Bioavailability of Nutrients and Other Bioactive Components from Dietary Supplements

What Do We Need to Know about Active Ingredients in Dietary Supplements? Summary of Workshop Discussion

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Overview

Key issues identified during deliberations of the group included the following:
• Identification of active ingredients.

The group concluded that in general with regard to dietary supplements directly composed of plants or animal-based substances or their extracts, rather than those composed of purified nutrients or minerals, active ingredients have not been fully characterized chemically or biologically.

The discussants cautioned that botanicals are likely to contain several potentially active ingredients even when derived from a single plant species. Consequently, it may be useful to apply the scientific strategy of reductionism with some caution.

In support of this caution, the group offered the following example. The Food and Drug Administration has recently approved a health claim that consumption of 25 g of soy protein per day may lower blood cholesterol. Crouse et al. (1999) showed that in subjects above median blood cholesterol, consumption of 25 g of soy protein containing 37 or 62 mg of isoflavones lowered cholesterol significantly, but soy protein containing lesser amounts of isoflavones did not lower cholesterol. This suggests that isoflavones are the active ingredients in the soy protein, but the effect might have been produced by an interaction between the protein and the isoflavones. Saponins are also potentially cholesterol-lowering components that would be likely to present in soy protein high in isoflavones. Thus, interactions among several soy protein-associated components might produce the biological effects responsible for cholesterol lowering by this product.

• The necessity for the identification of biomarkers to assess safety and to determine appropriate indications of use.

• In vitro or in vivo bioassays, including model systems that have meaningful short- to medium-term endpoints with respect to human diseases or that are otherwise relevant to predicting human disease outcomes may be useful potential screening tools. These should be used with caution and cannot be considered substitutes for clinical studies.

• Careful consideration of matrix effects on active ingredients and in subsequent studies of bioavailability of active ingredients should be used. The focus of this concern is the potential problems in interpretation of studies of active ingredients in their natural milieu versus those that have been isolated and/or synthesized.

The discussants concluded that the process by which active ingredients in dietary supplements are identified needs to developed with attention paid to the following caveats:
• Both chemical and biological characterizations of dietary supplements are needed. To accomplish this, investigators must recognize that analytical chemistry of active ingredients depends upon the chemical identification of numerous specific components of complex mixtures. For example, within soybeans, there are three major soybean isoflavones, daidzein, genistean and glycitein, each of which can exist as an aglycone, a glycoside or acetylated or malonated glycosides. Soybeans also contain at least 16 phenolic acids and several forms of saponins, just to name a few of the major classes of nonnutrient components present in these foods.

The group agreed that the identification of meaningful components was key. Meaningful was defined as "components that produce a biological effect." It was generally agreed that identification of meaningful components should precede study of their bioavailability.

• With specific regard to botanically derived supplements, the central question posed was: "Are traditional nutritional and pharmacological approaches applicable to herbal supplements?" The discussants agreed that in general such approaches would apply. However, the group provided the following caveat: the approaches would need to be technically sophisticated enough to recognize multiple biologically

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active substances in products, with the likelihood of multiple biological activity endpoints.

- Standards are an essential component for the analyses of active ingredients. Usually the most accurate methods for compound detection are relatively expensive and slow, involving complex and tedious extraction procedures. The methods depend upon the production and identification of standards. Standards may vary in stability and detectability. For example, soybean saponins may be detected by the presence of a moiety, 2,3-dihydro-2,5-dihydroxy-6-methyl-4H-pyran-4H-1, which is heat labile. The remaining compound has much less ultraviolet absorbance than do 2,3-dihydro-2,5-dihydroxy-6-methyl-4H-pyran-4H-1-containing saponins.

Methods may be facilitated by development of appropriate internal standards, but it is not always a straightforward task to find or develop stable inexpensive internal standards that are not present in the product to be assayed. Potential interactions among components must be considered. Such interactions might cause a component to in effect appear or disappear, depending upon conditions. Ultimately, development and maintenance of databases containing analytical information is desirable.

- Sampling strategies should be developed to identify and use the most commonly used products. Product formulations will be likely to change as knowledge of biological efficacy develops. Analytical methods may also become more sophisticated as the knowledge base grows. Therefore, continual maintenance and upgrade of databases are critical. An example of a relevant database is a soybean isoflavone database developed by scientists at the Nutrient Composition Laboratory (U.S. Department of Agriculture, Agricultural Research Services, Beltsville, MD) and Iowa State University (Available at: http://www.nal.usda.gov/fnic/foodcomp/data/soyflav/soyflav.html).

- Bioavailability studies. The discussants identified a number of issues to be considered in this context including:
  1. Although the active ingredients may exist in several forms, such as the soybean isoflavones, the relative bioavailability of all active forms needs to be estimated.
  2. Because it would be unusual for active ingredients not to undergo biotransformation, bioavailability studies must include the identification and analysis of the metabolites of active ingredient. These metabolites may be of greater or lesser bioactivity than are the parent compounds.
  3. Doses, dosing interval and duration need to be determined, based on common or recommended usage.
  4. Because bioavailability of presumably active ingredients may change with time, adaptive responses should be anticipated.
  5. Bioavailability may be affected by interactions with other ingredients or with other dietary components.
  6. Physiological state could also influence bioavailability (e.g., gender, ethnicity, age, health status) and, therefore, must be included in such states.

Conclusions and research recommendations

The workshop participants identified five research priorities.

1. The identification of meaningful (bioactive) components should be the main focus of research efforts at this time.

2. Databases are inadequate for botanicals, including analytical chemistry and databases on biological effects, health efficacy, dosages and common usage. Analytical database development was thought to be a significant issue. General informational databases include Natural Products Alert and International Bibliographic Information on Dietary Supplements. Although these are relatively good sources, the knowledge base needs to be expanded internationally. U.S. Department of Agriculture databases may serve as models (see above).

3. Bioavailability may be a key determinant of bioactivity, but determining biological effects should take precedence in nascent research on active ingredients.

4. Standard reference materials, preferably developed by a nonproprietary industry-based collaboration, should be the initial priority in this field of research. Reference materials including analytical standards, internal standards and standardized products are needed for research. Previous work that developed dietary fiber and fish oil standard products should be considered model approaches to the present problem. It was suggested that members of the botanicals industry should collaborate to develop standardized products on a nonproprietary basis, using a collective best first guess as to efficacy and safety as a basis for proceeding. U.S. Pharmacopeia certification would also be a useful step in standardization of the approach to develop this field of research.

5. Clinical studies focused on active ingredients likely to have meaningful effects and performed with standard reference materials should be the chief research aim at this time.

The discussants agreed that clinical trials were the gold standard for developing our knowledge of active ingredients. Because of their important role, clinical trials would be a major driving force for the need for standard reference products. The classical approach (phase I, II, etc.) was considered a reasonable starting place for the human studies needed in this area. Determining priorities for clinical trials is first a matter of selecting which agents, ingredients and/or products to study.

Suggested major criteria for clinical trials included: extent of use (i.e., which botanicals are used most commonly—ginseng, gingko, St. John’s wort, etc.): efficacy (i.e., botanicals that are thought to have some biological effect with respect to major public health problems, such as Alzheimer’s disease; colon, breast or prostate cancer; atherosclerosis; osteoporosis; type II diabetes); and safety (botanicals that are thought to be safest, have longest history of use with least reports of adverse effects or for which other safety data are available).

Ideally, short- to medium-term clinical studies and related bioassays examining biomarkers predictive of human disease were considered to be of great benefit in advancing this field of research. Some examples of useful biomarkers include blood cholesterol, prostate serum antigen and dietary n-3:n-6 fatty acid ratios, both of which may be predictive of certain human disease risks albeit with significant limitations. There has been little progress to date in extending the knowledge base of biomarkers, but such research is likely to be useful and, therefore, is a worthwhile priority.

LITERATURE CITED