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Japanese plant holds HIV– fighting promise of hope

Using chemical compounds found in a Japanese plant as a lead and the clever application of ultraviolet light, a Scripps Research Institute team has created a unique library of dozens of synthetic compounds to test for biomedical potential. Already, one of the compounds has shown great promise in inhibiting replication of HIV particles and fighting inflammation.

With the report of their work scheduled to appear in the online Early Edition of Proceedings of the National Academy of Sciences this week, the researchers now plan to optimize the compound's pharmaceutical potential so that it can be pursued as a drug candidate.

The plant Hypericum chinense, known in Japan as biyouyanagi, produces beautiful yellow flowers and, as it happens, potent chemical compounds known as biyouyanagins that have already shown promising anti-HIV and anti-tumor activity. That got the attention of K.C. Nicolaou, who holds the titles chair of the Department of Chemistry, Aline W. and L.S. Skaggs Professor of Chemical Biology, and Darlene Shiley Chair in Chemistry at Scripps Research. Nicolaou's interest was also piqued because the plant is from the same family that produces St. John's wort, and the biyouyanagins possess an intriguing molecular architecture.

"It was the perfect recipe for convincing a synthetic chemist to get into the game," said Nicolaou, who spearheaded the project in collaboration with a number of Scripps Research colleagues. "It seemed like there was so much to be discovered."

Within the biomedical field there are some researchers that argue natural products are the best route to new drug discovery. Others laud the potential of designing completely synthetic drugs. "I belong to both camps," says Nicolaou, because he prefers to start with natural products and then modify them in a variety of ways to create new synthetic products with improved potential. "The power of this method is that it allows us to build on the natural structures to make a whole new and diverse family of compounds."

An unexpected side result of the group's initial work was the discovery that the structure previously reported for the biyouyanagins was slightly off. With the proper structures in hand, the Nicolaou team recognized it could induce formation of critical bonds that join the two domains of the molecules by bombarding the right chemical building blocks with ultraviolet light.

This technique, known as photocycloaddition, allowed the scientists to synthesize the two known biyouyanagins as well as a third type not yet discovered in nature. The scientists then began combining a variety of different building blocks—some commercially available and others they produced in the lab—using the photocycloaddition to build a library of about 50 analogs, compounds similar to the originals but with significant chemical variations.

The resulting compounds then went in groups to various collaborating Scripps Research laboratories. Professor Dennis Burton's lab analyzed the compounds' ability to inhibit replication of HIV. Chair of the Department of Chemical Physiology Ben Cravatt's team looked at anti-inflammatory potential. Professor Juan de la Torre's group examined effects against LCMV, the prototype member of the arenavirus family that includes several causative agents of deadly hemorrhagic fever disease in West Africa and South America.

All of the compounds in the team's new library are, like aspirin, considered small molecules. Nicolaou believes these offer the best biomedical potential. Larger molecules such as proteins are finding new medical applications, but have to be injected and are often short-lived and very expensive.

"If you can discover small molecules that work, they're affordable and they last long enough in the body to do their jobs," he said. "Those are the magic bullets."

One compound from the new library, number 53, stood out. One side of its structure is essentially the same as that of a natural biyouyanagin, while the other side is a departure comprising a structural motif like the bases found in DNA. In the HIV testing, it compared favorably with the well-known AIDS drug AZT, though it is not yet as potent. In the anti-inflammatory tests, it was as potent or more so than commercially available products. This particular compound hasn't been tested for its potential against arenaviruses, but Nicolaou is hopeful the team will eventually find interesting activity there as well.

"We were certainly excited to see those results," says Nicolaou. "It's quite a promising lead." Next,

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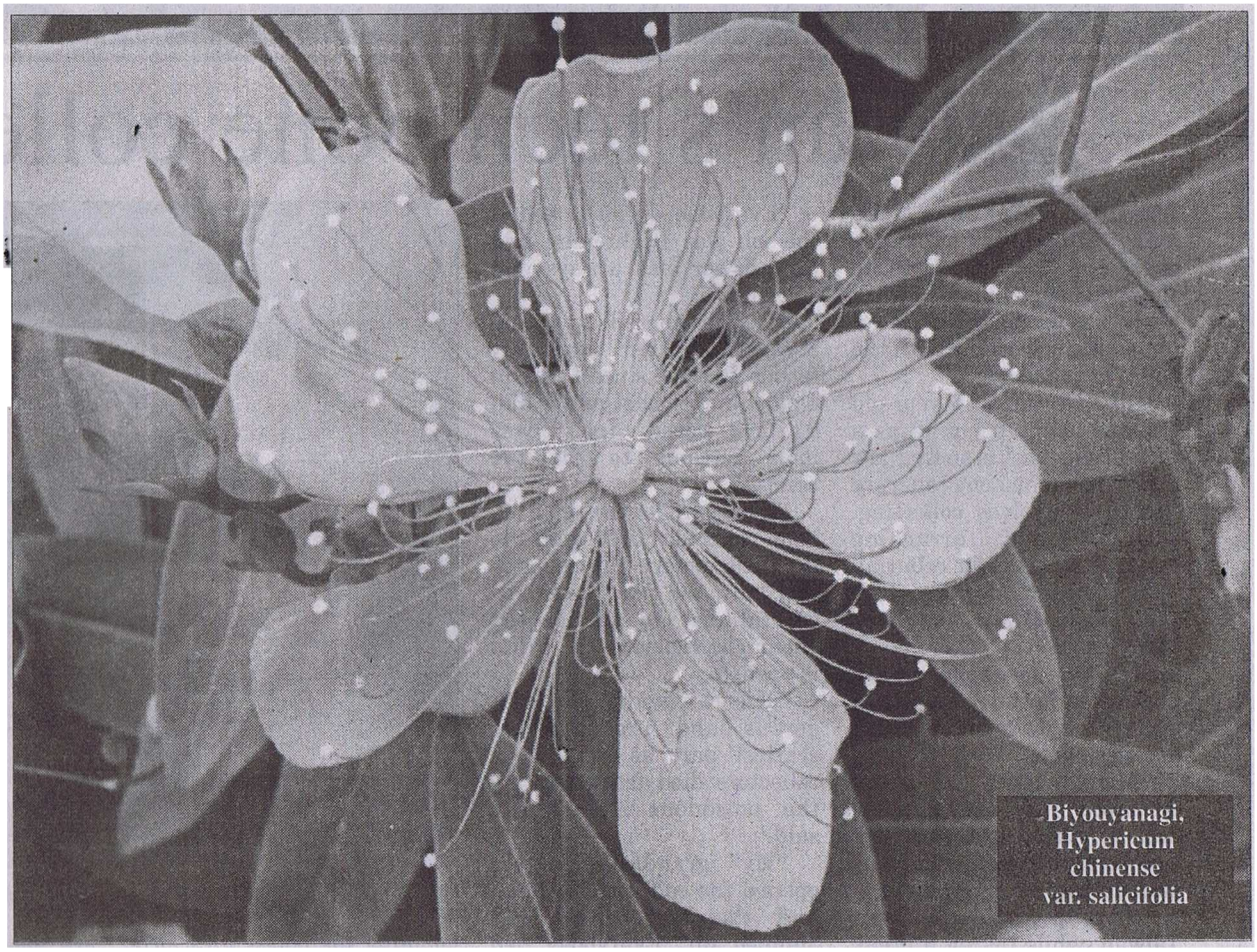
the team will tinker with 53's initial structure in search of modifications that will increase its potency. Once its biomedical activities are optimized, the group will consider pushing the compound toward the drug-testing process.



Biyouyanagi, Hypericum chinense var. salicifolia