Botanical Safety Consortium Introduction and Updates

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BOTANICAL SAFETY CONSORTIUM

Outline

Background
- Botanical Usage
- Current Challenges

Botanical Safety Consortium
- Mission & Objectives
- Initial Case Studies

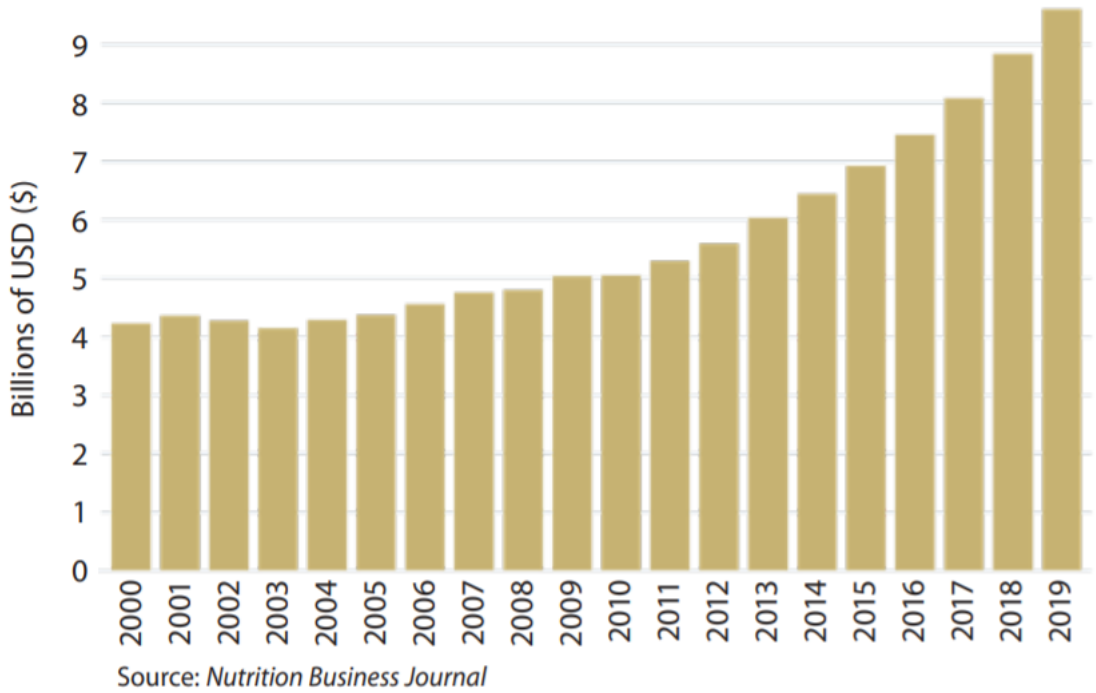
Botanicals are complex

- **Plants are chemical factories**
  - 28,187 plant species recorded as being of medicinal use*
    - Few (16%) cited in medicinal regulatory publications
  - Secondary metabolites exhibit a broad range of bioactivities
  - Many bioactive constituents from plants have been exploited by humans for use as pesticides, pharmaceuticals, poisons, or other consumer products

*Kew Royal Botanic Gardens State of the Worlds Plants Report, 2017.

Widespread botanical use

Figure 1. Total US Retail Sales of Herbal Supplements



Source: *Nutrition Business Journal*

US Supplement Sales Rise Sharply during First Six Months of 2020

COVID-19 pandemic boosts sales of medicinal fungi and herbs commonly used for immune health

By Tyler Smith

Systematic Review Article

Herbal Drug use in Sickle Cell Disease Management; Trends and Perspectives in Sub-Saharan Africa - A Systematic Review

Author(s): Michael P. Okoh*, Lukman A. Alli, Martti E.E. Tolvanen, Maxwell M. Nwegbu

Journal Name: Current Drug Discovery Technologies

Volume 16 , Issue 4 , 2019

BMC Health Serv Res. 2019; 19: 952. PMCID: PMC69

Published online 2019 Dec 10. doi: 10.1186/s12913-019-4739-0 PMID: 318

The importance of herbal medicine use in the German health-care system: prevalence, usage pattern, and influencing factors

ELSEVIER

Journal of Ethnopharmacology

Volume 215, 6 April 2018, Pages 184-190

Herbal medicine uses to treat people with epilepsy: A survey in rural communities of northern Peru

Emilie Auditeau [a, b], Luz Maria Moyano [a, b, c], Geneviève Bourdy [d], Mandy Nizard [a, b], Jérémy Jost [a, b], Voa Ratsimbazafy [a, b], Pierre-Marie Preux [a, b], Farid Boumediene [a, b]

Clarke et al. 2015; Smith et al., 2019. *HerbalGram; https://www.nutritioninsight.com/news/potent-botar*

Challenges with botanicals

- Toxicity testing, safety evaluation, and risk assessment processes was built around and optimized for single chemicals (drug, pesticides, etc.)

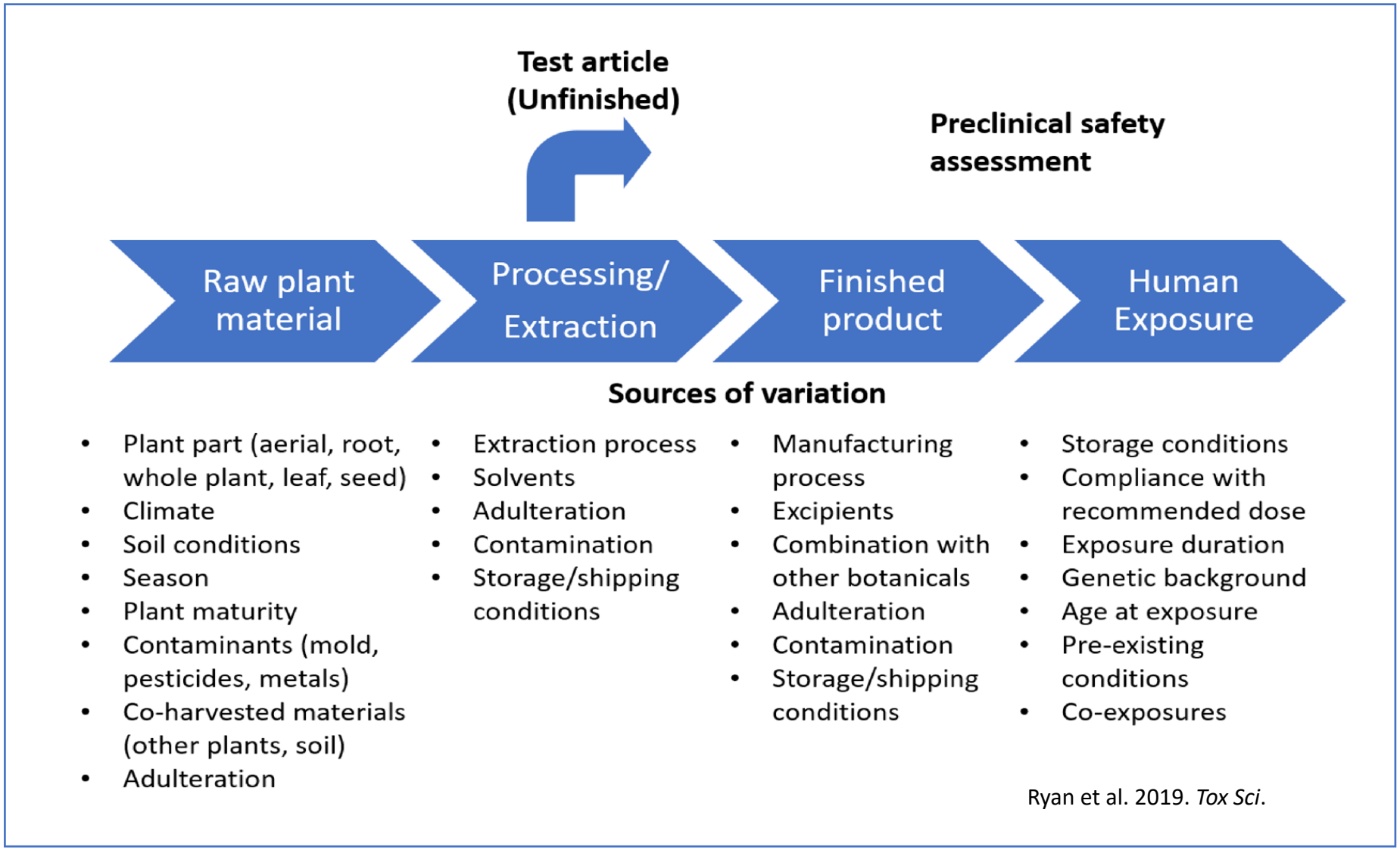
Drugs

- Regulatory structure aimed at ensuring safety and efficacy
- Assumed to be harmful until proven safe
- Simple and consistent
- Biological activity is associated with the constituent

Botanicals

- Regulatory structure aimed at ensuring access
- Assumed to be safe until proven harmful
- Complex and variable
- Biological activity is associated with the whole mixture

Inherent variation produces many potential test articles



Ryan et al. 2019. *Tox Sci*.

The problems…

- Limited botanical safety assessment methods and framework
  - Reliance on history-of-use data (food use vs supplement use)
  - *In vivo* toxicity testing to fill gaps (cost, time, and ethical concerns)
- Global botanical safety requirements are diverse and varied
  - Lack of global consensus regarding what comprises sufficient safety substantiation for a botanical
- Little toxicity data on formulated botanical products in the market
  - Existing toxicity data is often on constituents
  - Many multi-ingredient products have no toxicity data

The Botanical Safety Consortium

Applied In Vitro Toxicology, Vol. 5, No. 1 | Roundtable

Full Access

The Botanical Safety Consortium

Moderator: Amy L. Roe Participants: Joseph T. Dever, Stefan Gafner, Daniel S. Marsman, Cynthia V. Rider, and Sibyl Swift

Published Online: 13 Mar 2019 | https://doi.org/10.1089/aivt.2018.29018.rtl

View

FDA STATEMENT

Statement from FDA Commissioner Scott Gottlieb, M.D., on the agency's new efforts to strengthen regulation of dietary supplements by modernizing and reforming FDA's oversight

Share

I'm pleased to announce that we've recently created the Botanical Safety Consortium, ***a public-private partnership*** *that will gather leading scientific minds from industry, academia and government to promote scientific advances in evaluating the safety of botanical ingredients and mixtures in dietary supplements.*

BOTANICAL SAFETY CONSORTIUM

FDA Announces Convening of the Botanical Safety Consortium

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Constituent Update

November 14, 2019

The U.S. Food and Drug Administration (FDA) announced today that the Botanical Safety Consortium (BSC) has formally been convened. This milestone is the result of a Memorandum of Understanding (MOU) that was recently signed between the FDA, the National Institutes of Health's National Institute of Environmental Health Sciences, and the Health and Environmental Sciences Institute (HESI). This MOU establishes the framework for the BSC.

The BSC was originally announced in the FDA's February 2019 statement on the agency's new efforts to strengthen regulation of dietary supplements through modernization and reform. The Consortium's mission is to provide a forum for scientists from government, academia, consumer health groups, industry, and non-profit organizations to work collaboratively to generate a sound scientific basis for integrating existing safety data and the latest toxicology tools to evaluate botanical safety in dietary supplements. With the execution of the MOU, specific guidelines for membership and participation in the BSC will be established by early 2020.

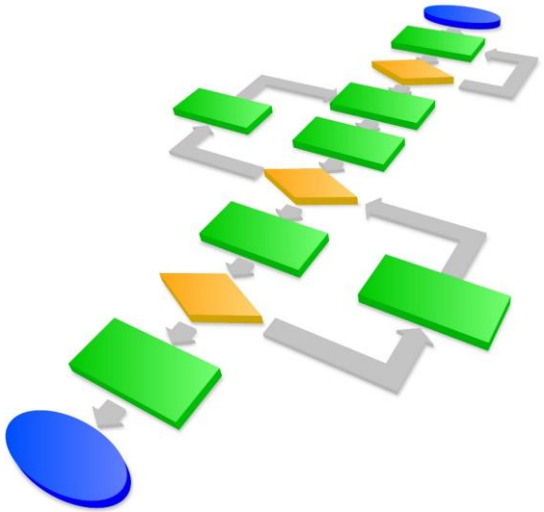
Problem Statements for the Botanical Safety Consortium

NOW

We do not know which approach methodologies can be used to evaluate botanical safety

WHERE WE WANT TO BE

We need a testing strategy & framework to evaluate botanical safety



Botanical Safety Consortium Objectives

- Engage with a broad group of global stakeholders to leverage the best scientific approaches
- Establish the appropriate levels of chemical characterization for complex botanical ingredients
- Identify pragmatic, fit-for-purpose in vitro & in silico assays to evaluate botanical safety
- Evaluate the application of these tools via comparison to the currently available safety information
- Integrate these tools and approaches into a framework that will facilitate robust evaluation of botanical ingredients

Current Charge of the Botanical Safety Consortium

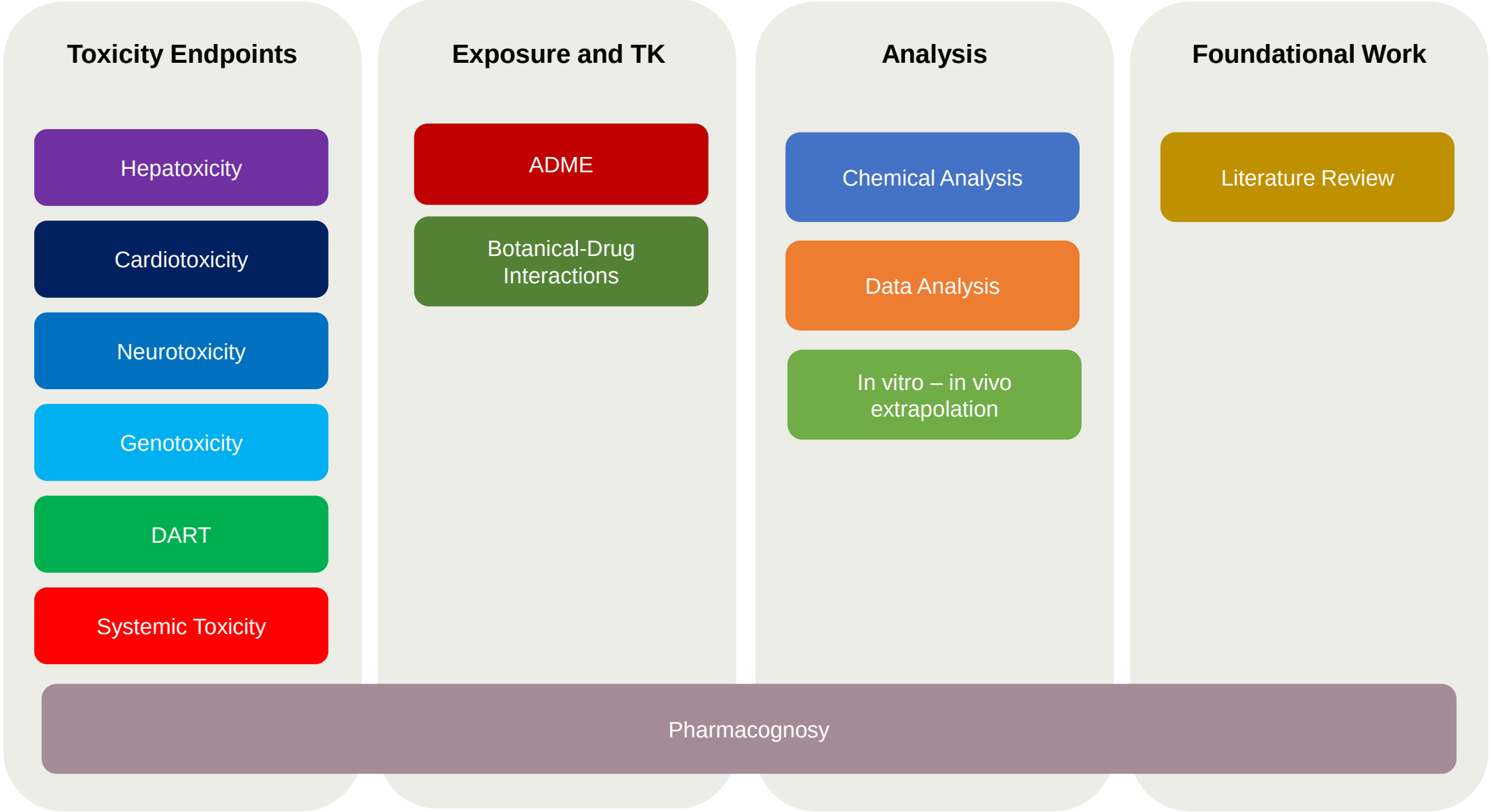
To evaluate the suitability of assays for botanicals as complex mixtures

BOTANICAL
SAFETY CONSORTIUM

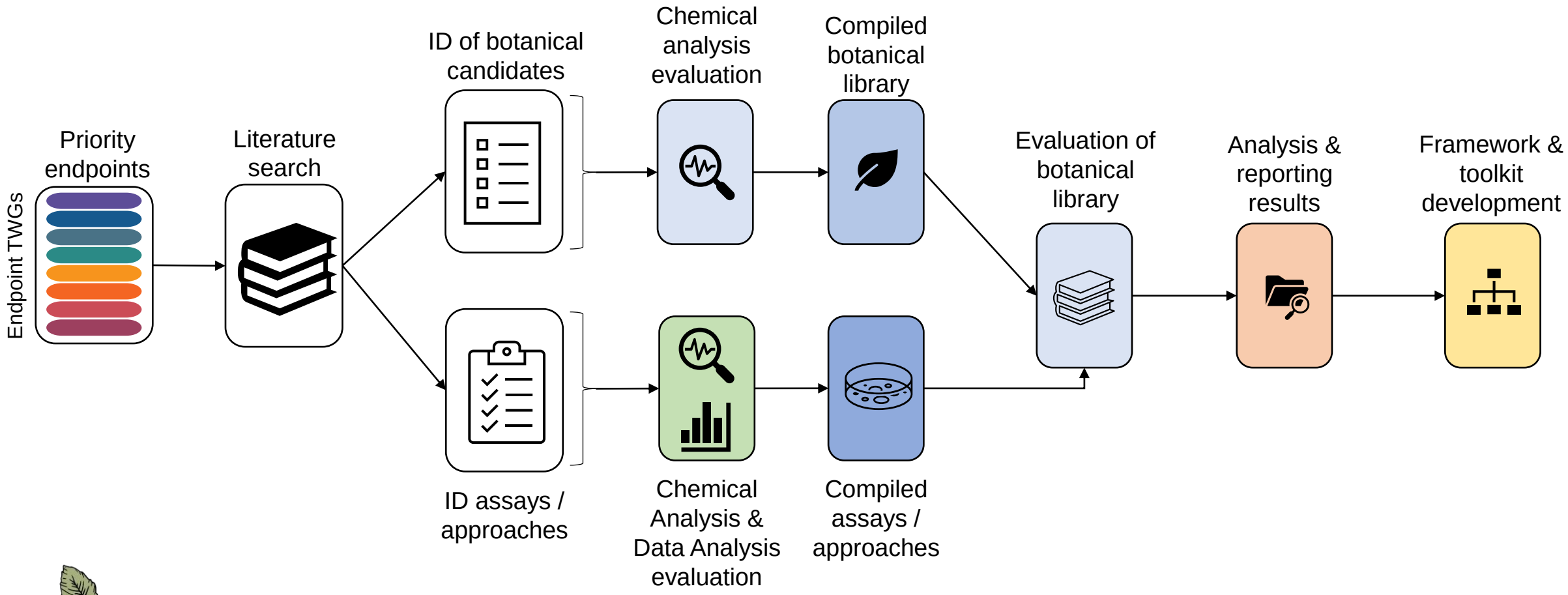
What we are NOT doing

- Making safety determination of botanical ingredients
- Making regulatory decisions
- Endorsing any particular method or product
- Testing ‘off the shelf’ products
- Testing individual constituents of botanicals (unless negative or positive controls)
- Looking at routes of exposure other than oral
- Performing mammalian *in vivo* studies
- Performing risk assessments
- Validating methods

BSC Current Working Groups: Thematic Focus



Strategy Details



BOTANICAL SAFETY CONSORTIUM

Assays

In Silico Methods

Assays for screening

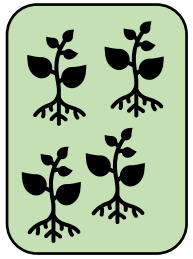
Assays for Mechanistic Follow-Up

Assay Guidelines

- Established and reproducible
- Relevant for key mechanisms for botanical-induced toxicity
- Suitable for botanicals as complex mixtures
- Accessible for use by many groups
- Available at a reasonable cost

Botanical Candidate Selection Process

Nomination of Botanical candidates



- In vivo *evidence (rodent)*
- *Clinical evidence (human)*
- In vitro *evidence*
- *Used in susceptible populations?*
- *Known toxic constituents*

- Genotoxicity
- Hepatotoxicity
- Drug-botanical Interactions
- DART
- Systemic Toxicity
- Cardiotoxicity
- Neurotoxicity

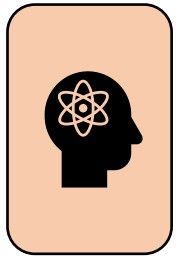
Chemical Analysis Evaluation

- *Identification of product*
- *Authentication of botanical*
- *Contaminants*
- *Nutrient Analysis / Mass balance*
- *Constituent Identification*
- *Marker quantification*
- *Material stability*
- *Dosing solution*

Literature Collection

- *Gather information from authoritative sources*
- *Create literature reviews for uses and toxicity data*

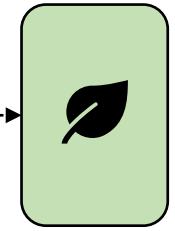
Pharmacognosy Advisory Information



- *ID of source / supplier*
- *Adverse events / effects*
- *Indications for use*
- *Recommended doses*
- *Type(s) of products / preparations*
- *Contaminants & adulterants*
- *Nomenclature / naming convention*

Additional discussions on feasibility / labs / suitability for assays

Compiled Botanical list for testing



Botanical Case Studies

Standardized Common Name	Scientific Name	Plant part(s)
Aristolochia fangchi	*Aristolochia fangchi* Y.C. Wu ex L.D. Chou & S.M. Hwang	Root
Ashwagandha	*Withania somnifera* (L.) Dunal	Root
Asian Ginseng	*Panax ginseng* C.A. Mey.	Root
Blue cohosh	*Caulophyllum thalictroides* (L.) Michx.	Root and Rhizome
Comfrey	*Symphytum officinale* L.	Root or leaf
Ephedra	*Ephedra sinica* Stapf	Aerial parts
Green Tea	*Camellia sinensis*	Leaf
Goldenseal	*Hydrastis canadensis* L.	Root and Rhizome
Kava	*Piper methysticum* G. Forst.	Root and Rhizome
Kratom	*Mitragyna speciosa* (Korth.) Havil.	Leaf
Milk thistle	*Silybum marianum* (L.) Gaertn.	Seed
Usnea lichen	*Usnea* spp.	Whole Plant
Yohimbe	*Pausinystalia johimbe* (K. Schum.) Pierre ex Beille	Bark

Asian Ginseng
Panax ginseng C.A. Mey

- Very robust history of use
- Comprehensive animal toxicology studies
- Many human clinical studies also available

- NEGATIVE control for assays

Milk Thistle

Silybum marianum (L.) Gaertn.

- Very robust history of use
- Comprehensive animal toxicology studies
- Many human clinical studies also available

- NEGATIVE control for assays

Han et al., 2019: doi: 10.3389/fphar.2019.00648
Grollman and Marcus, 2016: doi: 10.15252/embr.201642375

Aristolochia fangchi
Y.C. Wu ex L.D. Chou & S.M. Hwang

- Contains aristolochic acid (AA); many other *Aristolochia* species are used worldwide
- Human case reports, clinical studies, and adverse event reporting have clearly demonstrated:
  - Kidney damage [aristolochic acid nephropathy (AAN)] – end-stage renal failure
  - Bladder cancer (upper tract urothelial carcinoma)
- AA-DNA adducts are biomarkers of exposure
- Restricted / banned use in many regulatory jurisdictions

Photo by: Chen Binghui
http://www.efloras.org

Ashwagandha Root Extract *Withania somnifera* (L.) Dunal

- Multiple case reports describing hepatoxicity and one for cardiotoxicity
- Clinical trial data in humans pointing towards safe use
- In vitro evidence for alternation of developmental pathways in human cells

Blue cohosh

Caulophyllum thalictroides (L.) Michx.

- Not recommended for use in 1st trimester of pregnancy due to cardioactivity, teratogenic and embryotoxic risk
- Surveys & case publications re: human use during pregnancy point to caution needed (AHP, 2012; Romm, 2009)
- Demonstrated teratogenicity and embryotoxicity of constituents in animal models
  - Quinolizidine alkaloids (N-methylcytisine, taspine, anagyrine)
  - Livestock “crooked-calf” disease linked to anagyrine
  - In vitro studies in human cells with constituents; embryotoxicity plausible (Kennelly et al., 1999)
  - Fish model studies have shown teratogenicity (Wu et al., 2010)
- Nicotinic activity of N-methycytisine linked to cardiac effects in animal studies (though at concentrations much higher than seen in products)

AHP, 2012: https://herbal-ahp.com/collections/frontpage/products/blue-cohosh-root-rhizome
Kennelly et al., 1999: https://doi.org/10.1021/np9901581
Romm, 2009: https://elischolar.library.yale.edu/ymtdl/88/
Wu et al., 2010: https://doi.org/10.1021/tx100205a

Mei et al., 2005: doi: 10.1038/sj.bjc.6602420
Mei et al., 2010: doi: 10.1080/10937404.2010.509013

Comfrey
Symphytum officinale (L.)

- Contains pyrrolizidine alkaloids (PA) (Mei et al., 2005, 2010)
  - Hepatoxicity (humans, livestock, & laboratory animals)
    - Sinusoidal obstruction syndrome (SOS) / veno-occlusive disease
      - PAs metabolized to pyrrole metabolites with alkylating properties
      - Damage hepatic endothelial cells and cause sinusoidal obstruction → liver damage
  - Carcinogenicity
    - Hepatocellular adenomas and haemangioendothelial sarcomas (rat)
    - Mutagenic in rat liver
    - Tumorigenicity from PA genotoxicity
- Safety concerns have led to restrictions on oral use
  - Restricted / banned oral use in many regulatory jurisdictions

Ephedra (Ma-huang)
Ephedra sinica Stapf

- Contains ephedrine-type alkaloids with demonstrated cardiovascular and CNS stimulating effects (ephedrine & pseudoephedrine)
  - Sympathomimetic
  - Stimulation of α-, β1-, and β2-adrenergic receptors
- Human case reports, clinical studies, and adverse event reporting show CV (hypertension, palpitation, cardiac arrest) and cerebral (stroke, seizures) effects.
- Restricted / banned use in many regulatory jurisdictions

Al saeed et al., 2011: DOI:10.5530/pj.2019.11.68
EFSA, 2013. https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2013.3467

Green Tea Extract (GTE)
Camellia sinensis

- GTEs may contain hepatotoxic solvent residues, pesticide residues, pyrrolizidine alkaloids and elemental impurities
- GTE catechin profiles vary significantly with manufacturing processes.
- Published adverse event case reports associate hepatotoxicity with EGCG intake amounts from 140 mg to ~1000 mg/day
- "*Do not take on an empty stomach. Take with food. Do not use if you have a liver problem and discontinue use and consult a healthcare practitioner if you develop symptoms of liver trouble, such as abdominal pain, dark urine, or jaundice (yellowing of the skin or eyes*)."
- Metabolism/ BDI interactions

Goldenseal Root
Hydrastis canadensis L.

- Contraindicated in pregnancy unless otherwise directed by a qualified health professional expert in the use of this substance (AHPA)
- Contains berberine, a potent bilirubin displacer and metabolism inhibitor
- Evidence of in vitro inhibition of human P450 3A4 enzymes
- Carcinogenicity in animal and in vitro studies
  - Positive in rats - hepatocellular adenoma
  - Some evidence in male mice
  - Negative for mutagenicity in Ames test
  - Negative in in vivo micronucleus test

Kava Root
Piper methysticum G. Forst.

- Due to their tranquilizing, sedative, and anxiolytic properties, kava is widely used all over the world for recreational and medicinal purposes
- Cultivar can greatly change the chemical constituents
- Kava-related liver disease is a well-defined clinical entity that occurred in a few patients worldwide

Kratom

Mitragyna speciosa (Korth.) Havil.

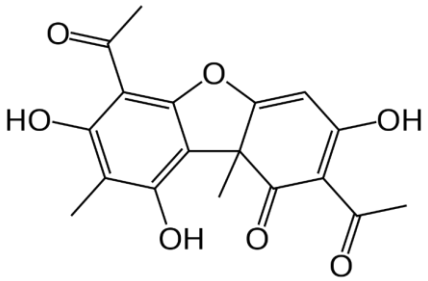
- Kratom is a natural psychoactive preparation
- Illegal in some countries (Australia, Malaysia, and Thailand) but legal in others
- Hepatotoxicity reports mostly linked to long-term kratom consumption or to its excessive intake.

Usnea Lichen

Usnea spp.

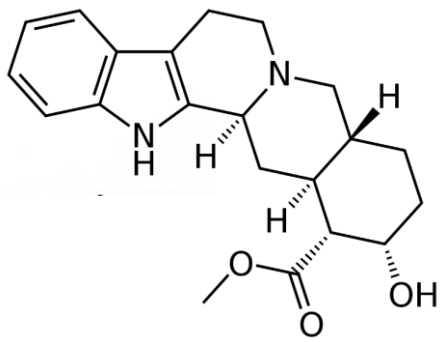
- Usnic acid produce by *Usnea* spp. is primarily marketed as a dietary supplement to promote weight loss
- Signals for reproductive toxicity in the National Toxicology Program Study

Usnic Acid
CARN 125-46-2



Yohimbe
Pausinystalia johimbe (K. Schum.) Pierre ex Beille

Yohimbine
CASRN 146-48-5



- Yohimbine and yohimbe extracts cause dilation of blood vessels, resulting in vasocongestion.
- Potential carcinogenicity from yohimbine based on read-across to reserpine

- Website: www.botanicalsafetyconsortium.org
- Email: botanicalsafety@hesiglobal.org