



In the process of purifying and testing the antimalarial agent artemisinin, phytochemist Youyou Tu realized that the age-old Chinese technique of boiling and high-temperature extraction destroys the artemisinin contained in *Artemisia annua* (*qinghao* in Chinese), a herb used in traditional Chinese medicine (TCM) for hundreds of years. So she redesigned the process for isolating artemisinin, performing it at lower temperatures (60 °C) and using ether as a solvent. Tu also removed a harmful component of the herb that did not contribute to antimalarial activity, discovered that the active ingredient is present only in the leaves, and worked out the best time to harvest it. Since its initial isolation in 1972, artemisinin and its derivatives have become the leading treatments for one of the world's most deadly diseases and saved countless lives. On 12 September 2011, Tu, who has since retired as a research fellow from the China Academy of Chinese Medical Sciences (CACMS) in Beijing, won the Lasker–DeBakey Clinical Medical Research Award for her pioneering work on this agent.

GRACIA LAM

The other classic example of a modern medicine that originates in TCM is arsenic trioxide, which was approved by the US Food and Drug Administration for use in leukaemia in 2000. Tingdong Zhang, a research fellow of Harbin Medical University in China, made a unique contribution to the development of this drug by separating a toxic component from the therapeutic compound. Tingdong Zhang used animal toxicological experiments to define the maximum safe dose, and changed the route of administration to intravenous delivery to maximize the effect.

“The discoveries by Tu and Tingdong Zhang are great examples of how to develop drugs from TCM,” says Bai Lu, vice-president of biology at GlaxoSmithKline (GSK) China in Shanghai. “Consciously or not, they were actually using modern scientific approaches for drug discoveries.”

Beyond the utility of these drugs as lifesavers, their development raised hopes in China that, with the help of modern science, TCM could become an equivalent — or perhaps even a more powerful counterpart — to modern medicines. But, despite decades of research and billions of yuan, TCM is still considered to be part of complementary or alternative remedies in most Western countries, its ingredients hard to define, and its efficacies difficult to evaluate.

#### ACTIVE INGREDIENTS

For decades, European and US regulatory agencies held the view that a drug must be either a highly purified or synthetic agent. Traditional medicines could not qualify under this definition because a TCM preparation is a concoction rather than a single compound, and the chemical structures of the active ingredients are undefined. Consequently, when it came to assessing a traditional medicine for efficacy, most effort went into identifying the principal agent within a herb or mixture of herbs and purifying it as a

#### MODERNIZATION

# One step at a time

*The repertoire of traditional Chinese medicine could offer rich pickings for modern drug developers, but researchers must first define and test herbal concoctions.*

BY ZHIGUO XU

single chemical compound. However, “academic scientists and the pharmaceutical industry have not been very successful at isolating the active substances in TCM preparations,” says Bai Lu.

Others share Lu’s dour outlook. “Few active ingredients are extracted from TCM herbs by modern scientific approaches,” says Yi Rao, dean of life sciences at Peking University in Beijing. “Those extracted effectively have not been demonstrated to be clinically successful.” Indeed, he says, “artemisinin and arsenic trioxide are perhaps the only two examples”.

This process is not helped by the insistence of many TCM researchers on using different measures of efficacy for TCM compared with modern medicines. “You can use different drugs or approaches, but all drugs and treatment strategies have to pass the same standards to show that they are effective,” says Rao, who is also an evaluator for the big-budget Innovative New Drug Development and Manufacturing project, which was launched in 2008 with more than 10 billion yuan (US\$1.6 billion) of public funding. The aim is to develop new TCM drugs by applying modern research and development techniques to TCM. Rao criticizes TCM researchers who adhere to traditional ways. “They think it’s too slow and troublesome to extract the active ingredients by modern scientific approaches, but in fact this was how Tu and Tingdong Zhang did it.”

A major drive of the central Chinese government is to sponsor projects that use modern drug discovery technologies to characterize the active parts of TCM formulae. For example, the 30 million yuan (\$4.7 million) Herbalome project, initiated in 2008 by scientists at Dalian Institute of Chemical Physics (DICP), part of the Chinese Academy of Sciences, is compiling a database of active agents in herbs from popular TCM recipes<sup>1</sup>. Researchers use liquid chromatography and other modern methods of separation to identify the components of a herb, then evaluate each one using high-throughput screening, toxicity testing and randomized clinical trials to determine both its active ingredients and toxic components. More than 10 scientists are involved in the project, which is set to last for 15 to 20 years.

Xinmiao Liang, a chemist at DICP and head

of the Herbalome, is confident about its prospects. “We can analyse 500 samples every day, and initial results are very good,” he says. “We have already extracted the active ingredient from one herb and identified its chemical structure.” Liang is applying for international patents, conducting animal experiments and writing papers about this newly identified analgesic compound, although he is yet to publish his findings. Liang hopes the Herbalome will uncover the next artemisinin or arsenic trioxide.

### COMPLEXITY

But within China, the Herbalome project has its sceptics. “Japanese scientists have tried to extract active ingredients from TCM herbs in



**Youyou Tu is bringing TCM into the modern clinic.**

past decades, but failed,” says Bengang Zhang, a researcher at the Institute of Medicinal Plant Development of the Chinese Academy of Medical Sciences (CAMS) in Beijing. Part of the problem is that standard laboratory technologies do not always match up well with TCM analysis. For example, Liang acknowledges that one of the major tools used by his team as part of the Herbalome — high-throughput screening — is not ideally suited to the task. That’s because TCM concoctions are mixtures of multiple active compounds, and a typical Chinese medicine is intended to hit multiple biological targets. Hence, even if a high-throughput screen shows a strong effect, it cannot identify the active ingredient — especially if it is a trace component. “In most cases, you don’t know what the targets and

mechanism are,” says Bai Lu. “Without that, you can only identify and isolate compounds based on phenotypes, which is extremely difficult.”

According to Bengang Zhang, the failure of the Japanese researchers was not because they were using poor methods or technology. “The instruments in Japan are sophisticated enough,” he says. The issue, in his view, is that both the human body and the formulae in the TCM repertoire are complex systems. Trying to simplify both, by extracting one active ingredient to hit one biological target, is a recipe for futility.

The difficulties have not deterred scientists keen to explore traditional medicines and untangle their many components. “This is actually an advantage of TCM,” says Bai Lu. Many common diseases, including diabetes and hypertension, are polygenic and their pathology follows multiple mechanisms. Alzheimer’s disease, for example, involves accumulation of toxic proteins (amyloid- $\beta$  and tau), neuronal death, loss of function in the synapses, and inflammation. A drug that hits a single mechanism, no matter how hard, might not work. Bai Lu adds: “The multiple components in TCM formulae offer a unique opportunity to attack multiple disease-causing mechanisms simultaneously — provided we know what they are and how to test them clinically.”

Taking advantage of complexity is one of the goals of Zalicus, a drug developer in Cambridge, Massachusetts. “Biological systems have evolved over millions of years to be able to resist a single insult and they have become very robust,” explains Margaret Lee, vice-president of research at Zalicus. “There is a redundancy and complexity in biology.”

Zalicus’s approach is to take existing molecules with known mechanisms of action, and combine them to look for synergistic activity. For example, Zalicus, in partnership with Sanofi Aventis of Paris, France, is developing Prednisporin — a combination of the glucocorticoid prednisolone acetate and the immunosuppressant cyclosporine A — for the treatment of inflammatory eye diseases.

However, working the other way around — starting with a complex herbal mixture and trying to “deconvolute the synergy” — is tough,

### FUTURE CHINESE TREASURES?

Several drugs are aiming to become the first authentic TCM-derived formula to get approval in the West.

Drug name	Manufacturer	Active ingredients (if known)	TCM formula	Diseases to treat	Status
Danshen dripping pill	Tasly Pharmaceutical	Danshensu, protocatechuic aldehyde, salviolic acid B	<i>Salvia miltiorrhiza</i> , <i>Radix notoginseng</i> , Borneol	Cardiovascular disease (especially chronic angina)	FDA phase II clinical trials
Kanglaite injection (KLT)	Zhejiang Kanglaite Group	Unknown	Coix seed oil (with soybean phospholipids and glycerol as excipients)	Cancer	FDA phase II/III clinical trials
Xuezhikang capsule	Beijing Peking University WBL Biotech Co.	Various natural statins, unsaturated fatty acid, ergosterol, alkaloids	100% Red yeast rice (Hong Qu), obtained through fermentation of with <i>Monascus</i> strains.	Coronary heart disease caused by hyperlipidaemia and atherosclerosis.	FDA phase II clinical trials
Fuzheng Huayu capsule	Shanghai University of TCM	Salviolic acid B, Adenosin	<i>Salvia miltiorrhiza</i> , peach seed, pine pollen, <i>Gynostemma pentaphylla</i> , <i>Schisandra chinensis</i>	Liver fibrosis	FDA Phase II clinical trials
Nongsuo Danggui Pill	Lanzhou Foci Pharmaceutical		Angelica root	Thrombosis, blood lipid levels and pain	Applying for registration in EU



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From rural farming to the lab: herb farming standards were introduced in China in 2002 to help standardize the raw ingredients of herbal remedies.

says Lee. “With a herbal medicine, there might be 10–15 different components in there.” A researcher would need to isolate the components, purify them, then add them back in various combinations until the entire effect of the mixture is recapitulated. And that is supposing it is possible to identify the components in the first place. “With a herb, where it’s grown and the environmental conditions can have an impact on the level of components,” she says. It would take repeated attempts to ensure all active ingredients have been isolated. “In theory, it should be possible. But in practice it can become very difficult.”

#### QUALITY ASSURANCE

Bai Lu says that consistency is an important challenge. For each recipe, “some sort of standardization criteria must be established to control batch-to-batch variation”, he says. Bengang Zhang agrees: he helped draft the TCM Good Agricultural Practice (GAP) guidelines for the State Food and Drug Administration (SFDA), the Chinese equivalent of the US Food and Drug Administration (FDA). He contends that poor agricultural practices lead to inconsistent quality of TCM products, severely affecting stability and therapeutic effects<sup>2</sup>. Bengang Zhang proposed that these problems can be addressed in part through a GAP approach, which standardizes various basic drug production processes, including the cultivation, collection and processing of TCM herbs. These techniques should improve the quality of the herbs and bring TCM in line with international practices.

GAP for herbal products was introduced in China in 2002. Although it is not mandatory for herbs, being GAP certified can promote the visibility of a manufacturer. In the eight years to 2010, the SFDA certified 99 production bases (about half of the total number), which ranged in size from around 13 hectares to hundreds of hectares.

There are still problems that GAP has not solved. The rural areas where most herbs are grown remain underdeveloped, and many young people leave the countryside to work in the cities.

The agricultural land is typically owned by the drug manufacturer, and even though the companies provide training, the GAP guidelines will not be properly implemented without an adequate labour force. Basic research into important herbal production technology is weak, Bengang Zhang says. Moreover, he points out, “the government has not yet enacted any provisions to enforce implementation of GAP for TCM herbs”.

#### NON-TRADITIONAL TRIALS

But even with standardized raw ingredients and consistent products, measuring the clinical efficacy of TCM formulae is a challenge. Multiple active compounds hitting multiple targets could also mean multiple criteria for judging whether the medication works. While scientists worldwide are becoming increasingly interested in the evaluation of TCM products based on clinical trials, few researchers know how to do it right. It is clear that double-blind, randomized clinical trials (RCTs) are needed.

**“Some sort of standardization must be established to control batch-to-batch variation.”**

to measure multiple clinical endpoints based on multiple disease mechanisms, especially when you cannot measure them separately.”

Aiping Lu, researcher into integrative medicine in the Department of Disease and TCM Pattern Correlation Research at CACMS, says that more than 100 clinical trials on TCM formulae were conducted in China from 2006 to 2010 — most of them RCTs — and that more are coming soon. “A large amount of TCM clinical research papers will be published in the next 2–3 years,” he predicts. Indeed, several drugs developed from TCM recipes are currently in clinical trials, registered with agencies in Western

countries (see ‘Future Chinese treasures’).

But the widespread adoption of such robust, modern testing techniques requires a significant change from today’s situation, says Bengang Zhang. “Only a few dozen new TCM drugs are approved by the SFDA each year. Some approved TCM formulae have to be reviewed again, because the registration and approval processes have become stricter.” He adds that many products “won’t be able to enter into clinical trials even if they are successful in animal experiments”.

Indeed, despite the popularity of TCM, there is clearly a long way to go before its drugs pass the rigorous scientific standards of Western pharmaceuticals. According to the SFDA’s Annual Report on Drug Registration Approval, only 81 TCM products were approved in 2010 — 8% of all drugs, and slightly lower than the figure for 2009. The overwhelming majority (89%) of drugs that were approved in China in the same year were synthetic or purified chemicals.

Modernizing Asian medicines will require more than just applying modern tools and scientific techniques to ancient practices. Simply extracting one active ingredient from a herb or herbal concoction and then trying to find its biological activity has produced few positive results in the past and is unlikely to work effectively in the future. The process will require a better understanding of how multiple ingredients act in synergy, and what effect they can have on multiple targets. If TCM is to take its place in the modern medicine cabinet, then it must develop modern ways to prove itself. “TCM is a great treasure,” says Bai Lu. “But the only way to bring its full values to society is using modern science and drug discovery technologies.” ■

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1. Zhang, X. et al. *Anal. Bioanal. Chem.* [Epub ahead of print] (2011).
2. Zhang, B. et al. *Planta Med.* **76**, 1948–1955 (2010).

## CORRIGENDUM

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### Corrigendum: Modernization: One step at a time

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A quote attributed to Yi Rao in this Outlook article incorrectly implied that he criticized the use of traditional Chinese medicine (TCM) techniques. Instead, Rao's intention was to question attitudes that apply different standards to TCM and modern medicine. The text "This process is not helped by the insistence of many TCM researchers on using traditional methodologies — such as water decoction, immersion, reflux extraction and distillation — to process herbs. "It is totally ridiculous," says Rao' should instead read "This process is not helped by the insistence of many TCM researchers on using different measures of efficacy for TCM compared with modern medicines. "You can use different drugs or approaches, but all drugs and treatment strategies have to pass the same standards to show that they are effective", says Rao'. This text has been replaced in the PDF and HTML versions online.