Published in final edited form as:

Clin Pharmacol Ther. 2018 September ; 104(3): 429–431. doi:10.1002/cpt.1088.

Getting to the Root of the Matter: Challenges and Recommendations for Assessing the Safety of Botanical Dietary Supplements

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Introduction

The National Toxicology Program's (NTP) mission is "to evaluate agents of public health concern, by developing and applying the tools of modern toxicology and molecular biology." Botanical dietary supplements (BDS) represent agents of public health concern due to widespread exposure to high doses, a lack of safety data for most products, variable quality, and reports of adverse events. This commentary will address lessons learned in NTP testing activities with BDS and recommendations for moving forward.

Background

The passage of the Dietary Supplement Health and Safety Act (DSHEA) in 1994 ushered in an era of unbridled growth in the BDS industry with sales in the U.S. reaching 7.5 billion dollars in 2016 (1). The regulatory framework for BDS, overseen by the Food and Drug Administration (FDA), includes requirements for product labeling, good manufacturing practices (GMP), and notifications for new dietary ingredients (2). However, any new product containing an ingredient or combination of ingredients represented in the market prior to 1994 does not require pre-market safety data. The lack of pre-market safety requirements, combined with public perceptions that plant-based products are 'natural' and 'safe', have contributed to the paucity of toxicity data available for safety evaluations of BDS. The NTP began a concerted effort to fill this void by developing a BDS testing program in the late 1990s (3). Over the past two decades, the NTP has evaluated numerous BDS by applying the latest tools of modern toxicology including sophisticated chemical analyses, comprehensive short-term and long-term animal studies performed according to Good Laboratory Practices (GLP) specifications, and targeted mechanistic studies using leading-edge *in vitro* technologies (Table 1).

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Conflict of interest: The authors declared no competing interests for this work.

Challenges

Assessing the safety of BDS presents many unique challenges (4). The two most important challenges are also interrelated - the natural complexity and variability in BDS products and the relatively lenient regulatory structure for BDS in the U.S. BDS are complex mixtures containing hundreds of constituents, often with a large fraction of the botanical material consisting of unknown constituents. There are multiple sources of variation in the raw plant material (e.g., plant part, soil conditions, season, harvesting process), extraction (e.g., technique, solvent composition), and manufacture (e.g., process, excipients). Additionally, there is the possibility of adulteration motivated by economics (addition of cheaper plant material) or performance (addition of approved pharmaceuticals or their structural analogs). Finally, contamination can occur through co-harvesting (e.g., weeds containing toxic pyrrolizidine alkaloids), application of pesticides to source material, presence of heavy metals in soil, or inappropriate storage conditions leading to mold or bacterial growth. Although the GMP guidelines are intended to prevent adulteration and contamination, the lack of pre-market safety requirements and ease of entrance into the market contribute to difficulties in enforcement. The current situation is one of easy consumer access to highly variable products.

Recognizing the inherent BDS challenges of complexity and variability, the NTP initiated internal discussions of its BDS portfolio to identify key areas that require research attention in order to improve our understanding of how BDS can negatively affect health. The three areas identified were: developing and applying approaches for identifying toxicologically-active constituents, developing and validating methods for determining “sufficient similarity” of complex BDS, and establishing recommendations for conducting evaluations of absorption, distribution, metabolism, and elimination (ADME) of BDS including the underlying kinetics of these processes. A 2016 workshop titled “Addressing Challenges in the Assessment of Botanical Dietary Supplement Safety” brought together experts from government, academia, and industry to provide external feedback on the identified research areas. Experts were tasked with discussing the current state of the science in each of the key areas and providing suggestions for the research required to fill existing knowledge gaps.

Identifying actives

Identification of the toxicologically-active constituent(s) can be useful in responding to adverse events with regulatory action. Knowledge of the active constituent, which could be either an intrinsic constituent of the botanical or an adulterant, allows for a complete ban, limit-setting and/or monitoring to prevent future adverse outcomes. For example, the banning of ephedra alkaloids in 2004, which are known constituents of ephedra or Ma Huang, was due to their association with cardiotoxicity. A recommended approach for identifying active constituents from complex BDS mixtures is bioassay-guided fractionation (5). This approach involves fractionation of constituents based on chemical properties, followed by testing fractions for biological activity in carefully selected bioassays. Biologically-active fractions can be further explored for candidate active constituents. It is important to note that biological activity of the complex BDS might be due to multiple constituents or classes of constituents, and their interactions. Therefore, BDS fractions or

isolated constituents may or may not reflect the activity of the whole mixture. While bioassay-guided fractionation has been applied for identifying pharmacologically-active candidates for drug discovery purposes, there are fewer examples of its application in toxicology. Instead, correlation studies between candidate actives and biological activity are more frequent in the toxicology literature, as in an example linking berberine content to genotoxic potential among a number of goldenseal samples (6).

Sufficient similarity of BDS

Considering the complexity and variability of BDS, characterization and authentication of study samples is an important part of research to evaluate the efficacy and/or toxicity of BDS. BDS testing at the NTP and elsewhere has typically involved the inherent assumption that the chemically- and toxicologically-characterized sample is representative of similarly labeled products in the marketplace (i.e., the tested 'green tea extract' is representative of all products labeled as 'green tea extract'). In order to provide scientific support for this assumption, a series of case studies was developed using *Ginkgo biloba* extract, black cohosh extract, and *Echinacea purpurea* extract to evaluate the chemical and biological similarity of nominally-related products. In each case study, the reference sample was compared to other unformulated samples from the marketplace, formulated products, and standard reference material. Methods to compare across samples included strength of evidence evaluations, statistical equivalence testing based on determination of a similarity region, and a visual interval evaluation which superimposed biological data onto the chemical relationships among samples (7). Preliminary findings offer convincing support for selection of samples for testing based on chemical analyses and comparison to reference materials.

ADME considerations

The term ADME is used broadly here to include ADME processes, toxicokinetics, and potential interactions among chemicals. ADME data for BDS are integral to evaluating safety and rarely available (8). Options for assessing ADME properties for BDS rely heavily on knowledge of toxicologically-active constituents. Without this knowledge, pharmacologically-active or abundant constituents have been used as markers for evaluating ADME of BDS with the understanding that findings may not reflect toxicological outcomes. Alternatively, a global and unbiased method to evaluate ADME properties of botanicals called polypharmacokinetics has been proposed (9). While promising, there are currently few examples of its application. Another key consideration in safety assessments is characterizing potential drug-botanical and botanical-botanical interactions. A framework involving *in silico*, *in vitro*, and clinical components has been proposed to provide stakeholders with options for making informed decisions about interaction potential (10).

Conclusions and recommendations

The current BDS scenario in the U.S. has been compared to the Wild West, with the public receiving little guidance on what products may or may not be safe and/or effective. The converging factors that cause concern over the safe use of BDS are the high doses (100s–

1000s mg per day) aimed at achieving pharmacological “efficacy”; widespread exposure to all populations including those with pre-existing conditions, the very young and the very old; lack of a robust regulatory structure such as that for pharmaceuticals; complex mixtures exhibiting high variability and questionable quality, and often containing a large unidentified fraction; and very little safety data available. There is clearly a need for research to better understand the hazards associated with BDS. Recommendations for continued progress include:

- Prioritization of BDS for toxicological assessment based on exposure and indications of potential toxicity from adverse event reporting and/or toxicity observed in efficacy studies.
- Comprehensive analysis of samples that are being used in toxicity testing including plant authentication, contaminant analysis, and untargeted and targeted chemical evaluation including quantitation of marker constituents.
- Increased efforts to identify active constituents through use of bioassay guided fractionation and whenever possible (i.e., when multiple samples have been evaluated) correlation of quantified constituents with bioassay results.
- Continued development and refinement of sufficient similarity methods with attention to developing rigorous statistical approaches that can be applied universally.
- Development of ADME case studies to better understand the value of current practices and incorporating polypharmacokinetic approaches when feasible.
- Greater emphasis on identifying drug-botanical and botanical-botanical interactions, which appear to be an important concern for many BDS.

Acknowledgments

Funding: We were grateful for funding from the Office of Dietary Supplements to support sufficient similarity case study development. This work was supported by the NIH, National Institute of Environmental Health Sciences.

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Table 1

Botanical dietary supplements assessed at the National Toxicology Program in rodent toxicity and carcinogenicity studies.

Completed studies	Ongoing studies
<i>Aloe vera</i> (non-decolorized whole leaf extract)	Black cohosh extract
Bitter orange extract	Bilberry extract
<i>Ginkgo biloba</i> extract	Dong quai
Ginseng	<i>Echinacea purpurea</i> extract
Goldenseal root powder	Evening primrose oil
Green tea extract	<i>Garcinia cambogia</i> extract
Kava kava extract	Gum guggul extract
Ma Huang	Valerian root extract
Milk thistle extract	
Senna	
<i>Usnea</i> lichen	