Botanical Safety
Discovering Common Struggles, Needs, and Solutions

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Broad consumer demand for natural health and nutritional products

• U.S. dietary supplement industry: $46 billion in annual sales.¹
• More than 170 million Americans take dietary supplements annually, including vitamins, minerals, botanicals, and specialty products.
• Half of dietary supplement users take at least one botanical product.
• Most popular Botanicals in dietary supplements include²:
  - Horehound (Marrubium vulgare)
  - Echinacea (Echinacea spp.)
  - Turmeric (Curcuma longa)
  - Elderberry (Sambucus nigra)
  - Green Tea (Camellia sinensis)
  - Ginger (Zingiber officinale)
  - Ivy Leaf (Hedera helix)
  - Garlic (Allium sativum)
  - Fenugreek (Trigonella foenum-graecum)
  - Black Cohosh (Actaea racemosa)
  - Saw Palmetto (Serenoa repens)
  - Flax Seed (Linum usitatissimum)

¹CRN; ²ABC
Botanicals with recognized pharmacologic and toxicologic properties

- In addition to plants as an essential part of the diet, plants are creative chemical factories, for good or harm.
Safety concerns

- Adulteration continues as a problematic reality
- Complexity and uncertainty also drive the Safety concerns.

**Few essential oils met label spec in recent test**

By Hank Schultz


This stimulant is banned in sports but found in dietary supplements. A doctor asks why

By ELIZABETH COONEY @cooney_lk / SEPTEMBER 6, 2018

Essential oil adulteration continues to be an issue in the marketplace, according to testing results revealed by a major dietary supplement manufacturer.
Botanicals are complex

- Plants are chemical factories
  - 28,187 plant species recording as being of medicinal use*
    - Very few (16%) cited in 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

Analytical Challenge

Red Clover
*Trifolium pratense*
Whole herb, EtOH extract

Complexity
- Isomers, co-eluting compounds

Variation
- Lot to lot, processing, seasonal, stability
- Large dynamic range of constituent levels
- Lack of analytical standards
- Limited or inaccurate literature data

Identify all of these components…
…and quantify them.
Agricultural practices drive additional complexity

- Good Agricultural Practice
- Harvest Conditions
- Botanical Parts
Botanical raw material processing adds additional complexity
Botanical products are variable

- **Source material**
  - Plant part (aerial, root, whole plant, leaf, seed)
  - Climate
  - Soil conditions
  - Season
  - Plant maturity
  - Contaminants (mold, pesticides, metals)
  - Co-harvested materials (other plants, soil)

- **Processing**
  - Extraction process
  - Solvents
  - Adulteration
  - Contamination
  - Storage/shipping conditions

- **Finished product**
  - Manufacturing process
  - Excipients
  - Combination with other botanicals
  - Adulteration
  - Contamination
  - Storage/shipping conditions
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Exposure
- Dose (use pattern)
- Length of dosing
- Life-stage
- Disease-state
- Nutritional status
- Background genetics
- Co-exposures
Testing scheme built on single chemicals

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

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Botanicals</th>
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<tbody>
<tr>
<td>- Regulatory structure aimed at ensuring safety and efficacy</td>
<td>- Regulatory structure aimed at ensuring access</td>
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<tr>
<td>- Assumed to be harmful until proven safe</td>
<td>- Assumed to be safe until proven harmful</td>
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<tr>
<td>- Simple and consistent</td>
<td>- Complex and variable</td>
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<td>- Biological activity is associated with the constituent</td>
<td>- Biological activity is associated with the whole mixture</td>
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Safe History of Documented Use: Hallmark of a botanical risk assessment

- Dietary use patterns provide essential bridge to safe human use
- Accurate historical records establish:
  - dose, duration, population size & diversity;
  - botanical part, species identity,
  - harvest conditions, extraction conditions, solvents...
- What if not identical?
Traditional toxicology tools are generally not fit-for-purpose for botanicals

For a novel botanical, the current safety qualification process is highly dependent on animal testing:

- Often a high degree of variability when evaluating mixtures,
- An insensitive tool for discerning minor variations,
- Resource and time intensive,
- Moral/ethical considerations.
New 21st Century methodologies are providing an improved path forward

- Advances in chemical analysis provide clearer picture of raw material composition and variance
- Differential analysis provides framework to evaluate relevant differences

Analysis of Grape Seed Extract
New 21st Century methodologies are providing an improved path forward

- Current Safety Methods (*in vitro, ex vivo, in silico*) provide a suite of new options
Finding Common Ground

C. L. Galli, et. al., Tox. Lett. 314:10-17, 2019

In silico approach to safety of botanical dietary supplement ingredients utilizing constituent-level characterization.
Common Struggles, Needs, and Solutions

- Growing demand for botanical products, and growing trend towards modified or specialty botanicals.
- Diverse botanical starting materials, coupled with variable agricultural and processing practices.
- Ongoing need for bridging to biosimilar materials, and a transparent discussion on qualification of new materials.
- Desire to apply 21st Century (non-animal) methodologies.
Mission of the Botanical Safety Consortium

To enhance the botanical safety toolkit and bring clarity to botanical dietary ingredient assessments for manufacturers and regulators.