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SELECTION OF PRIORITY NATURAL PRODUCTS FOR EVALUATION AS POTENTIAL PRECIPITANTS OF NATURAL PRODUCT-DRUG INTERACTIONS: A NaPDI CENTER RECOMMENDED APPROACH

Emily J. Johnson, Vanessa González-Peréz, Dan-Dan Tian, Yvonne S. Lin, Jashvant D. Unadkat, Allan E. Rettie, Danny D. Shen, Jeannine S. McCune, and Mary F. Paine

Center of Excellence for Natural Product Drug Interaction Research (Y.S.L., J.D.U., A.E.R., D.D.S., J.S.M., M.F.P.); Department of Pharmaceutical Sciences, Washington State University, Spokane, WA (E.J.J., V.G.P., D.D.T., M.F.P.); Department of Pharmaceutics (Y.S.L., J.D.U., D.D.S., J.S.M.) and Medicinal Chemistry (A.E.R.), University of Washington, Seattle, WA; Department of Population Sciences, City of Hope, Duarte, CA (J.S.M.)

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Running Title: Prioritizing NPs as precipitants of NPDIs

Corresponding author:

Mary F. Paine, RPh, PhD

PBS 341, PO Box 1495

College of Pharmacy

Washington State University

Spokane, WA 99210-1495

Telephone: 509-358-7759

Fax: 509-368-6673

E-mail: mary.paine@wsu.edu

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Abbreviations: AUC, area under the concentration versus time curve; DDI, drug-drug interaction; DIDB, Drug Interaction Database; NaPDI Center, Center of Excellence for Natural Product Drug Interaction Research; NP, natural product; NPDI, natural product-drug interaction; NCE, new chemical entity

ABSTRACT

Pharmacokinetic interactions between natural products (NPs) and conventional medications (prescription and non-prescription) are a longstanding but understudied problem in contemporary pharmacotherapy. Consequently, there are no established methods for selecting and prioritizing commercially available NPs to evaluate as precipitants of NP-drug interactions (NPDIs). As such, NPDI discovery remains largely a retrospective, bedside-to-bench process. This Recommended Approach, developed by the Center of Excellence for Natural Product Drug Interaction Research (NaPDI Center), describes a systematic method for selecting NPs to evaluate as precipitants of potential clinically significant pharmacokinetic NPDIs. Guided information-gathering tools were used to score, rank, and triage NPs from an initial list of 47 candidates. Triaging was based on the presence and/or absence of an NPDI identified in a clinical study (≥20% or <20% change in the object drug area under the concentration versus time curve, respectively), as well as mechanistic and descriptive in vitro and in vivo data. A qualitative decision-making tool, termed the 'fulcrum model', was developed and applied to 11 high-priority NPs for rigorous study of NPDI risk. Application of this approach produced a final list of five high-priority NPs, four of which are currently under investigation by the NaPDI Center.

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INTRODUCTION

Natural products (NPs), which include botanical dietary supplements and foods, can precipitate clinically significant pharmacokinetic interactions with conventional drugs. These interactions can manifest as enhanced or reduced pharmacological effect(s) of the object drug. Discovered ≥20 years ago, the pharmacokinetic interactions between St. John's wort and cyclosporine (Barone *et al.*, 2000; Breidenbach *et al.*, 2000; Mai *et al.*, 2000; Ruschitzka *et al.*, 2000; Moschella and Jaber, 2001), and between grapefruit juice and felodipine (Bailey *et al.*, 1989; Paine and Oberlies, 2007), are now textbook examples of clinically significant pharmacokinetic NP-drug interactions (NPDIs). Despite the clinical impact of these interactions, guidelines for systematically prioritizing commercially available NPs for NPDI investigations are nonexistent. As such, discovery of clinically significant NPDIs is left to chance and remains almost exclusively a bedside-to-bench process. This Recommended Approach, the first in a series of Recommended Approaches to be released by the Center of Excellence for Natural Product Drug Interaction Research (NaPDI Center) (citation for accompanying commentary), proposes a solution to this problem: a decision-making strategy for systematically identifying high-priority NPs that are likely to precipitate clinically significant pharmacokinetic NPDIs that warrant rigorous evaluation.

The need for development and widespread adoption of the aforementioned prospective strategy is evident. Historically, identification of clinically significant NPDIs has been driven by case reports of unexpected adverse drug reactions or loss of efficacy that were indicative of pharmacokinetic or pharmacodynamic perturbations of an object drug (Gardiner et al., 2008a). However, the value of these case reports for accurately identifying NPDIs is unclear. By one estimation, 68% of a representative sample of these case reports were inadequately documented such that determination of whether an NPDI occurred was not possible (Fugh-Berman and Ernst, 2001).

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Adverse event reporting is a similarly flawed and inefficient method of NPDI discovery. A survey of NP consumers indicated that just 30% of users would report any adverse reaction to either a drug or an herbal remedy to their primary care physician, and only 6-7% would report such an adverse reaction to their pharmacist (Barnes *et al.*, 1998). In addition, 26% indicated they would report an adverse reaction to a conventional drug, yet would not report the same adverse reaction to an herbal remedy (Barnes *et al.*, 1998). Adverse events to food have traditionally been reported more frequently to poison control centers than the FDA, but the FDA now administers reporting of dietary supplement-related adverse events and serious adverse events (SAEs) via MedWatch (Gardiner et al., 2008b; Frankos et al., 2010). Whether or not these reporting mechanisms lead to substantial advances in identification of NPDIs remains to be seen. Given the inherent limitations of anecdotal case reports and postmarket SAE reporting, a prospective and systematic research method for identifying high-risk NPs for NPDI studies is clearly needed.

The accompanying commentary (citation for accompanying commentary) introduces the premise, overarching goals, and objectives of the NaPDI Center and provides an anticipated list of Recommended Approaches to be released by the Center. These Recommended Approaches will present a coherent strategy for surmounting the unique challenges commonly encountered during the investigation of NPs as precipitants of NPDIs. This Recommended Approach, the first in the series, describes a systematic approach for identifying and prioritizing NPs that merit rigorous evaluation of NPDI risk.

CHALLENGES AND A POTENTIAL SOLUTION TO CURRENT PRACTICES

Current regulatory guidances for evaluating drug-drug interactions are not sufficient for evaluating NPDIs

Current draft regulatory guidances for evaluating drug-drug interactions (DDIs) recommend the following structured approach for testing a new chemical entity (NCE) as a pharmacokinetic DDI precipitant: (1) *in vitro* evaluation of the potency of the NCE as an inhibitor

or inducer of a standard panel of major drug metabolizing enzymes and transporters; (2) simulation of *in vivo* interaction potential using static or dynamic models, the latter including physiologically-based pharmacokinetic models; and, if necessary, (3) evaluation of the DDI in human subjects (EMA, 2012; FDA, 2017).

Although these guidances provide an essential framework for NPDIs, they are not fully suited for evaluating NPDIs, partly due to the inherent complexity of NPs. The diversity and complexity of NP composition is underscored by the inclusiveness of the definition established by the National Center for Complementary and Integrative Health: “a large and diverse group of substances from a variety of sources…produced by marine organisms, bacteria, fungi, and plants” encompassing both “complex extracts from these producers, but also the isolated compounds derived from those extracts.” (NCCIH, 2017) The typical commercial formulation of an NP is usually a complex botanical mixture consisting of a prodigious assemblage of phytoconstituents from multiple plant species and/or organs (Freedman *et al.*, 2011; Alolga *et al.*, 2015). Predictably, these mixtures often vary significantly in composition depending on sourcing and processing, thus complicating the selection of a single product, formulation, or constituent for NPDI studies (Ross *et al.*, 2000; Vandermolen *et al.*, 2013; VanderMolen *et al.*, 2014; Raclariu *et al.*, 2017; Raman *et al.*, 2017).

Basic experimental hurdles also preclude NPs from being evaluated in accordance with regulatory DDI guidelines. For example, authentic analytical standards do not always exist for quantification of the NP constituents or associated metabolites in human biologic matrices, and well-designed human pharmacokinetic studies of NP constituents and metabolites have not been routinely conducted. The complex stereochemistry of botanical constituents introduces additional challenges. Collectively, these experimental impediments have historically precluded development of a systematic approach for selecting NPs to study as potential precipitants of NPDIs. Thus, assessing and predicting the drug interaction liability of individual NP constituents

requires a strategic adaptation and/or inversion of the DDI assessment process for NCEs (Fig. 1).

Recommended Approach for identifying and selecting NPs as precipitants of pharmacokinetic NPDIs

The NaPDI Center, in consultation with the National Center for Complementary and Integrative Health, developed a systematic approach to select high-priority NPs for investigation as precipitants of clinically significant pharmacokinetic NPDIs (Fig. 2). The Center's Pharmacology Core developed the 'fulcrum model' (Fig. 3), a decision-making tool that is the crux of this approach. By facilitating a balanced evaluation of mechanistic and descriptive in vitro and in vivo data, the fulcrum model enabled visual identification of the final high-priority NPs. Currently, four of the remaining five high-priority NPs are under investigation by the NaPDI Center. Although the following strategy was developed with a focus on pharmacokinetic NPDIs involving the North American NP market, the approach is generalizable, and the accompanying tools also may be adapted to pharmacodynamic NPDIs.

Phase I: Screening of candidate NPs. An initial list of 47 candidate NPs (Table 1) was compiled from two sources: the 40 top-selling botanical NPs reported by *HerbalGram* (Smith, 2015) and seven from the University of Washington's Drug Interaction Database (DIDB), which houses the largest manually curated collection of *in vitro* and *in vivo* data related to drug interactions in humans (http://www.druginteractioninfo.org/) (DIDB®, 2018). Only human data were evaluated for the *in vivo* information gathering step due to the well-established species differences in common interaction targets (*e.g.*, drug metabolizing enzymes and transporters) (Baillie and Rettie, 2011).

DIDB Query Strategy. DIDB searches were conducted for each of the 47 initial candidates using the "Therapeutic Class Queries" tool, with the key words "Herbal Medications" as "Precipitants," and the condition as "In Vivo." The "Overall Effect" column of the resulting table was filtered using the term "20% effect" (*i.e.*, ≥20% change in the object drug area under the

concentration *versus* time curve, or AUC) to identify NPs that could potentially precipitate a clinically significant pharmacokinetic NDPI. When common names from the *HerbalGram* sales report did not coincide with those listed in the DIDB (*e.g.*, horny goat weed, feverfew, grass), the Latin or scientific name was used to query the DIDB. Rather than names of specific extracts or formulations, the broadest possible terms were used in queries.

Scoring. NPs for which no *in vivo* interaction data existed in the DIDB were triaged (n=24). An information-gathering form was subsequently used to compile query results for the 23 remaining NPs (Table 2). This form tabulated counts of the presence of an *in vivo* interaction (≥20% increase or decrease in object drug AUC), absence of an *in vivo* interaction (<20% increase or decrease in object drug AUC), and *in vitro* targets (*i.e*., drug metabolizing enzymes, transporters, nuclear receptors) for which data were collated in the DIDB.

Phase II: Identifying low-, intermediate-, and high-priority NPs. The 23 remaining NPs were binned into one of three priority levels – low, intermediate, or high – to triage NPs that were unlikely to precipitate interactions, or for which interactions were markedly under- or overstudied. A low priority was assigned if the DIDB query returned any of the following:

1) very high counts of the presence of an *in vivo* interaction, indicating that the NP was overstudied or well-characterized as an NPDI precipitant (*e.g*., St. John's wort, milk thistle);
2) counts of exclusively the absence of an *in vivo* interaction, indicating that the NP was understudied or had a low interaction liability (*e.g*., saw palmetto, valerian); or
3) counts of either the presence or absence of an *in vivo* interaction, but no counts of an *in vitro* interaction, again indicating that the NP was understudied or had a low interaction liability (*e.g.*, evening primrose oil).

An intermediate-priority was assigned if the query returned a ≥3:1 ratio of counts of the absence of an *in vivo* interaction relative to counts of the presence of an *in vivo* interaction (e.g., ginkgo, black cohosh). Based on these criteria, a high-priority was assigned to the remaining 11 NPs:

cannabinoids, cinnamon, garlic, ginseng, goldenseal, green tea, licorice, red yeast rice, resveratrol, *Schisandra spp.*, and turmeric.

Phase III: Gap analysis.

Data Mining. For each of the 11 high-priority NPs identified in Phase II, a systematic primary literature search and gap analysis was conducted by the NaPDI Center's Pharmacology Core, which is composed of experts in the fields of NPDIs and DDIs. Gaps were identified by evaluating the primary literature and reputable websites (*e.g*., the DIDB) to determine which of the following mechanistic or descriptive elements were missing or understudied: names and structures of known NP constituents, potential enzyme and/or transporter target(s) of NPDI-precipitating constituents, human pharmacokinetic studies, and current liquid chromatography/mass spectrometry bioanalytical methods. The gap analysis was précised into an executive summary (Supplement A). Brief summaries of each section of the gap analysis are provided below.

1) Known NP constituents. The first section of the gap analysis consisted of profiling constituents within NPs and determining whether these constituents had been evaluated for NPDI liability. Constituents containing functional groups with known potential to trigger time-dependent inhibition of the cytochromes P450 (CYPs) were flagged, especially if these constituents had shown NPDI potential (Table 3). Sub-structures associated prominently with time-dependent inhibition, including alkylamines and methylenedioxyphenyls, the metabolism of which can lead to "quasi-irreversible" metabolite-intermediate complexes that are known to feature in DDIs (Grimm *et al.*, 2009; Orr *et al.*, 2012), were reported in constituents of many NPs, including those in goldenseal and *Schisandra spp*. catechols, olefins, acetylenes, and α,β-unsaturated Michael acceptors, which may give rise to reactive intermediates that could impact CYP function (Kalgutkar et al., 2005), also were identified.

2) Potential enzyme and/or transporter target(s) and essential experimental systems. The second section of the gap analysis consisted of an evaluation of the strength of NPDI evidence

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for each constituent identified in section 1. Detailed categories of essential experimental systems, including panels of key drug metabolizing enzymes, transporters, and nuclear receptors, were defined by the Pharmacology Core (section 2.1). Next, experimental data for any potential targets within these categories were compiled (section 2.2). These data included details of experimental systems, NP source, probe substrate(s) used to test the NPDI, the form of the NP (*e.g.*, extracts and/or as isolated constituents), enzyme/transporter/receptor target(s), induction or inhibition parameter (*e.g.*, K_i, IC_{50}, E_{max}), and the data source. As the function, expression, and tissue distribution of key drug metabolizing enzymes and transporters exhibit known inter-species differences (Baillie and Rettie, 2011), only data from human-derived systems were included in this analysis. Missing elements were summarized as key gaps in the executive summary.

3) Human pharmacokinetic NPDI studies. The third section of the gap analysis consisted of the following data extracted from any report of an in vivo pharmacokinetic study for each constituent of the NP: formulation and route of NP administration, object drug(s), description of the study participants, pharmacokinetic outcome(s), and reference(s). These data were evaluated for gaps, such as unstudied major constituents, unknown pharmacokinetic endpoints, and unstudied interaction targets.

4) Bioanalytical methods. The fourth section of the gap analysis consisted of reports of LC/MS/MS-based bioanalytical method(s) for quantifying NP constituents in human biological matrices, including microsomes, hepatocytes, plasma, and urine. If a large number of LC/MS/MS methods were available for a given NP (*e.g.*, forensic methods for analysis of cannabinoids), the most recent reports (typically within the last five years) were recorded. Data elements collected from each report included the NP constituent(s), the biological matrix analyzed, any other pertinent data such as lower limits of detection, and the reference(s). If methods for some constituents were not found, this gap was noted in the executive summary.

5) Executive summary. Members of the Pharmacology Core compiled the gap analysis for each NP into an executive summary.

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Application of the fulcrum model. Mechanistic and descriptive data gaps from each executive summary were used to populate the fulcrum model (Fig. 3). This qualitative, conceptual decision-making tool was developed to facilitate identification of the final high-priority NPs. For this final triage, NPs with a large number of gaps were eliminated because completing the required *in vitro* and *in vivo* studies during the five-year funding period was not feasible. Conversely, NPs with a small number of gaps were triaged because additional experiments were unlikely to yield novel information. Finally, NPs with unbalanced gap categories were eliminated because (1) the existing evidence could not adequately guide future experiments or (2) at least one of the complementary categories of evidence was not sufficient to substantiate the other. Thus, NPs that balanced the fulcrum with a moderate quantity of gaps in each category were prioritized. A final list of five high-priority NPs emerged from application of this fulcrum model: cannabinoids, goldenseal, green tea, licorice, and turmeric. The first four NPs are currently under evaluation by the NaPDI Center (Kellogg et al., 2017; Tian et al., 2018).

SUMMARY

This NaPDI Center Recommended Approach provides one possible solution to the longstanding question of how to identify high-priority NPs for NPDI studies. The major labor-intensive aspect of this Approach is data extraction from both the primary literature and a curated database. In the future, this process could be partially automated with appropriate database querying methods (Wu et al., 2014). This Recommended Approach also suggests categories of evidence gaps that should be considered essential when evaluating NPs and their individual constituents as potential NPDI precipitants.

Application of this Recommended Approach identified five popularly consumed NPs for which existing evidence is sufficient to guide further investigation and currently warrants reasonable suspicion of clinically significant NPDI liability. Four of these NPs are now the subjects

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of targeted Interaction Projects, which are designed to fill essential scientific gaps related to NPDI potential and, if warranted, conduct clinical pharmacokinetic NPDI studies.

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AUTHOR CONTRIBUTIONS

Contributed to manuscript writing: Johnson, González-Peréz, Lin, McCune, Paine, Rettie, Shen, Tian, Unadkat

Contributed to Recommended Approach strategy: González-Peréz, Lin, McCune, Paine, Rettie, Shen, Unadkat

Participated in data collection: Johnson, González-Peréz, Lin, Paine, Rettie, Tian, Unadkat

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FOOTNOTES

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Reprint requests: Mary F. Paine, RPh, PhD

PBS 341, PO Box 1495

College of Pharmacy

Washington State University

Spokane, WA 99210-1495

Telephone: 509-358-7759

FAX: 509-368-6673

E-mail: mary.paine@wsu.edu

Current Address for EJJ: Providence Medical Research Center, Providence Health Care, Spokane, WA 99204

Current Address for VGP: Office of the Dean of the Graduate School, Princeton University, Princeton, NJ 08544

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FIGURE LEGENDS

Fig. 1. Pathways to drug interaction testing for new chemical entities and natural products. Comparison of drug interaction identification processes for new chemical entities (NCEs) (solid arrows) versus natural products (dashed arrows). Drug interaction testing for NCEs is an early step during preclinical assessment, which includes predicting pharmacokinetic drug-drug interactions using in vitro data and static or dynamic models to guide the need for clinical assessment. In contrast, drug interaction testing for natural products is not required and is typically conducted after case reports of unexpected adverse drug reactions or an unexpected loss of efficacy has been reported in humans.

Fig. 2. The NaPDI fulcrum model: balancing evidence in natural product-drug interaction prediction. A qualitative, conceptual decision tool, termed the fulcrum model, was developed to facilitate selection of the final list of high-priority natural products for drug interaction liability testing by the NaPDI Center. The magnitude of evidence gaps in mechanistic ("M") and descriptive ("D") data categories were balanced against each other. Natural products for which moderate levels of evidence gaps balanced each other were prioritized over those that had too few gaps (small circles), many gaps (large circles), and/or unbalanced gaps.

Fig. 3. Workflow for identifying natural products as high-risk precipitants of pharmacokinetic natural product-drug interactions (NPDIs). An initial list of natural products (NPs) was gathered from *HerbalGram* and the University of Washington Drug Interaction Database. A series of elimination steps were used to triage 42 of these NPs, leaving five for advancement to NPDI studies by the NaPDI Center.

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Table 1. Initial list of 47 candidate natural products to study as precipitants of pharmacokinetic natural product-drug interactions.

Rank	Natural Product	Rank	Natural Product
1	Horehound	25	Chia seed/chia oil
2	Cranberry	26	Turmeric
3	*Echinacea*	27	Maca
4	Black cohosh	28	Fenugreek
5	Flaxseed/flaxseed oil	29	Isoflavones
6	Valerian	30	Ginseng
7	Yohimbe	31	St. John's wort
8	Bioflavonoid complex	32	Green tea
9	Saw palmetto	33	Fennel
10	Ginger	34	Horsetail
11	Aloe vera	35	Tribulus
12	Milk thistle	36	White kidney bean
13	Garlic	37	Evening primrose oil
14	Cinnamon	38	Kelp
15	Rhodiola	39	Gymnema
16	Horny goat weed	40	Grass
17	Ginkgo	-	Berberine
18	Plant sterols	-	Cannabinoids
19	Red yeast rice	-	Feverfew
20	Elderberry	-	Glycyrrhizin
21	Guarana	-	Goldenseal
22	Coconut oil	-	*Shisandra chinensis*
23	Senna	-	Resveratrol
24	Ivy leaf		

Candidates 1-40 were obtained from the 2015 *HerbalGram* report of the top 40 herbal products by sales (Smith, 2015). Candidates without a sales rank were obtained from the University of Washington Drug Interaction Database (DIDB®, 2018).

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Table 2. Precipitant natural product candidates advanced to Phase II (n=23).[d]

Natural Product	Presence of In Vivo Interaction[a] (count)	Absence of In Vivo Interaction[b] (count)	Total In Vivo Interactions (count)	Total In Vitro Targets[c] (count)	Priority Level
Cannabinoids	9	7	16	11	High
Ginseng	5	3	8	5	High
Green tea	5	5	10	13	High
Berberine (from goldenseal)	5	3	8	12	High
Resveratrol	5	0	5	25	High
Garlic	4	9	13	5	High
Glycyrrhizin (from licorice)	3	1	4	14	High
Goldenseal	2	2	4	3	High
Cinnamon	1	0	1	2	High
Red yeast rice	1	1	2	1	High
Turmeric	1	0	1	3	High
Schisandra chinensis extract	1	0	1	1	High
Ginkgo	8	32	40	21	Intermediate
Echinacea	4	15	19	9	Intermediate
Cranberry (juice)	2	10	12	4	Intermediate
Black cohosh	1	5	6	4	Intermediate
St. John's wort	50	27	77	12	Low
Milk thistle (including *Silymarin* and silibinin)	31	17	48	54	Low
Evening primrose oil	1	0	1	0	Low
Echinacea (extract combination)	0	1	1	1	Low
Valerian	0	6	6	7	Low
Saw palmetto	0	6	6	6	Low
Ginger	0	3	3	2	Low

[a]Reports indicating ≥20% change in object drug AUC. [b]Reports indicating <20% change in object drug AUC. [c]Reports of *in vitro* enzyme-, transporter-, or nuclear receptor-mediated interactions (inhibition, induction, or activation). Data were extracted from the University of Washington Drug Interaction Database (DIDB®, 2018) and tabulated. [d]Entries are listed by descending priority level.

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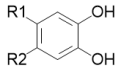
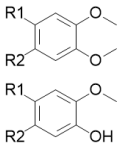
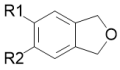
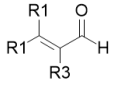
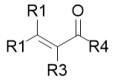
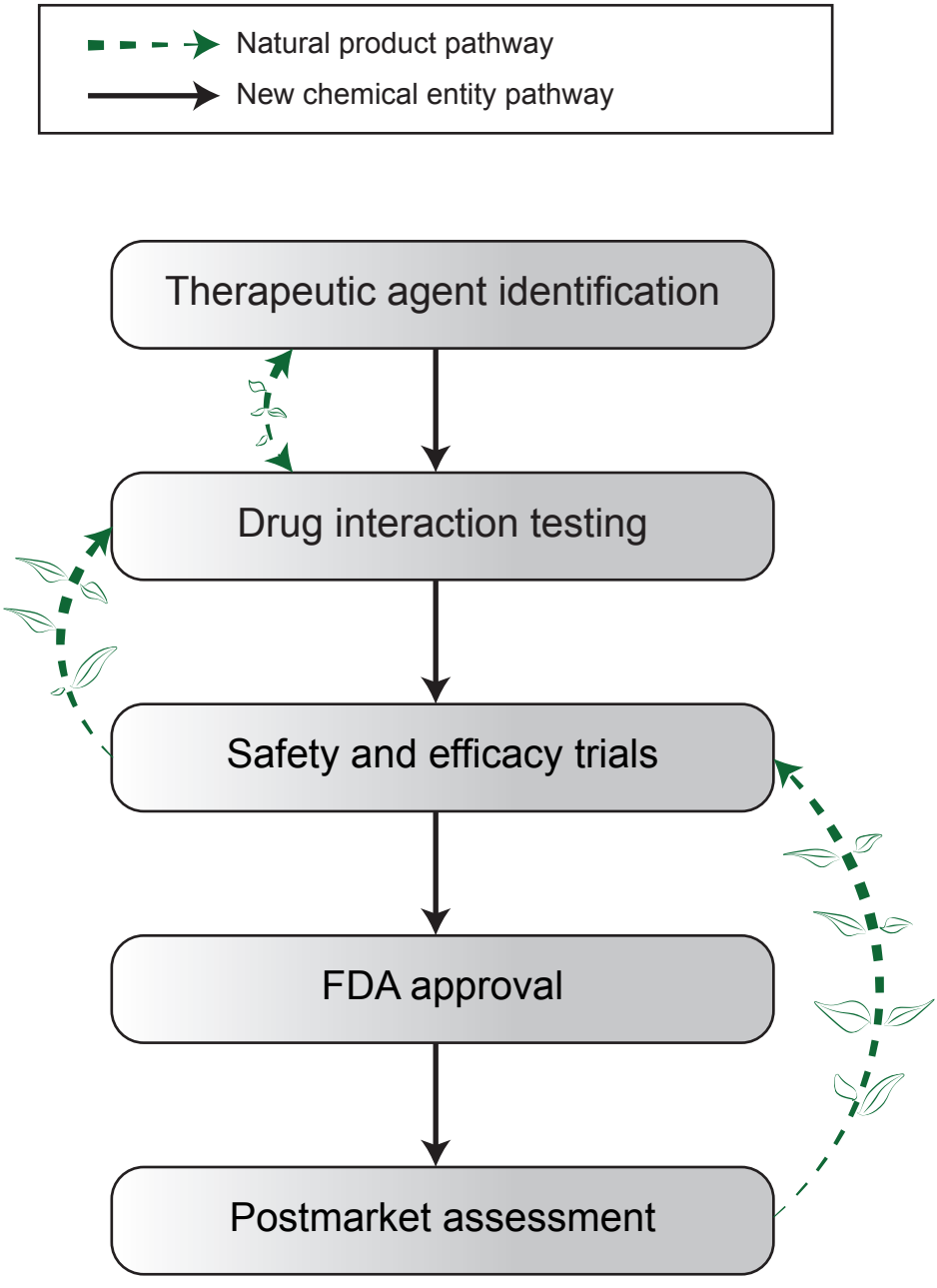
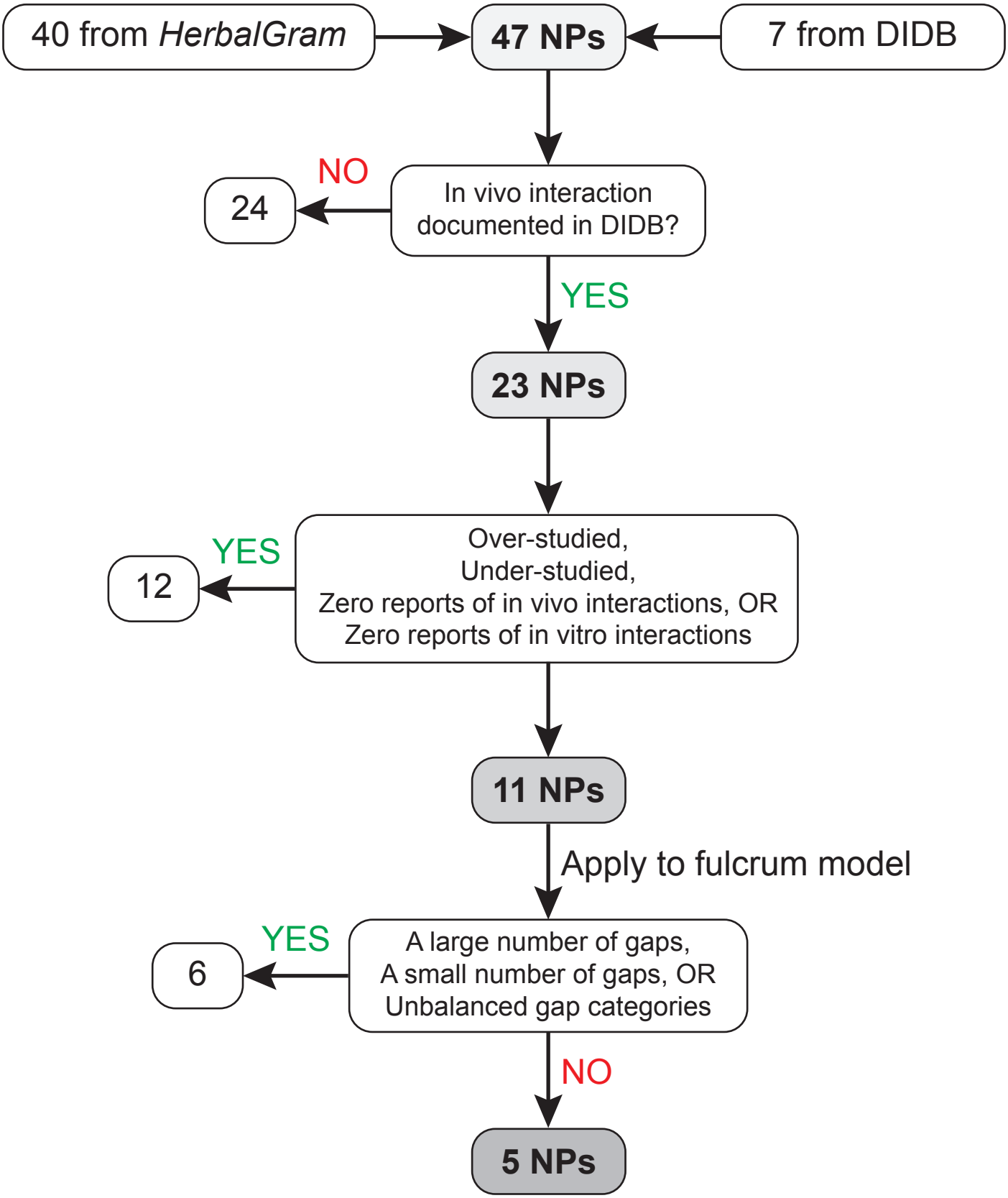
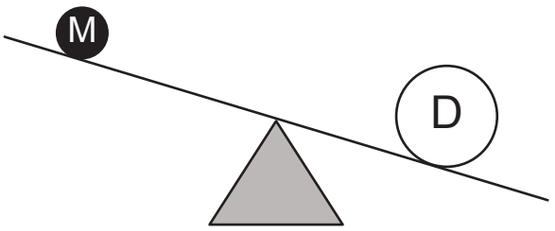
Table 3. Structural alerts for constituents in select natural products.

Constituent(s) / Natural Product	Structural Alert	Alert Substructure
Flavonoids, phenylpropanoids / *Echinacea* Glycyrrhizin, glycyrrhizinic acid / licorice	Catechols	
Isoquinoline alkaloids / goldenseal Terpenoids / cinnamon Curcuminoids / turmeric	Masked catechol	
Isoquinoline alkaloids / goldenseal Shizandrins / *Schisandra spp.* Gomisins / *Schisandra spp.*	Methylenedioxyphenyl	
Cycloartenol / black cohosh	Subterminal olefin	
Polyacetylenes / *Echinacea*	Terminal and subterminal acetylenes	
Terpenoids / cinnamon Diallyl di- and tri-sulfides / garlic	Terminal olefin	
Cinnamaldehyde / cinnamon	α,β-Unsaturated aldehyde	
Curcuminoids / turmeric	α,β-Unsaturated ketone	


Natural product pathway
New chemical entity pathway
Therapeutic agent identification
Drug interaction testing
Safety and efficacy trials
FDA approval
Postmarket assessment


40 from *HerbalGram*
47 NPs
7 from DIDB
NO
24
In vivo interaction documented in DIDB?
YES
23 NPs
YES
12
Over-studied,
Under-studied,
Zero reports of in vivo interactions, OR
Zero reports of in vitro interactions
11 NPs
Apply to fulcrum model
YES
6
A large number of gaps,
A small number of gaps, OR
Unbalanced gap categories
NO
5 NPs



Resveratrol
Schisandra

Unbalanced Minor to Moderate Gaps
- Overstudied
- Preponderence of mechanistic data
- Unlikely to yield substantial or novel NPDI findings

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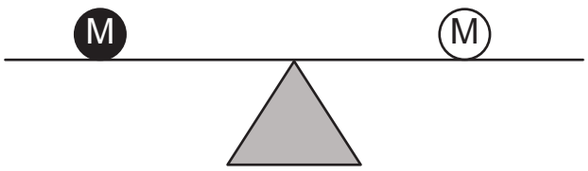
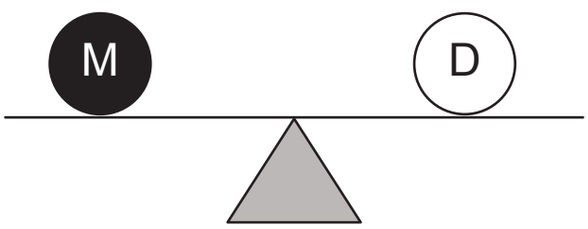


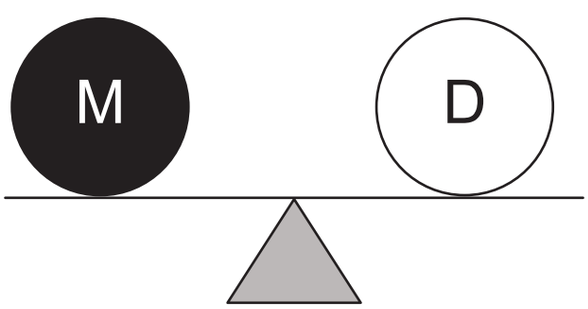
Garlic
Ginseng

Balanced Minor Gaps
- Overstudied
- Minimal evidence of NPDI
- Unlikely to yield substantial or novel NPDI findings



Cannabinoids
Goldenseal
Green tea
Licorice
Turmeric

Balanced Moderate Gaps (High Priority)
- Reasonably studied
- Reasonable mechanistic and descriptive evidence of NPDI
- Required studies feasible during funding period



Cinnamon
Red yeast rice

Balanced Major Gaps
- Understudied
- Minimal evidence of NPDI
- Required studies infeasible during funding period

Legend

M Mechanistic data gaps
D Descriptive data gaps