Cell

From Exotic Spice to Modern Drug?

The global demand for more affordable therapeutics and concerns about side effects of commonly used drugs are refocusing interest on Eastern traditional medicines, particularly those of India and China.

Curcumin, the phytochemical agent in the spice turmeric that gives Indian curry its yellow color and distinctive taste, is also a staple of traditional Indian medicine (including Ayurveda) (see Figure 1). Used for millennia as a wound-healing agent and for treating a variety of ailments, the antioxidant and anti-inflammatory properties of curcumin have only recently garnered the attention of researchers interested in its mechanisms of action and clinicians attracted by its therapeutic potential for treating diseases such as cancer and Alzheimer's disease.

Even as publications on curcumin's effects on cell lines and in animal models of disease increase dramatically, there are only 13 clinical trials underway worldwide (see the Essay by T.W. Corson and C.M. Crews, page 769 of this issue). Part of the delay is attributable to a US patent, granted in 1995 to researchers at the University of Mississippi Medical Center for curcumin's wound-healing properties, that prevented its development as a therapeutic. In a landmark case, the Indian Council of Scientific and Industrial Research (CSIR) spent two years arguing and finally proving that curcumin has been part of the Indian traditional system of medicine for centuries and that this knowledge should be considered "prior art" and hence in the public domain. The patent was finally overturned in 1997. However, many other patents still stand preventing widespread and rigorous development of traditional medicines into modern therapeutics.

To establish traditional medicines as "prior art" and so stem the tide of multinational companies rushing to patent herbal compounds, the Indian government has launched an initiative to document and digitize its traditional knowledge. Called the Traditional Knowledge Digital Library (TKDL), this encyclopedia currently contains 24 million pages, with more than 120,000 formulations from 100 ancient texts and will soon be made available in five languages to patent offices worldwide. "We are currently negotiating with the patent offices in the US, European Union, and Japan to make our library accessible to them for patent examination," says Vinod Kumar Gupta, the chief architect of TKDL and head of information technology at CSIR in New Delhi. Gupta estimates that about 2000 patents misappropriating Indian traditional resources are granted every year to multinational corporations and nonresident Indian researchers working abroad.

Figure 1. A Colorful and Flavorful Medicine
The curry spice turmeric (called *haldi* in Hindi) contains the yellow pigment curcumin, an Indian traditional medicine currently being investigated in clinical trials for treating a variety of diseases. Turmeric is obtained by grinding the roots of the plant *Curcuma longa*. Photographs courtesy of the Indian Institute of Integrative Medicine, Jammu.

Packaging an Ancient Spice

Overturning the patent on curcumin has only removed some hurdles to its development as a therapeutic. Given that public knowledge does not involve any intellectual property (IP), drug companies are not interested in its commercialization. "Unless there is an IP to make money, nobody will come forward," says Bharat Bhushan Aggarwal, whose research group at M.D. Anderson Cancer Center in Houston, Texas was the first to show that curcumin inhibits the master transcription factor NF-κB that is activated in many human tumors (see the Essay by Corson and Crews on page 769). However, the potential benefits of curcumin are sufficiently compelling that scientists are finding ways to overcome the lack of interest from big pharma. Although curcumin itself is no longer patentable, derivatives, formulations, delivery systems, and synthetic methods can be patented. For instance, Aggarwal founded a company in 2004 called Curry Pharmaceuticals that is developing drugs based on synthetic analogs of curcumin.

Another big hurdle to using curcumin clinically is its insolubility in water and hence its poor bioavail-

ability. For free curcumin to be effective as a drug, solubility is crucial so that it can be absorbed by the gut and enter the bloodstream. But since it is excreted from the gut, a patient on curcumin therapy would have to take oral doses of 12 to 20 g, a huge dose given that more than 10 g of curcumin leaves an almost unbearable aftertaste. Thus, scientists are busy developing new delivery mechanisms or combinations of curcumin with other compounds to render curcumin more suitable for clinical use.

Anirban Maitra at Johns Hopkins University School of Medicine in Baltimore, Maryland and Amarnath Maitra, a chemistry professor in India's Delhi University, have developed a "nano" formulation of curcumin that is soluble in water. They synthesized nanoparticles that are hydrophilic on the exterior and hydrophobic on the interior and then encapsulated curcumin within these particles. The hydrophilic exterior allows nanocurcumin to be soluble in water enabling it to enter the bloodstream where the biodegradable polymer nanoparticles break down. After positive results using nanocurcumin to kill pancreatic cancer cell lines in the lab, Anirban Maitra is ready to move into animal models. "These studies are aimed at two aspects of cancer—the treatment of established tumors using xenograft models and prevention of cancers in genetically engineered mice," he says. Meanwhile, Anirban Maitra and Johns Hopkins, which owns the nanocurcumin patent, already have the drug industry interested in their technology as it is easy to produce to GMP (good manufacturing practice) requirements. "A U.S. pharma company is close to licensing our nanocurcumin formulation to develop it for multiple indications, including Alzheimer's and cancer, and take it to the clinic," says Maitra.

Meanwhile a research group at the Indian Institute of Science (IIS) in Bangalore has filed a patent application for a new combination of curcumin and the antimalarial drug artemisinin, a Chinese traditional medicine (see the Essay by Corson and Crews on page 769). The group, supported by India's Department of Biotechnology (DBT) in New Delhi, is testing the combination preclinically and will start clinical trials later this year in India, which has about 2 million cases of malaria annually. Although artemisinin combined with other antimalarial drugs has been used to fight resistance of the malaria parasite to frontline drugs, most of the combinations are less than ideal because of side effects, pharmacokinetic mismatches, and cost. Researchers at IIS point out that the curcumin-artemisinin combination may circumvent some of these problems. "Both are from natural sources of long-term use and so far no resistance is known to curcumin," says Govindarajan Padmanaban, an IIS principal researcher. Moreover, curcumin is tolerated at very high doses without any toxic side effects, and hence there is potential to decrease the dose of artemisinin and lower the cost of therapy. The problem of poor bioavailability can be overcome by adding a low dose of piperine (from black pepper), which increases the uptake of curcumin by 2000% in humans. "We have an industry partner, Ipca Laboratories, which will manufacture the malaria drugs once the fast-tracked human trials are completed," says Padmanaban, who believes India will finally have the first "made-in-India" malaria drug at a much lower cost than offered currently by big pharma even with special reduced price programs.

Taking Traditional Medicines to the Clinic

With curcumin once more in the public domain, DBT launched eight multi-institution clinical trials nationwide in 2005 and 2006 to investigate curcumin's effects on squamous cell carcinoma of the head and neck, cervical cancer, oral premalignant cancer, oral fibrosis, and clearance of human papillomavirus. These multicenter trials involve nine hospitals and research institutions across the country, including the All India Institute of Medical Sciences in New Delhi, Tata Memorial Hospital in Mumbai, Rajiv Gandhi Center for Biotechnology in Thiruvananthapuram, and the National Cancer Institute in Kolkata, and are due to be completed within two to three years. These trials use curcumin formulations that are GMP compliant from two Indian companies: Arjuna Pharmaceuticals, which makes Biocurcumax (95% curcumin in turmeric oil), and Sami Labs, which makes Bio-prene, a preparation of curcumin with piperine.

Touted more as a social service for a disease that is expensive to treat in developing nations, DBT's large-scale cancer trials anticipate no proprietary benefits, but if they do see anticancer effects then there are plans to "convert the results in a nano-based delivery or better combinations that could be patented." "Our study primarily aims to show to the world that if we test this molecule in a systematic manner, we may provide a cheaper way to treat cancer," says Bindu Dey, director of medical biotechnology at DBT. And in the hopes of discovering profit-yielding formulations of curcumin, DBT is funding the National Institute of Pharmaceutical Education and Research in Mohali in northern India to research patentable formulations of curcumin.

Curcumin's potential therapeutic effects have also garnered interest beyond India's borders (see the Essay by Corson and Crews on page 769). Ongoing clinical trials worldwide include investigating curcumin as a treatment for FAP (familial adenomatous polyposis) at Johns Hopkins University in Baltimore, chronic psoriasis at the University of Pennsylvania, multiple myeloma at M.D. Anderson Cancer Center in Houston, Texas, and pancreatic cancer at Kyoto University in Japan (www.clinicaltrials.gov). A six month randomized placebo-controlled double-blind pilot clinical trial examining curcumin's effects on Alzheimer's disease in

34 patients at the Chinese University of Hong Kong has been completed. Patients were randomized to receive either 4g /day or 1 g/day curcumin or placebo. Researchers saw no difference in adverse events among the three groups. Scores on a simple test of cognitive function (MMSE) did not decline in any of the groups including placebo. "Interestingly, although the serum A-beta peptide level did not differ significantly among doses, the level did tend to rise in patients treated with curcumin, possibly reflecting an ability of curcumin to disaggregate A-beta deposits in the brain, releasing the A-beta for circulation and disposal," says the trial's principal investigator Lawrence Baum. Encouraged by the findings, Baum intends to start a larger two-year clinical trial with 100–200 Alzheimer's disease patients and using a more comprehensive cognitive function test (ADAS-Cog) to determine whether curcumin can slow cognitive deterioration.

Getting Back to Basics

As curcumin's beneficial effects are under scrutiny in clinical trials, researchers are trying to unravel the mechanisms underlying its potent antioxidant and anti-inflammatory activities. "Curcumin is the most effective inhibitor of NF-κB, through which it affects several downstream targets" including gene products involved in blocking apoptosis (Bcl-2, Bcl-xL, XIAP), invasion (MMP-9), angiogenesis (VEGF), and metastasis (adhesion molecules), says M.D. Anderson's Aggarwal.

Meanwhile, biochemist Gaurisankar Sa at the Bose Institute in Kolkata reported this year that curcumin's anti-tumor effects are mediated in two ways. "We show that curcumin not only boosts the immune system in tumor-bearing mice by restoring CD4 and CD8 T cells, but also increases production of proteins that cause immune cells to proliferate and reduces the production of proteins that destroy immune cells." Administration of curcumin to tumor-bearing animals resulted in restoration of progenitor, effector, and circulating T cells. "Our observations suggest that curcumin may be used alone or in combination with classical anti-tumor drugs to sustain the immune capacity of the host," says Sa.

Researchers say that most Ayurvedic plants, including curcumin, work by modulating the immune system through different molecular mechanisms. For instance, a polysaccharide in the Ayurvedic plant *Tinospora cordifolia*, traditionally used to treat throat cancer, induces mitosis of B lymphocytes, says Ashok Vaidya, a clinical pharmacologist and research director of Kasturba Health Society in Mumbai. Agents modulating a single pathway or cellular target may be less effective than a cocktail of botanicals to restore immune system homeostasis. But there are limitations. "You can derive good immunodrugs from traditional medicinal plants but you may never get a strong analgesic, a cytotoxic or a hypolipidemic drug from them," says Bhushan Patwardhan, professor and director of the Interdisciplinary School of Health Sciences, University of Pune.

Mining Traditional Knowledge

Several scientific measures have been taken by the Indian government to ensure that drug researchers drawing on the Indian traditional system of medicine start their investigation from standardized and safe botanical material. "A major scientific shift has been the adoption of "reverse pharmacology" for drug development from natural products," says Patwardhan, who also leads CSIR's New Millennium Indian Technology Leadership Initiative (NMITLI) program on Ayurveda-based herbal drug development. NMITLI was launched in 2002 for fast track, innovation-driven indigenous development of certain areas in science and technology, some of which derive from India's traditional knowledge. Among the first few deliverables of this initiative are three new botanicals for arthritis, diabetes, and hepatitis. "The usual drug development pathway, from laboratory to clinic, is actually reversed in the study of traditionally used herbal medicines. The strategy we are now following is 'from clinics to laboratories,'" says Patwardhan. In this approach, case studies, case series analyses, observational studies, including cohort studies, all provide data on clinical use and outcomes of Ayurveda. They also serve as clues for mechanisms and therapeutic effects of well-established herbal drugs.

Researchers say in this process safety remains the most important starting point and efficacy becomes a matter of validation. The process also reduces the time and cost of development, argues Patwardhan, who has four Indian drug companies as partners in CSIR's NMITLI program as well as several promising leads. For example, a compound for treating osteoarthritis derived from a fully standardized polyherbal (a combination of two or more plant extracts) is in a phase III trial at five Indian centers. "We are comparing our compound with the largest selling osteoarthritis drugs on the market, Glucozamine and Celecoxib. While it compares positively in bioequivalence, our compound shows an added property of chondro protection," says Patwardhan, implying that the new drug can prevent degeneration of cartilage by protecting the chondrocyte cells that build cartilage.

Promising as the polyherbal osteoarthritis drug may be, it could have a long road to approval in the United States. The U.S. Food and Drug Administration (FDA) traditionally has been reluctant to approve plant extracts or mixtures of different compounds. Currently, CSIR is building a case before the FDA for submission of an Investigational New Drug (IND) application for multiplant extracts. CSIR has a Memorandum of Understanding with the FDA-supported National Center for Natural Products Research (NCNPR) to provide mutual help in validating and promoting products derived from nature. "The NCNPR [and FDA] recognizes the poten-

tial of more solutions in Ayurveda for degenerative disorders and hence is keen on multi-plant extract research data that we have generated," says Ghulam N. Qazi, director of the Indian Institute of Integrative Medicine in Jammu, who is leading the CSIR discussions with the FDA. However, there is evidence that the FDA may be looking more favorably on polyherbals and botanicals. In November of last year, the FDA approved a special extract of green tea as a prescription drug for topical treatment of genital warts caused by human papillomavirus, making it the first prescription herbal (botanical) drug approved in the United States. Although this approved drug is a single plant extract, the FDA has received several INDs on multiplant extracts although none have yet been approved, says Qazi. The CSIR team hopes to file an IND for the polyherbal osteoarthritis drug before the end of the year.

Although Indian and Chinese traditional medicine has been used for millennia, their recent convergence with Western medicine is opening up fresh opportunities for developing new therapeutics and for boosting the effects of existing drugs.

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DOI 10.1016/j.cell.2007.08.024