RECOMMENDED APPROACHES FOR PHARMACOKINETIC NATURAL PRODUCT-DRUG INTERACTION RESEARCH: A NaPDI CENTER COMMENTARY

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Abbreviations: AUC, area under the concentration-time curve for the object drug; AUC_{NP}, AUC in the presence of a precipitating natural product; DME, drug metabolizing enzyme; FDA, United States Food and Drug Administration; NaPDI Center, Natural Product Drug Interaction Center of Excellence; NPs, natural products; NPDIs, pharmacokinetic NP-drug interactions in which the NP is the precipitant and an FDA-approved medication is the object; PBPK, physiologically-based pharmacokinetic

ABSTRACT

Sales of botanical dietary supplements and other purported medicinal natural products (NPs) have escalated over the past ~25 years, increasing the potential for NPs to precipitate clinically significant pharmacokinetic interactions with United States Food and Drug Administration (FDA)-approved medications (NP-drug interactions or NPDIs). Published NPDI studies to date often lack consistency in design, implementation, and documentation, which present difficulties in assessing the clinical significance of the results. Common hurdles include large variability in the admixture composition of phytoconstituents between and within batches of a given NP, limited knowledge on the pharmacokinetics of precipitant NP constituents, and use of animal and/or *in vitro* models which, in some cases, are not mechanistically appropriate for extrapolation to humans. The National Center for Complementary and Integrative Health has created a Center of Excellence for Natural Product-Drug Interaction Research (NaPDI Center) to address these unmet research needs. The NaPDI Center has two overarching goals: 1) develop Recommended Approaches to guide researchers in the proper conduct of NPDI studies, which will evolve over time concurrent with emerging technologies and new research data; and 2) apply the Recommended Approaches in evaluating four model NPs as precipitants of NPDIs with clinically relevant object drugs. The major objectives of this commentary are to 1) explain the rationale for creating the NaPDI Center; 2) describe the Decision Trees developed by the NaPDI Center to enhance the planning, rigor, and consistency of NPDI studies; and 3) provide a framework for communicating results to the multidisciplinary scientists interested in the NaPDI Center's Interaction Projects.

History and unique challenges of pharmacokinetic natural product-drug interactions.

Sales of botanical dietary supplements and other purported medicinal natural products (NPs) in the United States have more than tripled over the past ~25 years since passage of the Dietary Supplement Health and Education Act in 1994, nearing $7.5 billion as of 2016 (Gufford *et al.*, 2014; Smith *et al.*, 2017). Based on the general perception that 'natural' means 'safe,' the lay public often turn to NPs as a means to alleviate self-diagnosed illnesses, allay health care costs, and/or supplement prescribed therapeutic regimens, often without discussing with their health care practitioners (Blendon *et al.*, 2001). Consequently, patients frequently take NPs in conjunction with FDA-approved medications, potentially leading to NPDIs that may alter the safety or effectiveness of conventional medications. Despite considerable investigation, pharmacokinetic elucidation and clinical relevance of many of these complex interactions remain inconclusive (Gufford *et al.*, 2014).

Assessing the risk of NPDIs is more challenging than that of drug-drug interactions. Common difficulties include the large variability in the admixture composition of phytoconstituents amongst marketed products of supposedly the same NP and the relatively scant pharmacokinetic knowledge of precipitant NP constituents (Paine and Oberlies, 2007; Brantley *et al.*, 2014; Gufford *et al.*, 2014). Many purported NPDIs are based on studies with animal and/or *in vitro* models; it is difficult, and often not mechanistically appropriate, to extrapolate results from these preclinical models to humans and assess probable clinical relevance (Gufford *et al.*, 2014). Even when human studies are available, the data often are equivocal or conflicting due in part to 1) variable study design, which ranges from case reports to uncontrolled observational studies to controlled human studies, and/or 2) faulty study design or inadequate methods. Another difficulty is reports of mild to moderate NPDIs, particularly with widely-used drugs, which have unclear clinical significance (National Center for Complementary and Alternative Medicine, 2012) and often lead to the question of whether or not vulnerable sub-populations (*e.g.*, low prevalence genotype carriers, renally- and hepatically-impaired patients,

pregnant women, and elderly or pediatric patients) exist that would be uniquely susceptible to an NPDI. Clear standards for publication of NP-related research, including the NaPDI Center's Recommended Approaches, can mitigate some of these challenges. Such standards should spur other pharmacology journals to consider adopting practices similar to those of the ASPET journals.

Addressing NPDI research challenges. Feasible solutions to the aforementioned challenges of NPDI research are available; however, organized efforts to rally the research community to develop evidence-based, standardized approaches were previously lacking. The National Center for Complementary and Alternative Medicine, Office of Dietary Supplements, and National Cancer Institute jointly sponsored a roundtable meeting of experts and stakeholders on "Dietary Supplement-Drug Interactions" in March 2012 (National Center for Complementary and Alternative Medicine, 2012). The National Center for Complementary and Alternative Medicine (now the National Center for Complementary and Integrative Health or) subsequently put forth a Request for Application in June 2014 to create a Center of Excellence focusing on NPDI research methods; our investigative team was awarded this U54 cooperative agreement in September 2015. The overarching goals of the NaPDI Center are two-fold:

1) Develop a set of Recommended Approaches to guide investigators conducting NPDI research. These approaches are expected to be updated at regular intervals to reflect new research findings based on emerging technologies, including initial lessons learned from the Center's Interaction Projects (described below).

2) Apply the Recommended Approaches toward assessing the potential of four carefully selected NPs to precipitate clinically significant pharmacokinetic interactions with relevant object drugs in model studies referred to as Interaction Projects.

Creation of the Recommended Approaches will ideally lead to consensus on an evidence-based, standardized approach to address the unique challenges of NPDI research. Addressing these challenges requires a multidisciplinary team of clinical pharmacologists, natural products and analytical chemists, and biomedical informaticists.

The NaPDI Center consists of three Scientific Cores (Pharmacology, Analytical, and Informatics), along with an Administrative Core that coordinates activities among the Scientific Cores and liaises between NaPDI Center Investigators and National Center for Complementary and Integrative Health program officials. The Pharmacology Core will 1) use a systematic

evaluative approach to select four NPs as potential precipitants of NPDIs and 2) develop

Statements of Work for a coordinated series of studies, which are guided by evidence-based

Decision Trees, ranging from investigations with human-derived *in vitro* systems to static and

dynamic mathematical modeling to well-designed clinical studies. The Analytical Core will 1)

develop rigorous guidelines for the NP chemistry investigations, focusing primarily on

characterizing and sourcing NPs, and 2) analyze the biofluids (e.g., plasma, urine) obtained

from clinical interaction studies for the precipitant NP constituents and the object drug and its

metabolites. The Informatics Core will 1) create a repository of the data generated from the

Interaction Projects using the most up-to-date open-source technologies and cloud-based

infrastructure and 2) develop a public portal to inform researchers of the NaPDI Center's results.

The Cores will work together to achieve the NaPDI Center's two overarching goals. The main

innovation offered by the NaPDI Center is the combined deployment of state-of-the-art *in vitro*

cell-based assays, pharmacokinetic modeling and simulation, and clinical approaches to

improve NPDI research methods.

Recommended Approaches. There is a range of challenges (Table 1) associated with NPDI research that can best be addressed with evidence-based Decision Trees (Figs. 1-3). These challenges need to be tackled in a variety of ways, spanning from prioritization of which NPDIs should be rigorously evaluated, to NP characterization that accounts for structural isomers and metabolites of phytoconstituents, to only using human-derived *in vitro* systems for screening altered activity of drug metabolizing enzymes or transporters, to necessitating follow-up NPDI studies with narrow therapeutic index object drugs if a clinical NPDI occurs with probe substrates. The list of unique research challenges (Table 1), anticipated Recommended Approaches (Table 2), and Decision Trees (Figs. 1-3) developed by the NaPDI Center to date serve as a roadmap and toolset for addressing key NPDI research needs. Because of the numerous challenges associated with NPDIs, the Tables and Figures present how to address these challenges in various formats to provide a comprehensive overview from the perspective of the challenges (Table 1), the Recommended Approaches (Table 2), and how an individual NP will progress through the Decision Trees (Figs. 1-3).

The first charge of the NaPDI Center was to select and prioritize the NPs to be studied as potential precipitants of NPDIs. A systematic method was developed to identify four priority NPs that will serve as exemplars for the Recommended Approaches (Johnson, 2018). Beginning with a list of 47 commonly used NPs, these four NPs were selected based on existing *in vitro* and clinical data suggesting the potential to precipitate an NPDI. Each identified NP will be entered into the Decision Trees to evaluate the requirements for the Interaction Project.

Upon prioritization and approval of the NPs, the Pharmacology Core will develop detailed Statements of Work for each of the four NPs. These Statements of Work will include a comprehensive literature review and preliminary data to identify the particular needs for NP characterization and sourcing, details about the target drug metabolizing enzyme(s) and/or transporter(s) mediating the potential NPDIs, and, according to the Decision Trees (Figs. 1-3), build the plan for *in vitro* and clinical studies to determine the likelihood of an NPDI.

Evaluation of an Interaction Project begins with Part I of the comprehensive Decision Tree by asking the key question, *"Are the NP constituents commercially available?"* (Fig. 1). If such constituents are available, the Analytical Core will subsequently determine if the NP constituents meet their pre-determined reference standard specifications. If these two criteria are met, the Pharmacology Core will evaluate the available *in vitro* metrics, specifically the inhibition or induction parameters described in the FDA draft guidance on drug-drug interactions (Food and Drug Administration Center for Drug Evaluation and Research, 2017), published in the literature and other publicly accessible sources (e.g., New Drug Applications and medication labels). The Informatics Core will provide input, as necessary, regarding the availability of these data. If such constituents are not commercially available, the Pharmacology Core will work with the Analytical Core to isolate, purify, and scale-up sufficient quantities of the constituents for determination of the *in vitro* metric(s) using relevant human-derived systems. Once robust *in vitro* metrics are obtained, the Interaction Project will be advanced to Part II (Fig. 2).

Part II of the Decision Tree begins with the key question, *"Do in vivo human data exist about the concentrations of the NP constituent(s)?"* If the data do not exist, a 'Phase 0' human pharmacokinetic study involving selected NP formulations and doses will be conducted. The choice of formulation(s) will be decided by the Analytical Core. Once *in vivo* data are obtained, they will be combined with *in vitro* data from Part I and applied to a predictive static model based on an average steady-state concentration of the precipitant NP constituents; alternatively, a dynamic (*e.g.*, physiologically-based pharmacokinetic) model could be developed to simulate multiple NP and drug dosing regimens using the maximum tolerated dose of the NP. Modeling and simulations will be used to predict the likelihood and magnitude of an NPDI (Food and Drug Administration Center for Drug Evaluation and Research, 2017) under two circumstances: 1) if the maximum plasma concentration of one or more NP constituents is near or exceeds the *in vitro* metric (Food and Drug Administration Center for Drug Evaluation and Research, 2017) or 2) if the target drug metabolizing enzyme/transporter is pharmacologically important in the gut

(*e.g.*, cytochrome P450 3A, UDP-glucuronosyltransferase IA, P-glycoprotein, organic anion transporting polypeptide 2B1) (Won *et al.*, 2010; Won *et al.*, 2012) and the estimated gut tissue/lumen concentration is near or exceeds the *in vitro* metric. If an NPDI is predicted, the Interaction Project will be advanced to Part III (Fig. 3).

Part III of the Decision Tree begins with the task, *"Determine the NP dose needed to precipitate an interaction using PBPK modeling and existing in vivo or 'Phase 0' data from Part II."* Once the dose is determined, a clinical NPDI study will be conducted using a probe object drug or cocktail of object drugs. If the magnitude of the NPDI interaction (e.g., ratio of object drug area under the concentration-time curve (AUC) in the presence of the NP to the AUC in the absence of the NP, AUC_{NP} / AUC) is significant (*i.e.*, ≥30% (Food and Drug Administration Center for Drug Evaluation and Research, 2017), a follow-up NPDI study involving a different drug (*e.g.*, one with a narrow therapeutic index) will be considered. If the magnitude of the NP-probe drug interaction is not significant, PBPK modeling and simulation may be used to further assess the likelihood of a clinically significant NPDI in the following situations: a narrow therapeutic index object drug, human subjects carrying clinically important drug metabolizing enzyme/transporter pharmacogenetic variants, or vulnerable sub-populations. If the modeling and simulation suggest a clinically significant NPDI is likely, follow-up clinical studies with a different object drug or within different patient populations will be considered. All data generated from the Interaction Projects will be organized and archived into a repository that is publicly accessible through a web-based public portal created by the Informatics Core.

Future Directions. The NaPDI Center's Recommended Approaches for NPDI research are working documents that should be updated as new information comes forth from ongoing Interaction Projects and any ensuing studies. Priority and emphasis of NPDIs also will need re-considerations with major shifts in the dietary supplement and herbal product markets and changes in standard guidelines for the prescribing and use of the involved medications. As sales of NPs continue to increase annually, the NaPDI Center will continually strive to provide evidence-based recommendations that balance the risks of drug interactions against the benefits of NP.

AUTHORSHIP CONTRIBUTIONS

Wrote the manuscript: McCune, Paine, Shen

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FOOTNOTES

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FIGURE LEGENDS

Fig. 1. Decision Tree, Part I: Addressing challenges 1-3, 5-6 (Table 1). DME, drug metabolizing enzyme; NP, natural product; NPDI, natural product-drug interaction.

Fig. 2. Decision Tree, Part II: Addressing challenges 3-5 (Table 1). DME, drug metabolizing enzyme; NP, natural product; NPDI, natural product-drug interaction. PK, pharmacokinetic; PBPK, physiologically-based PK.

Fig. 3. Decision Tree, Part III: Addressing challenges 1 and 3-6 (Table 1). AUC, area under the concentration vs. time curve of the object drug; AUC_{NP}, AUC in the presence of the natural product; IC_{50}, the concentration of an inhibitor that reduces the velocity of the reaction by half at a single substrate concentration; NP, natural product; PBPK, physiologically-based pharmacokinetic.

Table 1. Unique challenges of NPDI research that will be addressed using the Recommended

Approaches (RA; Table 2) and Decision Trees (Figs. 1-3).

Challenge unique to NPDI research	RA	Decision Tree
1. NP characterization should account for structural isomers and metabolites of phytoconstituents.	2, 6	I
2. Human-derived *in vitro* systems should be used for screening drug metabolizing enzyme (DME) or transporter inhibition and induction by NP.	1, 3, 6	I
3. *In vitro* screening of isolated individual phytoconstituents and their admixture should be considered; identification of marker constituents predictive of the complex NP mixture would streamline pharmacokinetic modeling and simulations.	1, 2, 3, 5, 6	I
4. Positive controls should be included during both in vitro screening and the design of clinical NPDI studies to serve as benchmarks for judging NPDI magnitude.	3, 5	I, III
5. Clinical pharmacokinetic profiling (*e.g.*, bioavailability, metabolites) of key phytoconstituents should inform the screening strategy; interactions in the gut should be considered for phytoconstituents not available systemically.	3, 4, 5	II
6. The clinical NPDI study should consider chronic dosing of NP to assess induction and/or accumulation of precipitating constituents with long elimination half-lives.	3, 4, 5	II

7. Systemic exposure to NP constituent metabolites (particularly conjugated metabolites) should be assessed in the clinical NPDI study.	1, 4, 5	II, III
8. The clinical NPDI study should assess clinical relevance by considering the NP formulation and bioactive dose and identifying vulnerable sub-populations with covariates (genotypes, organ dysfunction, disease states, *etc.*).	1, 2, 5, 6	III
9. Additional clinical NPDI studies involving specific drugs (*e.g.*, drugs with narrow therapeutic indices) should be considered if the clinical NPDI study involving phenotypic probe(s) as the object drug(s) indicate a significant DME- and/or transporter-mediated interaction.	1, 4, 5, 6	III

NP, natural product; NPDI, NP-drug interaction

Table 2. Anticipated Recommended Approaches (RAs) for NPDI research, listed in the order by which an NP would move through the Decision Trees. Table 1 lists the challenges unique to NPDI research that will be addressed in the respective RA.

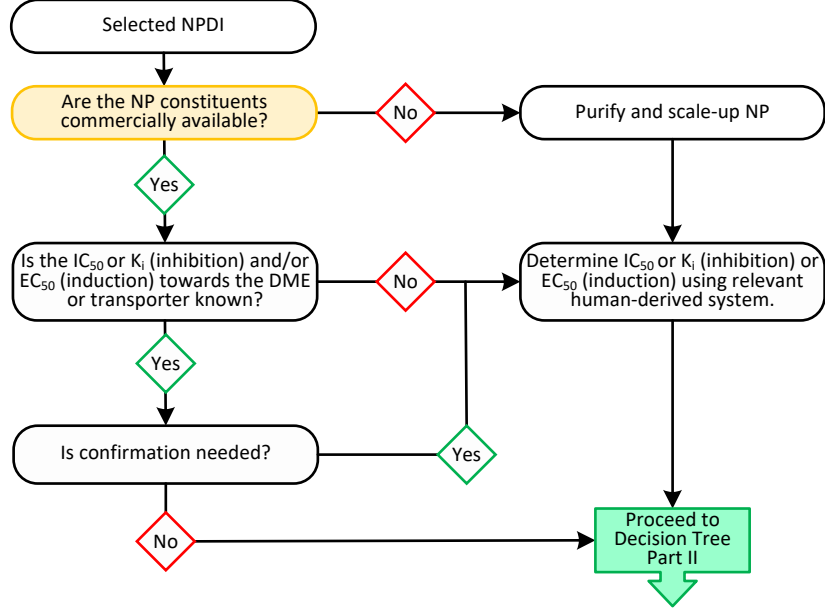| RA	Short Description	Addresses NPDI challenges
1	Selection of priority NPs for evaluation as potential precipitants of NPDIs	2-3, 7-9
2	Identification and characterization of optimal NP study materials for NPDIs	1, 3, 8
3	Evaluation of a potential NPDI using static and dynamic pharmacokinetic modeling of data obtained from *in vitro* systems and human pharmacokinetic studies	2-6
4	Design of "Phase 0" studies to understand NP constituent pharmacokinetics to inform design of a clinical NPDI study	5-7, 9
5	Design of clinical NPDI studies using appropriate NP formulation, object drug(s), and human subject group(s)	3-9
6	Design and creation of a data repository and public portal of the NaPDI Center's NPDI data for access by researchers	1-3, 8, 9

NP, natural product; NPDI, NP-drug interaction

Fig. 1

Fig. 2

Fig. 3

Determine NP dose needed to cause an interaction using PBPK modeling and existing *in vivo* or Phase 0 study from Part II

Conduct clinical interaction study using probe object drug (or cocktail)

Is the magnitude of the interaction (AUC_{NP} / AUC) significant?

Yes → Is the magnitude of the interaction clinically meaningful? → Yes → **Conclude clinical interactions are possible**

No → PBPK modeling and simulation

Narrow therapeutic index drugs

Pharmacogenetic considerations

Vulnerable populations

Is an interaction predicted?

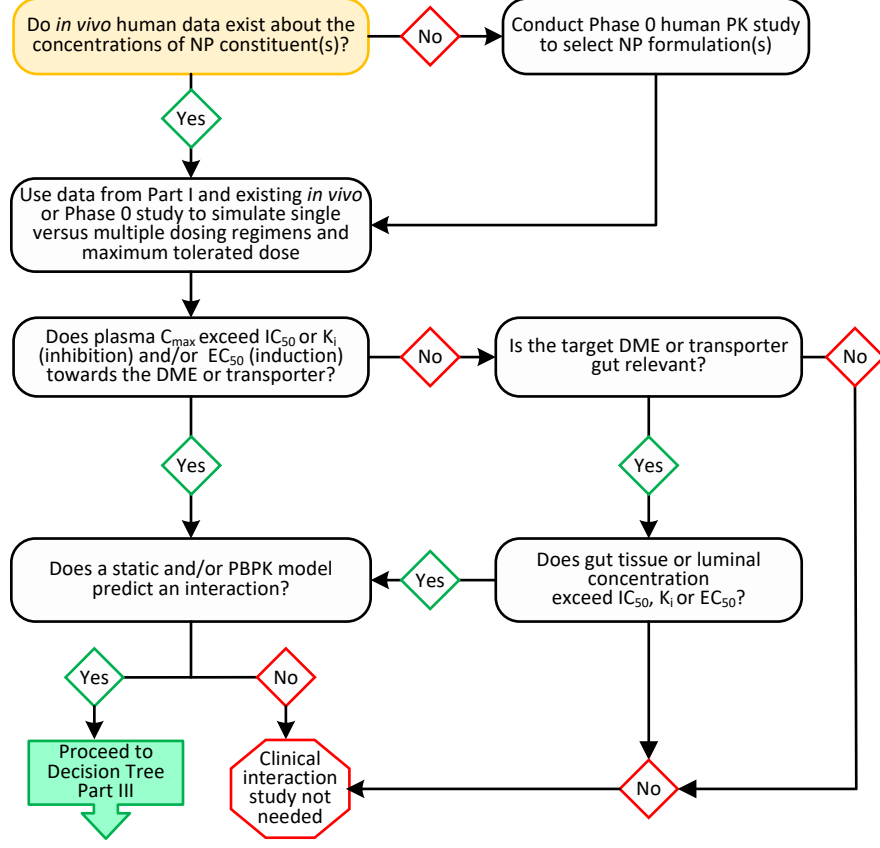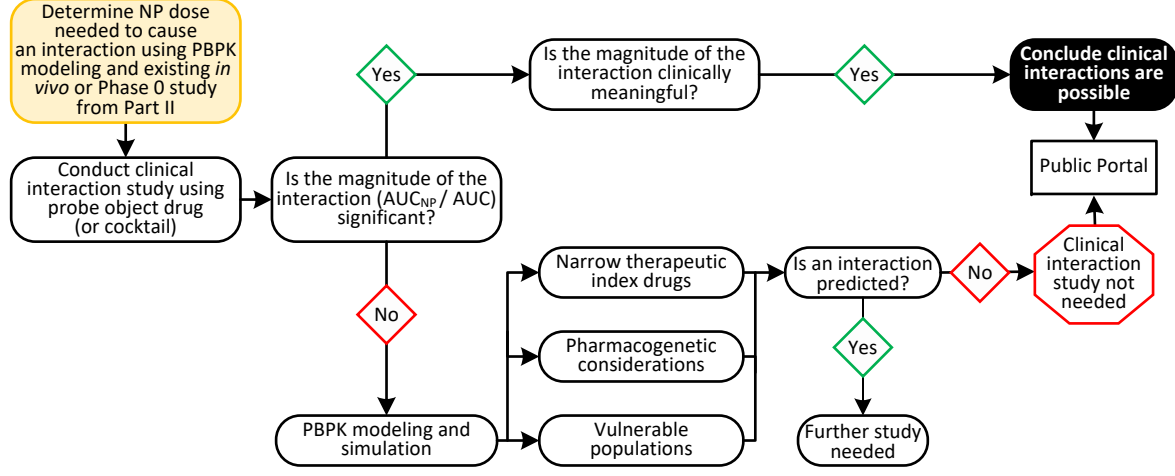No → Clinical interaction study not needed → Public Portal

Yes → Further study needed

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