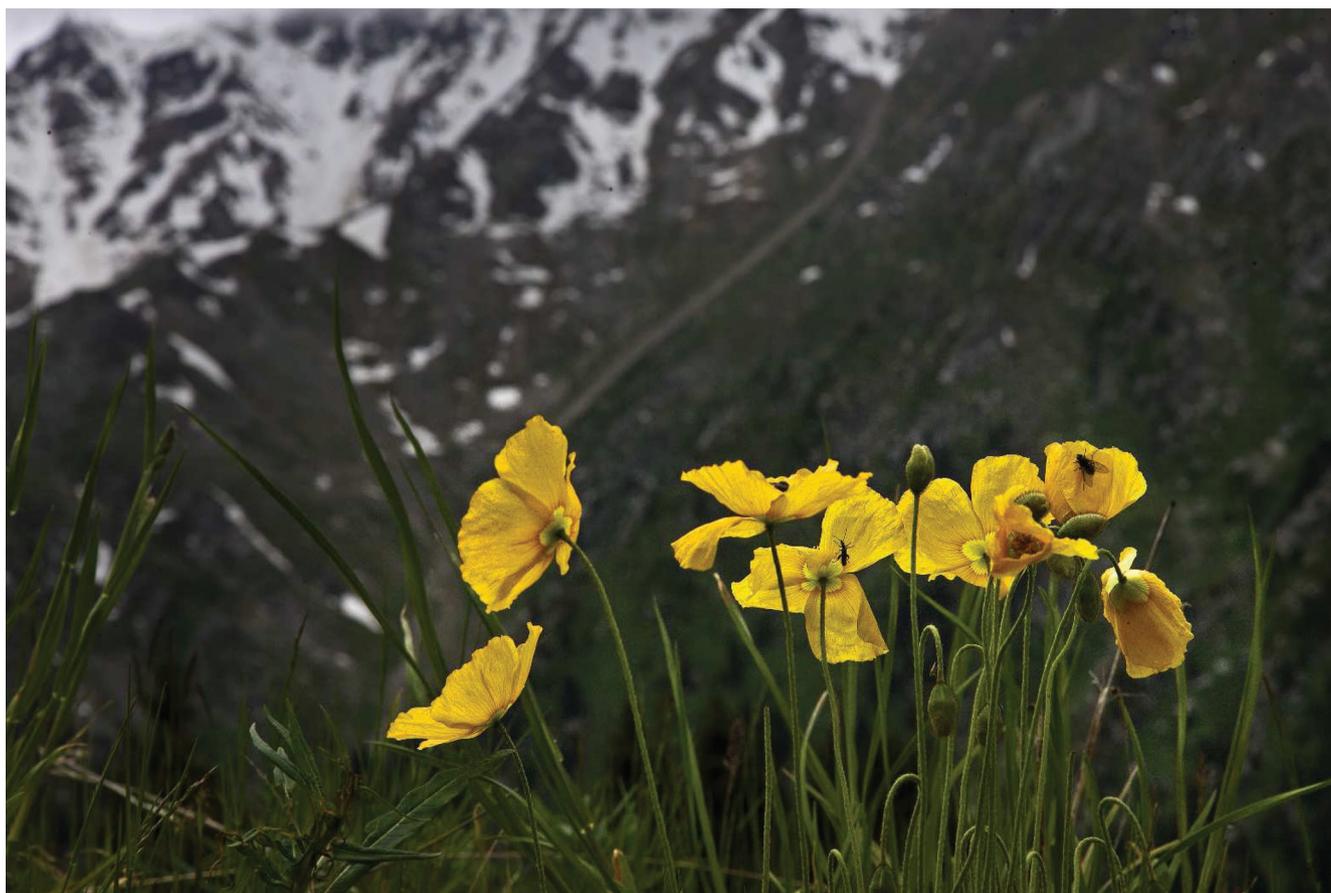


# Wild Medicine

CHERYL LYN DYBAS

## The search for cures from nature



*Wild poppies in Kazakhstan's Charyn Canyon, also called the Valley of Castles for its rock formations. Extracts from poppy seeds have led to medicines such as morphine and codeine. Photograph: Ilya Raskin.*

In the movie *Medicine Man*, biochemist Robert Campbell, played by actor Sean Connery, searches for new drugs in the Amazon's vast rainforests. There, Campbell finds a cure for cancer not in the rainforest's rare flowers but in an indigenous ant species. All is looking up until a logging company destroys Campbell's research station. Along with it, acres of rainforest

burn to the ground, taking the cure-containing ants with them. Campbell perseveres, however, convinced he will locate more ants and stop cancer in its tracks.

"As often happens in fiction, seemingly fanciful discoveries from nature are becoming biomedical realities," says biochemist Gordon Cragg, retired chief of the National Institutes

of Health's (NIH) National Cancer Institute Natural Products Branch. "Medicinal chemicals isolated from frog skin secretions, for example, come from the ants in their diet." In new research, scientists are working on less-toxic variants of a powerful analgesic called epibatidine.

Thousands of miles from the tropical rainforest and far from any movie



*Marketplace in Mary, Turkmenistan, an ancient oasis in the Karakum Desert through which caravans carrying herbal medicines have traveled for centuries. Photograph: Ilya Raskin.*

theater, other medicine men and women are on the path to cures—in this case, to metabolic syndrome, a cluster of conditions including high blood pressure, high blood sugar levels, and high cholesterol levels. Metabolic syndrome increases the risk of heart disease, stroke, and diabetes. Remedies could not come too soon: The overall prevalence of metabolic syndrome in adults in the United States, according to a 2015 issue of the *Journal of the American Medical Association*, is 33 percent.

### Scaling the roof of the world

In remote, mountainous countries such as Tajikistan, researchers are on the hunt for—and finding—pharmacological treasures. Molecular biologist Ilya Raskin, of Rutgers University, whose expertise is plants and human health, and plant biologist Vyacheslav Dushenkov, of Hostos Community

College, in Bronx, New York, are scaling the “roof of the world,” as Tajikistan is known. Raskin and Dushenkov visit the country’s high Pamir Mountains to locate plants in the genus *Artemisia*, or wormwood. They are evaluating *Artemisia*’s potential for treating metabolic syndrome.

*Artemisia annua*, or sweet wormwood, is known for its active component, artemisinin, which led to a new class of antimalaria drugs. Artemisinin’s discovery won scientist Tu Youyou in China the shared 2015 Nobel Prize in Physiology or Medicine. During Tu’s screening of herbal remedies, an extract from *Artemisia annua* emerged as a promising candidate. Tu revisited ancient Chinese literature and discovered invaluable clues in the quest to find answers. Raskin’s and Dushenkov’s efforts in Tajikistan are not so different. Tajikistan has a long tradition of using botanical therapies

for the prevention and treatment of disease, going back at least 1000 years.

Through an international research training grant from the NIH, the Center for Botanicals and Metabolic Syndrome (CBMS)—directed by Raskin and coordinated by Dushenkov, along with physicians Saidbeg Satorov, of the Tajik Research Institute of Preventive Medicine, and Yusuf Nuraliev, of the Avicenna Tajik State Medical University—is integrating training in Western medicine with traditional botanical knowledge.

“Through CBMS, we’re seeking to merge two medical systems—ancient and modern—for the benefit of Tajikistan,” says Raskin. “We’re fostering research scientists who can bridge these ways of thinking for the prevention and treatment of metabolic syndrome.” Dushenkov adds, “Tajikistan is one of the poorest countries in the world and is in critical need of

improved public health and training in medical research.”

The CBMS held its first Plants for Human Health International Workshop in Dushanbe in October 2015. Months before the meeting, Raskin and Dushenkov were in Tajikistan for meeting preparations and fieldwork on *Artemisia*. Of 235 species of *Artemisia* in the former Soviet Union, 114 are found in Central Asia, with about 70 in Tajikistan.

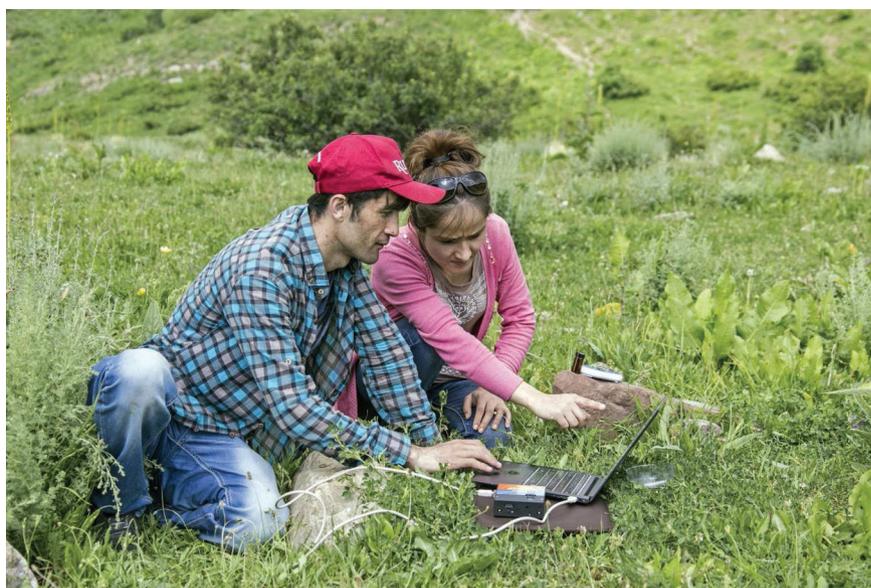
### Praying for *Artemisia*

To find *Artemisia*, Raskin and Dushenkov joined a group of Tajikistan residents on their way to the village of Sary-Khasor, in the Pamir Mountains. There, peaks reach elevations of more than 7000 meters. “First, you get on a four-wheel drive truck that doubles as a bus,” says Dushenkov. “The road, if you can call it a road, follows a river, sometimes just going along the riverbed itself.”

In Sary-Khasor, the researchers changed “cars” to a jeep. “These are quite durable—and notoriously unreliable,” quips Dushenkov. “You’re packed in a small vehicle and just pray for a happy ending.” He and Raskin stayed overnight in a small village. The night prayer—*Tarawih*—was conducted on a small terrace outside one of the houses. The biologists did not speak the dialect, but they were surprised to hear *Artemisia* repeated several times. They later learned that the locals were praying that the researchers would find *Artemisia* plants the next day.

*Artemisia scoparia*, or redstem wormwood, may be an answer to the Tajiks’ prayers, especially for those afflicted with metabolic syndrome, diabetes, and nonalcoholic fatty liver disease (NAFLD). The prevalence of NAFLD may be as high as 30 percent in developed countries and nearly 10 percent in developing nations, making it one of the most common liver conditions in the world, wrote Raskin and other scientists in a 2013 paper in the journal *Metabolism*.

The researchers report that experiments showed reduced liver fat in



*Parviz Sukhrov and Farzona Miskinova, students at the Avicenna Tajik State Medical University, use the Screens to Nature method to test Artemisia plants in Tajikistan. Photograph: Vyacheslav Dushenkov.*

mice given an extract of *Artemisia scoparia*. A Eurasian plant that is found from France to Japan, including in Tajikistan, *Artemisia scoparia* is one of several *Artemisia* species CBMS scientists are studying.

Tajikistan’s peaks and valleys endure widely ranging temperatures. To survive there, plants, including *Artemisia*, must adapt to extremes. All plants produce primary substances for growth and—if they live in stressful conditions—secondary compounds, or metabolites, to protect them in demanding environments. Leads for new treatments, says Raskin, are often contained in secondary metabolites.

The initial research to find these compounds may now be performed right where the plants grow. It is a new paradigm that Raskin calls *Screens to Nature*: bringing pharmaceutical screens to nature, in the form of field-deployable bioassays provided through Rutgers’ Global Institute for BioExploration, instead of bringing nature to pharmaceutical screens. “This new way of looking at medicinal plants,” says Satorov, “is important to our efforts to advance

medical research and education in Tajikistan.”

### Nature meets drug discovery

In the Screens to Nature antibacterial bioassay, for example, investigators identify and collect plants in the wild. Each plant’s location is recorded with a portable global positioning system (GPS) unit, and two small samples are obtained: one for extraction and one for identification, the latter to be kept as an herbarium specimen, wrote Raskin and others in a 2010 paper in the *Journal of the North American Colleges and Teachers of Agriculture*. Then, an extract is prepared from the parts of a plant that may have medicinal value, whether leaves, bark, fruit, or roots.

The screening involves placing a small, bacteria-laden saliva sample into each well of a 48-well plate, after which the plant extract is added. The plates incubate overnight. The next morning, they are ranked on a scale of zero to three—the higher the number, the less bacterial growth in the sample. If a plant shows few bacteria, laboratory-based assays often follow.



Scientists at the Uzbek Agricultural University in Tashkent, Uzbekistan, work on extracts from medicinal plants ready to be assayed for pharmacological activity. Photograph: Ilya Raskin.

Other Screens to Nature bioassays evaluate whether plant extracts might be used to regulate blood sugar levels, fight parasitic and viral infections, or increase immunity. “These bioassays can be performed without a lot of equipment and provide a simple platform that’s great for students and others to gain insights into the complicated path of drug discovery,” says Jim Miller, senior vice president for science and conservation at the Missouri Botanical Garden. Miller has run drug discovery programs in North America, the Caribbean, and Madagascar.

Screens to Nature is in keeping, says Raskin, with the Convention on Biological Diversity, also known as the Rio Treaty. The treaty, adopted in 1992, governs the conservation and sustainable use of biological

resources and equitable sharing of benefits. “Permanent ownership of all Screens to Nature data and discoveries is assigned to the country where the work was done,” Raskin says. He

and colleagues have used the method throughout Central Asia and in other locales, such as North Dakota and elsewhere in North America, Israel, and the Mediterranean region.

#### Further reading.

- The American Society of Pharmacognosy ([www.pharmacognosy.us](http://www.pharmacognosy.us))
- National Institutes of Health (NIH) Centers for Advancing Research on Botanical and Other Natural Products (CARBON) Program ([https://ods.od.nih.gov/Research/Dietary\\_Supplement\\_Research\\_Centers/](https://ods.od.nih.gov/Research/Dietary_Supplement_Research_Centers/))
- Newman, DJ, Cragg, DM. 2012. Natural products as sources of new drugs over the 30 years from 1981 to 2010. *Journal of Natural Products* 75: 311–335.
- NIH Center for Botanicals and Metabolic Resiliency ([www.botanical.pbrc.edu](http://www.botanical.pbrc.edu))
- Nutrasorb (<http://nutrasorb.com/>)
- Wang ZQ, Zhang XH, You Y, Tipton RC, Raskin I, Ribnicky D, Johnson W, Cefalu WT. 2013. *Artemisia scoparia* extract attenuates non-alcoholic fatty liver disease in diet-induced obesity mice by enhancing hepatic insulin and AMPK signaling independently of FGF21 pathway. *Metabolism* 62: 1239–1249.

### From cave medicine to combinatorial chemistry

Knowledge of botanical medicines probably goes back to the days of the Neanderthals, who disappeared between 39,000 and 41,000 years ago. Scientists have discovered evidence for the use of medicinal plants in a cave in what's now northern Spain, trapped in the remains of a Neanderthal's dental calculus.

In historical times, texts that included medicinal plants were written by Asian scientists Rayhan Muhammad ibn Ahmad Al-Beruni (973–1048 ACE) and Abu Ali ibn Sina (980–1037 ACE), also known as Avicenna. Their writings resulted in the most-referenced medical guides of their day, *Saydana* and the *Canon of Medical Science*, respectively.

Fast forward to the 1950s and 1960s: Those decades were heydays of modern drug discovery from natural products—the chemicals produced by living organisms. Many of the antibiotics and chemotherapies that are used today, such as the antibiotic gentamicin from a bacterium and the anticancer drug vincristine from the Madagascar periwinkle plant, were developed during that time.

Now, one-quarter of medicines are based on plants. The most common such drug is salicylic acid, or aspirin, extracted from the bark of the willow tree. Taxol, used to treat breast, ovarian, and other cancers, comes from the Pacific yew tree, which grows along the US West Coast.

“In the 1980s, the advent of computers totally changed the picture for medicines from the wild,” says Cragg. “Pharmaceutical companies suddenly had the ability to do very fast screening of molecules.” Industry chemists were able to study 1000 compounds or more each week. As companies ran low on compounds to consider, they used combinatorial chemistry to create libraries of thousands of molecules, wrote Cragg and scientist David Newman in March 2012, in the *Journal of Natural Products*.

Despite early high hopes, however, for new cures from nature's pharmacy,



**Lizard's tail plants in a southeastern US wetland. The plants are important in Creole traditional medicine and hold promise for the treatment of diabetes.**  
Photograph: Fredlyfish4.

many major companies closed their natural products divisions in the 1990s. Their libraries, which largely contained random molecules, had produced few new drugs, says Cragg. “Nature is a much better biochemist than we are, with hundreds of millions of years of practice.” Nonetheless, he

reported at the 2015 meeting of the American Society of Pharmacognosy, “We have a history of successes in drugs such as vincristine and taxol, with continuing promise for discovery and development.”

Genetic sequencing is rapidly moving that process forward, says Frank



A sign at the entrance to the Otero farm in Cuba states that “La medicina verde llegó para quedarse” (“Green medicine is here to stay”). The words are from a quotation by Raúl Castro, president of Cuba. Photograph: Brittany Graf.

Petersen, executive director of the Natural Products Unit at Novartis, a pharmaceutical company headquartered in Switzerland. “It’s now feasible to sequence the genes of pretty much anything,” Petersen says.

Novartis is one of the few major drug companies that has retained a keen interest in natural products, evidenced by one of its websites, *Beautiful Medicine*, which features botanical cures. The company is looking for the next Coartem or ergotamine, two of its most widely used drugs derived from nature. Artemisinin is the active substance in Coartem, a treatment for malaria; the antimigraine activity of ergotamine comes from a fungus that lives on rye and other grasses. “Ergotamine was the very first drug

Sandoz [part of Novartis] developed from nature’s medicine,” says Petersen. “That was almost 100 years ago, in 1921.”

To jumpstart new research, biochemists are investigating the promise of DNA-encoded chemical libraries. Scientists are using DNA to select and synthesize compounds that attach to targets such as enzymes and receptors. Compounds are labeled with short DNA fragments that act as barcodes. To identify those that bind successfully, researchers read the combined DNA sequence.

DNA barcode information is critical to progress in plant-based treatments, biochemists say. “Identification of plant species using DNA barcoding improves the quality of botanical

medicines by making sure the correct species is used,” says Raskin, “and in the right amount.” Medicinal plants can contain strong physiologically active compounds and may be poisonous, he and coauthors wrote in the introduction to the 2012 book *Medicinal Plants of Central Asia*. “Without the proper recommendations of a medical doctor, no preparations of medicinal plants should be taken.”

#### **Can an apple a day in fact keep the doctor away?**

The answer, biochemists believe, is yes—especially if that “apple” is a Concord grape, a swamp root, or a tree named *moringa*.

Along with physician William Cefalu, of Louisiana State University



*Vinales, Cuba, a region known for its medicinal plants, including malanga, a tuber that may benefit the human gut microbiome. Photograph: Ilya Raskin.*

(LSU), Raskin is coprincipal investigator of the NIH Center for the Study of Botanicals and Metabolic Resiliency, headquartered at LSU's Pennington Biomedical Research Center, in Baton Rouge. Scientists there are working to identify the active ingredients in botanical remedies for metabolic syndrome.

Among them is lizard's tail (*Saururus cernuus*), also called water dragon or swamp root. The plant grows in eastern North American wetlands and has long been used as an anti-inflammatory in Louisiana Creole folk medicine. Could it also treat insulin resistance and type-2 diabetes? To find answers, Cefalu and other researchers are combining cultural anthropology and botany with biochemistry and endocrinology. They are testing samples from Louisiana wetlands such as those along the Atchafalaya River to uncover the healing potential of

lizard's tail and other plants important in Creole cures.

Farther afield, Raskin and others are determining whether a small tropical tree called moringa (*Moringa oleifera*) is a viable alternative to cruciferous vegetables such as broccoli for maintaining normal glucose metabolism and managing inflammation. Moringa's range extends from India to Central America and the Caribbean, northern South America, and Southeast Asia. Results the group published in 2015 in the journal *Molecular Nutrition and Food Research* show that moringa may be an effective functional (also called medicinal) food for the prevention and treatment of obesity and type-2 diabetes. Testing on this and other plant species has led to a Rutgers spinoff company, Nutrasorb.

Other plants being studied by scientists at Rutgers and the University

of California, San Francisco, and collaborators include the Concord grape. Polyphenols in the grapes increase the growth of *Akkermansia muciniphila*, a beneficial human gut microbe. A 2015 paper in the journal *Diabetes* by Diana Roopchand of Rutgers, Raskin, and Peter Turnbaugh, of the University of California, San Francisco, suggests that Concord grape polyphenols are helpful to gut microbial community structure. "That leads to lower intestinal and systemic inflammation," says Raskin, "and improved metabolic outcomes."

The discovery caught the eye of companies that include Flagship VentureLabs, a venture capital firm that specializes in biomedicine. "We're very interested in what might be called 'microbiome modulation,'" says Jack Milwid, a senior associate. "This finding is a promising one we're following up on with Nutrasorb."

In a new project, Brittany Graf, of Rutgers, is taking a close look at a plant called *malanga* that grows in Cuba. With support from the Florida Keys Tropical Research Ecological Exchange (TREE) Institute, Graf and Raskin are conducting research on how *malanga*, a starchy tuber that resembles a potato, may benefit the human gut microbiome. At Cuba's Otero farm, the scientists study plants endemic to Cuba, including those in the genus *Garcinia*, sometimes called saptrees. They hope to learn more about how Cuba's flora is used in *medicina verde*, as plant-based medicine is known and widely practiced in Cuba.

A logical starting point for research on medicinal plants, Jim Miller believes, is on species that are important in traditional medicine. He thinks scientists need to investigate more such avenues. "Answers to a range of human diseases may be hidden in plain sight," Miller says.

### Is there a limit to what plants can provide?

Can plants offer an unending stream of new discoveries for human health? Miller calculates that there is likely a minimum of 500 new drugs waiting to be discovered from plants, with the actual number much higher. "But it's mostly a walk in the dark to find them," he says.

The journey can only happen, however, if plant diversity is protected, according to a 2015 report released by the Global Strategy for Plant Conservation (GSPC), a Convention on Biological Diversity program. In Europe, for example, populations of 31 percent of plants are declining. The GSPC's aim is "to secure a sustainable future where human activities will support the diversity of plant life, and where in turn the diversity of plants supports and improves our livelihoods and well-being."

How can science find the way down that path? According to Geoff Cordell, emeritus medicinal chemist at the University of Illinois at Chicago and president of the consulting firm



**Researchers from Israel and Spain collect medicinal plants near Jerusalem. Their project fostered cooperation among scientists in the United States, Greece, Spain, Palestine, and Israel. Photograph: Hadassah Academic College.**

Natural Products, Inc., a key question is, "How 'green' is our medicine?" In what Cordell calls ecopharmacognosy, scientists are starting to make use of developments such as "computer-aided design of natural-product derivatives and remote-sensing technologies that can assess natural materials non-invasively for critical constituents," he says.

### Plants as peacekeepers

If plants can treat individual ills, can they also cure maladies afflicting entire nations? A meeting in December 2014 might be the key to bridging the gulf among countries—and to new ways of viewing wild medicine. Scientists from the United States, Greece, Spain, Palestine, and Israel convened in Jerusalem to discuss the conclusions of a project named BioXplore. Funded by the European Commission under the European Neighborhood and Partnership Instrument Cross-Border Cooperation Mediterranean Sea Basin (ENPI CBC Med) Programme, BioXplore's researchers set out to discover the pharmacological potential of plants in the Mediterranean region.

"A land of wheat and barley and vines and fig-trees and pomegranates, a land of olive oil and honey"—so Israel is described in the Bible. Could cures to diseases common to Israelis and Palestinians, and their neighbors near and far, be found in the countries' botanical resources?

"The meeting brought us all together in one room to talk about results in the quest to uncover new treatments for age-old maladies," says immunologist Bertold Fridlender, president of Hadassah Academic College in Jerusalem and principal investigator of BioXplore. "We used science to communicate and to create trust."

Researcher Gili Joseph of Hadassah Academic College, along with Fridlender and others, collected plant samples from eight climate zones in Israel. The biochemists studied more than 1100 plant samples from 614 plants belonging to 85 families using Screens to Nature. Plants growing in extreme conditions showed more bioactivity than those in less harsh climates, says Fridlender. "Antibacterial, antifungal, and antioxidant activity were the most common results," he says. The findings

were published in 2014 in the journal *Biodiversity, Bioprospecting and Development*.

By testing plants from the Judean foothills, the mountains of Upper Galilee, the slopes of Mount Carmel, and the coast of the Dead Sea, the scientists discovered that

the Palestine oak, terebinth, golden chamomile, and Mediterranean stinkbush, for example, have antibacterial properties.

“We now have plans to pursue a further project with our Palestinian partners,” says Fridlender. “A win for science is, in this case, progress toward

something that may be as far reaching as potential new medicines: peace.”

---

*Award-winning science journalist Cheryl Lyn Dybas (cheryl.lynn.dybas@gmail.com), an ecologist and fellow of the International League of Conservation Writers, often writes for this and many other publications on conservation biology and medicine.*