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Workshop report

Assessing Natural Product–Drug Interactions: An End-to-End Safety Framework

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ABSTRACT

The use of natural products (NPs), including herbal medicines and other dietary supplements, by North Americans continues to increase across all age groups. This population has access to conventional medications, with significant polypharmacy observed in older adults. Thus, the safety of the interactions between multi-ingredient NPs and drugs is a topic of paramount importance. Considerations such as history of safe use, literature data from animal toxicity and human clinical studies, and NP constituent characterization would provide guidance on whether to assess NP-drug interactions experimentally. The literature is replete with reports of various NP extracts and constituents as potent inhibitors of drug metabolizing enzymes, and transporters. However, without standard methods for NP characterization or *in vitro* testing, extrapolating these reports to clinically-relevant NP-drug interactions is difficult. This lack of a clear definition of risk precludes clinicians and consumers from making informed decisions about the safety of taking NPs with conventional medications. A framework is needed that describes an integrated robust approach for assessing NP-drug interactions; and, translation of the data into formulation alterations, dose adjustment, labelling, and/or post-marketing surveillance strategies. A session was held at the 41st Annual Summer Meeting of the Toxicology Forum in Colorado Springs, CO, to highlight the challenges and critical components that should be included in a framework approach.

1. Introduction

Sales and usage of herbal products and other dietary supplements in Western countries including the United States and Canada, continues to increase across all age groups (CRN, 2014; US CDC, 2014; Smith et al., 2015). Individuals in these countries also have access to conventional medications, and polypharmacy is often observed, particularly in women and older adults (Djuv et al., 2013; Farina et al., 2014). Many patients are reticent to disclose natural product (NP)[1] usage to their healthcare providers, and many providers still do not inquire of their patients about such usage. Conversely, many healthcare providers are recommending alternative and/or complimentary NPs to counteract side effects of some drugs (Reddy, 2014). Thus, the potential for NP-drug interactions is high, and in many cases may be ignored in clinical practice because of the complexity of the problem.

Abbreviations: CYP450, cytochrome P450; Cmax, maximum concentration; DDI, drug–drug interactions; MDP, methylenedioxyphenyl; NP, natural products; PBPK, physiologically-based pharmacokinetics; UGT, UDP-glucuronodyl transferase; SCCH, sandwich-culture human hepatocytes.

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[1] The term "natural product(s), (NP(s))" will be used throughout this article and encompasses some country-specific and regional terms such as "dietary supplements", "nutraceuticals", "natural health products", "herbal/botanical products", "traditional medicines", "alternative/complimentary medicines", etc. In this manuscript, NP refers to products/ingredients used for non-nutritive health benefits such as prevention or treatment of health conditions.

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To further exacerbate the situation, individuals are faced with numerous reports in the popular media of potentially serious interactions between NPs, particularly prevalent dietary ingredients and supplements and conventional medicines. In parallel, healthcare providers seeking information in the scientific literature on the drug interaction potential of various natural ingredients may be discouraged with the lack of clinical relevance presented by most studies. The number of scientific literature reports related to NP-drug interactions has increased substantially in the past decade. The majority of these reports involve the use of *in vitro* systems such as hepatic microsomes or S9 cytosolic fractions, which alone may provide an overly conservative estimate of interaction potential. Follow-up studies are rarely performed to better predict clinical relevance; even if data are available, inconsistencies often exist for a particular ingredient across *in vitro*, *in vivo* animal, and/or clinical studies. For example, Won et al. reviewed a number of NP-drug interactions in which both *in vitro* and clinical data exist, and in many cases there was no correlation of findings (Won et al., 2012). In addition, there is sometimes poor analytical characterization of the natural materials used, contributing in large part to inconsistent findings across studies. Thus, it is not surprising that some have suggested that concerns related to NP-drug interactions may be exaggerated. To fully address the public's concern related to potentially serious interactions will require a sound scientific approach.

Various NPs, including dietary supplements in the U.S., are not subject to the same FDA regulatory guidelines for pre-market testing as prescription medicines. However, because there is no standard or systematic regulatory guidance on testing for NP-drug interaction potential, the scientific community has the opportunity to establish a set of best practices, or framework approach for conducting these assessments. Examples of key components that should be considered in such a framework relative to any particular NP ingredient(s) include its history of use, literature data, robust analytical characterization, and dose formulation characteristics. Follow-up studies may be warranted after review of data and information obtained from these various components. When testing is warranted, we can borrow where relevant, from the drug–drug interaction (DDI) guidances available for prescription medicines (FDA, 2012; European Medicines Agency, 2012). For example, intestinal and hepatic *in vitro* systems can be used to assess potential NP-drug interactions. Data from these studies can be incorporated into physiologically-based pharmacokinetic (PBPK) models to help forecast clinical relevance, and/or design clinical studies to further investigate interaction potential. Additionally, data could be utilized to perform formulation adjustments in specific NP ingredient content, provide labelling information, and guide monitoring for post-marketing signals related to NP-drug interactions in the marketplace. The remaining sections of this workshop report detail various components of a proposed framework approach for assessing NP-drug interactions.

2. Pre-clinical considerations

As with DDIs, mechanisms underlying NP-drug interactions can be pharmacokinetic, pharmacodynamic, or both. Pharmacokinetic mechanisms are the most extensively studied, of which inhibition of the pre-systemic and/or systemic metabolism of the 'victim' drug by one or more 'perpetrator' NP constituents predominates (Gurley, 2012; Gurley et al., 2012; Shi and Klotz, 2012). Pharmacokinetic NP-drug interactions pose challenges beyond those for DDIs because unlike drug products, NPs typically are mixtures of multiple constituents varying in quantity and identity, both between manufacturers and between batches from a single manufacturer (Brantley et al., 2014; Gufford et al., 2014; Markowitz and Zhu, 2012). In addition, because NPs are not regulated in the same manner as drugs, neither the pharmaceutical nor NP industry has incentive to assess the drug interaction liability of a given NP. Consequently, harmonized approaches to evaluate the magnitude and likelihood of NP-drug interactions remain nonexistent. The immense chemical diversity of NP constituents and ever-increasing number of diverse drug candidates further highlight the need for an efficient, systematic, and adaptive approach to evaluate potential NP-drug interactions. An integrated *in vitro-in silico-in vivo* approach involving human-derived *in vitro* systems, static and dynamic modeling, and proof-of-concept clinical studies provides a mechanistic framework to address these challenges.

As aforementioned, NPs consist of multiple constituents, which can alter drug disposition by multiple mechanisms. Inhibition of drug metabolizing enzymes, particularly the CYPs, has been investigated extensively (Gurley, 2012; Gurley et al., 2012; Brantley et al., 2013, 2014, 2010). Because NP constituents frequently are polyphenolic (e.g., some flavonoids, flavonolignans, curcuminoids, and ellagitannins), they are subject to extensive UDP-glucuronosyl transferase (UGT)-mediated metabolism in both the intestine and liver. As such, it follows that these constituents could alter drug disposition by inhibiting the UGTs, particularly those in the intestine, as this organ represents the first barrier to oral xenobiotic entry. Indeed, inhibition of intestinal UGT-mediated NP-drug interactions has not been evaluated rigorously in humans. Silibinin, a semi-purified extract of the popular herbal product, milk thistle (*Silybum marianum*), was selected as an exemplar NP to test this hypothesis due to reported *in vitro* inhibitory potency towards UGTs and the well-characterized nature of its constituents, the flavonolignans, silybin A and silybin B (Gufford et al., 2014; Sridar et al., 2004). Raloxifene, a selective estrogen receptor modulator, was selected as a clinically relevant victim drug due to an extremely low oral bioavailability (2%) resulting from extensive UGT1A-mediated first-pass metabolism in the intestine.

The saturation kinetics of raloxifene 4′- and 6′-glucuronide formation and inhibition kinetics of silibinin, silybin A, and silybin B towards raloxifene glucuronidation were recovered using human intestinal microsomes, human liver microsomes, and human embryonic kidney-overexpressing UGT1A1, UGT1A8, and UGT1A10 cell lysates (Gufford et al., 2015). The recovered parameters (Vmax, Km, Ki) were incorporated into a mechanistic static model, which suggested moderate to high clinical interaction risk according to regulatory guidances (FDA, 2012; European Medicines Agency, 2012). PBPK models were next developed using two platforms: the differential equation solver, Berkeley Madonna™ (v8.3; University of California at Berkeley, Berkeley, CA), and the population-based simulator, Simcyp® (v13.2; SimCYP Limited, Sheffield, UK). The Berkeley Madonna™ model predicted a 30% increase in the maximum concentration (Cmax) and area under the concentration–time curve (AUC) of raloxifene (60 mg) in the presence compared to the absence of silibinin (480 mg Siliphos® 3 times daily × 4 days) with minimal change in terminal elimination half-life (<3%). In contrast, the Simcyp® model predicted negligible changes (≤5%) in these pharmacokinetic outcomes. A proof-of-concept clinical study was designed to evaluate model performance. Healthy adult volunteers (8 men, 8 women) were enrolled to participate in an open label, single dose, randomized, two-period crossover study. Clinical study results will be used to assess not only model performance but also to refine the model and enhance predictive power (i.e., 'learn and confirm').

In summary, an integrated *in vitro-in silico-in vivo* approach was applied to an uncharted mechanism underlying NP-drug interactions in humans. This approach should prove useful in the evaluation of alternate combinations of NP perpetrators and drug victims, particularly for xenobiotics cleared predominantly by