



Traditional herbal remedies are typically prepared as tea.

For an unassuming-looking little herb, *Panax ginseng* has quite a reputation. Pulling the plant from the floor of the forests where it grows wild reveals the origin of its fame — the hairy ginseng root, prized for centuries by Asia people for its medicinal properties. Dried and ground, ginseng is a key ingredient in the traditional herbal medicines of China, Japan and South Korea.

PETER FRANK/CORBIS

Investigation shows that ginseng is rich in a family of steroid glycosides, dubbed ginsenosides. Equally clear is the fact that these compounds have no direct effect on the human body because the gut cannot absorb them<sup>1</sup>.

And yet, for many people, ginseng does have an effect. For although the human gut can't absorb the ginsenosides, some of the bacteria that live there can. After partly breaking down the compound for food, the bacteria excrete the remnants. It is these partly digested molecules that are used by the body and that have been proven to have a wide range of activity, from anti-inflammatory to anticancer effects.

The human gut is home to trillions of individual microbes representing thousands of species of bacteria and non-bacterial organisms called archaea<sup>2</sup>. The exact membership of this highly complex ecosystem, known as the microbiome, varies from person to person. Indeed, according to microbiologist Liping Zhao at Jiao Tong University in Shanghai, China, for around one-fifth of the population, ginseng will have no health benefit because the person doesn't have the right gut microbes to break it down.

Our microscopic passengers have long been suspected of being active participants in a mutually beneficial partnership. Integral to this picture is the interplay between gut bacteria and health. The global rise of chronic health conditions, ranging from obesity and diabetes to bowel disease and cancer, is increasingly being linked with perturbations in gut flora. And while modern medicine is struggling to tackle such multi-component diseases, the ancient medical philosophies and practices of Asia — particularly those of traditional Chinese medicine (TCM) — could offer an alternative approach. TCM's reliance on complex mixtures of compounds, and its philosophy of treating the human body as a whole, complete system that needs to be balanced, matches up well with the synergistic properties of the gut microbiome.

#### DUAL BENEFIT

Herbal medicines can affect health via the gut microbiota in two ways. Like ginseng, a host of herbal medicines are known to take effect only after being processed by bacteria in the gut. The list includes the dried fruits of *Gardenia jasminoides*, containing the compound geniposide, which is converted by gut microbes into its active form, genipin, another anti-inflammatory and anticancer compound. Similarly, the root of the liquorice

#### MICROBIOME

# That healthy gut feeling

*Many ingredients in traditional herbal medicines cannot be absorbed by the human gut. Could our microbial inhabitants do for us what we can't do ourselves?*

BY JAMES MITCHELL CROW

plant, *Glycyrrhiza glabra*, contains glycyrrhizin, which can be processed by microbes into 18 $\beta$ -glycyrrhetic acid — effective in the treatment of peptic ulcers, as well as having antiviral and antifungal activities<sup>3</sup>.

In the other type of interaction, certain ingredients in herbal medicines influence the balance of bacterial species living in the gut. For example, extracts from the *Ginkgo* leaf have been shown to increase the abundance of beneficial bacteria such as *Lactobacillus* and bifidobacteria in the gut. These bugs have been linked with a number of health benefits in the human host; in particular, they can modulate the immune system in ways known to reduce the risk of autoimmune diseases such as diabetes mellitus type 1 (ref. 1).

That at least some of the ingredients in herbal medicine exert their biological effects through interactions with our gut microbiota is not a new revelation. As long ago as the 1950s, Wei Xi, a microbiologist in the Dalian Medical University, China, proposed that the key to understanding the action of herbal medicines in the body was to consider their interaction with the microbes in our gut.

“People have appreciated for a long time that we carry this enormous community of microbes around with us,” says George Weinstock, a geneticist at Washington University in St Louis, Missouri. What has long limited our understanding of the role that the gut microbiota play in health was the overwhelming number of organisms present. The only realistic approach is to sample the whole bacterial community at once, says Weinstock. “It has only been in the last five years or so that the power of DNA sequencing instruments has got to the point where you can tackle that kind of project,” he says. Several large projects have already begun to chip away at the problem, including the US National Institutes of Health’s Human Microbiome Project, co-directed by Weinstock, and the European Commission-funded Meta-HIT project.

The next big step will be to link big-picture changes in microbiome makeup with particular patterns of disease, says Weinstock. Researchers are already starting to spot links between certain chronic diseases and the absence or presence of specific bacteria. For example, people with Crohn’s disease, a painful autoimmune disease affecting the bowel, tend to have low levels of a bacterium called *Faecalibacterium prausnitzii*, which is, therefore, suspected to play a protective role<sup>4</sup>. Another bacterium, a particular form of *Escherichia coli* called adherent invasive *E. coli*, is more prevalent in people with Crohn’s disease, raising the prospect it might be one of the bad guys<sup>5</sup>.

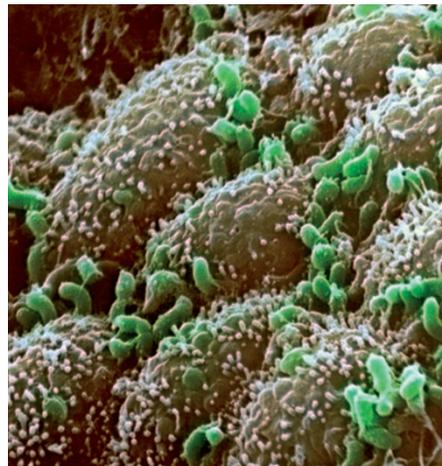
However, there is more to disease development than a single causative bacterium, says Weinstock. “It’s about the conversation between you and your microbes, and when that

conversation gets out of whack (for reasons that we don’t yet know) and if you have the right susceptibility genes, then disease can occur.”

It is this multifaceted nature of chronic diseases that makes them so hard to treat. “Western medicine is extremely good for treating acute diseases,” says Jan van der Greef, an analytical scientist from the Netherlands Organization for Applied Scientific Research (TNO) based in Delft, who helped establish the Sino-Dutch Centre for Preventive and Personalized Medicine in Zeist, the Netherlands. But the cell-based approach to medicine in the West is less effective for other kinds of ill-health, he says. “If you move towards chronic illnesses — or even to disease prevention and health promotion — our current way of thinking is really limiting what we can achieve.”

### TRUBLE ON THE WESTERN FRONT

Could it be that the traditional Eastern approach to health is better equipped to tackle chronic disease? “Because these complex diseases have multifocal problems, no single drug can treat them,” says Jeremy Nicholson, a biochemist at Imperial College London. “Chinese medicine is a polypharmacy, with multiple synergistically active compounds in the mixtures; the reason some of the medicines probably work is that they drug multiple targets at the



**Bacteria (green) settled on the small intestine.**

same time.” And in the gut, there are thousands of potential targets.

In fact, as far as chronic diseases go, modern medicines could be part of the problem, Nicholson adds. “Antibiotics don’t just kill bad bugs, they kill good bugs as well.” This disruption can still be detected in the gut microbiome at least two years after a patient has completed a course of antibiotics<sup>6</sup>.

Nicholson studies the interactions between gut microbiota and health using a whole-body systems biology approach that he invented called metabonomics — a systemic-wide version of metabolomics. “What we try to sample in metabonomics is the systemic response to some sort of intervention,” he says. The team uses analytical chemistry techniques such as

nuclear magnetic resonance (NMR) to map all of the metabolites — the chemical by-products of metabolism — in an individual’s blood, urine or stool sample, thereby capturing the cell’s metabolic output. By comparing the results before and after a treatment, metabonomics provides a read-out of the whole body’s response to a drug — whether that drug has worked directly on a cellular target or indirectly by interacting with the gut microbiome. This systemic view is the key difference between metabonomics and the standard scientific approach to examining metabolites using cell cultures.

For the past few years, Nicholson has been collaborating with Zhao, who is a leader in researching the interaction between herbal medicines and the gut. Zhao believes that metabonomics is uniquely placed as a tool for understanding how herbal medicines work, because it captures the whole-body response to what is, by intent, a whole-body treatment.

“We’ve done some work showing that herbal medicines produce notable shifts in gut microbial metabolism, and those shifts can be quite stable over quite long periods of time,” Nicholson says. Giving people chamomile, for example, changes the metabolite makeup of their urine. These effects remain even when the herb is no longer taken, implying that the change is caused by a lasting shift in gut microbe metabolism. “There is almost certainly a strong connection between microbiome activity and the activity of traditional Chinese medicines.” Not that herbal medicines were deliberately designed to work this way, he adds. “For TCM practitioners, it’s complete news to them.”

Zhao says that interactions with the gut microbiota could ultimately prove to be one of the main ways in which herbal medicines act on human health. “In Chinese medicine, many ingredients just pass through the gut, they don’t get into the bloodstream.” And yet some of these ingredients are known to have an effect, he says. So, much like ginseng, “it is most likely they work by changing gut microbiota.”

Given the emerging links between gut microbiome and human health, it is these types of glimpses that are inspiring scientists such as Nicholson to investigate traditional herbal medicines as a new way to treat chronic diseases. “If we can start to unravel how TCM works,” he says, “it might offer a completely new horizon on how you drug the human body.” ■

**James Mitchell Crow** is a freelance science writer based in Melbourne, Australia.

1. Zhang, X. *et al. Mod. Tradit. Chin. Med. Mater. Med.* **13**, 202–212 (2011).
2. Jia, W. *et al. Nature Rev. Drug Disc.* **7**, 123–129 (2008).
3. Kim, Y. S. *et al. J. Microbiol. Biotech.* **18**, 1109–1114 (2008).
4. Sokol, H. *et al. Proc. Natl. Acad. Sci. USA* **105**, 16731–16736 (2008).
5. Darfeuille-Michaud, A. *et al. Gastroenterology* **115**, 1405–1413 (1998).
6. Jernberg, C. *et al. ISME J.* **1**, 56–66 (2007).