis*
- *Rhizoma Arisaematis*
- *Rhizoma Pinelliae*
- *Semen Hyoscyami*
- *Semen Strychni*
- *Venenum Bufonis*
- *Radix Kansui*
- *Resina Garciniae Morellae*
Adverse Reactions of TCM Herbal Products

- Increase in number of adverse reactions
  - Increase use
  - Increase physician/consumer awareness
  - Improve surveillance system
  - Herb-drug interactions
  - Inadequate training of practitioners
  - Products lack appropriate standards (misidentification)
Chinese Patent Medicines
Concerns

- Many are manufactured overseas with little oversight
- Toxic ingredients
- Prescription drug products
- Unapproved drug products
- Controlled substances
- Treatment claims
Adulteration

- Synthetic drugs
  » Steroid, non-steroidal anti-inflammatory agents, anti-histamine, sulfonylureas, benzodiazepines...etc.

- Examples
  » PC SPES
  » Zhen Qi, Diabetes Angel (glyburide)
PC-SPES - Example

- PC SPES composed of 8 herbs
- Has shown clinical efficacy on prostate cancer
- Adverse effects include estrogenic effects and deep venous thrombosis and pulmonary embolism, which can be prevented using warfarin.
- Used when no other options or treatment alternatives are available
PC-SPES - Example

- PC SPES tested positive for warfarin, diethylstilbestrol (DES), ethinyl estradiol and indomethacin
- DES level is low and not considered therapeutic effective
- Manufacturer cannot provide testing records
- No Good Manufacturing Practices procedures
- No Quality Control procedures
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Detection Limit: 25 ppm

Detection Limit: 100 ppm

* No data due to insufficient sample

**None detected except on warfarin, indomethacin (see appropriate columns for results)

***None detected except on ethinyl

ND: none detected

All units are microgram per capsule (ug/cap)
NIH sponsored clinical trials on hold
Delay treatment for prostate cancer patients
Manufacturer closed
Criminal prosecution and class action lawsuit.
Herbs Prohibited From Imports

- CITES Appendix I (for endangered species)
- Plant Protection Act (Federal Noxious Weed (Cuscuta species))
- Unsafe herbs (Aristolochia fang chi)
- USDA lists (citrus product)
- EPA prohibited pesticide (Quintozene)
- Not ALL prohibited herbs are unsafe!
Examples of adverse reactions from herbs
Podophyllotoxin (Gui Jiu, Tao Er Qi, Ba Jiao Lian)

- Can be found in *Podophyllum emodi*, *Dysosma versipellis*, *D. pleianthum*.
- Topically used to treat genital warts. Systemically used for cancer treatment, as an abortifacient, antibiotics and antidote for snake bite.
Podophyllotoxin

- **MOA**
  - Antimitotic
  - Purine synthesis inhibition
  - RNA synthesis inhibition
  - Blocking of oxidation enzymes in the tricarboxylic acid cycle
  - Induces catharsis through irritation of intestinal mucosa.
  - Embryotoxic and possibly teratogenic.
Podophyllotoxin

- Lethal dose for podophyllum resin is estimated to be 350 mg (topical) and 10 gram (oral).
- Adverse reactions can appear from few hours to 13 hours after ingestion
  - severe abdominal pain, nausea vomiting
  - nephritis
  - altered mental status, confusion and hallucinations
Podophyllotoxin

- Adverse reactions
  - peripheral neuropathy, muscle paralysis, ataxia
  - hypotension
  - leukocytopenia and thrombocytopenia
  - coma, death
Podophyllotoxin

- Treatment - supportive and charcoal hemoperfusion
- Poisoning usually from misidentification of the herb, causing overdose
- Has been misidentified as *Clematis chinensis* (a commonly used non-toxic herb)
- Adverse effects can be permanent
Podophyllotoxin Case

- 61 years old female with history of hypertension, hepatitis A,B antigen
- complain of nausea, vomiting and diarrhea after ingest herbal tea for arthritic pain 4 hours before admission
- developed chest pain and 6 hours later, decreased level of consciousness.
Lab test: AST 676 U/L (14-36), ALT 462 U/L (11-66), Alk Phos 175 U/L (38-126), other chemistries are WNL, ABG and UA is WNL.

Day 2, patient’s neurological status deteriorated and non-responsive to pain.

No spontaneous movement in her extremities.
Podophyllotoxin Case (cont.)

- Day 3, patient had eyes open when commanded, still somnolent with no movement in her extremities.
- Liver enzymes show improvement
- Acute drop in hematocrit (15%) and platelet (200 K/uL). Discontinue heparin
- Day 7, patient had significant improvement of mental status.
Day 9, patient able to wiggle her fingers and toes, no reflexes and no further movement in the extremities.

DHS was notified.

Herbs supposed to consist of *Pyrola rotundifolia*, *Cibotium barometz* and *Clematidis chinensis* (approximately 30 grams each).

All are considered non-toxic.
Residual herbs are tested to contain podophyllotoxin and 2.7 ug of Ar in 316 grams of herbs.

*Clematidis chinensis* is tested to contain podophyllotoxin.

Patient sign & symptoms are consistent with podophyllotoxin ingestion.

Herbalist confirmed the identity of *Pyrola rotundifolia*, *Cibotium barometz* but not *Clematidis chinensis*. 
Podophyllotoxin Case (cont.)

- Most likely, *Clematidis chinensis* is substituted with *Dysosma versipellis* or *D. pleiantha*.
- Trace back to distributor in San Francisco and importer in Los Angeles.
- Likely imported from Hong Kong 2 years ago (BMJ 1996-But et al)
- No other cases are reported, therefore unlikely a misidentification problem affecting the batch.
- Patient still suffers from peripheral neuropathy.
Aconite (Monkshood, Wolfsbane, Fu Tzu)

- Found in the roots of *Aconitum carmichaeli*, *A. kusnezoffii*, *A. balfourii Stapf*, *A. szechenyianum Gay*
- Traditionally used as analgesic and anesthetic agents in the treatment of neuralgic and rheumatic diseases.
- Contains diterpenoid-ester alkaloids (aconitine)
Aconite

- **MOA**
  - Excitation and inhibition of the vagus and sensory nerves
  - Act directly on cardiac muscle inducing arrhythmia via the sodium channel
  - Analgesic effects is elicited through central nervous system (noradrenergic system but not the opiate receptor)

- **LD\textsubscript{50}** for IV of aconitine is 0.22 mg/kg in mice, 2 mg of aconitine po can cause death in human (1-4 gram of root/plant).
Aconite

Adverse reactions

» nausea and vomiting
» generalized paresthesia
» dizziness
» palpitation
» intolerance of cold
» irritability, delirium

» systemic paralysis
» hypotension, arrhythmia (ventricular tremor, atrioventricular block and myocardial damage) due to muscarinic activation.
» shock, coma and death
Aconite

- **Treatment**
  - In rabbits and guinea pigs, heart fibrillation reversed by IV calcium chloride
  - Hydrocortisone was effective in treating poisoning in rabbits
  - Amiodarone and atropine may be effective.
  - Cardioversion or extracorporeal techniques are likely to be ineffective.
- **Symptoms are reversible**
Aconite

- In traditional Chinese medicine, aconites are often processed at the factory to reduce toxicity
  - Soaking in water and prolonged steaming or boiling
- Aconitine alkaloids hydrolyzed to less toxic derivative such as benzoyl-aconines and aconines.
Aconite

- Patient prepares decoction by boiling the aconite herbs for some time before other herbs are added to ensure reduction of aconitine.
- Poisoning and fatality usually result in inadequate processing and overdose.
- Aconite responsible for most TCM poisoning cases and fatality.
Bufo Toxin (Chan Su)

- Toad venom from *Bufo bufo gargarizans* or *Bufo melanosticicus*
- Has cardiotropic effect, stimulates the central nervous system and local anesthetic effect
- Consists of bufotenine, bufotalin and a series of bufadienolides
- Traditionally used to stimulate the heart and as topical analgesic.
Bufo Toxin

- MOA: Inhibit myocardial Na\(^+\),K\(^+\) - ATPase activity and also a potent sodium pump inhibitor
- \(LD_{50}\) - IV aqueous extraction is 61 mg/kg for mice
- Bufotalin, an ingredient of bufotoxin, is similar to digoxin with common basic steroid nucleus structure.
- Cross reacts with digoxin immunoassays.
Bufo Toxin

Bufotalin

Digitoxigenin
Bufo Toxin

- Adverse reaction
  - affect the myocardium and produce dysrhythmias
  - ventricular ectopy
  - sinus bradycardia
  - atrial dysrhythmias
  - hyperkalemia
  - salivation, seizures and death
Bufo Toxin

● Treatment
  » digoxin specific antibodies (Digibind) for symptomatic patients
  » possibly IV propranolol in reversing ventricular fibrillation (in dogs)
Bufo Toxin case

- A 25-year-old Asian pregnant woman admitted to the emergency room
- Complain epigastric tenderness, vomiting and difficulty breathing immediately after consumption of herbal tea brewed from a prescribed Chinese herbal remedy mixture.
- She was in no apparent distress, though nauseated and drowsy
Bufo Toxin case

- 30 minutes after admission, became pale, bradycardic and hypotensive
- Cardiopulmonary arrest
- A grand mal type seizure
- Ventricular tachycardia
- Expired in 2½ hours
Bufo Toxin case

- Analytical assay identified herbal tea to contain bufotoxin.
- Bufotoxin (Ch'an Su) was placed in the herbal remedy instead of the prescribed Gelatinum Asini (from ass hide - animal product)
Aristolochic Acid

- Found in *Aristolochia fangchi* (Fang Chi), *A. contorta* (Ma Dou Ling), *A. debilis Sieb.* (Tian Xian Teng), *A. manshuriensis K.* (Guan Mu Tong)
- Widely used as diuretic and antirheumatic. Also has been used as an antitussive and antiasthmatic.
Aristolochic Acid

- **LD$_{50}$ is 48 mg/kg po in mice**
- **Adverse reactions**
  - Has both mutagenic and carcinogenic activity
  - Is a known nephrotoxin and has recently been reported to associate with interstitial nephropathy leading to end stage renal failure.
- It was assumed that *A. fangchi* has been misidentified as *Stephania tetrandra* (no aristolochic acid), causing interstitial nephropathy
Aristolochic Acid

- Traditionally, *Stephania* is used interchangeable with *A. fangchi*.
- There are no reported cases of renal failure associated with *Aristolochia* species in historical Chinese documents.
- Aristolochic acid is insoluble in water.
Aristolochic Acid

- Associated with nephropathy
- Two cases in California. In both cases, patients using the herb for over a few months.
- All related to unprocessed *Aristolochia fang chi*
- Wide spread use of *A. fang chi* in U.S., yet only few identified renal failure cases.
Aristolochic Acid

- FDA requires testing of all suspected imported herbs
- Why are there no previous reports in the Chinese literature?
- Germany use aristolochic acid as immunomodulatory agent without any reported adverse reactions
Aristolochic Acid

- Is low incidence of nephropathy due to:
  - Solubility? pH?
  - Other herbs presence to counteract toxins or contribute to nephropathy?
  - Rare allergic type reactions?
  - Inappropriate use and inadequate processing
  - Variability of aristolochic acid in botanical products
  - Individual or racial susceptibility to toxin

*Aristolochia fangchi* (Fang Chi)
Strychnos nux-vomica L.  
(Ma Qian Zi)

- Contains strychnine and brucine
- Traditionally used as analgesic, arthritis and paralysis
- MOA
  » strychnine and brucine are centrally-acting neurotoxins. Competitively antagonizes post-synaptic binding of the inhibitory transmitter glycine, leading to heightened reflex excitability of muscles.
**Strychnos nux-vomica L.**

- 30-50 mg of nux-vomica contains 5 mg of strychnine which can cause severe adverse effects, 1-2 grams of nux-vomica contains 60-90 mg of strychnine and can be fatal.
**Strychnos nux-vomica L.**

- **Adverse reactions**
  - restlessness, anxiety
  - increase sense perception and reflexes
  - stiffness and pain of neck and back
  - twitching, tonic spasms of jaw and neck muscle
  - convulsion
  - dyspnea, respiratory failure and cardiac arrest
Processed *Strychnos nux-vomica* L. as prepared in traditional method using heat (sand bath or frying in oil at 235 degree).

- Strychnine and brucine transformed into isostrychnine, isobrucine, strychnine N-oxide and brucine N-oxide, possibly with reduce toxicity.
Heavy metals

- lead (litharge [Mi Tuo Seng])
  - lead oxide
- arsenic (realgar[Xiong Huang], orpiment [Ci Huang])
  - arsenic sulfide, arsenic trisulfide
- mercury (cinnabar [Zhu Sha], calomel [Qing Fen])
  - mercuric sulfide or mercurious chloride
Heavy metals

- Traditionally used as antibiotics, seizure and sedative
- Most poisoning are due to oral ingestion from patent medicines
- Many are insoluble, however, even small amounts that leach out will be absorbed over time as the body acts as “sink” (shifting equilibrium) and absorb heavy metals
Heavy metals

- Difficult to diagnose
- Should perform routine heavy metal screening if herbal poisoning is suspected.
Advice For Consumers/Patients

- Treat herbal products as medicinal products
- “More” does not mean “better”
- Always consult your health care provider especially if you have serious diseases or are using pharmaceuticals (western drugs)
- Herbal products can interfere with absorption of pharmaceuticals (western drugs). Separate ingestion by at least 2 hours.
- Stop taking the herbal products if side effects develop
Advice For Patients

- Only purchase herbal products from reputable source (e.g. acupuncturist)
  - U.S. manufacturers or importer
  - name and address
  - phone number
  - expiration date/lot number
  - request information on testing
- price has no relationship to quality of product
Advice For Patients

- Do not use herbal products if pregnant or nursing unless as directed by your physician
- Do not use herbal products for infants or young children
- Use extreme caution if the claims sound too good to be true
- FDA or any regulatory agencies DO NOT approve any herbal products or manufacturers
Advice For Patients

- Do not use herbal products if allergic to sulfur
- Do not use herbal products for more than 4 weeks without the supervision of a health care provider
- Products with National Drug Code (NDC) number do not mean that they are approved by FDA
Uses of TCM Herbs

● General tonic use

● Used when no other alternative treatments are available (hepatitis C, diabetic nephropathy, morning sickness)
Uses of TCM Herbs

- For prevention of illnesses when directed by a physician or health care provider (acupuncturist)
- Clinical research has not supported many of herbal efficacy claim
  - problem with short term study
  - TCM treatment deals with total body (diet, lifestyle...etc), not just herbal use