Component Interactions for Efficacy of Functional Foods\textsuperscript{1,2}

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ABSTRACT The study of functional foods appears to hold the promise of improved quality of life, particularly for older persons who fight chronic disease. Many laboratories are studying the mechanisms of action of individual bioactive food components; but, relatively few studies are concerned with the interaction of the many components found in a single food or with a comparison between effects of the putative major bioactive component and the whole food. This overview is an introduction to the papers that follow, which were given as a symposium at the 2004 Experimental Biology meetings and which address the interactive effects of bioactive food components, particularly those in soy, broccoli, berries, and tomatoes. However, conclusions to be drawn go further than these 4 foods. The studies act as examples, identifying needed areas of focus in the study of functional foods and specifically the need for research into functional foods to encompass 3 areas of study: strength in chemical analysis, mechanistic studies carried out in cell culture, and animal studies comparing effects of dietary exposure to purified components and whole foods. Together, data from these 3 areas can give the solid scientific basis needed, so that clinical studies can be properly planned and executed. J. Nutr. 135: 1223–1225, 2005.

KEY WORDS: • functional foods • efficacy • component interaction

Epidemiological studies clearly show a relation between diet and health. Indeed, epidemiological studies that identify an association between a specific food or food group and lowered risk for a specific disease often lead to mechanism studies. Typically for such studies, scientists focus on a single component of a food rather than a whole food, to evaluate biological effects in cell cultures and animal studies. However, all too frequently, studies of individual components, or even mixtures of components, are found not to give the same effects as the whole food. Interactions between components are complex. Some component effects may be additive, but others may be synergistic, enhancing, inhibitory, masking, neutralizing or even opposing, causing competitive antagonism at a receptor, or sequestration of a component or any of multiple types of component–component interactions (Fig. 1). Some of these will only affect the efficacy under study, other interactions may precipitate additional positive effects or may produce negative, toxic effects. It is not possible to test the activity of the whole food in cell culture. However, all too often the type of animal study that defines and models future use in the population, such as those studies required for drug evaluation, are never carried out during preclinical evaluation of a functional food or a dietary supplement. Therefore, it may not be until clinical trials are underway that the activity of a single component, or even the sum of activities of several components estimated in cell culture, is found not to accurately reflect the activity of the whole food provided in the diet. A sound scientific basis is necessary if we are to integrate functional foods appropriately into the diet (1).

The following papers, presented as a symposium at the 2004 Experimental Biology meetings, highlight a number of such component interactions, particularly in soy, berries, broccoli, and tomato. These manuscripts may help to persuade us that the reductionist technology that served us well in identifying roles for essential nutrients during the last century may lead us astray if we try to jump to conclusions about the action of bioactive food components directly from cell-culture studies, without a solid scientific basis found in animal feeding studies of whole food, before human trials. This symposium also included presentations on how these research findings on foods and health are being translated into outreach and educational information for the public.

Soy

The presentation by Connie Weaver from Purdue University addressed the controversial issue of the effect of the whole soy protein fraction vs. soy isoflavones on bone health. She pointed out the difficulty in comparing effects across different

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parts of the life cycle, such as a young woman whose bones are growing, an adult, or a postmenopausal woman with no hormonal support. Yet, even if identical physiological models are used, an evaluation of specific isoflavones alone (e.g., genistein), a combination of isoflavones, or isoflavones together with lignans and other components within soy protein may provide very different patterns of activity. This same difference in effects of different soy fractions has also been reported for the effects of soy and soy fractions on growth of breast-cancer cells by Allred et al. (2). Weaver suggested that the lack of recognition of these differences and the categorization of many different products as "soy protein derivatives" or "soy isoflavones" can lead to apparently conflicting data and mixed messages that confuse not only scientists working in the area but also the public who are trying to use our findings. A recent publication addresses this issue and offers directives for researchers and reporters, in an attempt to overcome this concern (3).

The presentation by Ruth MacDonald (University of Missouri) further attested to the fact that studies comparing the effect of dietary soy protein and soy isoflavones are not in full agreement, even in her own laboratory. Teaming with agronomist David Sleper, they have shown that there are significant genetic × environment interactions during soybean growth, resulting in very different contents of bioactive isoflavones and saponins, both among varieties and within a single variety. Within a single variety, differences in content are considered to depend on growing conditions, with most differences being changes in magnitude of individual isoflavones, rather than changes in the isoflavone chemical profile. Having carefully analyzed the isoflavone mix, MacDonald carried out mechanism studies in cell culture, comparing purified genistein with a commercially available isoflavone-rich extract and found that genistein alone was more effective at inhibiting proliferation of Caco-2 cells than was the whole isoflavone extract used at a genistein-equivalent dose, suggesting the presence of an inhibitory, masking, or antagonistic factor in the mixture.

Berries

The study of the effect of plant-food components on human physiology requires interdisciplinary research. MaryAnn Lila (University of Illinois at Champaign-Urbana), a plant physiologist, has teamed with nutritional scientists Weaver and John Erdman to generate, through plant-cell cultures of berries and tomatoes, a broad array of secondary plant compounds ready for testing for possible bioactivity. In her presentation, Lila focused on the chokeberry, which grows under extremely stressed conditions. "Elicitation" is a term used by plant physiologists to describe stimulation of plant cells to upregulate synthesis of phytochemical pathways of interest. Lila and colleagues developed a plant-tissue culture system that, through elicitation, stimulates the biosynthesis of bioactive flavonoids in cells taken from berry plants. This technology has provided quantities of flavonoids that can be studied for bioactivity as a mixture or, after isolation, individually. Furthermore, incorporation of radiolabeled sugar into the growth medium is providing labeled flavonoids for important bioavailability and nutrigenetic work. Comparison of flavonoid profiles from plant-cell suspension culture and from whole foods shows a similar, but not an identical, profile mix. Comparison of bioactivity is ongoing, which will allow an evaluation of any similarities or differences between this mix of flavonoids and the mix that is present in the whole berry. This plant-cell culture tool, used for research so far, could readily be harnessed for food production. The potential for bioengineering dietary supplements is exciting but needs to be approached with caution, because novel metabolites with novel bioactivities might be generated during suspension culture.

Tomato

The paper by Carene-Adams and colleagues (University of Illinois at Urbana-Champaign) suggests that tomatoes and tomato products can play an important role in dietary prevention of both prostate cancer and cardiovascular disease (CVD). For some time, tomatoes have been known as a good source of the antioxidant lycopene. A comparison between the effects of dietary lycopene and dietary tomato powder found that lycopene was not as effective as tomato in preventing prostate cancer in an animal model, and the authors suggest there may be additional bioactive components in the whole
Outreach and education

Where should the study of bioactive food components go from here? In addition to building a scientific basis to understand how bioactive components function, a second important focus of the symposium began to look in a new direction—the need to pass on our knowledge of functional foods and dietary supplements to the public. Two presentations addressed this issue.

Glen Cameron and colleagues at the School of Journalism at the University of Missouri have studied the knowledge base of oncology nurses and their need for information on functional foods and dietary supplements. They found that knowledge is driven by personal interest rather than by professional training and that patients are turning to these nurses for information and advice on dietary choices, both during cancer therapy and after treatment, when many of these patients are at high risk for additional primary cancers, as in recurrence of melanoma, oral carcinoma, colonic polyps, and many other cancers. Thus, oncology nurses are sorely in need of continuing education in this area.

The other presentation was by Charles Santerre of Purdue University, who has focused his outreach research on another group of health professionals, registered dietitians. Whereas certain foods and food components have been associated with lowering the risk for cancer, there is a far stronger scientific basis for information on nutrition and CVD prevention. Starting with this knowledge base, Santerre developed an electronic interactive teaching tool, not just to teach registered dietitians, but to provide them with the information and materials to teach others about functional foods and prevention of chronic disease. This program, called Xtrain, includes a series of presentations on functional foods and CVD, as well as one on soy and bone health. Together with the other researchers from this program, Santerre is building a series of modules on nutrition and cancer prevention, which will be formatted for both registered dietitians and oncology nurses.

Before we can provide useful, relevant information on functional foods to health professionals so that they may in turn inform the public, much work remains to be accomplished. We need to know how much of a food must be ingested to gain an effect, how it should be prepared, how frequently one should take it, and for which individuals this is likely to have the greatest impact. Because both genetic and epigenetic factors can affect response to food components, dietary recommendations may need to be personalized. A cadre of plant scientists and food scientists are working to analyze and to quantify bioactive components within foods. Likewise, nutritional scientists, physiologists, and cancer biologists are working to generate the scientific basis that provides the mechanistic assurance that certain food components can provide protection at the cellular level. The link is clearly being forged between chemical analysis, cell-culture studies of mechanism, and animal studies that compare whole-food diets with the effects of individual bioactive components. We only need to look at the negative clinical trials on beta-carotene, with the resulting loss of interest in funding similar studies, or to the confusion among scientists about possible positive or negative effects of soy and soy components, to see how important it is to provide a solid basis in chemical analysis, mechanism studies, and animal feeding studies of sufficiently long duration before this area of research can safely mature to a clinical trial (Fig. 2). This is an exciting time to be studying the health benefits of foods and food components. With diligence, cooperation from funding agencies, and a clear vision of the steps that must be taken to reach our goal, we can make a difference both to the cost of health care and to the quality of life.

FIGURE 2 Interaction between in vitro studies, animal models, and physicochemical characterization research that is needed to be able to translate the results into clinical research.

LITERATURE CITED