**Summary of**

**Roundtable Meeting on**

# Dietary Supplement-Drug Interactions

March 27, 2012

Neuroscience Building
6001 Executive Boulevard, Room D
Rockville, Maryland

## PREFACE

This summary of the Roundtable Meeting on Dietary Supplement-Drug Interactions was prepared by the National Center for Complementary and Alternative Medicine (NCCAM), with JB Management Solutions, LLC, under contract no. HHSN263201100036I. The statements, conclusions, and recommendations contained in this document reflect both individual and collective opinions of the meeting participants and are not intended to represent the official position of the National Institutes of Health or the U.S. Department of Health and Human Services.

We at NCCAM would like to extend our sincere thanks to the panel members for generously contributing their time and expertise to these deliberations. We also appreciate the support of the National Cancer Institute (NCI) and the Office of Dietary Supplements (ODS) for their co-sponsorship and participation in this workshop. Lastly, we are extremely grateful to the members of the planning committee for all of their hard work in organizing this meeting.

## SUMMARY OF THE ROUNDTABLE MEETING

On March 27, 2012, NCCAM of the National Institutes of Health (NIH) held a "Roundtable Meeting on Dietary Supplement-Drug Interactions." The meeting was cosponsored by NCCAM, ODS, and NCI. Craig Hopp, Ph.D., program officer in the NCCAM Division of Extramural Research, served as chair.

The Roundtable Meeting brought together researchers and other experts on dietary supplements (including herbs, botanicals, and other supplements) and drugs to discuss outcomes, methodologies, the state of the research, and prioritization of a research agenda. The event comprised five thematic sessions; with four including presentations by one or two NIH-funded researchers (see Appendix A). Selected PubMed citations for speakers' major points are provided when available and are referenced in Appendix B.

### Background

NIH has supported a number of studies on interactions between natural products and drugs, recognizing the potential for, and importance of the consequences of, such interactions. Numerous surveys have found that many people take multiple dietary supplements and drugs together, which can produce adverse clinical effects and events.[1-3] The potential for natural products to influence the metabolism and disposition of drugs—e.g., anticoagulants, immunosuppressants, psychiatric medications, and oral contraceptives—has been recognized for decades, with St. John's wort and grapefruit juice as two prominent examples. In most studies, only about 30 to 40 percent of patients who use natural products as complementary health approaches reveal that use to their health care providers.[4, 5] This is a major driver behind NCCAM's "Time to Talk" educational campaign. Rigorous research is needed to yield further information on supplement-drug interactions, for purposes of safety. In addition, there have been lines of research suggestive of beneficial supplement-drug interactions—e.g., in chemoprevention, chemotherapy, and radiation therapy in cancer.

The Roundtable Meeting opened with welcomes to the members from Josephine P. Briggs, M.D., NCCAM Director; Paul Coates, Ph.D., ODS Director; and Jeffrey White, M.D., Director of the Office of Cancer Complementary and Alternative Medicine, NCI. Dr. Hopp provided the workshop overview and charge.

### Session I: Obstacles to Dietary Supplement-Drug Interaction Research

*Moderator: Craig Hopp, Ph.D., NCCAM*

### Presentation 1: Evaluation of Dietary Supplement-Drug Interactions: Limitations of *In Vitro* Methods

John Markowitz, Pharm.D., University of Florida

Natural products are complex, with multiple active constituents in each of at least 1 dozen major categories. This adds to the difficulty of *in vitro* screening for drug interactions.[6, 7] The

current research model for natural products, which parallels that of drug development, is mostly followed, and it was described.[6] Supplement-drug interactions can be of minor, moderate, or major clinical significance. Those of major significance are relatively rare; a larger concern is those of moderate significance that go unrecognized. While formal, normal-volunteer studies offer the most rigorous design for assessing these interactions, *in vitro* studies have predominated.

In choosing the bioassay, *ex vivo* may be most appropriate when measuring some pharmacodynamic interactions. In terms of *in vitro* systems for predicting metabolic clearance, liver microsomes, S9 fraction, and hepatocytes each have advantages and disadvantages.

The advantages of *in vitro* methods for screening for potential herb-drug interactions include that they are non-invasive, high-throughput, and relatively cost-effective and quick; present no risk to human subjects; can be carried out in most laboratories; and allow a specific mechanism to be evaluated in a controlled system. In principle, one can also forecast an interaction's magnitude. These methods also have many limitations and challenges that impact study design and interpretation.[8] They include:

- Natural products' complexity and variability, compared to drugs
- A lack of well-characterized pharmacokinetics (PK) and metabolites for most phytoconstituents
- Assignment of relevant hepatic concentrations of phytoconstituents
- The need to account for many factors—e.g., bioavailability, distribution, first-pass metabolism, and active-but-poorly-characterized metabolites
- A lack of authentic analytical standards, in many cases
- The difficulty of screening botanicals as mixtures to even somewhat approximate typical ingestion scenarios
- Solubility problems with botanicals.

In *in vitro* studies and bioanalysis, researchers need to be aware of the relative contributions of stereoisomers, including poorly characterized phytoconstituents that are present as isomers. Two examples were given of disparate effects, not only therapeutically but in terms of interactions, from isomers in the medicinal plants cinchona and milk thistle.[9, 10] Assessing all isomers for potential therapeutic and undesirable effects may be required.

An *in vitro-in vivo* disconnect exists with many natural products. *In vitro* methods are a powerful and cost-effective tool for initial screening procedures and other applied experiments. But, there are limitations in what can be learned, and the results must be placed in context with multiple factors such as therapeutic area and index, and administration route. Any appearances of metabolic inhibition or induction *in vitro* require confirmatory clinical studies in normal volunteers.

**Presentation 2: Evaluating the Clinical Relevance of Drug-Interaction Study Designs**

Bill Gurley, Ph.D., University of Arkansas for Medical Sciences

Three major categories of studies in this area exist—*in vitro,* animal, and clinical—each with advantages and disadvantages. Discerning the clinical relevance of studies can be confusing, often because many variables can affect outcomes. Recognizing those variables and incorporating proper controls may improve results and interpretation.

Dr. Gurley provided a brief overview of some known interactions and risks, e.g., St. John's wort interacting with cyclosporine and the risks to transplant patients[11], and of the biomedical literature in this area. The most-studied interactions are those having a PK mechanism via: (1) drug absorption, distribution, metabolism, and excretion (ADME); (2) modulation of drug-metabolizing enzymes in the liver and small intestine; or (3) modulation of drug-transporting proteins (transporters) in sites such as the small intestine, liver, and blood-brain barrier.

The most comprehensive means for discerning a potential interaction is *in vitro* screening followed by clinical studies to determine the existence and clinical significance of the interaction. Clinical studies address the shortcomings of *in vitro* and animal studies, and are the definitive assessment approach. Their disadvantages include cost, the significant resources and time that must be devoted to compliance monitoring, and possible difficulty in determining the underlying mechanism and specific phytochemicals involved. Their most typical design is a prospective, randomized crossover design, using patients and/or healthy volunteers who are not blinded. Often, one can observe induction only after multiple (vs. single) doses, and multiple dosing is desirable when studying several botanicals. Dr. Gurley's other recommendations with respect to design included:

- Participants' age, ethnicity, phenotype (e.g., extensive or poor metabolizer), medications, natural-product intake, smoking status, and dietary factors should all be considered.
- Characterize the dosage form for content and performance, including its dissolution profile and that of any marker compounds. Have product content independently verified by a laboratory; do not go by labels.
- Measure metabolic ratios; one benefit is to prevent participants' having to provide multiple blood samples.
- Include known CYP/transporter inducers and inhibitors (examples include rifampin and quinidine).
- Compare the phenotypic metabolic ratios of the probe drug and the intervention, especially if studying several botanicals.
- An appropriate washout period between active phases is 30 days.

Dr. Gurley presented examples of work by his team, including on (1) dissolution profiles of different formulations of goldenseal and kava;[12] (2) the effects of long-term supplementation of

goldenseal, black cohosh, kava kava, or valerian on activity of four CYP substrates, ultimately in terms of these botanicals' potentials to interact with drugs;[13] and (3) the effects of St. John's wort and Echinacea on the PKs of digoxin.[14] The latter illustrated how the dosages of different substances that are required to produce a similar effect can be different to a clinically significant degree.

**Session I Discussion** included suggestions to:

- Use a 30-day washout period for crossover studies of multiple botanicals.
- Qualify chemical profiles in systemic circulation.
- Perform more research on herb-drug interactions in elderly people.
- Explore whether a BCS-type system could be used to classify botanicals.
- Acidify and quickly freeze samples when they are drawn; this will make any future analyses easier.
- Develop a questionnaire for clinical study participants that asks about botanicals and yields data that could be applied in future studies with leftover samples.
- Perform genetic testing of study participants, especially when using repeat subjects in a study. Variable bioavailability affects transporters, which are genetically regulated.

**Session II: Roundtable Discussion on Improved Methodology**

*Moderator: Shiew-Mei Huang, Ph.D., U.S. Food and Drug Administration (FDA)*

Dr. Huang provided some background on the FDA's recent guidance for industry on drug interaction studies.[15] She noted that the FDA is favoring the use of dynamic, physiologically based PK models that consider enzymes, changes in population, age groups, etc., and allow examination of many system components. These models should be considered applicable to dietary supplements, while also posing challenges. At times, the FDA will label an interaction in the absence of a clinical study, if transporter and metabolism information is readily understood. Dr. Huang commented that her agency considers information on supplement-drug interactions to be vitally important. Furthermore, she requested feedback regarding whether or not the FDA should consider labeling foods and supplements, as it does for drugs, to alert the public about potential interactions.

*Roundtable Question 1: Are there any computational, i.e.,* in silico*, methods that can be employed to study interactions?*

Comments included that *in silico* is good technology, but many of its advocates also sell it, and thus one must be attentive to conflicts of interest. While there is potential for these methods, the amount of information that must be entered to adequately predict outcomes diminishes their value.

*Question 2: Does high throughput screening offer any insight into possible clinical drug interaction?*

Comments included that the human hepatocyte model is a good one with human tissue, and a reasonable procedure (including in cost) for screening many potential inducers. Even though many false positives will occur, the results can form the start of a database. If a response is seen using this method, a clinical study can then be performed.

*Question 3: How can we make animal models more predictive?*

Due to unavoidable differences in metabolic pathways between most animals and humans, using these models does not provide additional information that can be used in prioritizing specific combinations for clinical studies. The panel reached consensus that animal models have value, but are not predictive.

**Session II Discussion** comments included:

- NCCAM and other entities should consider investing in the determination of bioavailability levels for various substances. If very little of a supplement actually reaches systemic circulation, then preclinical studies become less relevant.
- Both induction and inhibition must be studied at the same time for a study to have predictive value.
- It was expressed that, although dietary supplement manufacturers are required to alert the FDA if they receive notification of an adverse event related to their products, sponsors would not likely provide evidence of interactions to the FDA. Doing so would not benefit the manufacturer.

**Session III: Pharmacokinetic Interactions**

*Moderator: Joseph Betz, Ph.D., ODS*

**Presentation 1: Predicting and Interpreting Drug Interactions with Nutrients and Natural Products**

David Greenblatt, M.D., Tufts University School of Medicine

Predicting and interpreting interactions between drugs and nutrients and/or fruit juices follow the same principles as for herbal products. Animal models are of little value, given numerous biological differences that are important in this topic area. There is often an *in vitro-in vivo* disconnect. In addition, many FDA guidelines for *in vitro* drug data do not translate well to nutrients and natural products.

In one study, Dr. Greenblatt's team evaluated *in vitro* and *in vivo* whether cranberry juice or brewed tea potentiated warfarin, via enzyme CYP2C9. As a substitute for warfarin, which is difficult to study in the United States, they employed flurbiprofen. They found that cranberry juice and tea impaired CYP2C9 activity *in vitro*, but none of the beverages affected CYP2C9's clearance of flurbiprofen in the clinical study. Thus, they concluded a PK interaction with

warfarin would be highly unlikely.[16] In the 10 years since this study, despite anecdotal reports to the contrary, numerous other controlled studies have also shown that cranberry juice does not meaningfully alter CYP2C9 phenotype or warfarin anticoagulation. Dr. Greenblatt noted he learned that using a positive control—here, fluconazole—is important.

One reason for the failure of many *in vitro* predictions arises from special characteristics of the human metabolic profile and rate for many natural products. One major issue is that *in vitro* studies are generally performed with aglycones; *in vivo*, however, methyl and sulfate conjugates from glycone are ultimately what reach the liver and systemic circulation, and are largely inactive. The ultimate question becomes, "What and how much does an enzyme see?"

Some enzymes, such as CYP3A, interact with drugs in the gastrointestinal (GI) tract as well as the liver. Dr. Greenblatt's team performed a controlled clinical study on the effects of furanocoumarins (FCs) in grapefruit juice on a CYP3A substrate, midazolam.[17] They found impairment of the enteric, but not hepatic, phase of presystemic extraction. Inhibition of CYP3A by grapefruit juice is irreversible. He noted that different results can be obtained from different levels of exposure (e.g., the amount of juice given and its concentrations, including of FCs) and different product-storage temperatures, which affect potency.

Dr. Greenblatt offered, as some other lessons learned, that *in vitro* studies of supplement-drug interactions may be misleading, as animal studies may be; clinical anecdotes have no worth for assigning cause and effect; and clinical PK studies are needed to answer these questions. Researchers who suspect an interaction need to answer three key questions:

1. Is it real?
2. If there is an interaction, how big is it?
3. Is it clinically important?

Even if an interaction meets the FDA's no-effect criteria, that does not mean that it is not important; for some drugs, even a very small level of interaction is important. In addition, statistical significance does not equal clinical importance. One must bring in supplemental data—e.g., on a particular population—to make that determination.

**Presentation 2: Transport-Mediated Dietary Supplement-Drug Interactions**

Reginald Frye, Pharm.D., Ph.D., FCCP, University of Florida College of Pharmacy

Drug transporters have recently emerged as an important factor in drug disposition and response. They control influx and efflux of endogenous and exogenous compounds and are widely expressed in the body, including in the intestines, liver, kidneys, and blood-brain barrier. Manipulating them will modulate drug content in the bloodstream. The two major types of transporters are:

- Efflux transporters or ATP-binding transporters. Examples include multidrug resistance proteins (e.g., P-glycoprotein, or P-gp, which is the most widely studied transporter and mediates many drug interactions); multidrug resistance-associated proteins (MRPs); and breast cancer resistance protein (BCRP). Inhibiting them will increase bioavailability.

- Uptake or solute-carrier transporters, which control influx. Examples include organic anion-transporting polypeptides (OATPs), organic cation transporters (OCTs), and organic anion transporters (OATs). They facilitate drug entry into the liver and intestine. Inhibiting them will decrease bioavailability.

Transporters can work with each other and/or with drug-metabolizing enzymes to modulate drug ADME.[15] FDA guidance notes that, as part of drug development and regulatory review, transporters' role in drug interactions should be evaluated. The International Transporter Consortium, with members from academia, industry, and the FDA, has developed decision-tree models intended to help guide clinical studies on the currently recognized most important drug transporter interactions.

Among the various examples Dr. Frye gave of transporter-mediated interactions were the following:

- In mice, administering a BCRP and P-gp inhibitor, GF120918, with oral topotecan significantly increased the systemic exposure to topotecan.[18]

- Elacridar is an inhibitor of P-gp and BCRP in the GI tract and can increase bioavailability of drugs that lack good bioavailability when ingested.[19]

- Grapefruit juice decreases bioavailability of fexofenadine[20, 21] through OATP transporters. The timing of juice administration is also an important factor, but few studies address this.

- Green tea has shown inhibitory effects *in vitro* on the four OATPs expressed in enterocytes and hepatocytes in humans.[22] Further work is needed to determine the clinical relevance.

**Session III Discussion** points included:

- If a substance inhibits a transporter, then one should perform a clinical drug-interaction study with a sensitive substrate. These can be difficult to find, however, compared with sensitive substrates for enzyme pathways. Clinical data is limited in this field of research.

- Genotypic variation may be important in transporters, as many have genetic variations. Genotypes' effects on the magnitude of drug interactions, however, have been little studied.

- *In vitro* data on transporters can be among the data used to prioritize clinical studies.

- How aging affects transporters is an important but understudied research area.

- Variability—e.g., in concentration, potency, constituents, and bioavailabity—can be problems in *in vitro* studies. Researchers must exactly define the substance they study. This will help create a more complex understanding of activity, expansion of the knowledge base, and extrapolation of results to the clinical setting.

- Studies at hyper exposure levels can provide evidence only on whether an interaction might happen. They cannot be extrapolated backward to normal exposures.

**Session IV: Pharmacodynamic Interactions**

*Moderator: Jeffrey White, M.D., NCI*

**Presentation 1: Botanicals as Adjuvant for Cancer Chemoprevention**

Chun-Su Yuan, M.D., Ph.D., Pritzker School of Medicine and Tang Center for Herbal Medicine Research, University of Chicago

Many patients in the United States, including cancer patients, take prescription drugs and herbal supplements concurrently. This co-administration can have negative outcomes. Yet, there can also be beneficial interactions. A variety of evidence has suggested that ginseng, for example, can potentiate chemotherapeutic agents, through synergistic effects. Dr. Yuan has been exploring herbs such as ginseng as adjuvants to conventional cancer therapy[23, 24]and whether they could improve drug efficacy, extend therapeutic index, and/or reduce toxicity. He noted that research on mechanisms of interactions is warranted for better understanding of the pharmacodynamics and pharmacokinetics, and that clinical studies are needed to verify utility of these compounds for this purpose.

The complexity of the research endeavor in this area is affected by many factors, including that herbal medicines have many different constituents and identifiers; produce effects individually and in combination; typically do not have PK data available; are largely unregulated; and are affected by various factors in cultivation, storage, distribution, etc. Research outcomes are often difficult to determine and/or unexpected.

Dr. Yuan discussed some of the preclinical and clinical studies by his team, including:

- In a 4-week, randomized, double-blind, placebo-controlled trial in healthy volunteers on the interaction of warfarin and ginseng, patients received warfarin in weeks 1 and 4 and either American ginseng or placebo beginning in week 2. After 2 weeks of ginseng administration, the ginseng group, compared to the placebo group, had a number of significantly lower measurements related to warfarin.[25]

- In human colorectal-cancer cells (HCT-116), American ginseng enhanced the chemopreventive effect of the drug 5-fluorouracil (5-FU) on cancer-cell growth.[26] So did panaxadiol, a specific saponin found in ginseng, in a combination with 5-FU, through regulating cell cycle transition and inducing apoptotic cells.[27]

- Also in HT-116 lines, panaxadiol enhanced antiproliferative effects *in vitro* of irinotecan. Increased activity of caspases 3 and 9 played a central role. Computer-based docking analysis shed light on the mechanism and confirmed synergistic apoptotic effects.[28]

Since botanicals are typically ingested orally, the roles of diet and gut microbiota are important, including in interactions. Researchers should also look at metabolites of supplements in interactions, because they almost always play a role.

**Presentation 2: Overcoming Therapeutic Resistance by Nutraceuticals**

Fazlul Sarkar, Ph.D., Karmanos Cancer Institute, Wayne State University

Therapeutic resistance is one of the major challenges in the treatment of human malignancies, especially solid tumors. At present, there are no avenues to overcome it. Carcinogenesis and tumor progression are complex processes that involve many molecular and cellular pathways. Cancer cells are dynamic, constantly changing, and highly drug-resistant, and contain heterogeneous cell populations. Preventive or therapeutic strategies with drugs typically require combining multiple agents with different modes of action that may target different cancer cell populations. However, this creates toxicity problems. Lowering dosages also impacts efficacy. Therefore, natural agents that are non-toxic and target multiple pathways may have a role in augmenting standard therapy for cancer.

In addressing drug resistance, there are emerging discoveries surrounding cancer stem cells, epithelial-mesenchymal transition (EMT)-type cells, and microRNAs (miRNAs). Among the dietary compounds of significant interest to this team are isoflavones, indoles, isothiocyanates, resveratrol, curcumin, lupeol, and silybin. By introducing a natural agent early on, Dr. Sarkar's group hopes to support chemotherapy or radiotherapy in "pushing" cancer cells' reaction toward death by the natural agent, instead of toward their own survival signaling. Among their findings to date:

- The results of an array of *in vitro* and *in vivo* studies suggest that genistein could enhance antitumor activities of chemotherapy drugs.[29] Further mechanistic, animal, and clinical studies are needed.

- A formulation of 3, 3'-diindolymethane (DIM) potentiated the apoptosis-inducing effect of erlotinib *in vitro*[30] and had a therapeutic effect *in vivo* in SCID (severe combined immunodeficiency) mice.[31] Moving from bench to bedside, a phase I clinical study of a formulation of diindolylmethane (B-DIM) in patients with rising PSA has been completed,[32] and a phase II study is progressing and near completion.

- Colony assay showed *in vitro* that a soy-isoflavone formulation boosts the effects of radiation.[33] The team tested the formulation in a controlled study in prostate-cancer patients undergoing radiation therapy. The soy group experienced improvement at the 3- and 6-month time points in several measures of urinary, intestinal, and sexual adverse effects of radiation.[34]

The Sarkar team has also been testing natural compounds with chemotherapeutic agents to target cancer stem cells and EMT-type cells, through targeting miRNAs, which are critical in regulating drug resistance.[34]

Dr. Sarkar recommended comparing the natural form of a compound with its possible variations, as their activities and levels of potential benefit may vary. A high-quality diet remains important in cancer prevention and in patient response to therapy.

**Session IV Discussion** included the following points:

- Dr. Yuan commented further on diets, intestinal microbiota, and microbiomes as they affect individuals' responses to natural products. He also noted that the research environment is complex when adding supplements to chemotherapy, e.g., given different binding sites and effects on pathways by supplements vs. drugs. Researchers do not know yet how to simplify these issues.

- Dr. Sarkar commented that the concept of combining natural agents with conventional applications is gaining momentum, with many trials being designed and conducted. Tumors in animal models may not translate well to clinical studies, because animal tumors tend to be more homogenous. To avoid this issue, his group did not use cell lines, but rather suspension cell cultures.

**Session V: Roundtable Discussion on the Path Forward**

***Questions 1 and 2: How should supplement-drug interaction research be prioritized? Where can NCCAM resources provide the greatest impact?***

Roundtable members' responses included the following suggestions:

- Review the top 20 or 30 supplements being taken in the United States. They should be agreed-upon, bioavailable, contemporary, and reasonable for study. Alternatively, since popularity is affected by pervasive marketing, select the compounds that show the most promise for therapeutic indications. Use and promise may or may not overlap, or have common elements.

- Next, determine what is in those substances, through collaboration where feasible (e.g., with natural product chemists). The focus could be on the top few components to which humans are exposed upon ingestion.

- Use *in vitro* screening to further refine the list, e.g., using CYPs, UDP-glucuronosyltransferases (UGTs), and transporters. This could be done at multiple research centers, using tissue, microsomes, cultured liver cells, and human cell lines, and assessing for induction and inhibition. Researchers should avoid overinterpreting such data, however (e.g., by assuming that CYP data applies to all humans).

- Determine bioavailability early. For example, if a substance inhibits *in vitro* but its bioavailability has not been determined, then that information is interesting but not necessarily useful, especially if there is an alternative in which bioavailability has been determined.

- After the above data is collected, convene another roundtable to collate the data and decide priorities for human studies.

- Select substances that appear *in vitro* to have one or more of the following qualities: is a potent inhibitor; is a recognized mechanism-based inhibitor; has good inductive effects; has good solubility properties; has existing case reports that lend credence.

- Pare natural products into several categories of major-disease states for which they are used. NCCAM, with its expertise in methods to study herbs, could partner with researchers who understand the underlying disease model. Natural-product chemists could assist with measurements of constituents.
- Seek input from surveillance colleagues. For example, many of the FDA's label warnings had their start as submissions to the MedWatch system, and the FDA does surveys before embarking on studies.

Needs in information management and sharing were also discussed. Points included the following:

- More sharing and publication of studies was encouraged.
- Panelists favored development of a single, authoritative repository for study results.
    - One major challenge would be the level of disparity in the existing data. It was commented that the International Transporter Consortium agreed upon certain criteria to use in sorting authoritative information for inclusion into a public database.
    - Another would be to have a standardized definition or description of each natural product. It was commented that a good study with a badly defined product produces no better information than a badly designed study.
- Two suggestions to obtain more clinical information were (1) European companies, given the long tradition of phytomedicine use in health care in Europe, and (2) naturopathic practitioners and their patients.

***Question 3: How can we best inform the medical community and patient population about the relative risk/benefit of any particular combination [involving one or more natural products]?***

Curriculum development is a need, and it would have a far-reaching impact. Potential tools that could be developed include standardized subject components, a curricular outline with literature references, and a sample set of slides. Conventional medical schools and pharmacy schools are among the important targets. A centralized repository was again mentioned, to provide the most updated and accessible information on interactions.

***Question 3: What types of research have the greatest potential to impact clinical practice?***

The two lines of research most favored were to (1) research the drug interactions of the 20 most-used dietary supplements and (2) study supplements that may offer beneficial interactions with drugs, since popularity-based lists change.

## Appendix A

## AGENDA

### Roundtable Meeting on Dietary Supplement-Drug Interactions

Tuesday, March 27, 2012
Neuroscience Building, 6001 Executive Blvd
Rockville, Maryland

**8:30 Welcome and Introduction**
Josephine Briggs, M.D., National Center for Complementary and Alternative Medicine
Paul Coates, Ph.D., Office of Dietary Supplements
Jeffrey White, M.D., National Cancer Institute

**8:50 Overview of Workshop/Charge to Attendees**
Craig Hopp, Ph.D., National Center for Complementary and Alternative Medicine

**9:00 Session I: Obstacles to Drug Interaction Research**
*Moderator: Craig Hopp, Ph.D., National Center for Complementary and Alternative Medicine*

*9:05 Evaluation of Dietary Supplement-Drug Interactions: Limitations of In Vitro Methods*
John Markowitz, Pharm.D., University of Florida

*9:25 Evaluating the Clinical Relevance of Human Dietary Supplement-Drug Interaction Study Designs*
Bill Gurley, Ph.D., University of Arkansas

*9:45 Questions and Discussion*

**10:15 Break**

**10:30 Session II: Roundtable Discussion on Improved Methodology**
*Moderator: Shiew-Mei Huang, Ph.D., U.S. Food and Drug Administration*

- *Are there any computational, i.e. in silico, methods that can be employed?*
- *Does high throughput screening offer any insight into possible clinical drug interactions?*
- *How can we make animal models more predictive?*

**11:15 Session III Pharmacokinetic Interactions**
*Moderator: Joseph Betz, Ph.D., Office of Dietary Supplements*

*11:20 Predicting and Interpreting Drug Interactions With Nutrients and Natural Products*
David J. Greenblatt, M.D., Tufts University School of Medicine

*11:40 Transport-Mediated Dietary Supplement-Drug Interactions*
Reginald Frye, Pharm.D., Ph.D., University of Florida

*12:00 Discussion*

**12:00 Lunch**

**1:30 Session IV: Pharmacodynamic Interactions**
*Moderator: Jeffrey White, M.D., National Cancer Institute*

*1:35 Botanicals as Adjuvant for Cancer Chemoprevention*
Chun-Su Yuan, M.D., Ph.D., University of Chicago

*1:55 Overcoming Therapeutic Resistance by Nutraceuticals*
Fazlul Sarkar, Ph.D., Wayne State University

*2:15 Discussion*

**2:45 Break**

**3:00 Session V: Roundtable Discussion on the Path Forward**

*Besides grapefruit juice and St. John's wort, are there other clinically significant adverse interactions?*

- *How should supplement/drug interaction research be prioritized?*
- *Where can NCCAM resources provide the greatest impact?*
- *How can we best inform the medical community and patient population about the relative risk/benefit of any particular combination?*
- *What types of research have the greatest potential to impact clinical practice?*

**4:00 Adjourn**

**WORKSHOP DISCUSSANTS**

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## Appendix B

## REFERENCES


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