

# Nutraceuticals

## Move In

These products, in a gray area of FDA regulation, are gaining on prescribed drugs.

BY CHRISTEN L. BROWNLEE

**T**HE FAMILY medicine cabinet is currently experiencing a revolution. Interspersed among the familiar myriad of over-the-counter pain medicines, cough syrups, and prescription drugs are a slew of newcomers: green tea capsules for antioxidants, garlic to boost the immune system, fish oil concentrate to maintain clean arteries, and ginkgo biloba to aid memory, to name a few.

These supplements, as well as vitamins, protein powders, and a whole range of “functional foods”, fall into the category of nutraceuticals—a gray area of FDA regulation. Not quite drugs, yet not exactly foodstuffs, these products enjoy the benefit of making healthy-sounding claims without having to be regulated as medicines. Business is booming for this sector because of companies hawking their particular products’ benefits, but it has not remained unchecked—media scares about dangerous reactions

linked to supplements, as well as several studies that indicate the likelihood of drug interaction between certain nutraceutical ingredients and standard medications, have jarred consumer confidence in the nutraceutical industry. However,

with the help of well-designed studies and the participation of prescription drug companies, many nutraceutical products may prove beneficial and financially profitable for years to come.

### Vague definition

The word “nutraceutical”, a composite of “nutrition” and “pharmaceutical”, was coined in the late 1980s by Stephen L. DeFelice. A physician and clinical pharmacologist, he started the Foundation for Innovation in Medicine in 1976. The purpose of this nonprofit organization was to accelerate medical discovery by establishing



a more productive clinical research community. Originally, DeFelice had hoped the name itself would stimulate an interest in the field so that researchers would want to study natural dietary substances.

However, what falls into the category of nutraceuticals is difficult to define—and the definition of the term varies depending on whom you ask. According to the Nutraceuticals Institute, a research, education, and outreach program formed through the partnership of Rutgers University in New Brunswick, NJ, and St. Joseph's University in Philadelphia, nutraceuticals are natural, bioactive chemical compounds that have health-promoting, disease-preventing, or medicinal properties. Vitamins, minerals, and herbal supplements fall into this category, as do some neurotransmitters, hormones, and animal products such as shark cartilage and glandular extracts. In addition to these examples, which are usually taken as separate supplements to the diet, nutraceuticals include “functional foods”—foods that tout a particular health benefit based on their ingredients.

“I think the thought is that it is something you can take in your diet as a foodstuff, but which provides a physiological benefit to you beyond basic nutrition—that is, beyond the calories, there are other benefits to be had from consuming such an ingredient,” says John Cardellina, vice president of botanical science and regulatory affairs for the Council for Responsible Nutrition, a Washington, DC-based trade association for the dietary supplement industry.

However, this wide-open definition leaves much room for improvisation. Although many companies would like to throw ordinary food products considered healthful, such as fresh vegetables and lean meats, into this category, others would just as soon remove their products from the mix for fear of further scrutiny from regulators that might consider them to be medicine.

For example, SoBe Beverage Co., a soft drink manufacturer based in Norwalk, CT, makes a variety of “healthy beverages” with added vitamins, minerals, or botanical ingredients—for example, their Exotic Teas line has added ginkgo, ginseng, and guarana. However, the company is hesitant to use the word nutraceuticals to describe its products. “We think consumers are into the idea of great-tasting, fun, better-for-you beverages. Whether this is related to ‘nutraceuticals’ is hard to determine,” said Kristine Hinck, a SoBe spokesperson. “SoBe is very careful never to make health claims for any particular ingredient,” she added.

## Industry regulations

Why is SoBe so hesitant to make health claims? Because, like other supplement and functional food manufacturers, its products fall under the jurisdiction of the Dietary Supplement Health and Education Act (DSHEA), a law crafted in 1994 to create a regulatory framework for the safety and labeling of dietary supplements. DSHEA amended the Federal Food, Drug, and Cosmetic Act issued in 1938.

Under DSHEA, “a firm is responsible for determining that the dietary supplements it manufactures or distributes are safe and that any representations or claims made about them are substantiated by adequate evidence to show that they are not false or misleading” (1). This means that dietary supplements do not need approval from the FDA before they are marketed. Except in the case of a new dietary ingredient, where premarket review for safety data and other information is required by law, a firm does not have to provide the FDA with the evidence the firm relies on to substantiate safety or effectiveness before or after it markets its products.

Although DSHEA does set some guidelines for the industry, it gives companies a certain amount of leeway in following them. An ingredient may be regulated as either a drug or a supplement depending on its intended use—how it's marketed, for what purpose, and what instructions are given to the consumer. For example, ma huang, an herb, and ephedrine, a drug (marketed as a cough and cold reliever, a sports-performance aid, or a weight loss aid), have the same active ingredient, ephedra alkaloid. Ephedrine is regulated under laws pertaining to drugs, yet ma huang passes under the much looser scrutiny of the DSHEA.

Also, while supplements cannot make specific health claims without proof, they are allowed to make amorphous health statements (e.g., “Kava kava *may* aid in relaxation”) or extremely general structure–function claims (e.g., “Calcium aids in the development of strong bones”).

## Proven benefits, proven harm

Despite the fuzzy health claims of some nutraceutical firms, many of these products are proving their worth in studies performed by academic institutions and the NIH, among others. Most of the ingredients attracting attention, such as cranberry extract and garlic, have been used as folk remedies for hundreds, even thousands, of years.

“When I hear the results of some of these studies, I think, ‘Listen to your mother.’ People have known for thousands of years that these foods or plants had a positive effect,” said Steven Yanicelli, registered dietician and director of continuing education at supplement manufacturer Pharmavite, based in Mission Hills, CA. “The chemistry didn't catch up, so no one really knew what the active ingredients were—what it was that had an effect on a person.”

In one recent study, researchers found that cranberry concentrate, a common but previously unproven folk remedy for urinary tract infections (UTIs), actually did have a positive effect in preventing illness when tested in women who commonly get the infections. Researchers from the Finnish Student Health Services at Oulu University recruited 150 women with persistent UTIs. Fifty drank 50 mL of cranberry juice a day for 6 months. Another 50 drank a preparation of *Lactobacillus*, a “friendly” bacteria that helps prevent yeast infections, and the final



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50 women were given no treatment. After six months, only 8 women taking cranberry juice had experienced a UTI, compared with 19 of those taking *Lactobacillus* and 18 not taking anything (2).

Also, when participants in another study took a pill containing 300 mg of garlic powder (equivalent to two cloves) daily, age-related stiffening of the aorta was delayed. Study authors theorized that the garlic raises blood levels of nitric oxide, which is a compound known to protect arteries and aid in blood flow (3).

However, on the flip side, other studies have shown popular nutraceuticals as having a detrimental effect or having no effect at all. For example, a recent study found that St. John's wort, an herbal supplement used to counter mild depression, may reduce the effect of a commonly used chemotherapy drug called irinotecan (4). Study authors also noted that St. John's wort combined with irinotecan appeared to increase the cancer drug's ability to suppress bone marrow cells, a potentially toxic side effect of the treatment that increases patients' susceptibility to infections.

According to Cardellina, St. John's wort is the leading prescription antidepressant in Germany, where it is regulated as both a supplement and a drug. It has been found to interact with numer-

ous other drugs in addition to irinotecan. Ironically, notes Cardellina, those drug interactions seem to affect those populations in the worst way who would otherwise benefit the most from its use.

“Organ transplant patients often tend to be mildly to moderately depressed because of their life condition. Some take cyclosporine to prevent rejection, but side effects of this medication are magnified in that population when they take St. John's wort,” said Cardellina. He added that the same is true in the case of AIDS patients taking protease-inhibiting drugs—other medications, including St. John's wort, limit the effect of protease inhibitors.

Another recent study slammed the popular supplement ginkgo biloba, touted as a memory aid, as being ineffective. The supplement, tested over a period of six weeks in a population over age 60 and in good mental health, did not appreciably change the mental acuity of these individuals (5).

### **Big business attracts pharmaceutical companies**

Despite the detrimental claims of such studies, nutraceuticals continue to be a huge business. After experiencing a boom in the early

to mid-1990s, the industry continues to grow. According to MarketResearch.com, an online market research firm, the retail dollar sales of nutraceutical foods and beverages reached \$17.2 billion in 2001. Sales of nutraceuticals grew a total of 19.4% between 1997 and 2001, and they are expected to top \$22.5 billion in 2006.

It is not surprising, then, that Big Pharma has decided to join in by making their own nutraceutical products. Bristol-Myers Squibb (BMS, New York), GlaxoSmithKline (GSK, London), and Johnson & Johnson (J&J, New Brunswick, NJ) have each created a line of "nutritional" products—functional foods and supplements meant to fill specific dietary needs. These products include several infant formulas, such as BMS's Enfamil line, but they also include many products made for adults, such as GSK's energy drink, Lucozade, and J&J's cholesterol-reducing margarine, Benecol.

Benecol contains plant stanol esters, which block absorption of cholesterol from the digestive tract. This, in turn, helps to lower blood levels of LDL cholesterol without affecting HDL cholesterol levels.

Also, prescription drug companies who own smaller subsidiaries that sell supplements and functional foods may be more likely to step up internal regulations so that these products are treated more like drugs. According to Yanicelli of Pharmavite, which is owned by Otsuka Pharmaceuticals based in Tokyo, his company



is working with the American Botanical Council to provide a pullout guide on all the herbs they sell. The guide, appearing this fall, will include information about each supplement similar to what is available for prescription drugs: who it is recommended for and who should not take it, contraindications, information for women who are pregnant or lactating, adverse events, and drug interactions.

Yanicelli says that these efforts, so far, are completely voluntary—no plans exist for such information to become mandatory for supplements made by other companies. "We hope it will improve consumer confidence in the whole industry," he said.

However, the information provided will only be as current as the most recent studies. As the number of people taking nutraceutical supplements continues to rise, so will the knowledge scientists receive on the products' benefits and safety.

#### References

- (1) FDA's DSHEA site; <http://vm.cfsan.fda.gov/~dms/supplmnt.html>.
- (2) Kontiokari, T.; et al. *Br. Med. J.* **2001**, *322*, 1571.
- (3) Breithaupt-Grogler, K.; et al. *Circulation* **1997**, *96*, 2549–2555.
- (4) Mathijssen, R.H.J.; et al. *J. Natl. Cancer Inst.* **2002**, *94*, 1247–1249.
- (5) Solomon, P. R.; et al. *J. Am. Med. Assoc.* **2002**, *288*, 835–840.

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