Dietary Supplement Safety
A 25-year Retrospective Assessment

Bill J. Gurley, Ph.D.
Shabana Khan, Ph.D.
Douglas MacKay, N.D.
Amy Roe, Ph.D.
Sibyl Swift, Ph.D.

INTERNATIONAL CONFERENCE ON THE SCIENCE OF BOTANICALS
University of Mississippi
Oxford, MS
April 9, 2019
Congratulations Craig!

CONGRATS VIRGINIA!

NATIONAL CHAMPIONS
Plants have been a source of drugs since time immemorial.

In the U.S. plants and plant extracts were a mainstay in medicine until after WWII. At that point, drugs transitioned from multi-ingredient plant-based products to synthetic, single-ingredient API.

By the late 1970’s, most colleges of pharmacy removed “pharmacognosy” courses (the study of plant-derived medicines) from their curricula.

In 1994, passage of DSHEA and the influx of botanical dietary supplements caught most health-care professionals unaware of how to deal with these new pharmacological entities.
Lessons learned from 25 years of botanical dietary supplement research

1. BDS are complex phytochemical mixtures that beget complex research problems and solutions (e.g., “Proprietary blends”).
2. Products must be independently verified for phytochemical content (e.g., “Content vs. label claim”).
3. Contamination and adulteration plague many BDS categories.
4. Human clinical pharmacokinetic parameters (e.g., clearance, bioavailability, half-life, etc.) for most unique phytochemicals are unknown (exceptions: caffeine, ephedrine alkaloids).
5. BDS can interact with conventional medications, although only a few appear to be clinically relevant.
6. BDS dosage form performance (e.g., disintegration and dissolution) is largely unknown and can adversely affect clinical study outcomes.
7. Significant disconnects exist between in vitro HDI predictions and in vivo realities.
8. Novel BDS dosage forms may enhance efficacy and/or toxicity.
9. Despite 25 years of use, health-care professionals are still largely ignorant of the positive and negative aspects of BDS.
Botanical Dietary Supplement (BDS) Safety: Overview

- Introduction.
- Historical overview with examples ("The Ephedra Wars")
- Basic BDS safety concerns: Most single ingredient BDS are safe
- Single-ingredient vs. “proprietary blends”
- Herb-induced liver injury
- Contamination and adulteration
- Herb-drug interactions: St. John’s wort and MDP-containing phytochemicals
- Dosage form performance and its influence on BDS safety
- Predicting BDS safety: methodologies and their utility
- A discomfiting legacy: health care professionals still know little about BDS
A lot has changed in 25 years: Global supply chain, Global marketing platforms (Amazon), novel products, etc. How do we get the minor players in the industry to become more concerned about product safety?

Should there be another tier/category of BDS products that have demonstrated adequate quality and safety? Can this “safety assurance” impart market exclusivity for “health safety” claims.

After 25 years, is there now a need for BDS CROs that can conduct the proper clinical “safety” studies for products aiming for this upper-tier category?
# Suplement Facts

**Serving Size:** Four Tablets  
**Servings Per Container:** 30

<table>
<thead>
<tr>
<th>Amount Per Serving</th>
<th>% Daily Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin C (as Ascorbic Acid)</td>
<td>120 mg</td>
</tr>
<tr>
<td>Niacin</td>
<td>20 mg</td>
</tr>
<tr>
<td>Vitamin B-6 (as Pyridoxine Hydrochloride)</td>
<td>2 mg</td>
</tr>
<tr>
<td>Pantothenic Acid (as Calcium d-Pantothenate)</td>
<td>10 mg</td>
</tr>
</tbody>
</table>

## Ultra Heat Matrix

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucuna Pruriens Seed Extract</td>
<td>500 mg</td>
</tr>
<tr>
<td>Ginger Root Extract (Zingiber officinale)</td>
<td>500 mg</td>
</tr>
<tr>
<td>Caffeine Anhydrous</td>
<td>200 mg</td>
</tr>
<tr>
<td>Boswellia Serrata Extract</td>
<td>250 mg</td>
</tr>
<tr>
<td>Capsimax™ Capsicum Seed Extract</td>
<td>100 mg</td>
</tr>
<tr>
<td>Cinnamon Bark Extract (Cinnamomum zeylanicum)</td>
<td>100 mg</td>
</tr>
<tr>
<td>Piper Longum Fruit Extract</td>
<td>2 mg</td>
</tr>
</tbody>
</table>

## Performance Enhancing Blend

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yerba Mate Leaf Extract (Caffeine 40 mg)</td>
<td>500 mg</td>
</tr>
<tr>
<td>Guarana Seed Extract (Paulinia cupana) (Caffeine 150 mg)</td>
<td>422 mg</td>
</tr>
<tr>
<td>MegaNatural® Gold Grape Seed Extract (Vitis vinifera)</td>
<td>200 mg</td>
</tr>
<tr>
<td>Black Tea Leaf Extract (Camellia sinensis) (Caffeine 10 mg)</td>
<td>100 mg</td>
</tr>
<tr>
<td>Schisandra Fruit Extract (Schisandra chinensis)</td>
<td>100 mg</td>
</tr>
<tr>
<td>Dill Weed Extract (Anethum graveolens)</td>
<td>100 mg</td>
</tr>
<tr>
<td>Sicilian Blood Orange Fruit &amp; Peel Extract (Citrus sinensis)</td>
<td>100 mg</td>
</tr>
<tr>
<td>Quercetin (as Quercetin Dihydrate)</td>
<td>50 mg</td>
</tr>
<tr>
<td>Turmeric Root Extract (Curcuma longa)</td>
<td>25 mg</td>
</tr>
<tr>
<td>Green Tea Leaf Extract (Camellia sinensis)</td>
<td>25 mg</td>
</tr>
</tbody>
</table>

## Metabolism Igniter Complex

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-Arginine</td>
<td>500 mg</td>
</tr>
<tr>
<td>Green Coffee Bean Extract (Coffee canephora robusta)</td>
<td>100 mg</td>
</tr>
<tr>
<td>resVida® Resveratrol</td>
<td>30 mg</td>
</tr>
</tbody>
</table>

* Daily Value not established.
Effect of SJW on CYP3A4 Phenotype

Young: [Average increase = 98%] (Range = 17%-240%)

Elderly: [Average increase = 141%] (Range = 58%-725%)

Gurley et al., Drugs & Aging 2006; 46:201-213
Effect of SJW on Cyclosporine Trough Concentrations

What makes St. John’s wort so problematic?

- **Mechanism:**
  Induction of CYPs (e.g., CYP3A4, 2C9, 2E1) and efflux transporters (e.g., ABCB1, ABCG2)

  Binds to hPXR to induce CYP and ABC gene expression

- **Responsible phytochemicals:** Hyperforin, adhyperforin

  Most potent hPXR ligand yet discovered! (Ki ≈ 25nM)

  More potent than rifampin!
Botanical Dietary Supplements (BDS): Herb-drug Interactions (Pharmacokinetic HDI)

Broken circle = methylenedioxyphenyl (MDP) moiety
Botanical Dietary Supplements (BDS): Herb-drug Interactions (Pharmacokinetic HDI)

Botanicals with phytochemicals containing MDPs that produce clinically relevant HDI are:

<table>
<thead>
<tr>
<th>Plant species</th>
<th>MDP-containing phytochemical</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Berberis</em> spp.</td>
<td>Berberine</td>
</tr>
<tr>
<td><em>Coptis</em> spp.</td>
<td>Berberine</td>
</tr>
<tr>
<td><em>Hydrastis canadensis</em></td>
<td>Berberine, hydrastine</td>
</tr>
<tr>
<td><em>Piper longum</em></td>
<td>Piperine, piperamides</td>
</tr>
<tr>
<td><em>Piper nigrum</em></td>
<td>Piperine, piperamides</td>
</tr>
<tr>
<td><em>Schisandra</em> spp.</td>
<td>Gomisins, schisantherins, schizandrols</td>
</tr>
</tbody>
</table>

Bioavailability of most phytochemicals is poor

Is poor dosage form performance a factor?

- cGMPs do not require dissolution & disintegration testing.
- USP dissolution standards **not** established for all botanical monographs.
- Few clinical studies of botanicals assess dosage form performance.
- Dosage form performance = disintegration and dissolution
  - Poor disintegration & dissolution can adversely affect bioavailability.
  - Dissolution often a function of physicochemical properties
    (e.g., molecular wt., aqueous solubility, permeability, etc.)
Bioavailability of most phytochemicals is poor
Is poor dosage form performance a factor?

Goldenseal extract (capsules)
Water solubility of hydrastine & berberine
~20 mg/mL

Kava extract (capsules)

Kava extract (liquid gel caps with lecithin)
Water solubility of methysticin & dihydromethysticin
< 0.8 mg/mL

Emerging technologies for improving phytochemical bioavailability

- Recognizing that many “active” phytochemicals have poor aqueous solubility and/or permeability, new formulation technologies have been implemented to improve dissolution and bioavailability.

  - Liposomes
  - Phytosomes (complexes of polyphenols and phosphatidylcholine)
  - Self-emulsifying drug delivery systems (SEDDS)
  - Nanoparticles
  - Phytochemical inhibitors of xenobiotic metabolism (e.g., piperine)

- None of these new botanical formulations have been evaluated for their drug interaction potential in humans.
Liposomal formulation greatly improves dissolution of milk thistle silymarin (A) and its oral bioavailability (B).

Today, BDS are for sale in pharmacies, health food stores, grocery stores, and various other retail outlets including the internet.

BDS are oral dosage forms (e.g., tablets, capsules, liquids, etc.) containing various types of botanical extracts (i.e., aqueous, non-aqueous, and mixed extracts).

Two major categories of BDS:

- **Single-ingredient products** (e.g., *Ginkgo biloba*, saw palmetto, echinacea, St. John’s wort, etc.)
- **Multi-ingredient products** (“Proprietary Blends”) (e.g., weight-loss aids, exercise performance enhancers [“pre-workout supplements”], sexual performance enhancers, etc.)
In 1994, ~4000 products were on the U.S. market and annual sales were <$100M

In 2019, roughly 75,000 dietary supplement products are on the market today, accounting for >$30B in annual sales. BDS sales are ~$10B annually. (Things have certainly changed in 25 years!)

Approx. 60-70% of U.S. population take some form of DS (i.e., vitamins, minerals & botanicals).
Surveys indicate that 20-30% of Rx drug users in the U.S. take botanical supplements concomitantly.

Less than 40% of patients reveal use of herbal dietary supplements to health care professionals.

Herb-drug interactions pose significant safety risks to consumers.
For the last 25 years, safety requirements for botanicals have been linked to intended their use (e.g., food, dietary supplement, cosmetic, botanical drug).

DSHEA provides the regulatory safety framework for dietary supplements, but growth and innovation in the supplement market may have challenged a law developed 25 years ago.

“I’m concerned that changes in the supplement market may have outpaced the evolution of our own policies and our capacity to manage emerging risks.” - Gottlieb 2019.
BDS Safety: Some questions to ponder

- Does DSHEA in its current form still provide a reasonable approach to monitoring BDS safety?

- If so, is there a better way to utilize the existing regulatory framework of DSHEA?

- If not, how best can we go forward with modifications to DSHEA with regard to improving BDS safety?
### BDS Safety: Events impacting BDS safety over the last 25 years

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>Dietary Supplement Health &amp; Education Act passed</td>
</tr>
</tbody>
</table>
| 1995 | Adverse events linked to ephedra use first reported  
Office of Dietary Supplements (ODS) at NIH begins operations |
| 1997 | FDA issues proposed ruling on adulteration of ephedra supplements |
| 2000 | Organ transplant rejection linked to interaction between SJW and cyclosporine;  
First jury trial involving an ephedra-related injury *(verdict in favor of plaintiff)*  
NCCAM funds first Botanical Research Centers |
| 2002 | Research into herb-drug interactions begins in earnest |
| 2004 | FDA rules ephedra supplements are adulterated and removes them from US market;  
Adverse events related to ephedra-free supplements first reported |
| 2006 | FDA establishes rules for adverse event reporting for dietary supplements.  
Dietary Supplement & Nonprescription Drug Consumer Protection Act passed |
| 2007 | FDA issues final ruling on dietary supplement GMPs |
| 2008 | Rash of reports finding BDS adulterated with undeclared drugs and anabolic steroids; FDA removes (and continues to remove) adulterated BDS from US market |
| 2010 | Food Safety Modernization Act passed enhancing FDA recall authority for food & BDS |
| 2013 | Spate of liver injuries linked to use of OxyELITE Pro (OEP); FDA deems OEP adulterated and removes it from the US market |

BDS Safety:
Events impacting BDS safety over the last 25 years

2014  Designer Steroid Control Act passed expanding list of anabolic steroids regulated by Drug Enforcement Agency

2015  NCCIH (formerly NCCAM) establishes Center of Excellence for Natural Product Drug Interaction Research; Using inappropriate testing methodology (DNA fingerprinting of finished BDS products), New York Attorney General erroneously targets major retailers for selling fraudulent BDS and demands products be removed from shelves.

2016  Department of Justice files criminal charges against the maker of OxyELITE Pro (USP Labs)

2018  FDA bans the sale of BDS containing highly concentrated or pure caffeine

2019  FDA Director expresses desire that DSHEA be revised to improve BDS safety oversight; USP Labs pleads guilty to criminal charges related to OxyELITE Pro

Several categories of BDS have posed significant safety concerns over the past 25 years.

- Weight-loss / Exercise performance enhancement BDS
  - Ephedra-containing BDS (Who in this room is not a veteran of the Ephedra Wars?)
  - Ephedra-free BDS (Adverse events similar to Ephedra-containing BDS)
  - BDS linked to liver injury (Lipokinetix, OxyELITE Pro, others)

- St. John’s wort (renders most medications ineffective)

- MDP-containing BDS (Berberis, Coptis, Piper nigrum, Schisandra, others)

- Adulterated/contaminated BDS
  - Pyrrolizidine alkaloids
  - Aristolochic acid
  - Prescription medications (Weight-loss, Pre-workout, Sex enhancement BDS)
  - Heavy metals
Botanical Dietary Supplements (BDS): Historical overview: Ephedra-containing BDS

Botanical Dietary Supplements (BDS): Historical overview: Ephedra-free BDS

Hypertensive Urgency Associated With Xenadrine EFX Use

Vasospasm and Stroke Attributable to Ephedra-Free Xenadrine: Case Report

Case report
Malignant hypertension and acute aortic dissection associated with caffeine-based ephedra-free dietary supplements: a case report

A Case of Severe Exercise-Induced Rhabdomyolysis Associated with a Weight-Loss Dietary Supplement
In 2013, a host of serious liver injuries, some requiring liver transplantation, and several deaths were linked to the use of OxyELITE Pro (OEP).

Marketed as an exercise performance enhancer, its ingredients had never been formulated together, and one (aegeline) had never been administered to humans.

Product contained no botanical extracts, only synthetic compounds (i.e., caffeine, aegeline, higenamine, yohimbine).

FDA removed the product from the market in 2014, sued the manufacturer (USP Labs) in 2016, defendants pled guilty in 2019.

Recent studies in mice demonstrated OEP hepatotoxicity at doses equivalent to that recommended in humans. OEP at doses 3X recommended dose were often deadly. (Narrow safety margin!)

Botanical Dietary Supplements (BDS): Single ingredient vs Proprietary Blends

- Botanical extracts are complex mixtures of numerous phytochemicals.

- “Proprietary blends” are BDS containing multiple botanical extracts, many of which have never been combined before as part of the diet.

- BDS formulations utilize concentrated plant extracts. Phytochemical exposure is much greater as an extract than consuming the plant in its natural state.

- Most phytochemicals have not been characterized for pharmacological activity, never mind combinations of multiple phytochemicals from multiple extracts.
Botanical Dietary Supplements (BDS): Single ingredient vs Proprietary Blends

A partial listing of phytochemicals present in St. John’s wort

<table>
<thead>
<tr>
<th>Naphthodianthrones</th>
<th>Flavonoids</th>
<th>Essential Oils</th>
</tr>
</thead>
<tbody>
<tr>
<td>hypericin</td>
<td>luteolin</td>
<td>methyl-2-octane</td>
</tr>
<tr>
<td>pseudohypericin</td>
<td>13,118-biapigenin</td>
<td>pinenes</td>
</tr>
<tr>
<td>protohypericin</td>
<td>amentoflavone</td>
<td>terpineol</td>
</tr>
<tr>
<td>protopseudohypericin</td>
<td>hyperin</td>
<td>quercetin</td>
</tr>
<tr>
<td>cyclopseudohypericin</td>
<td>catechin derivatives</td>
<td>kaempferol</td>
</tr>
<tr>
<td></td>
<td>epicatechin derivatives</td>
<td>hyperoside</td>
</tr>
<tr>
<td></td>
<td>quercetin</td>
<td>quercitrin</td>
</tr>
<tr>
<td></td>
<td>kaempferol</td>
<td>rutin</td>
</tr>
<tr>
<td></td>
<td>hyperoside</td>
<td>myricetin</td>
</tr>
<tr>
<td></td>
<td>quercitrin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rutin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>myricetin</td>
<td></td>
</tr>
</tbody>
</table>

**Xanthones**

- 1,3,6,7-tetrahydroxyxanthone
- kielcorin

**Phloroglucinol derivatives**

- hyperforin
- hydroperoxycadiforin
- adhyperforin

**Essential Oils**

- pinenes
- terpineol
- geraniol
- limonene
- caryophyllene
- humulene
Ephedra-containing BDS remain perfect illustrations of safety concerns inherent in “proprietary blends.”

Placing the burden of safety on the FDA or independent researchers, and not the manufacturer, is simply illogical from a safety perspective regarding complex phytochemical mixtures.

Many other variables impact the pharmacology of proprietary blends: age, genetics, exercise, prescription and/or nonprescription medications, others.
Current Good Manufacturing Practices (cGMPs), have significantly impacted the quality and safety of BDS.

Unfortunately cGMPs were not fully implemented until 2008.

While most DS manufacturers adhere to cGMPs, not all are fully compliant.

As a result, certain categories of BDS (e.g., weight-loss BDS, exercise performance enhancement BDS, sexual performance enhancement BDS) are frequently adulterated and/or contaminated.
**Rx adulterants:** anabolic steroids, barbiturates, benzodiazepines, corticosteroids, diuretics, NSAIDs, PDE-5 inhibitors, phenytoin, rimonabant, sibutramine, theophylline, thyroid hormones, many others.

**Economic adulterants:** plant extracts, essential oils, etc. that are not representative of the label claim but are easier and cheaper to acquire.

**Contaminants:** Bacteria, fungi, pesticides, heavy metals (Hg, Pb, Cd, As)
Refer to comments of the previous ICSB panel regarding this topic.
20-30% of Rx drug users in the U.S. take botanical supplements concomitantly.

Less than 40% of patients reveal use of herbal dietary supplements to health care professionals.

Herb-drug interactions pose significant safety risks to consumers.
Herb-drug interactions (HDI) can be categorized as either pharmacodynamic or pharmacokinetic.

Pharmacodynamic HDI involve phytochemicals whose pharmacological activity can either negate or enhance the activity of a prescription medication.
(e.g. Ephedra-free BDS containing high quantities of caffeine can increase blood pressure and thus can negate the effects of many antihypertensive drugs.)

Pharmacokinetic HDI involve phytochemicals that can either inhibit or induce the activity of drug metabolizing enzymes (e.g. CYPs, UGTs, sulfatases, etc.) and/or transporters (e.g. P-glycoprotein, OATP, OCT, etc.).
BDS noted for producing clinically relevant pharmacodynamic HDI include:

<table>
<thead>
<tr>
<th>BDS</th>
<th>HDI Risk</th>
<th>HDI Mechanism</th>
<th>Phytochemicals</th>
<th>Consequences</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ephedra-containing BDS</td>
<td>High</td>
<td>Pharmacodynamic Cardiovascular and CNS stimulant effects</td>
<td>Ephedrine alkaloids, caffeine, other natural stimulants</td>
<td>Increased BP, HR; increased risk of adverse cardiovascular &amp; CNS health effects</td>
<td>Avoid concurrent use with Rx antihypertensives and stimulants</td>
</tr>
<tr>
<td>Ephedra-free BDS</td>
<td>High</td>
<td>Pharmacodynamic Cardiovascular and CNS stimulant effects</td>
<td>Caffeine and other natural stimulants (e.g., yohimbine, synephrine, etc.)</td>
<td>Increased BP, HR; increased risk of adverse cardiovascular &amp; CNS health effects</td>
<td>Avoid concurrent use with Rx antihypertensives and stimulants</td>
</tr>
<tr>
<td>Liquorice Root* (G. glabra)</td>
<td>High</td>
<td>Pharmacodynamic Cardiovascular and CNS stimulant effects</td>
<td>Glycyrrhizic acid</td>
<td>Increased BP with prolonged use</td>
<td>Avoid concurrent use with Rx antihypertensives</td>
</tr>
</tbody>
</table>

* = This risk assessment does not apply to deglycyrrhizinated liquorice root products
Liquorice root extract

**Interaction mechanism:**
Chronic use leads to sodium retention, potassium depletion due to mineralocorticoid effect of glucyrhzoneic acid and its metabolite (monoglucuronyl-18β-glycyrrhetinic acid) which inhibits 11-β-hydroxysteroid dehydrogenase 2. (11βHS2 converts cortisol to cortisone.)

**Interactions:**
Antihypertensives (diuretics), antiarrhythmics

**Consequences:**
Hypertension, hypokalemia, arrhythmias
St. John’s wort (*Hypericum perforatum*) is perhaps the most problematic BDS with regard to pharmacokinetic HDI.

**Indication:** Anti-depressive

**Efficacy:** Good (product-dependent)

**Drug Interaction Risk:** Very High! Renders most drugs ineffective
Botanical Dietary Supplements (BDS): Herb-drug Interactions (Pharmacokinetic HDI)

- **SJW HDI Mechanism:**
  Induction of CYPs (e.g., CYP3A4, 2C9, 2E1) and efflux transporters (e.g., ABCB1, ABCG2)

  Binds to hPXR to induce CYP and ABC gene expression

- **Responsible phytochemicals:**
  Hyperforin, adhyperforin

  Most potent hPXR ligand yet discovered!
  (Ki \(\approx 25\text{nM}\))

  More potent than rifampin!
Unlike SJW, many phytochemicals containing methylenedioxyphenyl (MDP) moieties inhibit human CYP enzymes.

Inhibition of human CYPs by MDP-containing phytochemicals is “time-dependent” or “mechanism-based.”

This type of enzyme inhibition renders drugs more toxic, leading to clinically relevant HDI.
Most popular botanical supplements do not appear to pose a serious drug interaction risk; however, the vast majority have yet to be studied in a clinical setting.

Systemic effects of many botanical DS are minimal due to:
- poor dosage form performance
- extensive pre-systemic metabolism
• cGMPs do not require dissolution & disintegration testing.
• USP dissolution standards not established for all botanical monographs.
• Few clinical studies of botanicals assess dosage form performance.
• Dosage form performance = disintegration and dissolution
  – Poor disintegration & dissolution can adversely affect bioavailability.
  – Poor dosage form performance reduces efficacy but enhances safety.
  – Dissolution often a function of physicochemical properties
    (e.g., molecular wt., aqueous solubility, permeability, etc.)
**Definition:** Process by which a solid substance (drug/phytochemical) dissolves in a specified aqueous medium. Dissolution rate is amount of drug/phytochemical substance that goes into solution in a specified time under standardized conditions of liquid/solid interface, temperature, and solvent composition.

**Dissolution Apparatus:**
- Basket Apparatus
- Paddle Apparatus
- Reciprocating Cylinder
- Flow-Through Cell

Procedures and tolerances defined only for a **limited** number of botanical monographs: Plot percent dissolved vs. time
Goldenseal extract (capsules)

Water solubility of hydrastine & berberine
~20 mg/mL

Kava extract (capsules)

Water solubility of methysticin & dihydromethysticin
< 0.8 mg/mL

Kava extract (liquid gel caps with lecithin)
Recognizing that many “active” phytochemicals have poor aqueous solubility and/or permeability, new formulation technologies have been implemented to improve dissolution and bioavailability. None of these new botanical formulations have been evaluated for their drug interaction potential in humans.

- Liposomes
- Phytosomes
- Self-emulsifying drug delivery systems (SEDDS)
- Nanoparticles
- Phytochemical inhibitors of xenobiotic metabolism (e.g., piperine)
Liposomal formulation greatly improves dissolution of silymarin (A) and its oral bioavailability (B).
• **BENEFITS**: Improving phytochemical bioavailability through novel formulation technologies may lead to improved phytochemical efficacy.

• **RISKS**: With improved bioavailability may come an increased risk of toxicity and/or herb-drug interactions.

• **FUTURE**: Few randomized, controlled clinical trials have been conducted with these new novel formulations. The future of BDS may hinge on the success of these technologies.
At present, most single-ingredient BDS appear to be relatively safe.

A number of factors contribute to the safety of most single-ingredient BDS:

- Extensive pre-systemic metabolism
- Poor dosage form performance
- Consumption of BDS with food
- Quality control issues: “content vs. label claim”

“Proprietary blends,” however, often pose a greater safety risk.
At present, adverse event reports, case reports, poison control center calls, etc., are the principal “predictors” of BDS safety.

These methodologies, while infrequently submitted and imperfectly described, can provide insight into potential safety concerns, yet they remain “after the fact” descriptors.

Many other variables, usually not described in AERs, impact the safety of BDS, especially proprietary blends: genetics, exercise, concomitant use with prescription and/or nonprescription medications, others.
What other methods are available for predicting BDS safety?

Animal studies to predict safety can be easily performed on actual products, preferably prior to marketing.

While animal studies are not perfect, they can help identify problematic phytochemical combinations.

In vitro methodologies can also be useful in predicting BDS safety:
- Human hepatocytes
- Sandwich assays
- “Organ on a chip”
- Artificial intelligence / machine learning
- Others?
A tremendous body of literature documenting \textit{in vitro} HDI studies indicates that most phytochemicals can modulate drug metabolism and/or transport in model systems (e.g., human hepatocytes, Caco2 cells, microsomes, purified enzymes, etc.).

However, most \textit{in vitro} studies use physiologically irrelevant phytochemical concentrations or incorporate solubilizing agents (e.g., DMSO, ethanol, etc.), oftentimes both.

Few consumers take their BDS with DMSO!

The end result is that very few \textit{in vitro} results are clinically translatable. This has caused considerable confusion regarding HDI realities and botanical safety.
Despite a 25-year tenure on the U.S. market, the lay public and medical community remain largely ignorant of many aspects of BDS.

- Comments like “**BDS are natural and more safe than synthetic drugs**” are common among consumers.
- While “**BDS are unsafe and unregulated,**” are frequent refrains among health-care professionals.
- Educating the public and medical community to the facts about BDS remains a significant challenge.
Is DSHEA’s approach to safety, in its original form, still a reasonable expectation for Industry and for FDA?

Industry is responsible for establishing the safety of products in their finished form. However, if there is a concern, FDA has burden to prove there is evidence of harm. There are examples where FDA claims a product is unsafe and companies disagree and continue to sell the product, does this work?

Is a more aggressive application of New Dietary Ingredient (NDI) criteria needed?