Herbal Lottery

What's on a dietary supplement's label may not be what's in the bottle

Janet Raloff

Echinacea is a commercial success. The dietary supplement—made from the flowers, stems, and leaves of the purple coneflower—has become a popular and lucrative over-the-counter cold remedy. It's also one of the few nutraceuticals—natural products with medicinal reputations—that have substantial scientific evidence to support its purported functions: Various studies suggest that echinacea supplements can boost immunity or shorten the duration of colds.

Several years ago, however, Christine M. Gilroy of the University of Colorado Health Sciences Center in Denver was unsure whether to trust data from those experiments because few reports included biochemical proof of which species of purple coneflower had been used. That's important, she notes, because three species—Echinacea pallida, Echinacea purpurea, and Echinacea augustifolia—turn up in supplements "and only the first two have data indicating they might make colds better."

Curious about E. pallida's reputed power against colds, Gilroy designed a study and then ordered dried samples from three suppliers. She sent some of each delivery out for analysis of chemicals that were known to distinguish the species and that might even have therapeutic activity.

The data that came back put her study on hold. They showed no batch containing pure E. pallida. The one from a bulk wholesaler that supplies herbal-products companies contained almost no Echinacea from any species, and what little there was consisted solely of E. purpurea. The other batches, acquired directly from coneflower growers, did contain E. pallida—but also contaminating plants, including E. augustifolia.

Gilroy then turned to 59 commercial echinacea products from local stores. Her team's analyses, reported in the March 24 Archives of Internal Medicine, show that none offered consumers what had been promised by its label. Six contained no evidence of any echinacea, and 28 failed to contain the specific species that was listed on the box. Some offered echinacea in quantities exceeding or, more often, falling below the quantity on the label—sometimes substantially.

These findings call into question the conclusions of the many earlier studies of echinacea's purported cure for the common cold, says Gilroy. At the least, they suggest that health effects seen with one sample of supplement might not hold for others.

This is just the latest in a string of studies revealing variability in the ingredients of dietary supplements on the market today. Uniform products require consistent ingredients and processes throughout every stage of manufacturing. The troubling findings suggest that
many herbal-product makers aren't maintaining adequate quality control.

Several weeks ago, the Food and Drug Administration proposed rules designed to stem quality-control problems in dietary supplements, including nutraceuticals. The agency would mandate so-called good manufacturing practices, or GMPs, in the industry. Under GMPs like those now governing pharmaceuticals, all manufacturers of dietary supplements would have to chemically validate their ingredients and keep stringent records. These would include temperature readings from each batch as it's made and notes about any breakdowns of factory equipment.

However, representatives of the nutraceutical industry say they plan to call for amendments to the proposed FDA rules. They're currently analyzing the hundreds of pages of details before requesting changes. Moreover, any set of standard practices may be severely challenged by the complex makeup of herbal products, several scientists told *Science News*.

"For the most part, with [herbal] supplements, we still don't know what all the active ingredients are," so nobody knows the ideal formulation of most supplements, observes Bill J. Gurley of the University of Arkansas for Medical Sciences in Little Rock.

Says David J. Newman of the National Cancer Institute in Frederick, Md., "The bottom line remains *caveat emptor*," or let the buyer beware.

**Beyond echinacea**

There's evidence for poor quality control in the making of many dietary supplements, says Chien M. Wai of the University of Idaho in Moscow. His work focuses on those made from leaves of the maidenhair tree (*Ginkgo biloba L.*). Ginkgo supplements fight memory loss and reinvigorate blood flow in the brain, according to users of the herb.

Scientists have identified five purported active ingredients in ginkgo. In most cases, Wai finds, a product's label describes only how much bulk ginkgo tissue a tablet, powder, or tincture contains without quantifying the active agents. Concentrations of those agents can vary widely in plant tissue.

In 2001, Wai's group reported data showing that, for instance, supposedly equally potent ginkgo supplements could contain anywhere from 0 to almost 4 milligrams of active compounds. Brands varied in which active chemicals dominated them, and some brands exhibited large batch-to-batch variation.

His subsequent studies, Wai says, indicate "the situation is not getting better."

Consumers can't use his team's reports to avoid supplements with weak or erratic ingredients because the researchers haven't published any brand names. Companies challenge any implied criticism of their products, Wai explains, and "we can't afford the time to fight lawsuits."

Gurley has named brands in his published analyses of supplements containing the weight-loss stimulant ephedra and indeed "stirred up a hornet's nest," he notes. It started 3 years ago, when his team first surveyed 20 over-the-counter ephedra products. As Gilroy found...
with echinacea, the ingredients often didn't match label claims.

Tissues from the *Ephedra sinica* plant, like ginkgo, contain at least five purported active ingredients, which are in the chemical family named alkaloids. Each alkaloid has a different effectiveness as a stimulant, and its concentration varies among individual plants. Most supplements that are labeled with ingredient information claim only to have some specified quantity of mixed ephedra alkaloids—information too general to offer much gauge of potency, says Gurley.

Although one brand that his team tested contained none of the five stimulant alkaloids, most had several, but the amounts varied among brands. When the researchers tested several batches of a brand, some differed in concentration by up to tenfold. Only 13 of the 20 products listed a total quantity of alkaloids on the label; others just listed quantities of the raw source plant. In many cases, Gurley says, those values bore no relation to what was present. His group published its findings in 2000. Since then, the researchers' tests of 130 additional ephedra products found far fewer discrepancies between labels and contents, "although they do still occur," says Gurley.

His team has lately turned to St. John's wort (*Hypericum perforatum*), a possible antidepressant. The researchers are finding a wide range of concentrations of St. John's wort's purported active ingredient, which is called hyperforin. Batch-to-batch hyperforin differences in one supplement brand varied 15-fold.

Gurley acknowledges that some herbal-supplement companies reliably produce what their labels promise. The trick is identifying them, Gurley says, a task beyond the capability of most consumers.

Many explanations

Quality-control problems in herbal supplements often start with the hundreds of chemicals that plants contain. The type and quantity of these compounds vary in response to the environment in which a plant grew: its soil type and nutrition, water availability, excessive heat or cold, exposure to toxic minerals, degree of shading, and any hybridization.

One team is studying horticulturally triggered variations in several citrus compounds that are regarded as potential nutraceuticals because they've inhibited cancers in laboratory animals. Data collected by Bhimanagouda S. Patil and his colleagues at Texas A&M University in Weslaco show that concentrations of one such chemical—limonin glycoside—peaks midway through the crop's harvest season. So, when it comes to this agent, Patil says, "you must eat two grapefruit in May to get what one picked around Christmas will give you."

He's also been quantifying lycopene, a potential anticancer carotenoid that turns plants red. When his group planted Florida-derived rootstock of Star Ruby grapefruit in Texas, the fruit produced some 50 percent more of this carotenoid than it had in Florida.

Researchers at the University of Newcastle in Ourimbah, Australia, are studying effects of manufacturing techniques on nutraceutical quality. For instance, Douglas L. Stuart and Ron B.H. Wills report that high temperatures reduce concentrations of one of the potential therapeutic agents derived from *E. purpurea*. The scientists report in the March 15 *Journal*...
of Agricultural and Food Chemistry that drying the plant at 40°C results in one-third more cichoric acid than drying it at 70°C does.

Moreover, Wai's team has shown that whether oil, alcohol, or water is used can affect which chemicals are extracted from a plant. These products can have different potencies.

Even if purported active ingredients make it into a supplement, poor manufacturing techniques can yield tablets that don't effectively release those chemicals, notes Larry L. Augsburger of the University of Maryland in Baltimore.

Working with a synthetic version of melatonin, a hormone that promotes sleep, seems to fight jet lag (SN: 5/13/95, p. 300), and maybe even battles cancer (SN: 10/17/98, p. 252: http://www.sciencenews.org/sn_arc98/10_17_98/19981017fob.asp), his team showed that tablets don't always release their contents in a timely fashion. Although industry standards for the breakdown of conventional drugs is generally 30 minutes or less, his test-tube studies showed that some commercial melatonin supplements didn't disintegrate or release their contents for periods of 4 hours to more than 20 hours, by which time an ingested tablet may well have been excreted.

Help on the way?

In the early 1990s, nutraceutical manufacturers feared that FDA would challenge their label claims. Then, the 1994 Dietary Supplement Health and Education Act was passed, permitting the sale of nutraceuticals and other supplements that are nontoxic and make no curative claims.

Immediately following the act's passage, sales of herbal supplements skyrocketed, with many companies regularly reporting up to 11 percent annual growth. But by 2000, U.S. sales started flagging, observes Clare M. Hasler of the University of Illinois at Urbana-Champaign. Reports were emerging of health risks associated with some products, such as ephedra; uncertain efficacy of others; and quality-control problems in the industry.

Because that last item appears to be the easiest for manufacturers to fix, some nutraceutical makers have been voluntarily adopting GMPs of their own design, says Nancy Childs of St. Joseph's University in Philadelphia. These companies tend to be the large prescription-drug manufacturers that have entered the nutraceuticals market in the past half-decade, she adds.

Most nutraceutical makers are far smaller than those companies, notes Kim Smith, an attorney with the National Nutritional Food Association (NNFA) of Newport Beach, Calif. Since 1999, her trade group—which represents many nutraceutical makers with 20 to 500 employees—has provided guidance for developing voluntary GMPs. NNFA also officially supports FDA's March 28 proposal for mandatory GMPs. "It will go a long way toward improving credibility in the industry," Smith says.

However, she adds, small firms could have a hard time paying for stringent FDA-required monitoring and record keeping. The agency estimates that first-year costs for small firms will run about $100,000, with annual costs of $60,000 or so thereafter. In fact, Smith says, her group suspects FDA is substantially underestimating those costs.
Success in complying with mandatory GMPs, Hasler suspects, "is going to sort out the [nutraceutical industry's] major players from the fly-by-night companies and probably put some small players out of business." She adds, "I'm not sure that's a bad thing."

Allen Montgomery, executive director of the American Nutraceuticals Association in Birmingham, Ala., which represents pharmacists and other health professionals, agrees. He says, "I don't know of any other billion-dollar industry that makes ingested products for which [mandatory] GMPs are not in place."

Within the nutraceutical industry generally, Gurley charges, "there are so many bad actors right now, that it's giving the whole industry a bad name."

Fortunately, Montgomery notes, several independent groups—such as the U.S. Pharmacopoeia (USP) of Rockville, Md.—have already begun validating voluntary GMPs for several products. USP is the official standards-setting body for all U.S. medicines and dietary supplements.

Companies that want to carry the USP logo must submit products for a series of stringent tests of such features as a product's purity, potency, and consistency. Also, USP inspectors visit factories to confirm that GMPs are in place, notes Sherrie L. Borden, the organization's spokesperson. "Then we do postmarket surveillance [of a supplement] once a product is on the shelf. It's very rigorous," she notes, "because this mark carries a lot of credibility."

All this sounds comforting, Gurley says, except that pharmaceutical-grade uniformity in herbal products may be amazingly difficult to achieve, and FDA's new rules don't address the complexity of a plant's make-up. Synthetic drugs and vitamins tend to have only one or two well-characterized active ingredients, he explains, while herbal supplements "are a veritable pharmacological Pandora's box."

Indeed, the 48 nutraceuticals that USP recently vetted—all produced under the Nature Made or Kirkland Signature labels—contain only vitamins, minerals, or fish oil—not complex herbal products.

Since plant tissue may contain hundreds of compounds with perhaps dozens of active ingredients, Gurley asks, who knows which of these should be standardized in each product? This "truly daunting" problem would challenge the best pharmaceutical manufacturer, he says, let alone a 30-employee herbal-products company.

Wai and Newman say that they'd like to see the herbal-supplements market develop into a natural-products offshoot of the over-the-counter drug industry. They argue that the best route for making safe and effective nutraceuticals would be to identify each plant's active agents, isolate them for testing in the same kind of trials that conventional pharmaceuticals go through, and then package the proven chemicals in carefully measured doses.

An advantage to this approach for manufacturers, Newman argues, is that unlike an herb, the recipe for a cocktail of natural chemicals is patentable. Thus, it might be market forces after all that bring consistency to the nutraceutical marketplace.

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References and Sources

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Further Readings:


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