**Could Ancient Remedies Hold the Answer to the Looming Antibiotic Crisis?**

One researcher thinks the drugs of the future
might come from the past: botanical treatments
long overlooked by Western medicine.

BY FERRIS JABR

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On a warm, clear evening in March, with the sun still hanging above the horizon, Cassandra Quave climbed aboard a jalapeño-green 4-by-4 and started to drive across her father’s ranch in Arcadia, Fla. Surveying the landscape, most people would have seen a homogenous mat of pasture and weeds punctuated by the occasional tree. Quave saw something quite different: a vast botanical tapestry, rich as a Persian rug. On a wire fence, a Smilax vine dangled menacingly pointed leaves, like a necklace of shark’s teeth. Beneath it, tiny wild daisies and mint ornamented the grass with pink tassels and purple cornets. Up above, on the sloping branches of oak trees, whiskery bromeliads, Spanish moss and the gray fronds of resurrection fern tangled in a miniature jungle all their own.

Each of these species intrigued Quave enough to merit a pause, a verbal greeting, a photo. An ethnobotanist based at Emory University in Atlanta, Quave, 38, has an unabashed fondness for all citizens of the kingdom plantae. But on this evening, her attention lingered on certain species more than others: those with the power to heal, with the potential to help prevent a looming medical apocalypse.

Quave parked near the edge of a pond crowded with the overlapping parasols of water lilies. Here and there a green stem rose from the water, capped with a round yellow flower bud, like the antenna of some submerged mutant. Alligators had attacked dogs and ducks around here in the past. “But don’t worry,” Quave said, tracing the pond’s perimeter. “If we see one, I’m going to shoot it.” She wore lightweight cargo pants, a black tank top, a paisley bandanna wrapped around her head and a .357 Magnum revolver strapped to her hip.

After Quave gave the all-clear, her colleague Kate Nelson and I pulled on some tall rubber boots and proceeded cautiously into the water. I repeatedly plunged a shovel into the pond’s viscous floor of gray mud, just beneath the tenacious roots of a water lily — species name: Nuphar lutea — working it like a lever to loosen the plant as Nelson tugged on its stems. We seemed to be making good progress, until the roots suddenly snapped and Nelson fell backward with a splash. Thirty minutes later we emerged with boots full of water and several intact specimens. “Beautiful!” Quave said. “Hello, lovely.” The roots, which she had not seen properly until now, were large and pale like daikon, though much gnarlier and bristling with a mess of shaggy tendrils. Before this trip to Florida, while reading an old compendium on plants used by Native Americans, Quave had learned that a decoction of N. lutea’s roots could treat chills and fever, and that a poultice of its leaves could heal inflamed sores.

Ethnobotany is a historically small and obscure offshoot of the social sciences, focused on the myriad ways that indigenous peoples use plants for food, shelter, clothing, art and medicine. Within this already-tiny field, a few groups of researchers are now trying to use this knowledge to derive new medicines, and Quave has become a leader among them. Equally adept with a pipette and a trowel, she unites the collective insights of traditional plant-based healing with the rigor of modern laboratory experiments. Over the past five years, Quave has gathered hundreds of therapeutic shrubs, weeds and herbs and taken them back to Emory for a thorough chemical analysis.

By revealing the elemental secrets of these plants, Quave has discovered promising candidates for a new generation of drugs that might help resolve one of the [greatest threats to public health today](http://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf): the fact that an increasing number of disease-causing bacteria are rapidly evolving immunity to every existing antibiotic. Without effective antibiotics, common bacterial diseases that are curable today will become impossible to treat; childbirth, routine surgeries and even the occasional nick could turn lethal. The widespread emergence of resistant bacteria already claims 700,000 lives a year globally. Experts conservatively predict that by 2050, they will kill 10 million annually — one person every three seconds. “We’re standing on the precipice of a post-antibiotic era,” Quave says. “We just haven’t fallen off yet.”

**Wherever you are,**whatever you are doing, bacteria are beside you, on you and within you. And not just a few bacteria, but immense communities as dense, diverse and entangled as a rain forest. Relationships within these microbial societies are so intricate and volatile that they make more archetypal ecological associations — the cheetah and gazelle, the honeybee and flower — seem cartoonish in comparison. Depending on how many of its own kind are present and who else is around, and on the available territory and food, a given bacterial species will ignore, assist or obliterate its microbial neighbors. To cope with such a mercurial existence, bacteria have evolved an astonishing array of chemical lures, signals and weapons. In the early 20th century, [scientists discovered](http://www.microbiologysociety.org/publications/microbiology-today/past-issues.cfm/publication/antimicrobials/article/C1FD8C70-FA3C-4829-8E8DC35E8BD2F470) that some of these molecules, if isolated and replicated en masse, could wipe out certain disease-causing bacteria. In their modern forms, antibiotics appear entirely artificial. But most of them come from nature. We did not so much invent antibiotics as borrow them from the very creatures we were hoping to overpower.

Between the 1940s and 1960s, the golden age of antibiotic discovery, researchers and pharmaceutical companies harvested such molecules from soil microbes and chemically tweaked them into dozens of new commercial drugs. Some antibiotics, most famously penicillin, came from fungi, but soil bacteria were so abundant and so easy to collect that they remained the center of attention. Researchers soon discovered, though, that only about 1 percent of all bacterial species could be grown in sterile laboratory conditions. By the 1970s, scientists had squeezed almost every potential drug out of this small circle of amenable microbes. In subsequent decades, many large pharmaceutical companies turned away from nature as a source of antibiotics, diverting resources to the promising new field of synthetic drug development.

Combinatorial chemistry, which emerged in the 1980s and was adopted by the pharmaceutical industry in the 1990s, enabled chemists to rapidly generate immense libraries of potentially novel drugs by mixing and matching their molecular building blocks. Ultimately, however, human chemists have been unable to emulate the ingenuity and complexity of organic molecules produced by [eons of evolution](http://file.scirp.org/pdf/PP_2013062411214748.pdf). “The kind of evolution that happens in living things gives rise to unusual chemistry that is not straightforward to synthesize,” says Simon Gibbons, a medicinal phytochemist at University College London. “Nature is a superchemist. It’s been doing this for a lot longer than we or even mammals have been around. Plants have been doing this for about 400 million years.” That puts people — even very smart people — at a competitive disadvantage. Cedric Pearce, chief executive of the fungi-based drug development company Mycosynthetix, puts it this way: “Nature creates extremely effective but extraordinarily complex molecular structures that a chemist would look at and say, ‘Now, why would I ever think to design that?’ ”

Only a handful of truly novel antibiotics have made it to market since 1980. In the past two decades, Pfizer, Eli Lilly and Company, Bristol-Myers Squibb and other big-name drug companies have downsized or closed their antibiotic-research programs. The pharmaceutical industry lost interest not only because of the disappointment of synthetic chemistry as an engine for discovery but also because antibiotics are simply less profitable than drugs for more persistent conditions like cancer, depression and high cholesterol. Meanwhile, the world indulged in the existing array of antibiotics in such a reckless fashion that it’s hard to know where to place blame. Physicians are just as guilty of overprescribing antibiotics — even to mollify hypochondriacs — as patients are of demanding the drugs too often. Farmers grew accustomed to overmedicating livestock because a steady supply of antibiotics supposedly pre-empted infection and encouraged vigorous growth.

All those antibiotics were not simply treating isolated people and animals; they were transforming our shared ecosystems. Antibiotics fundamentally alter the invisible microbial landscapes in us, on us and all around us. Although antibiotics are designed to be as lethal as possible to dangerous bacteria, there are often a few inherently resilient microbes that survive and proliferate, passing on their genes — and grit — to their offspring. As subsequent generations of these microbial gladiators endure further onslaughts of drugs, they evolve even greater resilience, improving their defenses against antibiotics and sometimes spreading these adaptations throughout the microbial universe through the promiscuous exchange of DNA. By flooding our bodies, farms and hospitals with inordinate amounts of antibiotics — obliterating the weak and sparing the strong — we created exactly the kind of ruthless ecological arena most likely to drive the evolution of resistance.

With the world’s cabinet of useful antibiotics almost empty, scientists are rushing to discover replacements in a diverse set of natural resources. Some researchers are trying to mine the untapped potential of those noncooperative soil bacteria, devising new kinds of growth chambers that might allow unstudied species to thrive in the lab. Others are genetically engineering microbes to produce little-known compounds that could be useful for making drugs. Still others are scavenging the native antibiotics in ocean life, fungi and insects. “We’re at the end of the current era of antibiotics, and it’s getting really scary,” says Kendra Rumbaugh, a microbiologist at Texas Tech University who specializes in wound infections. “We’ve gotten all of the low-hanging fruit, and we’re going to have to work a lot harder. We have to go to the ends of the earth — the ocean, the ice shelf, the rain forest — anywhere we possibly can to find new natural products.”

No single strategy is likely to be sufficient, but ethnobotany offers a few distinct advantages. Instead of relying on random screenings of living creatures — an arbitrary scoop of soil or seawater — it is the only strategy that benefits from a pre-made guide to some of nature’s most potent drugs, honed by thousands of years of trial and error in traditional medicine. And as far as organic drug factories go, it’s difficult to beat the complexity and ingenuity of plants. Plants are nature’s chemical wizards. If a plant finds itself in an unfavorable situation — feasted on by pests, ignored by pollinators — it cannot kick up its roots and relocate. Instead, plants regulate the chemistry of their environment, perpetually suffusing the ground, air and their own tissues with molecular cocktails and bouquets intended to increase their chances of survival and reproduction.

The story of the malaria drug artemisinin is one of the most compelling testaments to the antimicrobial power of plants. In 1967, Mao Zedong initiated a secret military project to discover new treatments for malaria, which is caused by mosquito-borne microorganisms known as Plasmodia. The Vietnam War was raging, and China’s allies in North Vietnam were losing soldiers to the disease. These outbreaks were made worse by the fact that Plasmodia had developed resistance to chloroquine and other antimalarial drugs then in use.

Mao’s project recruited 500 scientists to find a new cure using two chief tactics: synthetic chemistry and ethnobotany based on traditional Chinese medicine. By analyzing ancient medical texts and more than 2,000 herbal remedies, the phytochemist Tu Youyou and her team identified a plant supposedly brimming with antimalarial compounds: sweet wormwood (Artemisia annua), a member of the daisy family that looks a bit like chamomile. Upon initial testing, the plant did not perform well. But a fourth-century handbook of prescriptions provided a vital insight: To extract the plant’s medicinal properties, it should be steeped in relatively cold water, rather than boiled like tea. Subsequent research identified wormwood’s primary active compound, which was eventually developed into artemisinin, one of the most successful treatments for malaria in history. In 2015, Tu [received the Nobel Prize](http://www.nytimes.com/2015/10/06/science/william-c-campbell-satoshi-omura-youyou-tu-nobel-prize-physiology-medicine.html)in Physiology or Medicine.

**Growing up in**Arcadia, Quave spent just as much time recuperating in hospital beds as she did in rough-and-tumble play outdoors. She was born with several deformities in her right leg: Her femur was much shorter than it should have been, and some of the bones in her ankle, as well as her entire fibula, were missing. When she was 3, surgeons amputated her right leg at the shin’s midpoint. A few days later, while she was recovering at home, her stub began to stink like “a dead rotting animal,” she recalls. Although doctors had told her mother not to remove the bandage under any circumstances, she unwrapped it to discover a wound with the consistency of Jell-O pudding. An emergency trip to the hospital revealed a staph infection in the bone and gangrene in the flesh. She underwent another surgery to excise the diseased tissue and spent months recovering at the hospital, periodically soaking in blood-red baths of Betadine, a rubber ducky floating on the surface.

As a toddler, she got around on a tricycle and a makeshift scooter — a carpeted board with wheels — until receiving her first prosthetic leg and foot, which she continually upgraded as she grew. Her disability never prevented her from exploring the outdoors with her sister and friends: They would climb trees, ride horses, chase goats and come back home covered in fire ant bites and mud and cow dung, so filthy they had to be hosed down. One time, Quave tried to drive her four-wheeler up a steep pile of dirt, rolling off and burning the back of her knee on the motor. Terrified of her mother’s ire, she kept the injury a secret, soothing herself with the cool, slimy pulp of a backyard aloe plant.

At school, Quave loved the sciences, and by the time she got to Emory for college, she was determined to be a surgeon. “I had been around medicine so much,” she says. “I wanted to emulate the doctors who had treated me.” So she proceeded on the pre-med track as a double major in biology and anthropology. In the spring of her junior year, to fill some vacant space in her schedule, she took a class on tropical ecology, which introduced her to ethnobotany.

Botanical medicine, Quave learned, not only predates civilization — it is older than humanity itself. Many animals appear to self-medicate with plants: In Panama, members of the raccoon family known as coatis rub minty tree resin through their fur to deter fleas, ticks and lice, and some great apes and monkeys swallow mildly toxic leaves seemingly to fight infestations of parasitic worms. Our earliest human ancestors continued such traditions, and until relatively recently, plants were our primary source of medicine. A Sumerian cuneiform tablet dating to circa 3,000 B.C. lists 15 prescriptions, many of which are made from plants — myrtle, thyme, willow — mixed with honey, beer or wine. The Aztecs searched far-off lands for new medicinal plants, returning with their roots carefully cocooned in balls of dirt. Between 50 and 70 A.D., while traveling with Emperor Nero’s armies, the Greek surgeon Dioscorides learned how to make balms, elixirs and anesthetics from about 600 plants, like peppermint, hemlock and cannabis. He published his findings in a pharmacopoeia eventually known as “De Materia Medica,” a standard reference for the next 1,500 years.

When European explorers infiltrated the lush New World at the end of the 15th century, they started a revolutionary era of botanical cross-pollination across the seven seas. The Columbian exchange introduced Europe not just to new foods and flavors but also to novel medicines, like the bark of the cinchona tree, which was eventually developed into quinine to treat malaria. It was not until the late 19th century — as medical knowledge advanced and appreciation for indigenous cultures increased — that ethnobotany as a formal discipline began to take shape. Starting in 1941, the American biologist [Richard E. Schultes](http://www.nytimes.com/2001/04/13/us/richard-e-schultes-86-dies-trailblazing-authority-on-hallucinogenic-plants.html?pagewanted=all), often regarded as the father of modern ethnobotany, spent 12 years living alongside indigenous peoples in the northwest Amazon Basin, participating in their rituals and ingesting numerous therapeutic and psychoactive plants. After returning to America, he trained several generations of ethnobotanists at Harvard University, some of whom are leaders in the field today.

Although ethnobotany and the longstanding co-evolution with plants that preceded it have provided us with some of our most essential medicines, their purified and generic final forms are so divorced from their origins that most of us are oblivious to this immense botanical debt. Aspirin is based on a compound found in the perennial herb meadowsweet; pseudoephedrine was inspired by the use of the dryland shrub Ephedra sinica in traditional Chinese medicine; morphine, codeine, thebaine and other opiates are still made from poppies; and many anticancer drugs come from plants, like vincristine and vinblastine, both extracted from the Madagascar periwinkle. As of 2003, at least 25 percent of modern medicines were derived from plants, yet only a tiny fraction of the estimated more than 50,000 medicinal plants used around the globe have been studied in the lab.

Quave’s personal discovery of ethnobotany culminated in two self-organized trips to a research station in Peru. There, she met a *curandero* — a traditional healer — named Don Antonio, who took her to villages of palm-thatched huts along the banks of the Napo River. Because village children drank unfiltered river water there, they were perpetually infected with large numbers of parasitic worms known as helminths, which live in the intestines and feast on blood. Although the Peruvian government had established a few small pharmacies to provide anti-helminthic drugs and other medicines, they were too distant and too poorly stocked to be of reliable benefit.

Don Antonio knew another way to dispel the parasites, using a natural remedy ubiquitous in the Amazon. He cut into the bark from one of the numerous fig trees growing in and around the villages, and a milky emulsion seeped out. Ingesting too much could cause severe cramping, but at the right dose it was highly effective. Don Antonio had learned this remedy from his family, who had trained him in plant-based healing from the age of 7. Since the introduction of pharmacies selling Western pills, however, much of traditional medicine had fallen into disrepute. Don Antonio was a healer by training, but history had reduced him to an entertainer in practice. The research station employed him to give talks to visiting scientists and tourists and to maintain a garden of medicinal plants that rarely grew into anything more than ornaments.

“That trip caused a shift in my worldview and in how I thought about medicine,” Quave told me. Even in the jungle, the dominance of modern Western medicine was overwriting vast stores of knowledge about powerful tonics hidden in surrounding ecosystems. “There’s chemical warfare around all of us all the time — in plants. When you’re really embedded in nature, you can see that.”

**On a sunny**afternoon, about halfway through the two-week field expedition in Florida, Quave, Nelson and I gathered in a circle to chop up several bags of gray tree branches studded with crinkled leaves and pale green flowers shaped like tiny beehives — the limbs of a wax myrtle, which has been used in traditional medicine to treat fevers, diarrhea and infections. Quave sat on an overturned bucket, the casing of her prosthetic leg partially exposed: a 3-D-printed calf-shaped silver shell with a lacy pattern of steampunk flourishes. She held a pair of garden clippers in one hand, which flashed through the air as she gesticulated, discussing her life after college and the botanical antibiotics she has discovered so far.

Quave’s trip to the Amazon was so inspiring that upon graduating from Emory, she turned down her acceptances to medical school and pursued ethnobotany instead. After working as an ethnobotanical research assistant in Ginestra, a tiny village in southern Italy; earning a Ph.D. in biology at Florida International University in 2008; and completing postdoctoral fellowships, Quave landed her current job as a medical ethnobotanist and assistant professor of dermatology at Emory in 2013. She has conducted most of her fieldwork with traditional healers in rural regions of Italy, Sicily, Albania and Kosovo. Quave has learned, for example, that leaving a bottle of olive oil and St. John’s wort to steep in the sun produces a scarlet solution that heals burn wounds, that immature green walnut can treat fungal infections and that the evergreen shrub Daphne gnidium can stop bleeding and rid dogs of fleas.

Around the globe, as people continue to abandon the countryside for urban areas, such botanical cures are increasingly forgotten or dismissed as old wives’ tales — and certainly some of them are. But to dismiss all of them, Quave thinks, would be a terrible oversight. “We’re showing it isn’t witchcraft or voodoo medicine,” she says. “It actually has some biological function.” In southern Italy, Quave discovered that healers use elmleaf blackberry to treat boils and abscesses. She gathered a few bags of blackberry roots, sliced and dried the samples, vacuum-sealed them in plastic bags and shipped them back to her lab in Atlanta, where her colleagues ground them to a powder in a mill and extracted organic molecules using various solvents. When they added different combinations of blackberry molecules to brothy wells of MRSA — a particularly antibiotic-resistant species of Staphylococcus bacteria — the botanical extracts did not kill the microbes as typical antibiotics do. Rather, they prevented the bacteria from forming slimy, intractable mats called biofilms, which allow them to adhere to living tissues and medical devices like catheters in hospitals.

And that, Quave says, is exactly the kind of antibiotic that can foil the evolution of resistance. A few lone bacteria drifting about are not particularly worrisome. It’s when pathogenic microbes team up that they become a greater threat. Bacteria rely on a form of chemical communication known as quorum-sensing: When they form a critical mass, they start churning out toxins, exchanging genes for antibiotic resistance and protecting themselves with a thick shell of sugar molecules that are impermeable to many drugs. But if an antibiotic could disrupt bacteria’s ability to collaborate, instead of killing them outright, it could render them more vulnerable and “sidestep resistance,” as Quave puts it. “It’s like a magician’s trick. You’re distracting the bacteria, saying, ‘Look over here!’ Meanwhile your own immune system can clear away the microbes.” Because such an antibiotic would not be directly responsible for the microbes’ death, there would be much weaker evolutionary pressure to develop resistance against it. “Ever since Fleming discovered penicillin, we’ve been in the mind-set that we need to kill microbes,” Quave says. “What we need to do is find a balance.”

Recently, Quave and her research team have discovered that an extract of Brazilian peppertree berries — an invasive species common in many warmer parts of the United States — prevents MRSA from forming skin lesions in mice and shrinks biofilms formed by the bacteria. “I really believe these kind of inhibitors are a major part of the solution to antibiotic resistance,” Quave says. “We can shut down bacteria’s most dangerous machinery without killing them.” She envisions using such drugs as prophylactics in surgeries with a high infection risk, or in combination with other antimicrobials if a serious infection is already established.

Given such promise and the desperate need for new antibiotics, you might think that the path from lab to pharmacy would be expedient. It is anything but. In many cases, plant-based remedies work best as complex mixtures of many distinct molecules, as opposed to a highly refined one- or two-molecule extract. In the past decade, the Food and Drug Administration has approved just two commercial botanical drugs: Veregen, a medley of green-tea-leaf compounds used to treat genital warts, and Fulyzaq, an antidiarrheal derivative of tree resin with so many molecular constituents that some remain unidentified. Despite these successes, there is continued opposition in the pharmaceutical industry to developing complex botanicals because they are perceived as too messy and too difficult to evaluate and standardize for mass production. University scientists often rely on drug companies to fund the costly and time-consuming clinical trials required for approval from the F.D.A., and major pharmaceutical companies have little interest in antibiotics. If a candidate antibiotic is some motley herbal treatment — if it has the whiff of mumbo-jumbo folklore — the opposition is stronger still.

The difficulties don’t end with regulators. Per the ethics of their field, ethnobotanists would also need to ensure that some of the profits from drug sales reach the people who originally developed a traditional botanical remedy. In 1992, more than 150 governments [signed](https://www.cbd.int/information/parties.shtml) the Convention on Biological Diversity, a treaty establishing that nations retain sovereign rights over their indigenous medicines and that such resources should be shared only after mediation of equitable benefits.

But above all else, the apathy of the pharmaceutical industry remains the biggest immediate roadblock. “The odds are sometimes disheartening,” she admits. “But this is my field, and I’m not going to abandon ship because today the market is not supporting antibiotic research. In the near future they’ll have to. Western medicine will stop without antibiotics.”

Consider, for instance, that over the past eight years, Thailand, Cambodia and other Asian countries [have reported](http://www.nejm.org/doi/full/10.1056/NEJMoa1314981#t=articleBackground) increasingly common cases of artemisinin-resistant malaria. Yet a recent study demonstrates that feeding rodents sweet wormwood leaves in their entirety — as opposed to a synthesized derivative — overcomes this resistance. The modern, stripped-down version of this ancient medicine may very well sacrifice some beneficial chemical synergy present in the whole plant.

If Quave is right, the impending medical crisis will eventually jump-start antibiotic research and development. But it can take more than a decade for a standard antibiotic to transition from discovery to pharmacy, let alone an entirely novel concoction or seemingly convoluted treatment. Meanwhile, we will be stuck with a dwindling stock of extant antibiotics, our only recourse against increasingly armored pathogens.

 In the early evening of our penultimate day in Florida, while driving along the edge of an orchard, with the scent of orange blossoms wafting through the car’s open windows and the lime-green sparks of fireflies blinking around us, Quave suddenly cried out to stop the car. She flung open the door, rushed forward and stooped to inspect a small rosette of dandelionlike leaves surrounding a few stalks furred with teensy maroon flowers. Most people would have regarded the three-inch-tall plant as a completely unremarkable weed, if they noticed it at all. Quave was rapt.

During her two-week expedition in the marshes, wetlands and forests of Florida, Quave had already collected close to 175 species — primrose willow, carnivorous sundew, toothache grass, gallberry, black nightshade — but she could not pass this one up. “This is Plantago!” she said. “It’s known for applications for skin infections.” One species of the plant, she later explained, can stop a bleeding wound; another can heal abscesses. “It’s easy to dig up,” she continued, turning back to the car. “Let’s get some bags. Grab as much as you can.”

Ferris Jabr is a writer based in Portland, Ore. He last wrote for the magazine [about breeding wheat](http://www.nytimes.com/2015/11/01/magazine/bread-is-broken.html) for more flavorful and nutritious bread.