Back to Nature: Extinction of Medicinal Plants Threatens Drug Discovery

By Vicki Brower

During the past few decades, as researchers developed new molecularly targeted cancer treatments, including trastuzumab, bevacizumab, and cetuximab, it has been easy to forget that many cancer drugs originated in plants, fungi, and soil and marine microorganisms.

Plants, such as the Pacific yew (*Taxus brevifolia*) and the Mayapple (*Podophyllum peltatum*), have been used to develop powerful anti-cancer drugs, but experts warn that many plants may become extinct before scientists can discover their medicinal properties.

Although early drugs came from plants—aspirin from willow tree bark, morphine from poppies, digitalis from foxglove, penicillin from mold—contemporary drug discovery has largely moved beyond natural products to the development of synthetic compounds and monoclonal antibodies. But natural-product experts who continue to develop cancer drugs from plants and other natural products insist that nothing beats nature for finding drug leads. They note that more than 60% of cancer therapeutics on the market or in testing are natural product based.

However, a new report by UK-based Botanic Gardens Conservation International warns that many plants and organisms are being lost through the destruction of rainforests, coral reefs, and other natural habitats. This trend will affect the discovery of cancer drugs, according to the report.

"Many medicinal plants are being destroyed at an unprecedented rate and are threatened with extinction," said Belinda Hawkins, author of the study, "Plants for Life: Medicinal Plant Conservation and Botanic Gardens," which was published in January. "The destruction of plant species is occurring at a rate unmatched in geological history. … Current extinction rates are at least 100 to 1,000 times higher than natural background rates, with a quarter of the world's coniferous trees … in jeopardy, and as many as 15,000 medicinal plants threatened," the author writes.

"Today, plants remain an important and continuing source of novel chemotypes," said Josh Rosenthal, Ph.D., deputy director of the division of international training and research at the Fogarty International Center at the National Institutes of Health. "While researchers have not yet described or analyzed most plant species and genera, they are rapidly disappearing at a time when research tools are much more powerful."

Early Plant-Based Anticancer Drugs

"Cancer has a long history of depending on natural products for drugs," Rosenthal said. Cancer therapeutics from plants include paclitaxel, isolated from the Pacific yew tree; camptothecin, derived from the Chinese "happy tree," *Camptotheca acuminata*, and used to make irinotecan and topotecan; combretastatin, derived from the South African bush willow; and etoposide from podophyllum, found in the eastern U.S. and the Himalayas (*see* Table, p. 839).

The search for anticancer drugs from natural products began in earnest in the 1950s, with the discovery and development of the vinca alkaloids, vincristine and vinblastine, from the Madagascar periwinkle, said Gordon Cragg, Ph.D., former director of the National Cancer Institute's natural products branch. In 1960, the branch established a repository of plant and animal samples from around the world, which is now the world's largest collection of natural products.

"Nature has produced wonderfully complex molecules that no synthetic chemist could ever dream up," Cragg said. These molecules evolved over millions of years as chemical defenses by plants, animals, and microorganisms, enabling them to survive attack by fungi, viruses, and other threats. An estimated 50,000–70,000 plant species alone are thought to have medicinal qualities.

Interest in Natural Products Waxes and Wanes

During the 1990s, when scientists developed new biotechnology drugs such as monoclonal antibodies and the buzz of promising new cancer targets grew, attention and resources were diverted from plants and other natural products as sources of anticancer drugs. But that trend is changing, said David Newman, Ph.D., chief of NCI's natural products branch.

"With the rise of combinatorial chemistry in the 1990s, interest in natural products waned, and only a few companies maintained their research groups," Newman said. "With a few exceptions, most pharmaceutical companies believed that this technology, which can generate thousands of compounds rapidly, would replace slogging

Natural products forming bases of cancer drugs

Natural product	Source	Activity
Halichondrin B (Eisai)	South Pacific sea sponge	Blocks tubulin formation
Yondelis	Sea squirt	Interferes with cell division, blocks transcription
Paclitaxel	Pacific yew tree	Stabilizes microtubule formation
Combretastatin	South African bush willow	Targets tumor vasculature
Vinblastine and vincristine	Madagascar periwinkle plant	Inhibits tubulin formation
Camptothecin	Chinese *Camptotheca acuminata* tree	Inhibits DNA topoisomerase I
Homoharringtonine	*Cephalotaxus harringtonia*, an evergreen tree	Inhibits protein synthesis
Etoposide	*Podophyllum peltatum* plant (mayapple)	Inhibits topoisomerase II
Thapsigargin	Ibizan *Thapsia garganica* plant	Induces apoptosis
Bryostatin 1	Marine moss protozoa	Activates protein kinase C
Dolastatins	Indian Ocean sea hare	Inhibits mitosis

through the rainforest, which is time-consuming and very costly." Finally, however, combinatorial chemistry did not fulfill the promise of delivering many new drug leads, he said, but has yielded one approved drug to date, sorafenib, an oral multiple kinase inhibitor approved in the U.S. for inoperable liver and advanced kidney cancer.

Although apparently not very effective for new-drug development, combinatorial chemistry is indispensable for optimizing leads found in natural products research, Cragg said.

"By starting with the chemical 'backbone' of a natural product, researchers are redesigning drugs for better efficacy, side effect profiles, and improved solubility," Newman added. Of 177 drugs approved worldwide for cancer, more than 70% are based on natural products or mimetics, many of which were improved with combinatorial chemistry.

NCI's Natural Products Push

Paclitaxel and camptothecin—and most natural product–based drugs—were discovered by an exploratory plant screening program sponsored by NCI, which began collecting samples in temperate regions in 1955 and then in the tropics in 1986. "In the late 1980s, the NCI recognized the need to collect natural products—marine, microbial, and plant collections—on a systematic basis by using contractors and standardized methods," Newman said.

Today, NCI has amassed 15,000 samples of marine invertebrates, more than 4,000 samples of marine algae, 65,000 plants, and 30,000 plant fungi, and it has screened tens of thousands of samples. NCI runs the National Cooperative Drug Discovery Group program, which promotes local, academic, and industrial collaboration efforts worldwide. Some agents that failed earlier trials are also now being restudied and redesigned using new technologies to determine whether they can be modified for better efficacy and fewer side effects. "Maytansine, isolated in the early 1970s from the Ethiopian plant *Maytenus serrata* looked promising in preclinical testing but was dropped in the early 1980s from further study when it did not translate into efficacy in clinical trials," Newman said. Later, scientists isolated related compounds, the ansamitocins, from a microbial source. A derivative of maytansine, DM1, has been conjugated with a monoclonal antibody and is now in trials for prostate cancer, Newman said.

The Fogarty Center's international cooperative biodiversity program also guides collaborative natural-product drug discovery around the globe. The program enables local communities to reap benefits from their biological resources while preserving and sustaining biodiversity. Most fieldwork and research in natural products is funded by the NIH, and several biotechnology and pharmaceutical companies are also active in this area. Memorial Sloan-Kettering Cancer Center in New York also has a large natural-product discovery team that is developing microbial metabolites of paclitaxel, the epothilones, and other drugs.

"We have come full circle, back to nature, with chemists now making synthetic drugs more natural product-like," said David Kingston, Ph.D., a professor of chemistry at Virginia Polytechnic University in Blacksburg. "We need to continue natural product discovery because it has been so successful."

Beyond Plants

The disappearance of plants also threatens a newer area of promising research, Rosenthal said. "Plants are hosts for multiple organisms, such as endophytic fungi and insect life, which we are discovering, in some cases, are actually responsible for producing active compounds such as Taxol [paclitaxel], rather than the plants themselves." Though somewhat controversial, this area of research underlines what is at stake. "We are losing materials whose value we don't yet know," Newman said.

Genomics is also revealing that certain medicinal plants have "hidden" sets of genes that, when found and expressed, yield more compounds with therapeutic properties.

But the greatest biodiversity may not be in found in plant life, Newman said, but in the sea. Dolastatins, isolated from Indian Ocean sea slugs, are being investigated in clinical trials. Sponges, sea squirts, blue-green algae (cyanobacteria), and other marine micro- and macroorganisms are also sources of many new drugs being tested in clinical studies.

Because plants often serve as the structural anchors of an ecosystem, their disappearance affects symbiotic organisms living on them, and marine life as well, Rosenthal said. The rapid loss of plant life, as highlighted by the new report, may be just the beginning, adversely affecting future cancer drug discovery.

 DOI: 10.1093/jnci/djn199