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Getting to Know Nutraceuticals

Claims for some of these food-based dietary supplements stand up to scientific scrutiny, but others falter

By Thomas Hayden

We live in an age when good nutrition practices—eat lots of whole grains, fresh fruits and fresh vegetables; hold the fatty meat and hydrogenated vegetable oils—are simple, straightforward and widely available. But visit a well-stocked health food store, pharmacy or supermarket, and you'd never know it. The variety of dietary supplements can be overwhelming, with dozens of vitamins, minerals and extracts offered alone and in combinations targeted at every possible intersection of age, sex and activity. And that selection is a nutritional desert compared to the tropical rain forest–level diversity of supplements at more specialized stores.

Dietary supplements are big business in the U.S.: consumer sales in 2006 were estimated at $22.5 billion, with some 60 percent of Americans taking at least a daily multivitamin. But thanks to a regulatory structure designed more to promote the availability of supplements than to ensure that they deliver on their promises, it can seem impossible to figure out what—if anything—you should be taking. The options range from the almost appetizing juxtaposition of garlic, cranberry and soy concentrates to the downright macabre "glandulars." And if cramming pituitary, prostate and pancreas extracts into a single pill doesn't count as overkill, then surely another product containing vitamins, minerals and most of the biochemical intermediates of the cellular Krebs cycle must. The skeptical browser could be tempted to ask where to find the snake oil aisle.

But whereas some, or perhaps many, nostrums are no more likely to improve longevity, alertness and athletic performance than the cure-alls of old were to ward off dropsy or nervous agitation, not all can be so easily dismissed. Several once exotic dietary supplements have been the focus of investigation for more than a decade now, and a select few can boast strong quantitative support as a result. One group in particular, the nutraceuticals, is attracting the attention of health advocates and scientists alike.

Occupying a space somewhere between essential nutrients (those nutrients critical to normal health, such as vitamins) and drugs with defined impacts on specific diseases, nutraceuticals are bioactive chemicals derived from foods but taken as supplements at much higher concentrations than diet alone could provide. They include antioxidants from fruits and berries, fatty acids found in cold-water fish, and potentially disease-fighting compounds from common spices such as cinnamon and turmeric. Claims have been made for their role in everything from fighting cancer and cardiovascular disease to maddeningly vague notions about "supporting healthy living."

"The category of nutraceuticals is really very broad, and their effects may be subtle," says Paul M. Coates, director of the Office of Dietary Supplements (ODS) at the National Institutes of Health. "That gives you a clue to the scientific challenges of understanding them. They range from supplements where we don't even know what the active ingredients are to compounds that are well characterized chemically but where the mode of action is still unknown."

To date, most nutraceuticals have been the subject more of marketing hype than of methodical clinical testing, and for many, it is not even yet known whether they provide more benefits than risks for consumers. But in at least a handful of

cases, the science is starting to catch up with the health claims.

The Fishy Benefit of omega-3s

Probably the best known of the nutraceuticals, the omega-3 fatty acids, are also the most intensively studied. Like all fatty acids, the building blocks of fats and oils, omega-3s are linear molecules with a carboxylic acid "head" at one end trailing a "tail" of linked carbon atoms. Those links can be made with either single (saturated) or double (unsaturated) chemical bonds. "Omega-3" simply refers to a double bond in the third position from the end of the carbon tail. Starting with alpha-linolenic acid (ALA, an essential nutrient common in many nuts and vegetable oils), our bodies can synthesize all the omega-3 fatty acids they need to build cell membranes and carry out a host of cellular functions.

But evidently we could stand to make a lot more of at least a couple of them. Beginning in the 1970s, epidemiologists started to notice that Eskimo and other groups of people who ate a lot of cold-water fish tended to have low levels of heart disease and stroke. Oil from such fish is packed with two unusually long omega-3s, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA).

"The epidemiological evidence was strong enough that it led to a whole series of clinical studies and randomized control trials with fish oil," says nutritionist Penny M. Kris-Etherton of Pennsylvania State University. By 2002 the results were positive enough for the American Heart Association panel on which Kris-Etherton sat to issue a statement recommending increased fish consumption for the general public and daily consumption or supplements of fish oil for coronary heart disease patients. Since then, Kris-Etherton says, "the evidence has just grown stronger for a cardioprotective effect from marine-derived omega-3 fatty acids."

Stronger, yes, though not necessarily less complicated. In a 2006 review of 842 scientific papers on omega-3 fatty acids and cardiovascular disease, a research team based at the Tufts–New England Medical Center in Boston concluded that only EPA and DHA seemed beneficial—ALA, their plant-produced precursor, was not. And while the studies showed clear evidence that fish oil helped to prevent heart attacks and cardiac deaths, especially among patients who had already suffered one heart attack, the effects on stroke were all over the map. For people who have pacemakers, too, "there is a mixed bag of evidence," Kris-Etherton says. "One study shows a benefit, one shows an adverse effect and one shows no benefit." It is a common issue with nutrition studies, she notes—given the vast diversity of human research subjects, variations in the concentration or mixture of supplements, and often uncontrolled factors such as baseline diets or preexisting illnesses, "it's not unusual to see different studies canceling each other out."

Understanding exactly how DHA and EPA work would help, but the molecular pathways underlying the fatty acids' heart-protective activity are still unknown. They seem to lower blood levels of triacylglycerol (often called triglyceride), keep cholesterol from gumming up arterial walls, and help to control unwanted blood clotting and inflammation, among other risk factors. Given that fish oil has now been linked to improvements in everything from asthma and rheumatoid arthritis to type 2 diabetes and neurological diseases, there is almost certainly more than one molecular mechanism in play and almost certainly a bright future for omega-3 fatty acids on the supplement shelf.

Science Sours on Favorites

The outlook is not quite so rosy for all the early candidates for nutraceutical stardom, however. In many ways, lycopene was a food manufacturer's dream compound. Grocery profit margins are notoriously slim, and adding nutraceuticals to staple foods has been prohibitive: consumers who will pay $20 for a bottle of fish oil pills balk at shelling out an additional dollar for a loaf of bread supercharged with omega-3 fatty acids. But lycopene, a deep-red plant pigment and powerful antioxidant, not only shows up in plants such as tomatoes for free, its bioavailability is actually increased by the boiling, squeezing and other rigors of food processing.

Early epidemiological studies suggested that men who ate diets rich in tomato products enjoyed lower than average rates of prostate cancer, and lycopene was identified as the likely reason. The ironic result is that while ketchup may not be the school lunch "vegetable" President Ronald Reagan once claimed it to be, for a while even a foil packet of the stuff had a legitimate shot at being declared a dietary supplement.

Ulrike Peters isn't happy that she had a hand in placing ketchup back in the condiment aisle. A nutrition and genetics epidemiologist at the University of Washington and the Fred Hutchinson Cancer Research Center in Seattle, she had high hopes for lycopene's cancer-fighting ability.

But when her research team analyzed blood lycopene levels of participants in a large cancer study, including 692 men who had developed prostate cancer and 844 randomly selected men who had not, they found no association between

the antioxidant and the malignancy. Even more troubling, her study found a link between high blood levels of lycopene's chemical cousin, beta-carotene, and an increased risk of aggressive prostate cancer—not enough to justify avoiding carrots and other food sources of beta-carotene but an ominous sign that not all food-derived compounds are necessarily benign when taken at higher doses.

"The results were very disappointing," Peters says. "It would be great to have such an inexpensive way to lower prostate cancer risk, but our study dampens that possibility. Unfortunately, it often happens that health claims get out in front of scientific evidence."

Whether that has also been the case with another, much more popular supplement is still unclear. Glucosamine, a simple amino sugar, is well known to biochemists as the precursor for a wide range of important structural components of the body, including the protein collagen in tough connective tissues such as tendons and ligaments. Collagen is also a major component of the cartilage that makes up the smooth layer that protects and lubricates the bones in joints. Early observational studies suggested that glucosamine could be helpful in combating the pain and cartilage destruction of osteoarthritis, and it is widely available as a supplement derived from shellfish, often in combination with the biochemicals chondroitin sulfate, which helps to make collagen spongy, and methylsulfonylmethane (MSM), a potential anti-inflammatory agent.

Consumer sales reached an estimated $818 million for glucosamine and chondroitin sulfate in 2006, according to the Nutrition Business Journal. Observational studies, while sometimes contradictory, have suggested that arthritis sufferers do indeed benefit from using the supplements. That possibility led to a large NIH-funded clinical trial of the supplements involving patients with knee osteoarthritis. For 24 weeks, 1,583 participants in the aptly named GAIT (Glucosamine/chondroitin Arthritis Intervention Trial) were given one of the following treatments: glucosamine, chondroitin sulfate, both in combination, a placebo, or the COX-2 inhibitor Celebrex (celecoxib) as a control. (COX-2 inhibitors have since been linked to negative cardiovascular side effects.)

The results, published in 2006, were underwhelming. True, almost 67 percent of the patients taking glucosamine plus chondroitin sulfate reported a significant decrease in knee pain—but so did fully 60 percent of those taking the placebo. Only in patients with moderate or severe knee pain at the outset did the supplements show a significant advantage over the placebo, with almost 80 percent of that group reporting a significant improvement, compared with 54.3 percent who took the inert pills. That favorable result is nothing to sneeze at—nor, for that matter, is a placebo effect of 60 percent—but it's far from warranting a blanket recommendation.

Simple Foods Aren't So Simple

Even if ketchup is one day recognized as a nutritional powerhouse, it's not likely to topple tofu from its shimmering, gelatinous perch atop the health food heap. High in protein and low in sugars and unhealthy fats, soybeans and the bean curd produced from them have long been lauded as a sound substitute for animal proteins. But they are also loaded with bioactive compounds, and the science is not yet in on whether consuming them at nutraceutical doses is a good or bad thing. The most investigated of those are a group of hormonelike polyphenols called isoflavones, which seem to have effects on everything from kidney and cardiovascular disease and various cancers to hot flashes, bone calcium loss and other symptoms of menopause.

Connie Weaver, a Purdue University nutritionist and director of that institution's Botanicals Research Center for Age Related Diseases, first became interested in soy isoflavones in 1999. "I went to a local health food store," she recalls, "and there were 13 different supplements that claimed to be effective for bone loss." But when she checked the research, Weaver recalls, "the literature was pathetic. I decided we'd better start doing some studies."

What she and other researchers have found is a vast swamp of complexity. Of the two main isoflavones, genistein and diadzein, the former seems to be more effective in preventing osteoporosis. Unless, that is, the person consuming it happens to have bacteria in the gut that convert the compound diadzein into another one called equol, which might offer more bone protection than either of the soy isoflavones—or might not. And there's even some worry that the soy compounds could boost rates of breast cancer, just as estrogen supplements used in hormone replacement therapy can.

"Nutritionally you've got to appreciate soy," Weaver says, "but there are also all these bioactive substances in there." At high concentrations, she adds, "the problem is that they do some good things, some other things, and some who-knows-what things." The goal, Weaver asserts, "is to figure out what combinations have advantageous impacts on bone health, heart health, and so on, without deleterious impacts." At least three long-term trials testing the effects of soy isoflavones on bone health are in progress, Weaver notes, "but we've got a long way to go before we can say what works and what

doesn't."

That conclusion means more research, of course, and dozens of nutraceutical trials are under way, many sponsored by ODS and other branches of the NIH. But some investigators fret that vital studies are being rushed or overlooked because of limited research funding. Peters worries that lycopene's lackluster performance to date may mean that it never progresses to clinical trials—a situation that could leave millions of consumers paying for supplements that might not be doing them any good. "We can't recommend using lycopene based on the current evidence," Peters says, "but that doesn't mean it has no benefit. There are some important studies that haven't yet been done."

Similarly, Greg M. Cole, a researcher at the University of California, Los Angeles, who sees great promise in using omega-3 fatty acids to prevent Alzheimer's disease and other forms of age-related dementia, expresses concern that current clinical trials lack funding to target the most promising patient population—people who have not yet started to show signs of those problems. "The risk of Alzheimer's doubles with every five years after age 65," he says, "and we've got a generation of 75 million people heading into that. We can't afford to miss something that might help with prevention just because we couldn't find the money to study it."

Not-So-Helpful Guidelines

In the meantime, patients, physicians and just plain folks will have to do the best they can to make smart choices with incomplete and potentially misleading information. The oversight of dietary supplements is loose: FDA regulations allow for several different types of efficacy claims to be made on labels, including fairly robust "significant scientific agreement" claims that the nutrient in question has a direct effect on a specific disease, but also so-called qualified health claims, where phrases such as "some evidence suggests that" are added. There's even room for "structure/function" claims: "calcium builds strong bones" is a noncontroversial example—which are not even evaluated by the FDA. (The claims do have to carry a footnoted disclaimer to that effect, however, a stipulation that can result in supplement labels with more asterisks than a Major League Baseball record book.)

"The danger of pseudoscience and quackery is very real," says Jeffrey I. Mechanick, an endocrinologist at the Mount Sinai School of Medicine who has written extensively about the use of dietary supplements in the treatment of diabetes and other metabolic diseases. "Dietary supplements in general should not be supplanting proven therapies," he cautions, "but I don't see any reason to use words like 'alternative' or 'complementary' to describe them. I just use 'proven' or 'unproven,' and that proof is what should guide patients and their physicians."

For many nutraceuticals, the most compelling evidence for efficacy remains anecdotal or, at best, based on hints of benefit from small or poorly controlled studies. Still, Weaver says, that doesn't stop several of the researchers at her institute from using nutraceutical supplements themselves. "Anecdotal evidence really shouldn't be very convincing to scientists," she says, "but people remain hopeful." That hope, to a large degree, is what fuels the popularity of dietary supplements. But it's good science that ultimately will determine whether the hope is well placed or not.