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June 22, 2018 Dustin Grinnell

How Chinese medicine uses the potency of herbs – Dustin Grinnell

In 221 BC, Qin Shi Huang became the first emperor of China after conquering the warring states and unifying an immense territory. A leader of colossal vision, Qin oversaw the building of the Great Wall, constructed a national road system and standardized China's currency. To protect him in the afterlife, the emperor spent almost forty years building a mausoleum in his imperial city of Chang'an in central China, guarded by the Terracotta army.

Obsessed with immortality, Qin commissioned alchemists to scour the country in search of an “elixir of life,” a concoction that would cure all diseases and stave off death. These alchemists brought back plants, minerals, animals, insects and metals from every corner of China. After repeatedly ingesting small silver balls of mercury, a highly poisonous metal, the emperor grew increasingly ill. On a tour of eastern China, he died of mercury poisoning, killed by the very elixir he had hoped would grant him eternal life.

The practice of ingesting chemicals sourced from nature has a rich and storied history in China, albeit generally with less dramatic consequences. Such natural remedies (*yaocao*) fall under the umbrella of Traditional Chinese Medicine (TCM), which includes a broad range of medical practices, including therapeutic massage (*tuina*), exercise (*qigong* and *tai chi*), and dietary therapy (*shiliao*). As China celebrated National Medicine Day on March 17, it is timely to reflect on how for over two millennia, TCM practitioners have used mind and body practices alongside herbal remedies to treat or prevent a wide range of diseases, from diabetes to cancer.



The author undergoing traditional Chinese medicine treatments to boost his qi and remove toxins from the body

Today, many Chinese routinely undergo traditional treatments to promote general health and wellbeing. Acupuncture (*zhenjiu*) is the first of five treatments aimed at stimulating meridian points in the body and boosting “qi,” or the body’s life force. The second, scrape therapy (*guasha*), involves scraping the neck with a comb-like tool to stimulate circulation and relax the cervical vertebra. The third, cupping (*bagua*), involves putting heated glass cups on the back to create a tight suction, drawing the skin upward to mobilize blood and energy in the region. The fourth is moxibustion (*aijiu*), which involves applying burning moxa (*aicao*, similar to mugwort) just above the skin to help ease pain, tension or digestion.

TCM practitioners have long used herbal therapies to treat a wide range of ailments. There are over 13,000 medicinal substances used in China, and over 100,000 herbal recipes recorded in the ancient literature. Most of these substances are derived from plants – leaves, roots, stems, flowers, and seeds. These medicinal formulas are served as teas, capsules, liquid extracts, granules, or powders. Once ingested, in theory the herbal therapy’s active components divide and conquer to achieved the desired pharmacological effects. And some of those components, as confirmed by science and Western medicine, are truly potent.

“There are over 100,000 herbal recipes recorded in the ancient literature”

For example, realgar (*indigo naturalis*) is a traditional Chinese herbal medicine used to treat leukemia. The formula contains three active components: realgar, indigo and sage root. When ingested, these compounds kill cancer cells through three individual pathways: the arsenic in realgar fights destructive proteins in leukemia cells; the indirubin in indigo slows the growth of leukemia cells; and the tanshinone in the sage root helps repair damaged pathways, preventing the spread of cancer cells.

In China's over 2,000 years of prescribing herbal remedies, traditional doctors have published their vast medical knowledge in roughly 20 classic texts, the earliest of which is *The Emperor's Classic of Internal Medicine (Huangdi Neijing)*, dated to between the 5th and 3rd century BC. These ancient medical texts are still assigned reading in Chinese medical schools. The first book to cover herb-based treatments was the *The Divine Farmer's Materia Medica (Shennong Bencaojing)*, supposedly written between 200 and 250 AD by Shen Nong, a mythical sage ruler of ancient China. The three-volume work details the distribution, collection methods, indications, dosage and health benefits of 120 medicinal substances.

For another example, we can turn to the *Modern Study of Traditional Chinese Medicine* (1998), and read about the medicinal properties of “red flower”. According to the text, this plant “purges fire, dispenses heat, and removes blood stasis,” which is another way of saying it treats cardiovascular disease. Some ancient therapies in *The Compendium of Materia Medica (Bencao Gangmu)* are still used today. The *Compendium* was written in 1578 by China's greatest herbologists, Li Shizhen, who spent 30 years experimenting with the therapeutic potential of plants, minerals, insects and animals. The book is one of the most comprehensive documentations of the use of medicinal substances, containing 1,892 therapeutic compounds and 11,000 prescriptions, complete with drawings, pharmacological properties, symptoms and side effects.



The Compendium of Materia Medica

In the 1960s, the Chinese phytochemist Tu Youyou sifted through over 2,000 Chinese texts searching for a malaria cure. In *The Prescription for Emergencies* (~341 AD), Youyou found a herb, sweet wormwood (*artemisia annua*), that was observed to relieve malaria-like symptoms in humans. In the lab, she noticed sweet wormwood's leaves reduced parasite numbers in the blood of a rodent. Years later, her research team isolated the active metabolite known as *artemisinin* that significantly reduced the mortality rates of malaria in humans and remains the best weapon modern medicine has against the global killer. Youyou's discovery won her the 2011 Lasker Award, and in 2015, she won the Nobel Prize in Physiology or Medicine.

“China's greatest herbologists, Li Shizhen, spent 30 years experimenting with the therapeutic potential of plants”

Far and away, natural products from plants have proven to be the best source of medicine. In the 1940s, Sidney Farber discovered the first chemotherapeutic agent at the Harvard Medical School, when he gave the plant-derived metabolite *aminopterin* to children with acute lymphoblastic leukemia, causing temporary remission. The active metabolite in aspirin, known as salicylic acid, was derived from the bark of the willow tree and is used to treat pain, fever and inflammation. Salicylic acid also interacts with platelets, making the blood less ‘sticky’ and susceptible to clotting, which helps prevent heart attack and strokes. Paclitaxel, a drug used to treat ovarian and breast cancer, was derived from bark of the Pacific yew tree.

Pharmaceutical companies have spent decades exploiting nature’s wisdom to develop blockbuster drugs derived from plants, such as morphine and the anti-cancer drug Taxol. Of the 175 small molecules approved by the FDA for treating cancer since 1940, 74.8% have not been created synthetically, and 48.6% have been natural products derived from plants. In 2010, 50% of the drugs approved by the FDA came from plants.

Why are plants the best source of medicines? Plants didn’t evolve fangs, claws or legs, so for 400 million years they relied on chemistry to combat environmental stressors, using their complex metabolisms as a source for inventing tailor-made metabolites to defend against ultraviolet rays, droughts, and assaults from insects, pathogens and herbivores. Many of these metabolites have beneficial effects in humans, when isolated and harnessed.

It’s challenging, of course, to pinpoint which compounds in a plant-based concoction contribute to its effectiveness. When we ingest a plant, we don’t just ingest the active component, but thousands of other chemicals at the same time. A single plant contains a myriad of metabolites, which have different targets and can work synergistically to achieve their pharmacological effect. To complicate matters further, a herbal remedy in Chinese medicine is typically a cocktail of many different plants, often ground up into a powder and drunk as tea.

“Plants didn’t evolve fangs, claws or legs, so for 400 million years they relied on chemistry”

Natural products chemistry is a field of science that transforms plants into their individual metabolites. The natural products field is booming in China, whose government has allocated large funds to research on probing the pharmacological properties of plants used in ancient medicine (\$4.9 billion in 2012). Dr. Peicheng Zhang, a medicinal chemist at the **Peking Union Medical College** at the *Institute for Materia Medica* in Beijing, is a world leader in natural products chemistry. His lab acquires medicinal plants, many of which have been prescribed in China for centuries, and then uses advanced chemistry and sophisticated tools to purify an extract to its most basic chemical constituents. It’s molecular exploration. Like cartographers, they map the chemical landscape of plants.



Lonicera japonica, “golden silver flower,” used in TCM to “remove inner heat” and treat the common cold, seen here on the corresponding page about the flower in the *Compendium of Materia Medica*

Winnowing a plant down to its metabolites isn't as simple as grinding leaves with a mortar and pestle. The compounds are first extracted through a method known as ultrasonic heating, then isolated via high-performance liquid chromatography (HPLC), and finally identified with several sophisticated spectrometry techniques. For example, Zhang's lab separated out the active metabolites in Japanese knotweed (*polygonum cuspidatum*), a plant that has been used to treat Lyme disease, joint pain, bronchitis, jaundice, amenorrhea and hypertension. After picking the knotweed in the wild (literally from a mountaintop), the plants are brought to a factory

and subjected to two hundreds gallons of ethanol. After the mixture evaporates, a two-pound mass remains. This solid extract is brought to Zhang's lab where medicinal chemists pass the extract through tall columns to isolate the plant's metabolites. Using Nuclear Magnetic Resonance (NMR) spectrometry, scientists purified about 60 compounds, 23 of which were new to chemists, and many of which showed anti-diabetes, anti-inflammatory, anti-oxidization, anti-tumor, hepato-protective, neuro-protective and cardio-protective properties.

The Western medical establishment has slowly embraced the potential of using modern tools to understand the medicinal properties of ancient Chinese herbal remedies. The National Institutes of Health (NIH), for example, founded the National Center for Complementary and Integrative Health. Some pharmaceutical companies are exploring traditional Chinese medicine for drug candidates, including GlaxoSmithKline, which has its research headquarters in Shanghai. The FDA recently approved *sinecatechins* as a cream for genital warts, which is derived from green tea extracts, even though the ingredients responsible for its efficacy are still unknown.

Yet the odds are stacked against this approach to drug-making. Most drugs fail in the drug discovery process, not because they're unsafe, but because they simply don't work, often for reasons that are not fully understood. The drug development model is mechanism-based, a one-molecule-for-one-target approach that works well for acute diseases and infections, but poorly in the treatment of chronic and degenerative diseases, such as cancer and Alzheimer's. These complex human diseases have foiled drug-makers, because they are multi-faceted, driven by a myriad of genetic and biochemical mechanisms, and are exceedingly clever in adapting to most pharmacological interventions.

“Like cartographers, they map the chemical landscape of plants”

Traditional Chinese practitioners have been much less interested in why a herbal remedy works. Throughout history, their process has been trial and error. They gave patients herbal medicines – concoctions of plants, minerals and animal parts – and then watched what happened. If a herbal

remedy did nothing for a patient's symptoms, or made a patient sick, the therapy or concoction was tweaked. If a remedy worked, it became front-line therapy. The fact that the doctors didn't know exactly how the mixture affected underlying biology didn't matter if a fever broke, or a wound healed.

The skepticism that surrounds traditional Chinese herbal remedies isn't lost on its advocates. The Western medical and scientific community is traditionally critical of anecdotal evidence, or findings that can't be measured, often deeming traditional therapies as pseudoscientific. TCM has also faced **scandals** for using toxic ingredients that have made patients sick and even killed them. Deemed 'unscientific' by modern standards, ancient practices are often viewed critically, which is why scientists intend



A TCM diagnosis in ancient China, by feeling for the pulse of a patients' meridians or energy channel

to continue publishing solid, irrefutable data proving efficacy. "Once we produce valuable results, I think people will be convinced of this work's value," said Dr. Jing-Ke Weng, PhD, a biochemist who studies the origin and evolution of metabolic systems in plants at the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts.

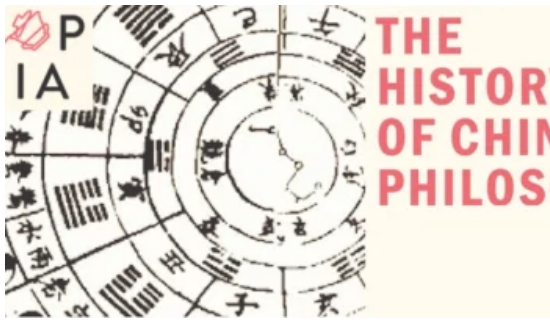
The natural products field, which got a tremendous boost with Tu Youyou's Nobel Prize win in 2015, seems poised for major breakthroughs. Holding *The Compendium of Materia Medica* in his office at MIT, Dr. Weng contemplated the 30 years of tedious experimenting that Li Shizhen, the Ming dynasty herbologist who compiled it, carried out to complete his life's work. Although the book was written in the 16th century, it might still hold further clues to the discovery of new medicines to treat complex diseases. Dr. Weng admitted that the task of sorting through the many galaxies of metabolites within the plant kingdom will take much longer than it took Li Shizhen to identity the plants' healing properties. But he's up for the challenge. ■

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