Medicine of the masses

Viewed askance by scientists for decades, herbal remedies are finally entering the mainstream. Gunjan Sinha explores the new face of centuries-old medicine.

In the late 1990s, the cancer community began buzzing with anecdotal reports that a mixture of eight Chinese herbs called PC-SPES could shrivel prostate tumors. As many as 10,000 men were swallowing the supplement and seeing some success, went the rumors. Doctors were initially skeptical. But as the stories multiplied, some scientists decided to test the mixture in clinical trials.

The first studies were overwhelmingly positive. The supplement appeared to reduce markers of prostate cancer, cut pain scores and shrink prostate tumors[1,2].

But shortly after, talk of serious side effects and contaminated products began circulating among patient groups. The complaints prompted the California Department of Health Services to investigate. Their chemical analysis revealed something shocking: the supplement was laced with three different prescription drugs—including an artificial estrogen used clinically to treat prostate cancer. By late 2002 the company that made PC-SPES went bankrupt and the herb was no longer available.

The scandal embarrassed researchers who had rushed to clinical trials without first studying the supplement. Even more humiliating, the US National Center for Complementary and Alternative Medicine (NCCAM) had funded four studies of the supplement that had to be shut down immediately. The bottom line was clear: scientists need to show not just that herbal drugs are effective, but that they are safe and of consistently high quality.

For years, the incident left many scientists wary of herbal medicines. But the botanical supplement landscape is now on the brink of a paradigm shift. Fueled by patients' growing obsession with alternative medicine and escalating reports of manufacturers peddling snake oil as miracle cures, scientists are finally diving into the field.

In the US, NCCAM is supporting several clinical trials to test whether botanicals hold up to their claims. Some scientists are developing long-overdue techniques to assess quality and consistency, and others are investigating the power of herbs from China and other countries to fight off specific diseases. Their hope is to move alternative medicine into the mainstream without repeating the mistakes of the past.

"There are some unscrupulous people in this industry that make it bad for the people who are trying to do honest work," says Norman Farnsworth of the University of Illinois at Chicago College of Pharmacy who studies herbals. "The basis of much of our research is that any plant material extract should be chemically authenticated and chemically and biologically standardized."

Reuters/Kin Cheung

Modern techniques are lending traditional medicines new credibility.

Untapped potential

PC-SPES is not the only herbal supplement that soured the field. Some supplements have been found to be contaminated with dangerous heavy metals or bacteria, others vary wildly in their content from bottle to bottle[3]. The negative publicity has sunk sales since the 1990s, says Stephen Morrissey, chief executive officer of Botanica BioScience in Ojai, California.

But despite the bad press, many scientists are confident of herbs' potential to treat disease. "The payoff will be huge," says Robert Tilton, vice president of science and technology at PhytoCeutica, Inc. The New Haven–based company is a spin-off from Yale University and is investigating Chinese herbs that fight cancer. It is also part of the Consortium for Globalization of Chinese Medicine, which includes 19 other academic institutions in the US, China, Hong Kong, Taiwan and Singapore.

"A lot of Chinese herb mixtures have proven themselves effective over many years. But we need to refine the evidence from subjective descriptions to objective verifiable data," says Paul Tam, associate dean of medicine at Hong Kong University.

Preliminary studies suggest that PhytoCeutica's lead target, PHY909, may boost the potency of several chemotherapeutic drugs and reduce side effects such as nausea and diarrhea. PHY909 is a mixture of four herbs that the Chinese first developed more than 1,500 years ago to treat gastrointestinal distress. The company is recruiting patients for a dose-escalation study in liver cancer patients.

PHY909 isn't new, but the idea of combining it with chemotherapeutic drugs is. The US Food and Drug Administration (FDA) last June issued new guidelines for marketing botanical drugs. The agency will allow companies to market herbals exclusively for up to five years after approval.

For herbs that have been widely in use, the agency is will also accept well-documented historical evidence that the herb is safe for use in healthy populations. Companies can therefore bypass extensive animal toxicity studies and quickly move into clinical trials.

"These FDA guidelines for the first time outline a roadmap for future botanical drug approval," says Tilton. "They are a major step forward."

New paradigm

Unlike pharmaceutical drugs made by packaging single molecules into pills, botanicals contain a number of active compounds "that work synergistically," says Tilton. No one phytochemical has shown to be very potent by itself, he adds, but together they pack a punch. "It's likely that they work on different pathways," he says. The company has some insight as to how PHY909 works, he says, but it is not a priority. Instead the primary focus is on establishing the consistency of their herbs.

To that end, PhytoCeutica has patented software, to be shared among consortium members, which creates a three-dimensional chemical fingerprint (see Figure, page 10) of herb mixtures based on chemical analyses from mass spectrometry and other technology. The fingerprint

appears as a series of peaks, each representing a single molecule. Researchers then treat cells with the herb extract and measure mRNA expression on a microarray to find the specific phytochemicals that are biologically active. In this way, the company can identify the important biologically active subset of molecules in the mixture. The fingerprint serves as a reference to which subsequent batches can be compared to assure quality.

Herbals represent a new model of drug development. According to the FDA's new guidelines, the agency will not require companies to identify an herb's mechanism of action for approval. This is also the reason that pharmaceutical companies have shied away from such research. "This multi-medicine approach is very foreign to them," says Tilton, who had previously worked for the pharmaceutical industry. "When they find an effective botanical, they want to isolate out the single molecule."

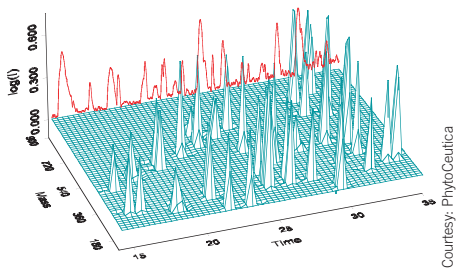
If approved, PHY909 will become the first botanical in the US to be available by prescription. But it will quickly be followed by many others, predicts Tilton. "I think when the first herbal drug gets approved for an indication that western medicine is not very effective," he says, "we will see a big turnabout."

In the next few years, says experts, herbs will join traditional drugs as therapeutics. This model already exists in Europe, where some countries such as Germany and the Netherlands require clinical evidence of an herb's efficacy as stated on its label, and where herbal drugs are prescribed.

Herbs that work

Unraveling how an herbal works is a challenge, but some scientists are trying to understand how supplements affect the body. For instance, scientists at the University of California in Los Angeles are examining the anticancer ability of less-exotic plants. "As a clinician, you really want to know how this [herb] is going to work," says Mary Hardy, associate director of the university's Center for Dietary Supplements Research.

In a recent study, researchers at the center found that green-tea extracts, which have been touted as cancer-fighting elixirs, turn down the expression of many genes involved in cell growth and crank up the expression of many genes involved in apoptosis[4].



Courtesy: PhytoCeutica

Chemical fingerprints can help identify the active ingredients of herbal mixtures.

The group is also planning to examine breast and prostate tissue for the presence of green-tea phytochemicals and to investigate the anticancer properties of an herb called *Scutellaria baicalensis*. Gene expression studies suggest that the herb interferes with a cell's production of tubulin—a protein required for cell division—and may affect the expression of Cox-2, an enzyme implicated in many cancers.

Botanicals are also being recruited to fight other problems. One NCCAM-funded project is examining the potential of Chinese herbs to treat addiction. "Because of the opium trade, China has over 100 years of experience in herbs for withdrawal symptoms," says project leader David Yue-Wei Lee at McLean Hospital in Belmont, Massachusetts. Opium addiction was a huge problem in China, Lee adds. "Even my grandmother offered it to her guests."

Lee's collaborators at other institutions have also studied the ability of various herb mixtures to curb drinking in rats. In one study, the University of Minnesota's Elhabib Benlhabib showed that the kudzu root extract reduced drinking in rats predisposed to alcoholism[5]. A small-scale placebo-controlled study, now in press, also suggests that kudzu root can reduce drinking in people.

Making supplements safer

Because concerns about quality have stunted herbal research in the past, academic researchers are trying to help improve good manufacturing practices for dietary supplements. For instance, Lee and Hardy are both investigating quality control methods for their herbal mixtures. But this presents a potential problem: with each team relying on its own system, there are no accepted academic standards to assess quality and update existing guidelines.

Supplement companies are not required to follow the guidelines, but regulatory agencies are relying on the market to police itself. As more companies have their products certified, market pressure will hopefully weed out the imposters, says Hardy.

It is too soon to predict whether this will make supplements safer. In the meantime, experts say, one thing is clear: herbal medicine can no longer be shoved aside as the work of charlatans, or as peddling a placebo effect. Some herbs have valid medicinal uses, says Hardy. "We are not only providing the justification for the further pursuit of these things in science, but their study will also give us direction for their medical use," she says. "They will eventually be integrated into the broader medical paradigm."

Gunjan Sinha is based in Frankfurt.

No more free lunches

When medicinal herbs on the market come from a foreign country, who profits? Although there are no international laws to mandate profit sharing, the Convention on Biological Diversity, established in 1992 and ratified by 187 countries—the US has yet to sign—establishes countries' sovereignty over their own genetic resources. The treaty leaves it to each country to legislate and enforce rules for access to plants and benefit sharing.

The University of Illinois at Chicago, for example, recently negotiated an agreement for bioprospecting in the rainforests of Vietnam and Laos for plants with anticancer abilities. Half of the net revenue from a marketed product will be paid to the country from which the plant originated. But this arrangement can present ethical issues when indigenous knowledge helps to develop a drug. Unless mandated by the government, there is no guarantee that the indigenous population will benefit. The World Intellectual Property Organization (WIPO) is developing guidelines to protect traditional knowledge and help member countries establish laws, says Antony Taubman, head of traditional knowledge at WIPO.

But some good models for profit-sharing already exist. In the late 1990s, Paul Cox, director of the Institute for Ethnobotany at the National Tropical Botanical Garden in Hawaii, discovered that a compound extracted from tree bark native to the South Pacific had antiviral properties. Traditional healers in Samoa had long used the bark to treat hepatitis infections and had pointed Cox towards the tree. The bark compounds have been transformed into a drug that is being tested as adjuvant therapy for AIDS patients. If the drug is approved, the government of Samoa, the village where Cox conducted his research and descendents of the healers will all share in the profits.

"That's very enlightened thinking," says Mary Hardy at the Center for Dietary Supplements Research at the University of California in Los Angeles. "It's a model we should all strive for."

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