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Brushing Up On Plant Riches

Phytochemicals get boost from advanced chemical analysis, synthesis

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Aspirin, belladonna, digoxin, morphine, pyrethrum, quinine. The names read like a litany of the tonics, infusions, and other remedies people have turned to over the ages for their aches and pains.

istockphoto
Plant Power The bottlebrush is the root of a Syngenta herbicide.

All are phytochemicals derived from plants or inspired by plant chemistry. Either as extracts or as purified compounds, such medicines have been used for centuries to protect or treat people, animals, and crops.

Far from being old school, the field of phytochemistry is being revitalized by sophisticated analysis, derivatization, and synthesis techniques. Armed with these tools and a new appreciation for the effectiveness of traditional remedies, companies are bringing a new clutch of phytochemicals to the market.

The spur here is economic, particularly as costs soar for research into pharmaceuticals and crop protection chemicals. "Researchers are recognizing their limitations as well as the great expectations on research," says David Evans, an agrochemicals consultant who retired in 2003 as head of research and technology for Syngenta, a crop protection and agribusiness firm.

"We put our shot in the air and hope the target flies in—it's like skeet shooting, not target shooting," Evans said in opening remarks at a conference organized in November by the pest management group of the U.K.-based Society for Chemical Industry. The conference, held at Syngenta's Jealott's Hill R&D center near Oxford, addressed various aspects of plant-derived natural products.

"The best way, still, to get leads," Evans argued, "is targeted screening. We are taking clues from nature."

Among the examples he cited is pyrethrum, which is derived from chrysanthemum and has been used as an insecticide since antiquity. Pyrethrum inspired the development of synthetic pyrethroids, including permethrin. The same is the case for azoxystrobin—an analog of strobilurin, which is a naturally occurring fungicide found in woodland fungi. This compound "is probably the most successful fungicide ever," Evans pointed out. "But it took about 700 compounds to get there."

To ease the search for new and intriguing phytochemicals, a team at London's Royal Botanic Gardens at Kew is developing a taxonomic approach to finding plants with previously unknown active compounds.

According to conference speaker Monique Simmonds, head of the sustainable uses of plants group at Kew, her team is using Kew's herbarium of more than 8 million samples and garden of some 33,000 plants to run DNA sequencing analyses. The scientists use the results to sort plant species into clades, or related groups, using inferred evolutionary relationships.

The sophisticated application of such relationships, Simmonds suggested, allows researchers to efficiently test hypotheses about the relevance of specific plants to different disease states. The work builds "a more robust framework" for deciding which groups of plants are closely enough related to be worthy of investigation. Researchers can in turn "deselect" plants that needn't be bothered with, Simmonds added.

Serendipity, though, still plays a big role in phytochemical development. A case in point is work at Syngenta that eventually led to the herbicide Callisto. According to Glynn Mitchell, group leader in the firm's U.K. agrochemicals labs, Callisto's roots are in a casual 1977 observation by a researcher in California who noticed that the plant known as bottlebrush bush and that was growing in his garden had only a few weeds sprouting around it.

Subsequent work on the bottlebrush, *Callistemon citrinus*, pointed the way to a series of triketones, synthetic analogs that are about 1,000 times more active as herbicides than the plant's own herbicidally active compounds, Mitchell said. That work in turn led to the development of mesotrione, 2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione, as a herbicide for corn.

Syngenta launched the herbicide in the U.S. in 2001 under the trade name Callisto, with a logo that acknowledges the inspirational bottlebrush. It is now the firm's biggest crop protection seller, with sales pushing $400 million per year.

As the herbicidal potential of the triketones was being recognized, other researchers at Syngenta's forebearer companies followed the chemistry along pharmaceutical lines. They developed nitisinone, a drug now used in the treatment of hereditary tyrosinemia Type 1, a severe but extremely rare disease affecting the liver. The drug subsequently was licensed to Swedish Orphan International.

Serendipity also underlies the formation of Phytopharm, according to Daryl Rees, the firm's chief executive officer.

In the early 1990s, a group of clinicians at Great Ormond Street Hospital, London's major children's hospital, was treating children with eczema. The physicians there were seeing good results, but they eventually realized these results were due not to the drug treatments they were administering, but to treatment by a Chinese herbalist whom parents were taking the children to.

The herbalist, Rees says, was using a mixture of more than 20 plant extracts in various tailored combinations and doses. The clinicians were able to identify a set of 10 components that were used in all of the treatments, and they formed a consortium to test the individual and combined effects of purified components on patients. Phytopharm emerged from that consortium with a mission to supply a wider range of purified extracts and plant chemicals for testing and development into marketable products.

The company's first product is based on its eczema extract work, but with a twist: It's for dogs. In January 2006, Phytopharm licensed its eczema extract to Schering-Plough, which introduced it to the U.K. veterinary market and plans to roll it out in other European countries in the near future. The product, Phytoptica, is sold as granules that pet owners sprinkle onto their pet's food.

The company also is close to striking gold with *Hoodia gordonii*, in-licensed from South Africa's Council for Scientific & Industrial Research (CSIR). A succulent plant that grows in the Kalahari Desert, hoodia is used by the San bushpeople as a source of water and an appetite depressor in hard times.

In the 1960s, CSIR had done a toxicology screen on many of the plants used by indigenous peoples. They found that hoodia, although not toxic, caused rats to lose their appetite. Analytical chemistry at the time wasn't advanced enough to pursue the finding down to its chemical details, so the discovery was shelved, Rees relates. Then in the 1990s, CSIR developed its chemical knowledge to the point that it could be patented. "But CSIR isn't a product developer, so it turned to us," Rees says.

In turn, Phytopharm has looked to the multinational giant Unilever to develop the hoodia extract as an additive for yogurts, margarines, and other foods. Clinical trials are ongoing, Rees says.

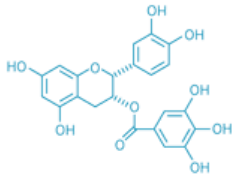
Next up for Phytopharm, Rees says, is development of Cogane, a potential pharmaceutical active ingredient obtained from a Chinese tonic.

"We were able to isolate a single chemical and then make it by a nice three-step synthesis," he says. The molecule is a potential treatment for Alzheimer's disease. The company has also completed Phase I trials of plant-derived compounds that may treat Lou Gehrig's disease and Parkinson's disease.

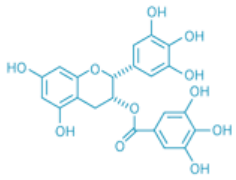
Much of the phytochemical industry's plant identification and assessment builds on work done in Southeast Asia and China, where herbal medicines are well-known and often well-characterized. The plant resources of Africa, however, are less explored and characterized.

One effort to remedy this dearth of information has begun. The Association for African Medicinal Plants Standards (AAMPS) is a collaboration of scientists from 14 countries working to compile an African herbal pharmacopoeia for 53 of the most important African species.

COUSINS An extra OH group is all that distinguishes two tea-derived flavonoid molecules.



(–)-Epicatechin-3-gallate (ECG)



(–)-Epigallocatechin-3-gallate (EGCG)

The association has established a first-phase list of 23 herbal profiles. The remaining 30 plants will be covered in a subsequent second phase. Earlier this month, the group received funding for the second phase, reports Kobus Eloff, a professor in the University of Pretoria's phytomedicine program. "There is also an application for funding to strengthen AAMPS as an organization," Eloff says.

Phytopharm's Rees points out that his firm will not spend time and money to develop a product that it cannot ultimately patent. That's one reason why it has passed on trying to develop products from perhaps the most ubiquitous source of phytochemicals going: tea.

Other companies, though, are finding tea to be a rich brew. One example is DSM's nutritional products unit, which has a focus on green tea and its extracts. Unlike black and oolong tea, production of green tea does not involve fermentation of the tea leaves, the company points out. Rather, green teas are produced by steaming fresh leaves at high temperatures that inactivate fermenting enzymes and leave intact the polyphenol content of the tea.

DSM has patented a process that permits extraction of a particular polyphenol, (-) -epigallocatechin-3-gallate, in concentrated form. DSM boasts that EGCG, marketed under the trade name Teavigo, is "the most active component of green tea in pure form." It has been launched as an ingredient for a broad range of health-enhancing applications in the food industry.

As effective as it seems in many applications, EGCG has a structural cousin, (-)-epicatechin-3-gallate, or ECG, that is more effective in the realm of antimalarial activity, says an Italian research team based in Rome. According to the team's early research, both ECG and EGCG exhibit effects against *Plasmodium falciparum*, the mosquito-borne organism responsible for malaria. But ECG was in general more active than EGCG, the team reports. The findings were particularly notable for strains that are resistant to the common antimalarial drug chloroquine.

In a paper just published in *Biochemical & Biophysical Research Communications* (**2007**, 353, 177), the team noted that it also analyzed the possible pharmacological interactions between artemisinin—a clinically established antimalarial drug-and the two catechins. The results of the analysis, the team concluded, suggest that the catechins enhance the effects of artemisinin.

Meanwhile, even companies in the ultra-specialized field of controlled drugs are keeping busy. Many of these drugs are age-old compounds based on opium, but manufacturers now are using a newer generation of products in an effort to bring marijuana-based products into the arsenal of respectable, albeit controlled, pharmaceuticals.

Earlier this month, the London-based firm GW Pharmaceuticals granted Japan's Otsuka Pharmaceutical an exclusive license to develop the marijuana-derived drug Sativex in the U.S. Sativex contains Δ-9-tetrahydrocannabinol and cannabidiol, which are thought to act via cannabinoid receptors that are distributed throughout the central nervous system and in immune cells. The agreement includes a signing fee of $18 million and milestone payments to GW of up to $273 million.

GW, which was founded in 1998, operates under license from the U.K. Home Office, the British government department responsible for internal affairs, to research and develop cannabinoid drugs that alleviate pain in patients with serious ailments. GW has two additional license agreements for Sativex-with Bayer HealthCare in the U.K. and Canada and with Almirall in Europe outside the U.K.-worth as much as $156 million.

According to GW, cannabinoid modulators show promise in chronic painful conditions, in movement disorders, and in cancer, as well as therapeutic promise in disorders of behavior and mood.

That promise also underpins some of the recent work by Germany's Boehringer Ingelheim, which celebrated its centenary in phytochemicals-particularly controlled drugs-in 2005.

The firm has been registered by the U.S. Drug Enforcement Administration to make Δ-9-tetrahydrocannabinol, the same compound being pursued by GW, to treat anorexia, nausea and vomiting from chemotherapy, and weight loss in AIDS patients.

However, Boehringer Ingelheim has developed a fully synthetic process for the hydrocannabinol that does not use any DEA-controlled raw materials or involve extraction from marijuana or other plant species, the company points out.

Whether plant-derived or synthetic analog, the phytochemical active ingredients coming up now are taking their place on the world stage. It's worth considering over a soothing cup of tea.