

# Adulteration: Context, history and responsibility

#### **IADSA Botanical Roundtable**

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### Adulteration in context: Foods



"Today's rising food prices and the global nature of the food chain offer the opportunity for criminals to sell counterfeit and substandard food in a multi-billion criminal industry which can pose serious potential health risks to unsuspecting customers."

### 30 March 2016 Largest-ever seizures of fake food and drink in INTERPOL-Europol operation

- 10,000 tons + 1 million liters of counterfeit and substandard food seized in 57 countries
  - Italy: 85 tons of olives 'painted' with copper sulfate to enhance color
  - Australia: 450 kg of blended or adulterated honey
  - Australia: Peanuts repackaged and relabeled as pine nuts
  - South Korea: Weight loss products labeled as "natural" but containing an undeclared prescription drug
  - Bolivia: Thousands of cans of sardines with fake labels of a famous Peruvian brand
  - Hungary, Italy, Lithuania and Romania: Counterfeit chocolates, sweets and non-alcoholic sparkling wine
  - UK, Greece, Burundi, Zambia: Fake labels of wine and other alcoholic beverages



### Adulteration in context: Foods

NOTE: In 2007, melamine spiking of wheat gluten from China used in pet foods was associated with the deaths of 100s of cats and dogs in the U.S.; a similar incident may have occurred in Korea and Taiwan in 2004.

9 September 2008 AEs associated with melamine in infant formula first reported (Shanghai Daily)

- Kidney and urinary tract AEs affected about 300,000 Chinese infants and young children; 6 deaths reported
  - Melamine found to be added to diluted milk to increase nitrogen levels and protein analysis
- 22 Chinese infant formula makers' products (including Sanlu Group) found to contain melamine
  - Melamine-laced milk ingredients exported from China to at least 47 countries; later found in many finished products with milk ingredients (candy, cookies, etc.)



# Adulteration in context: Drugs



"It's a sad and cruel fact that drug and device counterfeiting and adulteration pose serious threats to public health."

- 16 April 2015 Counterfeit Botox found in U.S.; distributed by an unlicensed supplier, possibly nationwide
- 21 January 2015 Counterfeit Cialis found entering U.S.; mailed to a single individual
- 5 February 2015 Counterfeit cancer drug (bevacizumab) found in U.S. containing none of the drug; sold by unlicensed wholesaler; FDA informed almost 800 doctors
- 29 May 2012 Warning issued to consumers and healthcare professionals re: counterfeit Adderall in which analysis showed actual APIs absent; sold on Internet
  - 14 February 2012 Counterfeit Avastin (cancer drug bevacizumab) found in U.S. containing none of the drug; sold by unlicensed distributor
  - 1 January 2007-31 May 2008 Acute reactions and as many as 179 deaths (U.S. alone) in dialysis patients receiving heparin injections; found to be contaminated with synthetic over-sulfated chondroitin sulfate; "intentionally contaminated ... to reduce the cost."



### ...not a new problem

# Robert Fortune. Two visits to the tea countries of China and the British Tea Plantations in the Himalaya (1853)

As many persons in Europe and in America have a peculiar taste for coloured green teas, I will now give a "full and particular account" of the colouring process as practiced in the Hwuychow green-tea country upon those teas which are destined for the foreign market...:

"The superintendent of the workmen managed the colouring part of the process himself. Having procured a portion of Prussian blue, he threw it into a porcelain bowl, not unlike a chemist's mortar, and crushed it into a very fine powder. At the same time a quantity of gypsum was produced and burned in the charcoal fires which were then roasting the teas. The object of this was to soften it in order that it might be readily pounded into a very fine powder, in the same manner as the Prussian blue had been. The gypsum, having been taken out of the fire after a certain time had elapsed, readily crumbled down and was reduced to powder in the mortar. These two substances, having been thus prepared, were then mixed together in the proportion of four parts of gypsum to three parts of Prussian blue and formed a light-blue powder, which was then ready for use.



## ...not a new problem

# Robert Fortune. Two visits to the tea countries of China and the British Tea Plantations in the Himalaya (1853)

"This colouring matter was applied to the teas during the last process of roasting. About five minutes before the tea was removed from the pans—the time being regulated by the burning of a joss-stick—the superintendent took a small porcelain spoon, and with it he scattered a portion of the colouring matter over the leaves in each pan. The workmen then turned the leaves rapidly round with both hands, in order that the colour might be equally diffused.

... "It seems perfectly ridiculous that a civilised people should prefer these dyed teas to those of a natural green. No wonder that the Chinese consider the natives of the west to be a race of 'barbarians.'



### ...not a new problem

# Robert Fortune. Two visits to the tea countries of China and the British Tea Plantations in the Himalaya (1853)

"One day an English gentleman in Shanghae, being in conversation with some Chinese from the green-tea country, asked them what reasons they had for dyeing the tea, and whether it would not be better without undergoing this process. They acknowledged that tea was much better when prepared without having any such ingredients mixed with it, and that they never drank dyed teas themselves, but justly remarked that, as foreigners seemed to prefer having a mixture of Prussian blue and gypsum with their tea, to make it look uniform and pretty, and as these ingredients are cheap enough, the Chinese had no objection to supply them, especially as such teas always fetched a higher price!



# Drug-spiking: An international issue

- Products "...masquerading as" dietary supplements (Michael Levy, FDA)
- Main product categories:
  - Male enhancement (sildenafil and analogs)
  - Weight-loss (sibutramine; diuretics; laxatives)
  - Athletic performance (steroids)
- International in scope: Australia, Austria, Canada, China, Denmark, Ireland, Israel, Italy, Malaysia, Mexico, Singapore, Switzerland, UK
- Three criminal actions in U.S. in 2015



#### KEEPSUPPLEMENTS CLEAN.ORG

**Key Product Categories** 

Info for Consumers

Info for Industry

International Enforcement

#### **FDA** enforces against tainted products masquerading as supplements

Products that contain vitamins, minerals, herbs and other health-promoting ingredients are sold in countries all over the world. These products may be marketed as a category of food, as is the case with dietary supplements in the U.S., or in a drug category, such as the natural health products sold in Canada. These products are sold in full compliance with the legal and regulatory statutes in effect in various countries around the world.

The vast majority of dietary supplement products fully comply with applicable laws and are properly sold to consumers. However, some unscrupulous companies have threatened consumer confidence by selling tainted products that contain undeclared prescription drugs and other chemicals. Since 2008, FDA has identified nearly 400 such products. These unlawful ingredients have been found in capsules, tablets, powders, teas, and coffees. While these tainted products represent a tiny minority of all dietary supplements sold, it is important that consumers have confidence when buying their products from reputable companies.

The U.S. Food and Drug Administration called attention to this problem with the following statement:

FDA has identified an emerging trend where over-the-counter products, frequently represented as dietary supplements, contain hidden active ingredients that could be harmful. Consumers may unknowingly take products laced with varying quantities of approved prescription drug ingredients, controlled substances, and untested and unstudied pharmaceutically active ingredients. These deceptive products can harm you!

The American Herbal Products Association (AHPA) has created this website to keep the dietary supplement industry informed on issues related to illegal tainted products being sold as "dietary supplements".

### What responsible supplement companies need to know

On December 15, 2010, FDA announced that it is working with U.S. trade associations, including AHPA, to make sure that supplement companies comply with the law. FDA also issued a letter to industry that addresses roles and responsibilities of companies to ensure that their products do not contain undeclared ingredients that would cause them to be adulterated. More specifically, FDA's letter:

- Reminds dietary supplement companies of their obligation under current good manufacturing practice (cGMP) to establish and meet specifications on those types of contamination that may adulterate or lead to adulteration of the finished batch of dietary supplement (see 21 CFR 111.70(b) and 111.75(a)).
- Notes that a strong program of qualifying





Western District of North Carolina

FOR IMMEDIATE RELEASE

Wednesday, April 1, 2015

#### Maker of Erectile Dysfunction Products Sentenced To Nine Years In Prison For Misbranding And Selling Drugs As "All-natural" Herbal Supplements

The Products Contained Pharmaceutical Compounds Smuggled from China

CHARLOTTE, N.C. – Kamraz Rezapour, 53, formerly of Creston, N.C. was sentenced today to 108 months in prison for defrauding consumers of nearly \$5 million by misbranding erectile dysfunction drugs and selling them as "all natural" herbal supplements, announced Jill Westmoreland Rose, Acting U.S. Attorney for the Western District of North Carolina. Chief U.S. District Judge Frank D. Whitney also sentenced Rezapour to three years of supervised release and ordered the defendant to pay a \$15,000 fine and \$44,100.52 in restitution. The Court also ordered the forfeiture of the proceeds of Rezapour's crimes, including over \$1.5 million in seized funds, gold and silver coins, along with a condominium located in Tampa, Florida.





#### Office of Public Affairs

FOR IMMEDIATE RELEASE

Monday, October 19, 2015

#### Owner of Pennsylvania Diet Supplement Business Sentenced to 30 Months Imprisonment for Selling Misbranded Drugs as Weight Loss Products over the Internet

The U.S. Attorney's Office of the Middle District of Pennsylvania announced today that Cheryl Floyd, age 52, of Harrisburg, Pennsylvania, owner of Floyd Nutrition LLC, was sentenced to 30 months in federal prison by U.S. District Court Judge Sylvia H. Rambo of the Middle District of Pennsylvania today in Harrisburg for introducing misbranded drugs into interstate commerce and money laundering. Judge Rambo also ordered Floyd to pay \$10,000 in fines and \$7,530 in restitution.

According to summaries presented to the court by Assistant U.S. Attorney Christy H. Fawcett of the Middle District of Pennsylvania in connection with the guilty plea and the sentencing hearing, Floyd, also known as Cheryl Floyd Brown, was the owner and operator of an internet-based business known as Floyd Nutrition LLC, based at her Harrisburg residence and with warehouse facilities in the Harrisburg area.

The items offered for sale between 2010 and 2014 were purported all-natural dietary supplements sold as weight loss products. They contained the drugs sibutramine and phenolphphthalein which are not listed as ingredients in the product labels.



# Ingredient adulteration

- Digitalis lanata leaf as unintentional substitute for plantain leaf; one EU import widely distributed in U.S. in 1997
- Parthenium integrifolium root as substitute for Echinacea purpurea due to common name confusion (both called "Missouri snakeroot"); not an issue with cultivated sources
- Various materials as substitutes for Hoodia gordonii; all imports in powder form; market spike has passed
- Triclosan (and other synthetic microbicides) labeled as "grapefruit seed extract"
- Ginkgo biloba leaf extract w/added rutin or Sophora japonica fruit; deliberate substitution to affect chemical analysis
- Bilberry fruit extract w/ added synthetic amaranth (red) dye; deliberate addition to affect spectrophotometric assay
- Etc.; all above and others are posted on AHPA's website and generally well known to responsible manufacturers



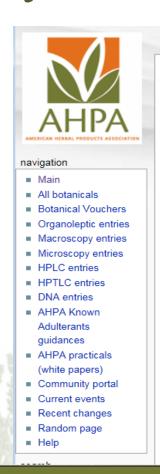
# Tools for responsible industry

- Regulatory compliance
  - U.S. FDA cGMP for dietary supplements (21 CFR 111) is modeled after food and drug cGMP
  - Requires "at least one test or examination" to verify identity of every ingredient
  - Also requires specifications to limit "those types of contamination that may adulterate" a finished product
- Additional resources
  - Many professional contract analytical labs
  - AOAC / Method validation
  - AHPA Botanical Identity References Compendium (<a href="http://www.botanicalauthentication.org/">http://www.botanicalauthentication.org/</a>)



# The AHPA Compendium

- - Nomenclature
  - Voucher specimens
  - Organoleptic characteristics
  - Macroscopic characteristics
  - Microscopic characteristics
  - HPTLC methods and images
  - Other chromatographic methods
  - Newly including DNA sequencing
  - AHPA known adulterants
  - Literature references



Main Page

#### Welcome and About the AHPA Botanical

history

delete

The AHPA Botanical Identity References Compendium is mair with the support of many individuals and organizations with a cherbal materials.

The AHPA Compendium is a cooperative and centralized soul and experienced analysts to determine the identity of plant spi

#### Scope of content

discussion

The particular botanical species included in the AHPA Compe materials known to be subject to misidentification, and several added as requested and as resources allow.

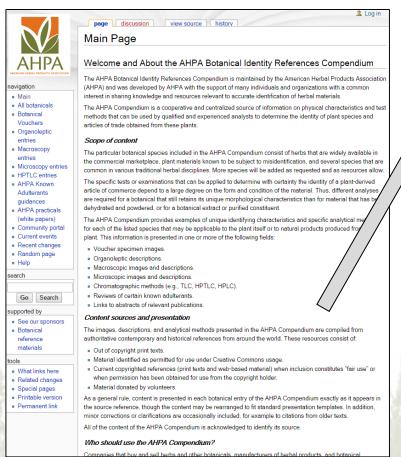
The specific tests or examinations that can be applied to deter degree on the form and condition of the material. Thus, differe characteristics than for material that has been dehydrated and

The AHPA Compendium provides examples of unique identify be applicable to the plant itself or to natural products produced

- Voucher specimen images.
- Organoleptic descriptions.
- Macroscopic images and descriptions.
- Microscopic images and descriptions.



# The AHPA Compendium



Expert sources

- Out of copyright texts
- Creative Commons works
- Copyrighted references ("fair use" or with permission)
- Donated material



- Both textual, commercial sources of information and methods
- Entries can include multiple images from multiple sources
- Thorough attribution provides direct references to each source and contributor

#### Organoleptic Characteristics

Color: Unpeeled – yellowish or purplish brown to dark brown externally and yellowish internally. Peeled – pale ye

Source: Natural Remedies Pvt Ltd [3]

Aroma/Odor: Characteristic Flavor/Taste: Sweet, sugary

Source: American Herbal Products Association. March 2013. Organoleptic Analysis of Herbal Ingredients. AHPA:

#### Macroscopic Characteristics

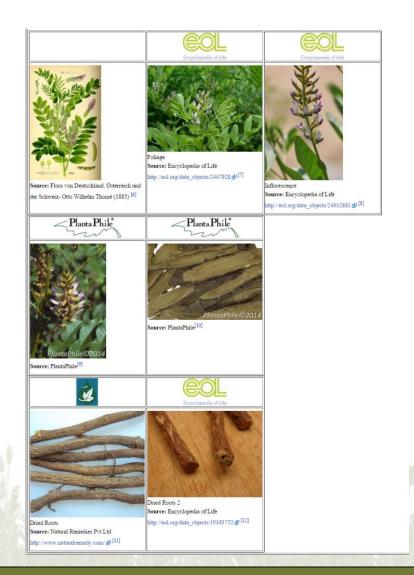
"...Root nearly cylindrical up to 2 cm in diameter, externally wrinkled with patches of cork. Fracture, coarsely fibrou

Source: Natural Remedies Pvt Ltd [5]





- Macroscopy
  - Organized by scale
  - Particular focus on providing references to articles of trade





- Microscopy
  - Additional literature source references included when possible
  - Images from a variety of contributors and references across the site

#### Microscopic Characteristics

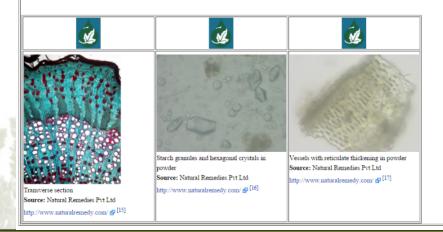
"Transverse section of stolon more or less rounded. Phellem severeal layered with tabular cells; outer layers filled with reddish brown contents, inner colour Phellogen indistinct; phelloderm three to five layered, collenchymatous; some of the cells contain calcium oxalate and minute starch grains. Secondary phlo numerous concentrically arranged bundles of phloem fibres and surrounded by a parenchymatous sheath containing prisms of calcium oxalate. Medullary re distinct, bi-to multiseriate, parenchymatous, in continuation with those of xylem. The rays are narrower in xylem and wider in phloem region. Xylem consists vessels, fibres and lignified wood parenchyma. The unpeeled drug shows the presence of polyhedral tubular brownish cork cells. In case of stolons, the pith present and is parenchymatous. The root is characterized by the presence of tetrarch xylem and absence of pith.

Powder: It shows plenty of starch grains, hexagonal crystals vessel elements are with reticulate wall pitting."

Source: Natural Remedies Pvt Ltd [13]

"The powder is identified by (1.) The character and location of starch-grains and crystals; (2) the very numerous bast-fibers of peculiar appearance and the wood-fibers; (3) The peculiar sieve-tissue. The starch-grains are irregularly spheroidal, mostly solitary, and range from 1.5 ore 2 to 20 microns in diameter. in medullary-ray and parenchyma-cells, and are often associated in the same cell with the monoclinic prismatic crystals of calcium oxalate, sometimes also bast- and wood-fibers are yellow, thick-walled, and doubly pointed. Part of the sieve-tubes have their cavities nearly or quite obliterated by cell-wall thickenia.

Source: Hare, Caspari, Rusby. National Standard Dispensatory (1905) [14]

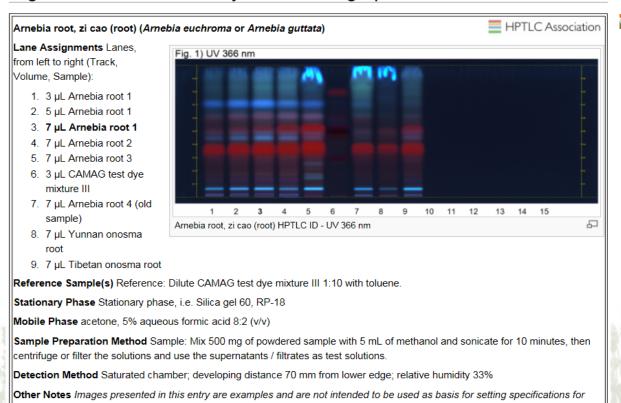




quality control purposes.

### Section Overview

High Performance Thin Layer Chromatographic Identification

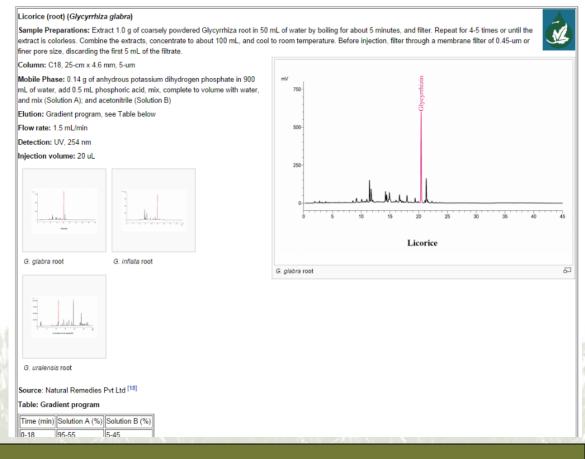


- High PerformanceThin LayerChromatography
  - Sample plates
  - Comparative methods
  - Multiple reference comparisons with analysis



- High Performance Liquid Chromatography
  - Information required to reproduce the methods
  - Citations to scholarly papers

#### High Performance Liquid Chromatographic Identification



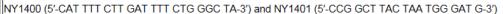


- New growth area!
- DNA-based identification
  - Recent research
  - Compendium format allows for easy additions as further developments proceed

#### **DNA Identification**

#### Black Cohosh (Actaea racemosa)

#### Amplification primers:



# THE NEW YORK

#### PCR reaction mixture:

15 μL final volume containing 1.5 μL PCR buffer (200 mM tris [pH 8.8], 100 mM KCl, 100 mM (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>, 20 mM MgSO<sub>4</sub>, 1% [v/v] Triton X-100, 50% [w/v] sucrose, 0.25% [w/v] cresol red), 0.2 μM dNTPs, 0.025 μg/μL bovine serum albumin (BSA), 1 μM of each primer, 0.25 units of *Taq* polymerase, and 0.5 μL template DNA.

PCR program: 95°C for 2.5 min; 35 cycles: 95°C for 30 s, 58°C for 30 s, 72°C for 30 s; 72°C for 10 min.

Sequencing primers: Same as amplification primers.

Sequence: 5'-TCT TTC AAG TGT ACG AAA AAA TCC TTC GGT GGT AAG GAG TCA AAT GTT AGA AAA TTC ATT TAT TAT AGA CAT TGC TAT TAA TAA GTT TGA TAC TAT AGT CCC AAT TAT TCC TTT GAT TGG ATT ATT GGC TAA AGC GAA ATT TTG TAA CTT ATC GGG G-3'

#### Diagnostic positions:

A. arizonica	156794678902344470 266921179239667960	3334444444455566667 5590004567900501130 2777892010701063662 GCACATTACGCTCACTACG
A. asiatica	TT	'A.GT
A. biternata	TG	ATT.TT
A. cimicifuga	TGT	AGT.G
A. cordifolia		
A. dahurica	<b></b> тт	ACCTGT.G
A. elata	T	ATGG
A. pachypoda	TT	A
A podocarpa	т с	
	AND RESIDENCE TO SERVICE A SERVICE ASSESSMENT AND RESIDENCE ASSESSMENT ASSESS	<del></del>



# Not a static reference - Contributions welcomed

AHPA recognizes other valuable resources exist regarding the identity of Aesculus hippocastanum.

To submit a suggestion or contribution, please contact

Merle Zimmermann ......

- Information can be contributed by outside experts
- Templates available to make contribution process easier
- Welcome partnerships and additions at scale
- Offered contributions are reviewed prior to addition by AHPA staff
- Clear attributions of every contributor or editor sourced

April 25, 2016 2<sup>--</sup>



# **THANK YOU!**

#### Michael McGuffin

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**American Herbal Products Association** 

THE VOICE OF THE HERBAL PRODUCTS INDUSTRY