

Asian governments hope that high-volume screening and rigorous clinical trials will unlock the secrets of ancient herbal remedies—and that the results will pass muster with Western scientists

The New Face of Traditional Chinese Medicine

Tokyo—Epidemiologists had long suspected that the low cancer rates in southeast China might be related to coix, a grasslike relative of maize that is a dietary staple in the region and a key ingredient of many traditional Chinese herbal medicines. But no one had as much faith in coix as pharmacologist Li Dapeng, who in 1975 began trying to coax the anticancer compounds out of the plant's seed. Twenty years later, Li won government approval to market the fruits of his research, a drug he calls Kanglaite, to help cancer patients fight their disease and reduce the side effects from other treatments.

Although scientists still don't know how it works, the injected drug has been taken by more than 200,000 patients and is China's best-selling cancer treatment. This year, the U.S. Food and Drug Administration approved a phase II trial to test its efficacy in treating non-small-cell lung cancer. It's the

first drug derived from a traditional Chinese herbal remedy to go into clinical trials in the United States, and officials and scientists in mainland China, Hong Kong, and Taiwan are betting it won't be the last. All three regions are ramping up efforts to screen the 10,000 or so plants described in the Chinese herbal medicine literature. In addition to searching for new drug leads, they are investigating the herbal remedies themselves.

Traditional Chinese medicine (TCM) has also made it onto the region's political agenda. Hong Kong Chief Executive Tung Chee Hwa has laid out a 10-year plan for making the city an "international center for Chinese medicine," and his government is currently funding 18 TCM research projects that

include clinical trials, developing quality standards, and basic pharmacological studies. The Hong Kong Jockey Club Charities Trust is equipping research labs and donating \$64 million to get research started at a new Institute of Chinese Medicine. Last year, Taiwanese President Chen Shui-bian proposed spending as much as \$1.5 billion over 5 years to develop Taiwan's Chinese medicinal herb industry, although a detailed spending plan is still pending and will need legislative approval. China's Ministry of Science and Technology has made the modernization of TCM one of 12 focal points in its current Five-Year Plan, with \$3.6 million budgeted for screening both conventional chemical compounds and medicinal herbs for drug leads.

Officials see these efforts as a way to use rising research budgets to boost domestic biotechnology research efforts and capitalize on a cultural treasure. "Screening [herbal remedies] is a way for China to try to catch up with Western

Rooting around for drugs. Shanghai's Li Dapeng found the active compound for his cancer-fighting Kanglaite drug in a traditional medicinal herb.

countries in developing new drugs," says chemist Yang Xiuwei, director of the National Research Lab of Natural and Biomimetic Drugs at Beijing University of Medical Sciences.

The timing is right, says biochemist S. D. Kung, who is coordinating herbal medicine

Qinghao (*Artemisia annua*, sweet wormwood)

Traditional use: To treat fevers.

The source of artemisinin, an antimalarial compound that may also have anticancer properties.



research at Hong Kong University of Science and Technology (HKUST). A new generation of Western-trained scientists is eager to take on the challenge of "demonstrating the efficacy [of traditional remedies] to [meet] the standards of the U.S. Food and Drug Administration," he says. Chinese researchers and officials also want to stay ahead of the growing Western interest in herbal medicine. "This is our culture!" says Yang Ning Sun, director of the Institute of Agrobiotechnology at Academia Sinica in Taipei. "We should be interested in making good use of it."

Ironically, as interest in herbal remedies and acupuncture has boomed in the West, the Asian public is turning increasingly to modern medicine. According to a 1999 survey by the Hong Kong government, only 22% of outpatient medical consultations in the city were provided by Chinese medicine practitioners. Officials think the percentage in mainland China is even lower, and they believe that safety concerns are driving people away from TCM. To address that problem, Hong Kong is drawing up regulations to ensure the quality of herbal medicines and the qualifications of practitioners. "Once the regulatory system is in place and we upgrade professional standards, I'm sure the usage rate [for TCM] will increase,"

CREDITS: (LEFT TO RIGHT) ZHEJIANG KANGLAITE PHARMACEUTICAL CO.; ILLUSTRATION: C. SLAYDEN

says microbiologist Edmund Lee, who heads the new Hong Kong Jockey Club Institute of Chinese Medicine.

How well the efforts will pay off—and how soon—is a matter of debate. Even optimists concede that it could take a decade before the work results in marketable pharmaceuticals. Many Western scientists remain skeptical, however, and some believe that the efforts are misguided. Relying on the traditional Chinese medicinal texts for hints to effective remedies for specific diseases, or even direction on what plants to screen, is wishful thinking, says Wallace Sampson, professor emeritus of clinical medicine at Stanford University and editor of *The Scientific Review of Complementary Medicine*. “Those empirical observations on herbs are unreliable, fanciful, false, [and] irrelevant,” he says, adding that any promising leads would arise purely by chance.

A few successes

The belief in the promise of herbal remedies rests on an admittedly minimal track record. The first compound derived from Chinese herbal remedies to enter the Western pharmacopoeia was ephedrine, an amphetamine-like stimulant. A Japanese scientist isolated it in the 1880s from the Chinese medicinal herb mahuang (*Ephedra sinica*), which was used to treat congestion. It’s a common ingredient in over-the-counter decongestants and prescription medications for bronchial asthma, among other products. (Mahuang is also used alone or in combination with other herbal compounds in nonprescription dieting aids, and as a legal way to get high, often under the label “herbal ecstasy.” But a lengthening list of adverse effects has led several countries to ban nonprescription uses, and the United States may soon join them.)

The next significant pharmaceutical derived from a Chinese medicinal herb didn’t appear until a century later, but it may be a far more important find. In the 1970s, Chinese scientists isolated a compound called artemisinin from qinghao, or *Artemisia annua*, a relative of the sweet wormwood found in North America. The traditional texts identified qinghao as beneficial for fever; the researchers found that artemisinin killed even chloroquine-resistant strains of *Plasmodium*, the parasite that causes malaria. Recent work in U.S. and European labs suggests that artemisinin may also have anticancer properties. But although artemisinin may be a boon to humankind, the original Chinese researchers earned nothing but bragging rights for their efforts. Zhou

Weishan, a chemist at the Shanghai Institute of Organic Chemistry who led the efforts to synthesize artemisinin, says they never patented any part of the work.

Chinese researchers vow not to repeat that mistake when developing the next drug. When Li decided to take Kanglaite global, “our very capable patent attorneys soon got a process patent and a use patent on the Kanglaite Injection,” says John Harmer, chief executive officer of Salt Lake City–based Kanglaite USA, a subsidiary of Li’s Zhejiang Kanglaite Pharmaceutical Co.

The phase II trial will pair Kanglaite with another chemotherapy to treat non–small-cell lung cancer, following on Chinese results suggesting that Kanglaite enhances the efficacy of chemotherapy and mitigates side effects such as fatigue, nausea, and hair loss. Not as far along in the drug pipeline is a compound derived from huangchi, or yellow root (*Astragalus membranaceus*), that, like Kanglaite, ameliorates the side effects of cancer chemotherapy. Taiwanese biochemist T. S. Jiang started screening fractions of yellow root more than a decade ago, after observing its traditional use in patients supposedly suffering what could be translated as a deficiency of vital energy, or “qi.” To Jiang, that sounded exactly like the lethargy and weight loss that often accompany chemotherapy.

The compound, called Xue Bao PG2, has been approved for use in China as a chemotherapy adjuvant treatment and will soon enter phase III clinical trials in

drugs into a flood. The most ambitious program is at HKUST’s Biotechnology Research Institute (BRI), which in 1999 set up a \$1.6 million High-Throughput Drug Screening Center for Traditional Chinese Medicine, with support from the government, the Hong Kong Jockey Club Charities Trust, and other local charities and private companies. The center is taking

Mahuang (*Ephedra sinica*, country mallow)

Traditional use: To treat respiratory congestion.

The source of ephedrine, an amphetamine-like stimulant used in decongestants and asthma medications.



aim at neurological diseases, including Alzheimer’s, Parkinson’s, amyotrophic lateral sclerosis, and diabetic neuropathy. Catherine Wong, BRI’s research projects coordinator, says neurological disorders were chosen because “no good cure is available for most neurorelated diseases yet, and [HKUST] had assembled a critical mass of [neuroscience] experts.”

The center spent 3 years setting up equipment and developing its own assays before beginning to screen crude herbal extracts, active fractions, and pure compounds for bioactivity. The plants being screened were picked “mainly based on the clinical experience as recorded in the voluminous Chinese medicine literature,” Wong says. She declined to reveal details of what she calls a number of promising hits, adding that they have drawn interest from “major pharma and biotech companies.” Beijing University of Medical Sciences’ Yang is similarly circumspect about screening efforts, which he says have already led to at least one patent application.

It’s not surprising that traditional remedies are yielding useful drug leads, Chinese scientists say. But herb enthusiasts think that screening misses the point, because traditional remedies rely on the joint actions of up to 20 herbs. They even worry that screening could produce negative results: “Extracting only some of the ingredients from the herbs might impair the original effectiveness and cause more serious side effects,” says Bian Baolin, director of research and development at the Institute of Herbal Medicine, China Academy of Traditional Chinese Medicine, in Beijing.

Traditional herbal remedies still suffer a credibility gap in the West because the claims made for them rest largely on anecdotal



Huangchi (*Astragalus membranaceus*, yellow root)

Traditional use: All-around tonic to boost energy.

The source of the active compound in Xue Bao PG2, which ameliorates the side effects of chemotherapy. Approved by China, preparing for phase III clinical trials in Taiwan.

Taiwan. Jiang, president of Taipei-based PhytoHealth Corp., created to commercialize the drug, hopes to find a partner to help him penetrate the U.S. and European markets. He says the company is also investigating a drug derived from an herb that is applied traditionally to ease arthritis-like symptoms.

Full speed ahead

Scientists in the three regions hope that modern screening efforts will turn this trickle of

dots and clinical observations instead of randomized, double-blind, placebo-controlled trials. Edzard Ernst, a professor of alternative medicine at the University of Exeter, U.K., and colleagues at the Chinese University of Hong Kong (CUHK) reviewed more than 2000 clinical trials reported in mainland Chinese journals and found them almost universally flawed. "What were called randomized clinical trials really weren't, because they didn't have control groups," says Ernst. "We were very disappointed." The track record for Western trials is not much better, says Tony Mok, a clinical oncologist at CUHK. Although hundreds of trials have been conducted in the United States and Europe in recent years, he says, "only one or two have been worthy of publication in high-quality, peer-reviewed journals."

Mok and more than a dozen colleagues at CUHK hope to fill in some of the missing data. They are conducting 20 randomized, double-blind, placebo-controlled clinical trials of traditional herbal remedies and acupuncture, with another dozen in the planning stage. The trials focus on ailments often treated with herbal remedies: asthma, insomnia, drug dependence, Alzheimer's disease, and osteoporosis, among others. "These trials are being led by orthodox clinicians and researchers," says Mok, who trained abroad, like most of the principal investigators, earning his M.D. from the University of Alberta, Canada, and working in clinical oncology at the Princess Margaret Hospital in Toronto. "The traditional practitioners don't have the training to conduct modern clinical trials," he says.

To ensure consistency, most of the trials are using generic herbal formulations. But Mok's trials—one using herbal remedies to counter the side effects of cancer chemotherapy and one pairing herbs and chemotherapy to treat

lung cancer—give more scope to traditional methods. All patients are seen not only by an oncologist but also by a traditional practitioner, who prescribes an individualized herbal recipe. Then, depending on a code known only to a pharmacist, the patient gets either the actual



Iijen (*Coix lachryma-jobi*, Job's tears)

Traditional use: To treat tumors.

Source of the active compound in the Kanglaite Injection. Approved in China as an anticancer drug, preparing for phase II clinical trials in the United States.

remedy or a placebo. Each patient's response is graded on standard measures used in FDA-approved cancer trials, which Mok hopes "will maintain a high standard of quality so we can publish in mainstream scientific journals."

A higher bar

Academic researchers are not the only ones testing the efficacy of traditional remedies. Sometime next year, Taipei-based Cathay Biotech Co. expects to launch FDA-approved, phase II clinical trials of an extract drawn from a collection of 15 herbs as a treatment for hepatitis B. Winston Town, Cathay's chief operating officer, says the multiherb extract is the result of 10 years of work, primarily in China. Starting with a remedy identified in the Chinese medical literature as useful for viral infections, Cathay scientists varied the ingredients, testing different combinations on human subjects until they arrived at a standard formulation. Their extract, given orally as a capsule or injected, has been used clinically in China since 1996. FDA trials will be randomized, double blind, and placebo controlled.

Cathay's strategy sidesteps two problems that have hindered wider clinical use of herbal remedies: trouble with patents and quality control. Because most herbal remedies are not new inventions, they cannot be patented, and companies have little incentive to pay for the clinical trials that might prove efficacy. Town says Cathay created a novel, non-obvious combination of herbs not described in any of the traditional texts and patented it. Four additional patents are pending on the processing technologies. Cathay also might

have solved the second big problem: It chemically characterizes both the raw herbs and the finished product to ensure quality and batch-to-batch consistency.

Quality control remains a big issue, affecting herbs, formulations, and even the practice of TCM itself. TCM supporters say its diminishing popularity in Asia is due more to lax enforcement of standards than to a failure of the remedies themselves. "I think the majority of scientists in Hong Kong believe [TCM] works," says Ge Lin, a CUHK pharmacologist studying the pharmacology of herbal remedies. "The problems are in the practice."

Ge and others say that spotty regulation leads to inconsistent herb quality, unsubstantiated claims for secret formulas, unqualified practitioners, and both deliberate and inadvertent mislabeling and adulteration, sometimes with fatal consequences. "There are a lot of fake [Chinese] medicines out there," says HKUST's Kung.

To restore both local and global faith in the traditional herbal approach, Hong Kong is moving to regulate every aspect of the business. Beginning this year, no one can practice Chinese medicine without a license, which requires completing an approved course of study and passing a test. Herbal pharmacists will soon face similar licensing. On the advice of a new Chinese Medicine Council, 31 potentially toxic herbs can now be dispensed only with prescriptions. The council is also studying ways to regulate the quality of raw herbs and formulations. "Hong Kong is spot on in its approach to regulating Chinese medicine," says Alan Bensoussan, an associate professor of health sciences at the University of Western Sydney, Australia.

The screening, trials, and regulations should bring much-needed modern scientific rigor to traditional herbal medicine, says the Institute of Chinese Medicine's Lee. That's even more important today, he notes, as the competition to capitalize on herbal remedies heats up not only among the three Chinese regions but among companies and institutions in North America and Europe as well. "Whenever you approach a subject scientifically, you are bound to generate new knowledge, new analytical techniques, and new methods of quality control," says Lee. The key, he adds, is making sure that the new, herb-based formulations meet the same standards of safety and efficacy as conventional pharmaceuticals.

—DENNIS NORMILE

With reporting by Ding Yimin in Beijing.



Ramping up. Hong Kong University's High-Throughput Drug Screening Center churns through thousands of compounds every week seeking the bioactive components of medicinal herbs.