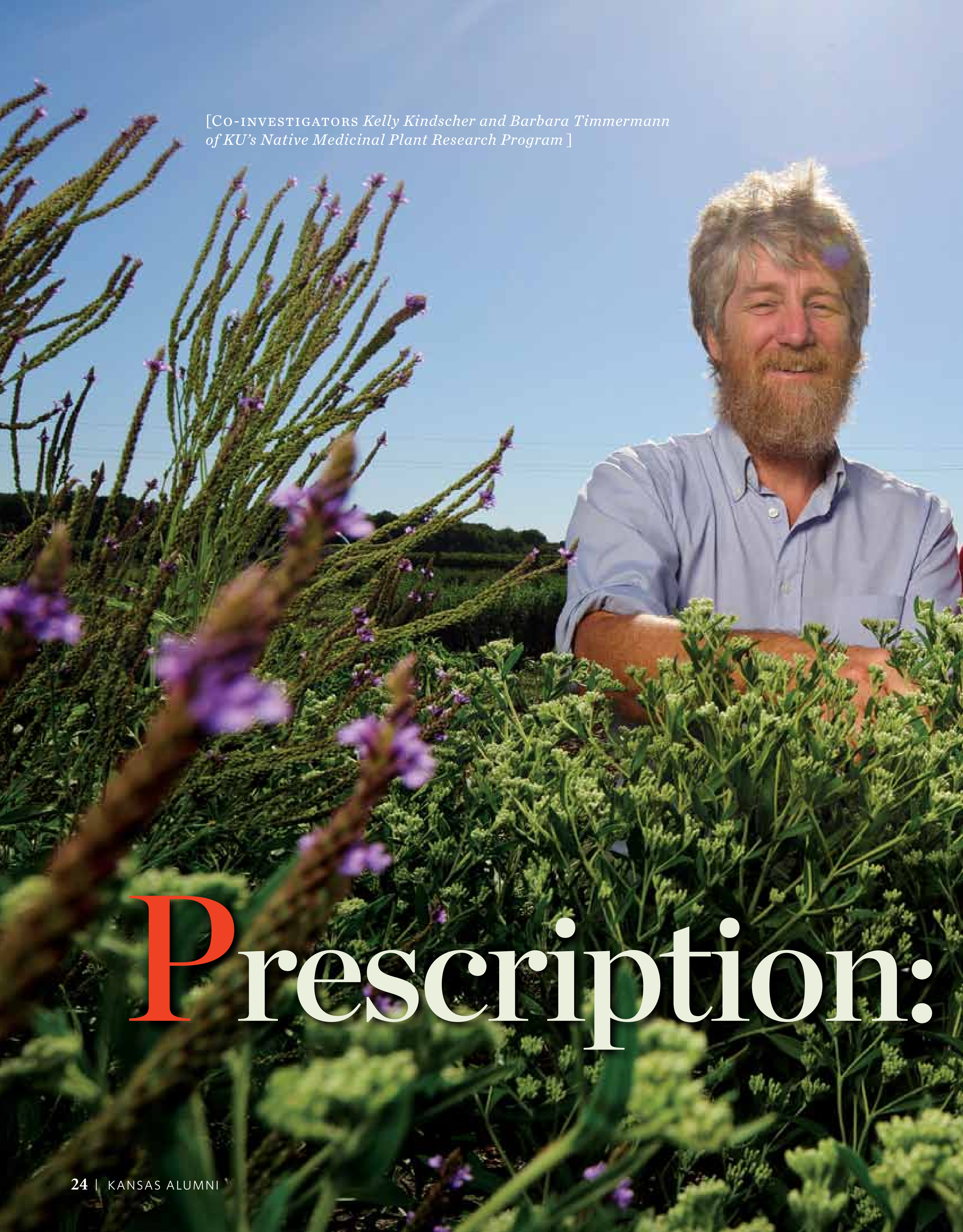

[Co-investigators *Kelly Kindscher and Barbara Timmermann of KU's Native Medicinal Plant Research Program*]

Prescription:

STEVE PUPPE

Searching for new drugs and health supplements, KU researchers take a fresh look at old medicine—the native plants of the Great Plains.

The 80-odd souls huddled under a canopy at KU's Native Medicinal Plant Research Garden are looking for something that's in short supply on this patch of prime Kansas River bottomland: shade. Open fields separate the river from the rumpled hills north of Lawrence, and the rich topsoil deposited by centuries of flooding is what soil scientists call Class I. This was Kansa Indian land, and the riparian bands of forest that once shadowed the riverbanks two miles south and west may have extended this far into the prairie at one time, but the cropland swells that roll toward every horizon now grow mostly corn and beans. Hours earlier, a thunderstorm packing 70-mile-per-hour winds strafed the county, felling trees and cutting power. But as a Saturday tour gets underway, skies are clear and the June sun already, at 10 in the morning, burns black-skillet hot.

"Around 3 a.m. I thought we might not be doing this," Kelly Kindscher tells the crowd, who've come to learn about the 25 species of native plants that Kindscher, senior scientist at the Kansas Biological Survey, and his colleagues are growing here on KU Field Station land near the Lawrence airport. "I thought we might get out here and find everything flattened. But prairie plants are tough."

Tough indeed. Blazing sun and bitter cold; too much rain and too little; high winds; grazing herbivores and nibbling insects; microbes, bacteria, fungi; wildfires and ice storms—these are but a few of the threats prairie plants must cope with. It's not easy being green.

Plants survive these hardships, Kindscher explains, without the benefit of a strategy employed by nearly all other life forms—mobility. "Plants can't run," he says. Tall boneset and purple coneflower and butterfly milkweed can't dodge bison or bugs, can't move to shade or seek high ground in a flood. They have to stand and fight.

To cope, they arm themselves with weapons of their own making, which vary from plant to plant. Some species develop structural defenses, spines or burrs or prickles that dissuade attackers, or thick skins that store and conserve water. But many fight back with a chemical defense of sorts, manufacturing potent organic compounds—individual molecules made up of carbon, hydrogen, oxygen and sometimes nitrogen—that help the plant cope with stresses.

"Plants produce hundreds of chemical compounds," says Barbara Timmermann, University Distinguished Professor and chair of medicinal chemistry. Primary compounds, which enable the plant to grow and reproduce, are present in large quantities. "But plants also make chemicals in very small amounts that have biological activity," Timmermann says. These are secondary compounds—so called because scientists once believed they had no function or were of secondary importance. "Today we know they have a very important role in the plant for defense against herbivores and protection against stress."

Some screen out harmful ultraviolet rays, some aid in drought survival and others act as natural pesticides that ward off insects. "They are very biologically active," Timmermann explains, "and some act pharmacologically." Which is to say these potent chemical compounds, so valuable as defense mechanisms for the plant, can also be powerful weapons for human health. In fact, secondary compounds from plants or synthetic compounds modeled on plant molecules are the source of 25 percent of the prescription medication dispensed in the U.S. today, Timmermann says.

Understanding these health benefits and working to develop products such as herbal remedies, food additives, pet foods and pharmaceutical drugs are the focus of the Native Medicinal Plant Research Program, a collaboration between Timmermann's Natural Products Chemistry Laboratory and Kindscher's botany lab. Launched two years ago with a five-year, $5-million grant from the Kansas Bioscience Authority and Heartland Plant Innovations, the program targets plants of the Great Plains region used by Native American tribes for medicinal purposes. In addition to the labs of the two principal investigators, the program enlists researchers at the KU Medical Center in Kansas City and the High Throughput Screening Lab on West Campus. It is using modern science to peer deep into the chemical structures of plants to discover the compounds responsible for their healing properties and determine which might have wound-healing, anti-inflammatory, antioxidant and even anti-cancer powers that could benefit human health.

"People have been using these plants for certain ailments, so it's not at all surprising that we find, chemistry-wise, that almost all the plants Native Americans historically used for medicine do have active medicinal constituents."

Kindscher, c'79, PhD'92, grew up in Newton and on his family's homestead farm near Guide Rock, Neb., and it was there he first experienced the power of the prairie and the plants that would become the core of his academic career. Working on his master's thesis at KU, he spent time on the Rosebud Indian Reservation in South Dakota, learning from the Lakota Sioux about their medicinal use of prairie plants; that work developed into his second book, *Medicinal Wild Plants of the Prairie—An Ethnobotanical Guide,* in 1992. An earlier book, *Edible Wild Plants of the Prairie—An Ethnobotanical Guide,* appeared in 1987.

Ethnobotany—the study of a people's traditional knowledge and customs in the use of plants—offers a kind of head start for Kindscher and Timmermann in their hunt for medicinally useful species. By focusing on plants traditionally used by American

[ECHINACEA PURPUREA, *purple coneflower*]

STEVE PUPPE

HILLARY LORING

Kirsten Bosnak, Hillary Loring and Maria Pontes Ferriera collect Fremont's goosefoot *(Chenopodium fremontii)* in Nebraska's Oglala National Grassland. Quinn Long hoists a bush morning glory *(Ipomoea leptophylla)* at the end of an hourlong dig.

Indians for healing, they are essentially drawing on results honed by centuries of trial and error.

"You already have human tests, in a way, just not quantifiable," Kindscher says. "People have been using these plants for certain ailments, so it's not at all surprising that we find, chemistry-wise, that almost all the plants Native Americans historically used for medicine do have active medicinal constituents."

Kindscher and his botany team are compiling an ethnobotanical database that catalogs more than 1,000 plants used medicinally by 256 tribes, and they spend their summers crisscrossing the Great Plains, searching for plants in that database that show promise for human health. During the first year alone, field collections gathered more than 200 plants native to Kansas and the Great Plains. Roots, stems, leaves and fruits are dried in the field or back at Kansas Biological Survey on West Campus, an exacting process that must be carefully controlled to preserve specimens and maintain accurate data. Samples of each species are carefully archived in KU's McGregor Herbarium, but the bulk of the dried plant material is ground (to a coarse consistency similar to the dried oregano in your spice rack) and bagged. A 1-kilo sample is sent to Timmermann's lab, and there chemists apply solvents to this biomass to get a crude extract, a "goop" of hundreds of chemicals that can be separated further using various other solvents to break the chemical soup into smaller samples. These smaller samples, each with a different chemical makeup, are called fractions, and those showing promise are sent to High Throughput Screening to undergo more specialized tests.

"Some of the assays they use are very novel; they've just been invented," says Rob Gallagher, a research technician in Timmermann's lab who coordinates the testing at High Throughput Screening. "They have some absolutely amazing instrumentation, robotics and such. It's like science fiction." Techniques employed by Kindscher, botanist Quinn Long, PhD'11, and other collectors in the field, on the other hand, are old-school. Though GIS mapping and other high-tech tools inform their searches, they still rely on a plant press, newspapers and stiff herbarium sheets to preserve samples, a traditional technique akin to pressing flowers between the pages of a book.

Results from High Throughput Screening generate what Timmermann calls "heat maps," which point to specific areas of biological activity—antioxidant capability, say, or cancer-fighting potential—that demand further study. As the chemists drill deeper and deeper into the plant, hoping to isolate at the molecular level a single chemical compound responsible for its health benefit, the botanists begin scrutinizing the plant's taxonomy—its family tree—to see what other close relatives might be sources of the coveted compound, adding these plants to their target list.

And with that, the biological treasure hunt, the search for a native-plant source of healing balm, begins anew.

To get the necessary kilo of biomass to present to the chemists, botanists must gather about 20 pounds of plant material. Each trip collects as many plants as possible, which creates "a lot of volume," Kindscher notes—and some interesting situations on the road.

"We'll be drying plants in some hotel room, with the Do Not Disturb sign up, and a maid comes in and then we have to talk to someone about that 'herb' we're drying," Kindscher grins. "It hasn't happened, but I can imagine being pulled over on I-70 and having to admit there's several kilos of herb in the back of the truck. Clearly it's not illegal, but it's unusual."

Volume is also a problem for the chemists. As in, too little.

"Many secondary compounds are produced in very, very small quantities," Barbara Timmermann explains. "Some as low as .0004 percent in the plant."

To get a significant amount of such a compound would require consuming huge quantities of a plant—an impractical and

DAVID McKINNEY-UNIVERSITY RELATIONS (2)

QUINN LONG

potentially dangerous gambit because secondary compounds beneficial to humans sometimes coexist with toxic compounds that aren't so nice.

Thus the importance of isolating the single molecule that delivers health benefits. Single compounds are what pharmaceutical drugs are made of. "When you get down to the single compound you can determine the proper dosage and how to deliver it," Timmermann says. "When you have the compound in a mixture with other compounds, as in dietary supplements, they are very much diluted. They can't be used to treat a condition, but are more to prevent."

Combinatorial chemistry, a form of synthetic chemistry in which molecules can be created in a short time in the lab, at one time seemed a promising source of secondary compounds, Timmermann notes. "In the 1980s that became the big thing," she says. "We were going to find new drugs by combinatorial chemistry, by creating artificial molecules. Pharmaceutical companies stopped working with natural products because combinatorial chemistry was going to solve all the problems. Millions of compounds were produced, but because they didn't interact with biological systems, they weren't useful as medicines."

Plants, it turns out, are more effective chemists than people are. So effective that even the most state-of-the-art tests can fail to unravel the riddles of healing compounds. Researchers still haven't figured out which compound generates echinacea's immune system boost.

"Plants can do things that a chemist just can't," Rob Gallagher says. "Sometimes it's just a simple thing, a simple change done by an enzyme, but we look at it and say, 'Really? How does it do that?'"

And, Gallagher adds, "the compounds that are the most interesting are also extremely difficult to synthesize." So when chemists succeed in isolating a promising compound, they can't always synthesize it in the lab. (Morphine, for example, cannot be synthesized but must be derived from the opium poppy.) When

Greg Beverlin, c'11, and Jason Hering, c'11, use a high-tech grinder to transform plants dried at Kansas Biological Survey labs into 1-kilo samples for chemists. Peter McDonald at KU's High Throughput Screening Lab examines plant extracts from Barbara Timmermann's lab, and uses a signal detection instrument to measure the effect of each plant extract on human cells.

KIM SCHERMAN

STEVE PUPPE

[Monarda fistulosa, *beebalm, horsemint or wild bergamot*]

"The ultimate goal of this program for me is to demonstrate that Kansas biodiversity—even Kansas, even the prairie—has great value, historically and today."

—Kelly Kindscher

chemists do manage to synthesize compounds, they often get impractically small yields (the volume problem again) that makes the process prohibitively expensive. “Sometimes,” Timmermann says, “it’s much simpler to get what you need directly from the plant.”

To study a plant, you must first find ample populations of it—often a difficult task, as Timmermann knows well.

Before she came to KU, in 2005, she spent 25 years at the University of Arizona, where she was a Regents professor and studied plants in the rainforests and deserts of Latin America and Asia. She built an international reputation as a natural products chemist and worked with the United Nations to foster access to biological resources under the Convention on Biological Diversity. Signed by 150 governments at the 1992 Rio Earth Summit, the treaty recognizes the value that biological diversity holds for people as a source of medicines, food security and a healthy environment.

“I’ve had many cases in South America where I would go to collect something, and I’d get to the site after traveling half the world around and the whole place is chopped down. You can’t find the plant, can’t complete the work.”

Pondering the move to KU, she looked at the academic literature and felt the prairie was under-studied. After meeting with Kindscher and examining the ethnobotanical history, she realized the grasslands of the Great Plains might be a research “gold mine.”

“After working for years in exotic places,” Timmermann says, “I’m working in the prairie, which seems so innocent and pretty—little flowers, little plants. And in such a short time I’ve found things much faster and more interesting perhaps than in the rainforest.”

Early results have been promising indeed. Timmermann’s lab discovered more than a dozen new molecules, and at least one plant shows promise as a potential cancer fighter. A large food company is interested in a plant with antioxidant properties that could be an ingredient in cereal. With academic papers underway, invitations to present findings at conferences, and a patent application pending, Timmermann and Kindscher won’t discuss specifics, but they agree that the pace of discovery has been unusually rapid.

Rainforests are routinely touted as great stores of future pharmaceuticals and herbal remedies, but the prairie holds great promise too. Yet like the rainforest, the prairie is a finite resource that’s shrinking daily.

Tallgrass prairie once covered 140 million acres in North America, but today only 4 percent remains. In the 1850s Douglas

KIM SCHERMAN

The Native Medicinal Plant Research Garden welcomes visitors during daylight hours, hosts open house events and arranges special tours by request. Recent tour groups have included KU Mini College participants, Douglas County master gardeners and (above) KU Continuing Education Osher Institute lifelong learners.

How their gardens grow

The five-acre Native Medicinal Plant Research Garden site, at 1865 E. 1600 Road in Douglas County, hosts several gardens, each with a different purpose but a common theme. “All are projects that honor the land one way or another,” says Kirsten Bosnak, g’93, g’11, communications and outreach director for the Native Medicinal Plant Research Program and manager of the garden, which is part of the KU Field Station.

Open to visitors from dawn to dusk, the site meets research, education and outreach goals for the Native Medicinal Plant Research Program, drawing people interested in gardening, the prairie, land conservation, herbal medicine and more.

“All those people can talk to one another,” Bosnak says. “I see this as a place where conversations get started.”

Research plot: 25 native plant species, including blue wild indigo, butterfly milkweed, yarrow, field mint, beebalm and purple coneflower. Some end up under the microscope in KU chemistry labs, providing comparative data to wild plants; others produce seeds. As research progresses, investigators can grow larger quantities of species that show particular promise for medicinal uses.

Demonstration garden: Native and European medicinal plants (like sweetflag, dogbane, rattlesnake master and mad-dog skullcap) historically included in the U.S. Pharmacopeia and National Formulary. Similar species also grow in a

STEVE PUPPE

[*Asclepias tuberosa, butterfly milkweed*]

County alone included 285,000 acres of prairie; by 2005 about 1,400 acres were left, mostly in scattered remnants. Secondary compounds were of course no defense against the steel plows of settlers, who viewed grasslands much as they viewed the forests they'd conquered back east: barriers to be removed to make way for cash-crops. Some of that attitude persists today.

"We're still seeing prairies plowed or houses built on them," Kindscher says. "I get greatly concerned seeing land use changes. And who knows what's coming down the pike with global warming, but that doesn't sound good, especially for keeping plants where they are on the landscape."

So while researchers work to find chemical compounds that can improve human health, they also hope to improve the health of the region's native plant communities, by educating the public on the true value of the plants around them. They tout the potential for healthier lives and a healthier economy these discoveries could bring. And they are taking additional work and seeking other funding for the Native Plant Research Program, which, as *Kansas Alumni* went to press, awaited word on a possible 50-percent or more cut in its annual grant from the Kansas Bioscience Authority, which researchers attribute to a shift in research priorities at the KBA.

"The ultimate goal of this program for me is to demonstrate that Kansas biodiversity—even Kansas, even the prairie—has great value, historically and today," Kindscher says. Not only do native grasslands hold important aesthetic and cultural appeal, but there's also economic value in the potential for medicines and herbal products. "This is an opportunity to look at nature and say, 'Nature does indeed have value, including the nature right around us.'"

People driving across Kansas see a flat, dry, boring landscape, Kindscher says. The state's western reaches seem inhospitable, barren. But for producing secondary compounds, he notes, you could hardly ask for a better scenario.

Secondary compounds are defense mechanisms, remember, weapons that plants use to fight for survival. When the environmental stress is high—as it is across much of Kansas—plants need to fight harder, and they produce more of these weapons. The basil in your garden is a tasty example of this concept.

"Basil is tender in June, but it will pack more flavor in August," Kindscher says. "It's secondary compounds that provide that bite, and it takes the stress of summer heat to bring that out."

In fact, plants coddled too much can lose their potency. Farmers growing echinacea for European markets, which value the coneflower root as an herbal supplement, learned a tough lesson about stress and secondary compounds when they tried cultivating it on an irrigated, fertilized center-pivot field in Kansas. Wild harvest echinacea has been a leading export crop for the state, but the cultivated root failed to meet Europe's standards. "They were used to wild-harvest," Kindscher says. "The cultivated crop had a higher yield but the actual content [of secondary compounds] was lower."

Adds Kindscher, "With our climate—a drought-prone landscape that still has great soil and some rain—I think there are more discoveries to be made here."

Those discoveries could lead to growth for Kansas companies and jobs for Kansas people, research breakthroughs and spinoff technologies for KU, and better health for all.

It may yet turn out that the prairie's most valuable crop has been here all along.

For more information visit nativeplants.ku.edu

garden planted by the program at the pharmacy building on West Campus.

KU student farm: Students, staff and faculty members sign up for one of 25 plots in this vegetable-and-flower garden, conceived by students for a class project in 2010 and launched this spring.

Natural dye garden: Textiles student Neil Goss researches traditional dyes made of coreopsis, sunflower, indigo and other native plants in an independent study project.

Prairie Moon herb garden: Students at neighboring Prairie Moon Waldorf School get a garden corner to grow culinary and medicinal herbs. "It's educational outreach to the youngest schoolkids," Bosnak says, "who are right next door and interested and curious."

—S.H.