

# Spice Healer

By Gary Stix

Searching for new drugs by milling through ancient folk pharmacopoeia or by just picking a plant while walking in the woods has a decidedly checkered history. Many well-established therapeutic compounds originated in trees, shrubs, mollusks, even dirt. Aspirin came from willow bark, cholesterol-lowering statins from a mold, and the antimalarial artemisinin from a shrub used in traditional Chinese medicine. Yet after raising \$90 million during the 1990s in a much publicized bid to tap indigenous knowledge for new drug leads, Shaman Pharmaceuticals had to lower its sights until it was doing nothing more than selling its products as nutritional supplements before finally shutting its doors for good a few years ago.

Now the trend may be reversing itself again. Recently a number of natural compounds—such as resveratrol from red wine and omega-3 fatty acids from fish oil—have begun to receive close scrutiny because preliminary research suggests they might treat and prevent disease inexpensively with few side effects.

**TURMERIC**  
(*Curcuma longa*)  
grows rhizomes,  
tuberous under-  
ground stems,  
from which the spice  
of the same name  
is produced.

DANIELA NAOMI MOLNAR



Turmeric, an orange-yellow powder from an Asian plant, *Curcuma longa*, has joined this list. No longer is it just an ingredient in vindaloes and tandooris that, since ancient times, has flavored food and prevented spoilage.

A chapter in a forthcoming book, for instance, describes the biologically active components of turmeric—curcumin and related compounds called curcuminoids—as having antioxidant, anti-inflammatory, antiviral, antibacterial and antifungal properties, with potential activity against cancer, diabetes, arthritis, Alzheimer's disease and other chronic maladies. And in 2005 nearly 300 scientific and technical papers referenced curcumin in the National Library of Medicine's PubMed database, compared with about 100 just five years earlier.

Scientists who sometimes jokingly label themselves curcuminologists are drawn to the compound both because of its many possible valuable effects in the body and its apparent low toxicity. They ponder how the spice or its derivatives might be used, not just as a treatment but as a low-cost preventive medication for some of the most feared ailments. As a treatment, it also has some enticing attributes. Because curcumin targets so many biological pathways, it could have benefits for cancer therapy: malignant cells may be slow to acquire resistance to

taken another approach to seeking cancer treatments. That work led him circuitously to the compound.

In the 1980s Aggarwal and his team at Genentech were the first to purify two important immune molecules—tumor necrosis factor (TNF) alpha and beta—that have been identified as potential anticancer compounds. These molecules can, in fact, kill cancer cells when deployed in localized areas, but when circulated widely in the bloodstream, they take on different properties, acting as potent tumor promoters. The TNFs activate an important protein, nuclear factor kappa B (NF kappa B), which can then turn on a host of genes involved in inflammation and cell proliferation.

This link between inflammation and the unchecked proliferation of cancer cells prompted Aggarwal to return to his roots. In 1989 he moved to the University of Texas M. D. Anderson Cancer Center and began looking for compounds that might quell inflammation and have an anticancer effect. Remembering from his youth in India that turmeric was an anti-inflammatory in the Ayurvedic literature, he decided to give the spice a try. "We took some from the kitchen and threw it on some cells," he remembers. "We couldn't believe it. It completely blocked TNF and NF kappa B."

Aggarwal has gone on to publish studies showing that blocking the NF kappa B pathway with curcumin inhibits the replication and spread of various types of cancer cells. This work has served as a jumping-off point for early, small clinical trials at M. D. Anderson using curcumin as an adjunct therapy to treat pancreatic cancer and multiple myeloma. Trials are beginning or under way elsewhere for prevention of colon cancer and Alzheimer's disease, among others. And early cell-based or animal studies have shown that curcumin may act against a range of inflammatory diseases, including pancreatitis, arthritis, inflammatory bowel disease, colitis, gastritis, allergy and fever. It has also shown some promise for diabetes and autoimmune and cardiovascular diseases.

So far the large clinical trials needed to prove efficacy against cancer and other diseases have yet to be conducted. But Aggarwal has nonetheless become an aggressive champion for a spice that Vasco da Gama brought back to Europe from his voyages eastward. Aggarwal's chapter in a new textbook that he co-edited is entitled "Curcumin: The Indian Solid Gold."

M. D. Anderson, a world-leading cancer institution, has also begun to promote the use of curcumin more than would be expected for a treatment that has not gone through the rigors of full clinical trials. The "frequently asked questions" section on its Web site recommends buying curcumin from a specific wholesaler, for which Aggarwal has served as a paid speaker. That company even issued a press release declaring that its product is the "ingredient of choice" of M. D. Anderson.

The FAQ section suggests that cancer patients gradually work up to a daily dose of eight grams a day, some 40 times the amount consumed in the average Indian diet. Most phar-

## Can an ingredient in curry treat diseases from Alzheimer's to cancer?

it and so might have to go through multiple mutations to avoid the substance's multipronged attack.

But is the compound ready for widespread use? Some work offers grounds for caution. Among the more than 1,700 references to curcumin in PubMed are studies showing how a compound that can affect so many biological pathways can sometimes hit the wrong switch and actually help to foster disease.

### Long Medical History

KNOWN AS HALDI IN HINDI, *jiang huang* in Chinese, *manjal* in Tamil (and just plain "yuk" as the yellow stain on a white T-shirt from the splatting of ballpark mustard), turmeric has a medicinal history that dates back 5,000 years. At that time it was a key medicament for wound healing, blood cleansing and stomach ailments in India's Ayurvedic system of medicine.

The first record in PubMed of research on the biological activity of curcumin dates back to 1970, when a group of Indian researchers reported the effects of the compound on cholesterol levels in rats. The pace of studies picked up in the 1990s; one of the leaders was Bharat Aggarwal, a former scientist at Genentech who, before turning to curcumin, had

maceuticals, in contrast, are meted out in milligrams. At one point, the Web site had even asserted: "By the end of eight weeks, a significant improvement is expected." Asked whether he was worried that any side effects might emerge at a dosage of eight grams, Aggarwal said that small clinical trials at other institutions have dosed up to 12 grams and that patients would have notified him if any untoward effects had occurred with the dosage recommended by M. D. Anderson. The researcher, who takes a curcumin pill every day, shuns the caution typical of investigators before well-controlled, large-scale clinical trials have been conducted. "People take a lot of other supplements, and I don't think you need anything else if you're taking this," Aggarwal says.

### Does Curcumin Abet Cancer?

THE M. D. ANDERSON FAQs and the stream of press releases from various institutions on the wonders of curcumin ignore a small portion of the literature that points to a dark side: the possibility that this spice may sometimes actually encourage the survival of cancer cells. In 2004 Yosef Shaul in the department of molecular genetics at the Weizmann Institute of Science in Rehovot, Israel, was studying an enzyme, NQO1, that regulates the amount of a well-known protein called p53. When p53 levels increase in cells, the protein institutes a defensive maneuver for the organism by inducing cancerous or damaged cells to stop dividing or even to commit suicide.

Shaul and his colleagues had found that an anticoagulant, dicoumarol, and related compounds blocked NQO1, which prevented p53 from doing its job. The researchers wondered what would happen if they exposed p53 in normal and myeloid leukemia cells to antioxidants such as curcumin and resveratrol. To their surprise, curcumin, by inhibiting the same enzyme, stopped p53 from sending aberrant cells to the gallows, a finding that was reported in 2005 in the *Proceedings of the National Academy of Sciences USA*. A few other researchers have published similar results. Aggarwal responds to this body

of work by pointing to studies that show the opposite, that curcumin actually activates p53.

Clinical researchers will now have to address whether Shaul's work in cell cultures relates to what happens when a person ingests the compound. The curcumin concentrations used by the Weizmann team in cell cultures—measuring 10 to 60  $\mu\text{M}$  (micromolar)—are roughly comparable to levels reached in some of the test-tube experiments conducted at M. D. Anderson. But because curcumin is absorbed poorly from the gut into the bloodstream and is also broken down in the body rapidly, a patient consuming eight grams would probably end up with a concentration in blood plasma no higher than about 2.0  $\mu\text{M}$ , Shaul notes, although that level could range higher in the gastrointestinal tract and in the liver. It could also remain elevated if researchers develop various means of increasing the concentration of curcumin in the bloodstream.

M. D. Anderson's FAQs might convey the impression of certitude by prescribing an eight-gram dose. But the low presence of curcumin in the blood—and the corresponding need to elevate the amount consumed if the substance does indeed fight disease—is a challenge that will continue to nag curcumin researchers. The animal studies that investigators cite as suggestive of curcumin's diverse benefits have generally used less than the equivalent of eight grams in humans, and blood concentrations have usually been in the nanomolar range. "We don't know how to explain how such low concentrations of curcumin can be beneficial in animals tested," Shaul states.

Dose is everything for a new drug—any therapeutic agent, including aspirin, turns toxic at high levels. For most new pharmaceuticals, the best dose for achieving the desired blood plasma levels is usually found through round after round of preclinical trials in cell cultures and mice. Yet drug companies are not battling one another to be the first to conduct these tests on curcumin. They have a preference for highly targeted therapeutics: hitting a specific receptor, for instance, may treat disease while lowering side effects, whereas a drug with multiple ac-

## Recent Studies Show Possible Benefits from Curcumin ...

CONDITION	FINDINGS	INSTITUTION	PUBLICATION
Rheumatoid arthritis	An extract of turmeric root inhibited joint inflammation and destruction in rats	University of Arizona College of Medicine	<i>Arthritis and Rheumatism</i> , November 2006
Alzheimer's disease	In test-tube studies, curcumin helped immune cells degrade components of Alzheimer's plaques	U.C.L.A. and the Veterans Administration	<i>Journal of Alzheimer's Disease</i> , October 9, 2006
Colon cancer	In cell cultures, curcumin blocked the activity of a hormone tied to development of colon cancer	University of Texas Medical Branch at Galveston	<i>Clinical Cancer Research</i> , September 15, 2006
Colorectal polyps	A combination of curcumin and the plant compound quercetin reduced the size and number of precancerous lesions in five patients	Johns Hopkins University and Cleveland Clinic	<i>Clinical Gastroenterology and Hepatology</i> , August 2006
Cognitive impairment	More than 1,000 elderly subjects from Singapore who reported eating curry at least occasionally had better scores on a cognitive test than did those who rarely or never ate the dish, an effect that might be attributed to curcumin	National University of Singapore and other institutions	<i>American Journal of Epidemiology</i> , November 1, 2006

## ... But Some Research Suggests Possible Cancer-Promoting Effects

CONDITION	FINDINGS	INSTITUTION	PUBLICATION
Myeloid leukemia	Curcumin at high doses in cell culture spurs degradation of a protein, p53, that prevents replication of cancer cells or induces their death	Weizmann Institute of Science, Rehovot, Israel	<i>Proceedings of the National Academy of Sciences USA</i> , April 12, 2005
Colon cancer	Curcumin inactivates p53's tumor suppressor role in colon cancer cells	University of Utah	<i>Carcinogenesis</i> , September 2004
Breast cancer	Curcumin inhibits several chemotherapeutic drugs from inducing cell death both in cell culture and in animal models	University of North Carolina at Chapel Hill	<i>Cancer Research</i> , July 1, 2002



tions could, in theory, increase the chance that an unwanted effect will occur. Another reason is the nettlesome issue of property rights for folk medicines.

Turmeric is a poster child for one of the most noted intellectual-property cases on biopiracy, which pitted an Indian government-supported research organization against a 1995 patent issued to the University of Mississippi for the use of the spice for wound healing. The U.S. Patent and Trademark Office invalidated the patent after the Indian Council for Scientific and Industrial Research questioned whether one criterion for patentability—that an invention be new—had been met. The council objected by pointing to a 1953 Indian journal article about the spice and by offering a citation about turmeric's healing properties from an ancient Sanskrit text.

The patent office has subsequently issued patents for specific uses for curcumin as an isolate. But the rejection means that drug companies will never obtain a "product" patent with a much broader scope that would help them to fend off competitors for drugs based on the spice. A few small companies

are still trying to exploit the substance's promise by changing its chemical composition to enhance activity and, by creating a novel compound, to bolster intellectual-property protection.

AndroScience in San Diego plans to enter the first phase of clinical trials this year with a drug candidate for acne based on compounds derived from curcumin that were discovered in collaboration with the University of North Carolina at Chapel Hill. Similarly, Curry Pharmaceuticals in Research Triangle Park, N.C., is trying to raise financing to move curcumin derivatives from Emory University into clinical trials. But in an age of targeted pharmaceuticals, venture capitalists, leery of side effects, have been hesitant to back new drugs that act on multiple pathways. For his part, Aggarwal, even though he is a co-founder of Curry Pharmaceuticals and holds patents on curcumin, asserts that chemists may have trouble improving on nature: modifying curcumin may only introduce unwanted side effects in patients, he says.

If the multitude of developmental hurdles can be overcome and safety can be assured, curcumin might provide an inexpensive alternative to mainstream pharmaceuticals. Based on positive results in rodents, Greg Cole of the University of California, Los Angeles, and the Veterans Administration, is organizing a clinical trial in humans to test whether curcumin can prevent the buildup of amyloid plaques that burden the brains of Alzheimer's patients. If successful, he and his collaborator (and wife), Sally Frautschy, plan to come up with formulations that could be mixed in cooking oil (to enhance bioavailability) and eaten as part of a meal to impede plaque accumulation—a recipe that might be affordable for both rich and poor in an aging world. ■

### MORE TO EXPLORE

**Inhibition of NAD(P)H:Quinone Oxidoreductase 1 Activity and Induction of p53 Degradation by the Natural Phenolic Compound Curcumin.** Peter Tsvetkov et al. in *Proceedings of the National Academy of Sciences USA*, Vol. 102, pages 5535–5540; April 12, 2005.

**Multiple Biological Activities of Curcumin: A Short Review.** Radha K. Maheshwari et al. in *Life Sciences*, Vol. 78, pages 2081–2087; 2006.

**The Molecular Targets and Therapeutic Uses of Curcumin in Health and Disease.** Edited by Bharat B. Aggarwal, Young-Joon Surh and Shishir Shishodia. Springer (in press).