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FOOD AS A SOURCE OF HEALTH ENHANCING COMPOUNDS

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Molecular nutrition is becoming an increasingly important scientific discipline of human nutrition. The systematic dissection of food into its molecular components followed by studying individual molecules in animal model systems and humans to investigate their nutritional and health benefits is evolving rapidly. The identification, production and marketing of these food-derived bioactives will not only have a significant impact on the development of new regimens for disease treatments but will lead the way into a new era of preventing or postponing the onset of severe chronic diseases. Sound scientific principles, rigorous clinical trials, and science-based regulatory processes will facilitate and help to define a new space in diet and dietary compound-based management of health and disease conditions.

Key words: biotechnology; cholesterol; diet; food; functional foods; human nutrition; nutraceuticals; vascular health, vitalins.

Our understanding of the biology of a diverse number of living species, ranging from microbes to humans and plants has grown tremendously during the last century and particularly during the last decade. Chemistry and genetics have provided a solid foundation for understanding the metabolic processes which play a pivotal role in maintaining the growth and health of living systems as well as interactions between the environment, food, genetics and health. The advent of molecular biology and modern biotechnology has vastly facilitated the process understanding the molecular and genetic basis of a wide range of physiological reactions and our ability to translate this rapidly growing knowledge into meaningful products for our society. Just about twenty years ago, introduction and expression of single genes in microbes, and complex multicellular organisms like plants and animals, was considered a feat that could only be accomplished in a few specialized laboratories around the world. Today, we are beginning to gain insights into the genetic make-up of a whole host of living organisms including bacteria, plants, animals, and humans – to identify and understand the specific genes and their corresponding gene products, and their respective contributions to health, disease, or disease initiation states in humans. We also are beginning to understand their contributions to yield and productivity in plants and productivity of fermentation systems. A large number of laboratories, academic, government, and industry-based, are now engaged in leveraging the tools of molecular

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biology, genetics, genomics and biotechnology to address issues of food, feed, fiber and health (DellaPenna, 1999; Mazur *et al.*, 1999; Moffat, 1999). It is our objective to link these rapidly evolving technologies to the science of human nutrition, a field which we will refer to as molecular nutrition.

Functional Foods Or Vitalins?

Human nutrition is more than a hundred year old science – this science has led to the discovery of many essential vitamins, minerals, amino acids, and fatty acids required for normal metabolic functioning of the human body. However, food contains nutrients which are not only capable of meeting caloric and general metabolic needs but can also affect specific metabolic functions which can either initiate or retard the process of degeneration of the cells and tissues of the human body. Identification of these bioactive, molecular constituents of food allow us to study their intrinsic health benefits and to provide them to people in pill form or as a food supplement. In addition, it puts us in a position to apply modern biotechnological approaches to enhance benefits of food by either including or excluding these bioactives from our most common food sources. A number of names have been coined to refer to these classes of molecules – "nutraceuticals" is a commonly used name although other names such as "phytoceuticals", "phytonutrients", "phytomedicines" are used. Both nutraceuticals and functional foods refer to either whole food products or bioactive ingredients that positively affect physiological functions of the human body. We feel that none of these terms adequately describe the nature of activity associated with the molecules that we are describing here. We propose a new name – "vitalins" – to these molecules of dietary origin which help preserve vital functions and, thus, vitality of the body. "Anti-vitalins" are those molecules which have the opposite effect, i.e., one of accelerating the degenerative process. Vitalins are therefore a class of nutrients and anti-vitalins are a class of anti-nutrients. Functional foods are foods containing one or more of these vitalins or foods depleted of anti-vitalins – they are more functional in their ability to meet metabolic needs of either the whole body or specific organs of the human body; in a context which includes vitality in addition to general metabolic activities.

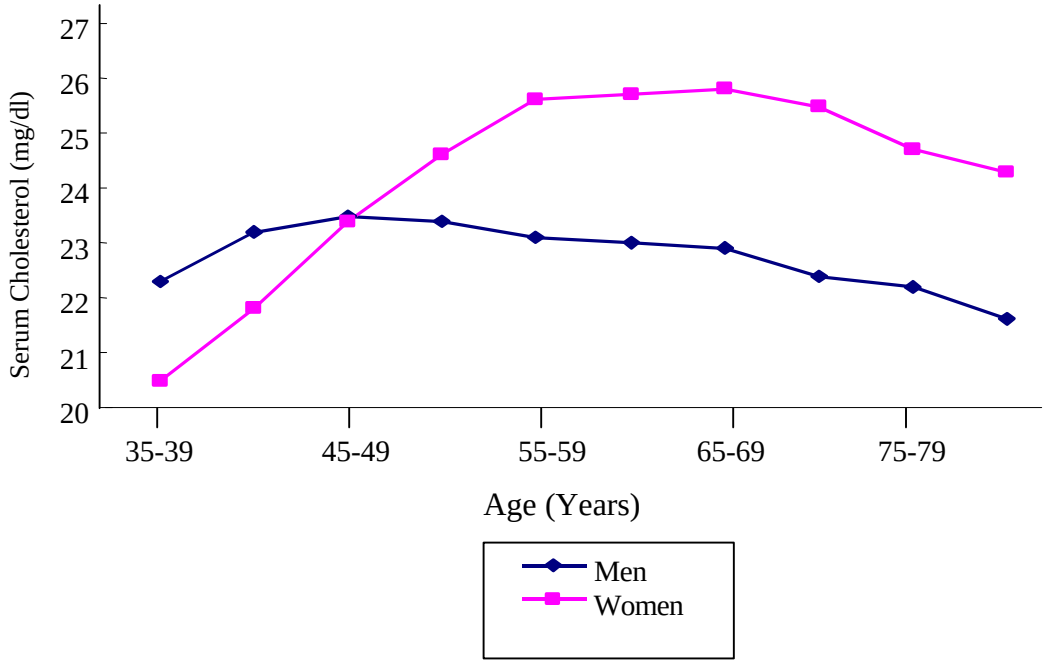
From a societal perspective, we feel that the science of molecular nutrition is urgently needed to address the growing needs of the population and escalating health care costs. Prevention of diseases by proper diet and exercise is a well-accepted paradigm but the process for identifying proper diets is either empirical or traditional. The causative factors of morbidity and mortality in human populations throughout this planet are essentially similar – vascular diseases, cancer, infectious diseases and inflammation account for a majority of the deaths in all populations. We are beginning to understand the biochemical basis for most of these diseases. This opens the door to a systematic process for dissecting food into its molecular components and to study either its vitalin or anti-vitalin activities in animal model systems and humans. Furthermore, since biomarkers for several of these diseases are becoming more widely known, it is possible to prevent the progression of a disease from an early stage by active diet-based therapy. Dietary solutions can also dramatically increase the role of people in self-directed management of their own health, reduce the cost of health care and very importantly, add quality of life to the longevity that has been obtained by enhanced availability of food during the last century.

Going To The Market

Our research at this time is directed towards introducing products of dietary origin into the market place which can be used for managing vascular health. Since vascular diseases of the cardio and the cerebral system in humans account for nearly 55% of all deaths in developed countries and also detract

from the quality of life, we felt that this is an excellent starting point for our studies. Our first objective was to determine if we could identify compounds in food which had the potential to improve cardiovascular health. Serum cholesterol levels, are a good indicator, and a widely accepted biomarker of arterial health (Kritchevskey, 1995). In addition, mean serum cholesterol levels increase in the average population by age, in particular in women (figure 1). Therefore, we and many other academic, biotechnology, and industry laboratories, have focused our research and development efforts on this important biomarker of health.

Figure 1: Age Trends for Mean Serum Cholesterol Levels in Men and Women.

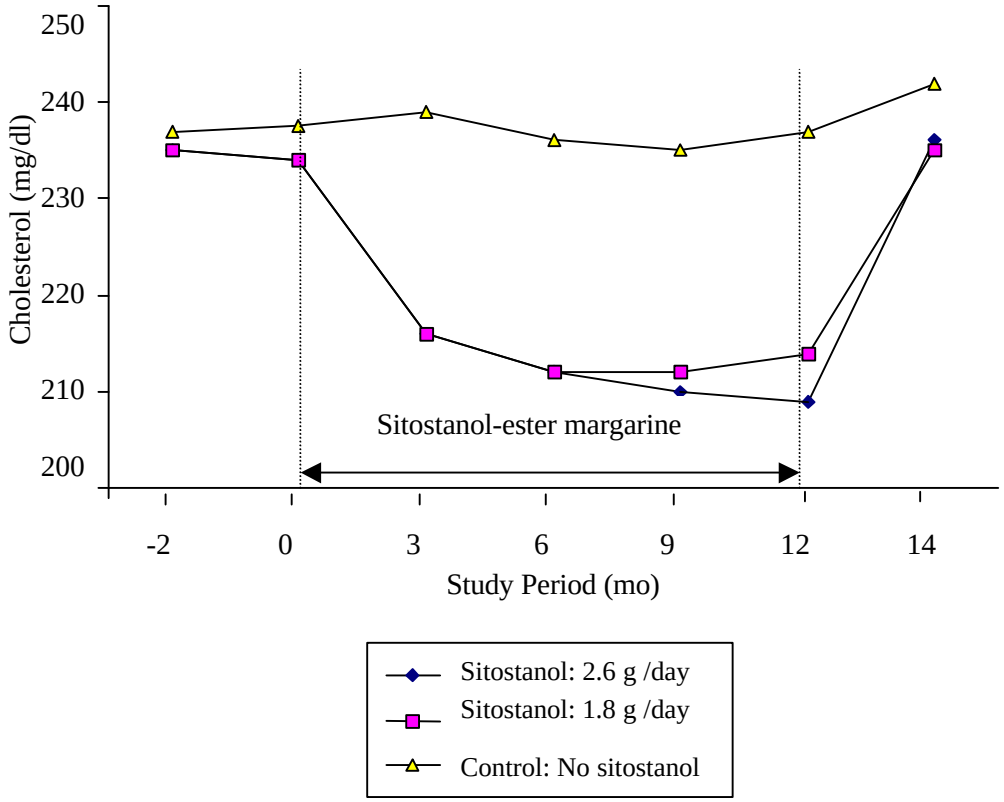


Cholesterol is a lipid found throughout the body in all tissues including blood. It plays a central role in the formation of cell membranes, is required for the formation of bile acid in the liver, and the production of hormones, such as steroid hormones in the adrenal glands. Cholesterol is thus an essential molecule which is centrally involved in multiple processes and pathways within a healthy body, both in animals and humans. At the same time, it is well established that higher levels of circulating cholesterol can dramatically affect arterial health increasing the risk of diseases, such as atherosclerosis, heart attacks, and strokes. There is overwhelming evidence that for every one percent rise of cholesterol above 160 mg/dl, the risk of coronary heart disease rises by 2-3 percent. Maintaining cholesterol below 200 mg/dl has been a priority for health care professionals and the national government. If cholesterol levels rise above 240 mg/dl, physicians recommend various drug therapies. However, if the cholesterol is in the range of 200-239 mg/dl, diet and exercise are the most widely recommended treatment regimens to reduce cholesterol levels in patients to a healthier level. Most often this initial attempt to lower blood cholesterol fails and is followed by the prescription of drugs. Recently, research into wood pulp, soybean extracts, and components of food has led to the discovery of cholesterol-lowering vitalins. The first products of this nature have just been identified, characterized, and shown to be safe and efficacious in human clinical trials (Miettinen *et al.*, 1995; Hallikainen & Uusiupa, 1999; Jones *et al.*, 1999; Gylling & Miettinen, 1999; Hendriks *et al.*, 1999). They are just now entering the market place and are offering people the choice of maintaining or

lowering their cholesterol levels through enriched foods, in addition to diet and exercise plus prescription drugs, depending upon the cholesterol levels of the individual.

In early clinical studies, a plant sterol, sitosterol and its derivatives such as sitostanol or acylated esters, all of which are natural components of vegetable oils and fats, have been demonstrated to lower cholesterol levels in patients by 10-12% (Farquhar *et al.*, 1956; Lees *et al.*, 1977). In addition to lowering total cholesterol, these studies also established that LDL-cholesterol can be reduced by 10-15%. More recent clinical studies have confirmed these initial results and have shown that both plant sterol and stanol esters can effectively lower cholesterol (figure 2) levels in humans (Miettinen *et al.*, 1995; Hallikainen & Uusiupa, 1999; Jones *et al.*, 1999; Gylling & Miettinen, 1999; Hendriks *et al.*, 1999). Both sitosterol and sitostanol appear to function by inhibiting the absorption of biliary and dietary cholesterol in the gastrointestinal tract (Heinemann *et al.*, 1991) and, thus, effectively lower circulating levels of total and LDL-cholesterol. Neither compound has any effect on HDL-cholesterol and triglycerides, other biomarkers of cardiovascular health.

Figure 2: Serum Cholesterol Levels Before and After the Consumption of Margarine With and Without Sitostanol Ester for 12 Months.



Note. Adopted from Miettinen *et al.* (1995).

Take Control™ (active ingredient: plant sterol esters derived from soybean) and Benecol™ (active ingredient: plant stanol esters derived from wood pulp of pine trees) are two products that have reached the market place in recent years making use of the well established beneficial cholesterol-lowering properties of stanols and sterols. We are applying molecular biology and biotechnology approaches to

produce soy and canola oils enriched with sitostanol which reduces both raw material and delivery costs of these important products (Kishore & Shewmaker, 1999). By expressing the gene encoding the rate-limiting enzyme for sterol synthesis, hydroxymethylglutaryl-CoA reductase, in seeds of crop plants, vegetable oils containing 2-5% phytsterols/stanols have been generated (Venkatramesh et al., 2000). This research will result in the production of more "cardio-healthy" vegetable oils than we have in the market at this time.

The examples of stanol and sterol esters illustrate the strategy and value of dissecting foods and plants into their molecular components followed by studying the individual molecules in animal model systems or humans. This strategy is instrumental in identifying and characterizing the properties of naturally occurring molecules of dietary origin. This scientific approach is a prerequisite for unraveling the potential nutritional and health benefits intrinsic to specific, food-derived, naturally occurring molecules. We are currently identifying and characterizing other food-derived compounds that can reduce total and LDL-cholesterol in humans by a number of different mechanisms. The well-established tools of the pharmaceutical industry are helping us to identify these molecules. In addition to cholesterol, bioactives that can reduce blood pressure, circulating levels of glucose, reduce inflammation, or enhance levels of anti-oxidant enzymes are being identified in a number of laboratories. Once these molecular components of food have been identified and characterized, pre-clinical and clinical studies will be used to evaluate and demonstrate the intrinsic health benefits associated with specific molecules. Food-derived molecules will play a significant role in future health care and disease prevention. A prerequisite will be that these molecular components of food are shown to be safe and efficacious. The safety and the therapeutic or disease prevention effects of these molecules must be carefully evaluated by well-designed, randomized, double-blind, placebo-controlled studies involving a significant number of human subjects. Anecdotal reports of utility of plants or food extracts are of interest, particularly in providing ideas for the design of potential proof of concept studies in animals and humans; however, they will no longer be viewed as a substitute for detailed clinical trials with specific extracts or individual food-derived molecules. It is also important to evolve a nomenclature for vitalins so that their biological activity can be effectively communicated within the nutritional scientific community as well as to the health care professionals and general public.

Concluding Comments

While scientists continue to dissect food and determine its molecular components that deliver nutritional and health benefits at an unprecedented pace, there is a growing need for science-based regulations that will help to distinguish science-based nutrition and disease prevention from quackery and anecdotal stories (Tyler, 1999). The current regulations in the United States (U.S.), and other developed countries appear to be adequate but they have to be enforced based on sound scientific principles. The distinction between food and medicine is beginning to blur. As we begin to identify the medicinal, healing and disease-preventing properties of food and its components –based on sound scientific principles – it is important that a system is established for taking the fruits of this research to the general public and consumers without creating confusion and compromising on scientific principles. The U.S. Food and Drug administration (FDA) has the challenge of defining this new space in diet and dietary component-based management of health conditions; this space has been historically allocated to drugs. It is becoming more and more obvious that molecular components of food not only have the ability to treat but prevent disease conditions. By creating the new space of vitalins, it is our belief that rigorous scientific principles can be used for identifying and communicating their intrinsic and natural health benefits, as well as potential risks, and introducing these dietary components into the market. We believe a "systems" approach for dealing with health, involving whole food, dietary ingredients and xenobiotics is urgently needed to meet the growing needs of our growing, aging population.

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