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Quest for new plant drugs gains momentum

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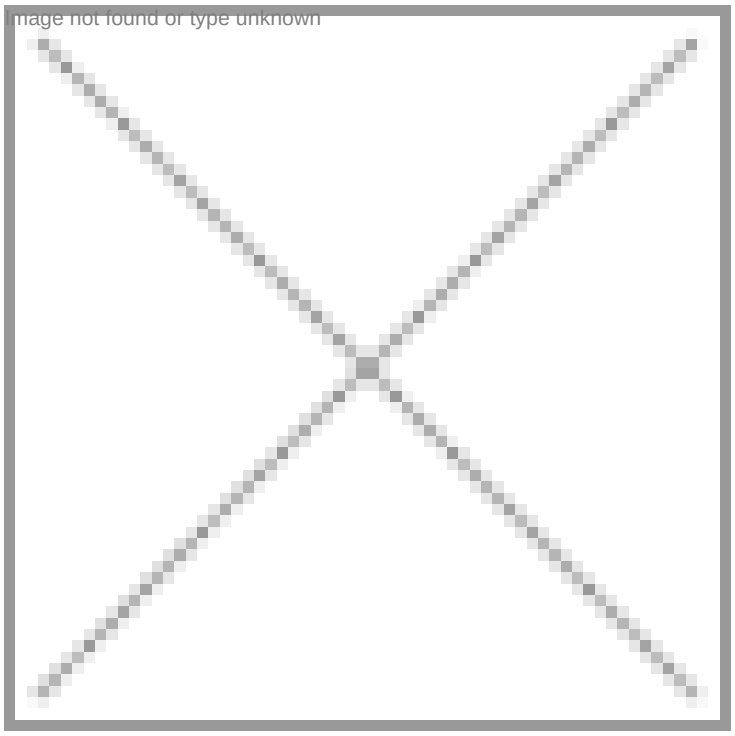

Quest for new plant drugs gains momentum

The School of Ecology and Conservation, with support from the DBT, has embarked on a program to identify alternate and high yielding sources of Camptothecin (CPT), an important anti-cancer compound, from among the plant resources of the Western Ghats. The results of this work may have implications in developing sustainable models for the extraction of CPT.

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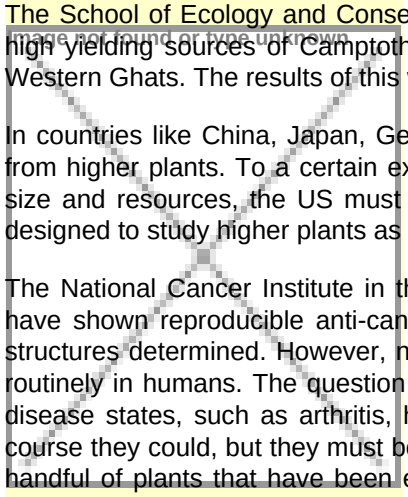

Prof. R Uma Shaanker

In countries like China, Japan, Germany and India, there is a great deal of interest in the search for new and useful drugs from higher plants. To a certain extent, virtually every country seems to be active in this search. However, in the light of its size and resources, the US must be considered as an underdeveloped country with regards to productivity and programs designed to study higher plants as sources of new drugs, both in terms of industrial and university-sponsored research.

The National Cancer Institute in the US has tested 35,000 species of higher plants for anti-cancer activity. Many of these have shown reproducible anti-cancer effects, and the active principles have been extracted from most of these and their structures determined. However, none of these new drugs have yet been found to be safe and effective enough to be used routinely in humans. The question then arises, could any of these 35,000 species of plants contain drugs effective for other disease states, such as arthritis, high blood pressure, acquired immune deficiency syndrome (AIDS), or heart trouble? Of course they could, but they must be subjected to other appropriate tests to determine these effects. In reality, there are only a handful of plants that have been exhaustively studied for their potential value as a source of drugs, i.e., tested for several effects instead of just only one. Thus, it is safe to presume that the entire flora of the world has not been systemically studied to determine if its constituent species contain potentially useful drugs. This is a sad commentary when one considers that

interest in plants as a source of drugs started at the beginning of the nineteenth century and that technology and science have grown dramatically since that time.

Various avenues

There are many approaches to the search for new biologically active principles in higher plants .One can simply look for new chemical constituents and hope to find a biologist who is willing to test each substance with whatever pharmacological test is available. This is not considered to be a very valid approach. A second approach is simply to collect every readily available plant, prepare extracts, and test each extract for one or more types of pharmacological activity. This random collection, broad screening method is a reasonable approach that eventually should produce useful drugs, but it is contingent on the availability of adequate funding and appropriate predictable bioassay systems. The last major useful drugs to have reached the marketplace based on this approach are the so-called vinca alkaloids, vincristine sulfate (leurocristine) and vinblastine sulfate (vincaleukoblastine). Vincristine is the drug of choice for the treatment of childhood leukemia; vinblastine is a secondary drug for the treatment of Hodgkin's disease and other neoplasms.

Vincristine was discovered by Gordon H. Svoboda at the Lilly Research Laboratories. In January 1958, Svoboda submitted an extract of the Madagascan periwinkle plant Catharanthus roseus to a pharmacological screening program at Lilly. This was the fortieth plant that he selected for inclusion in the program. Vincristine was marketed in the US in 1963, less than five years after a crude extract of C. roseus was observed to have anti-tumor activity. In 1985, total domestic and international sales of vincristine and vinblastine were approximately $100 million, 88 percent of which was profit for the company.

This discovery of new drugs from higher plants is one of the few that has evolved from a random-selection broad pharmacological screening program. For example, in the very expensive research and development effort undertaken by the National Cancer Institute, not one useful drug has emerged.

A cause for concern

Higher plants have been described as chemical factories that are capable of synthesizing unlimited numbers of highly complex and unusual chemical substances whose structures could escape the imagination of synthetic chemists forever.

One of the widely and highly demanded biochemical intermediate in the recent past is shikimic acid â€“ an important precursor for the synthesis of aromatic acids. The focus on shikimic acid has immensely increased since it is the key material of Tamiflu, a remedy against avian flu caused by H5N1 virus. Shikimic acid is used to make a generic drug called Oseltamivir - best known commercially as Tamiflu - which is used to fight many types of flu viruses. Some health experts believe that this and similar antiviral drugs could help save lives by slowing the spread of the virus in the absence of a bird flu vaccine, which is still in development.

Shikimic acid is found naturally in plants and can yield various esters and salts like inositol and quinic acid. Shikimic acid is widely used as a chiral building block for the synthesis of pharmaceuticals, an important example being Tamiflu. At the moment, the most satisfactory commercial route to extraction of shikimic acid is from fruits of Chinese star anise (Illicium verum Hook f., Illiciaceae). However, this plant, a small tree up to 10 meters tall, is extremely difficult to cultivate and also attains maturity at a very slow rate, in that it flowers only after 6 years. With shikimic acid being used in bulk in various industrial sectors, it becomes highly essential to find new sources to meet the demand. There is a skyrocketing demand for Tamiflu, but some experts fear there won't be enough of the drug to treat everyone if a worldwide pandemic occurs. The supply problem resides in the drug's source.

Novel venture

At School of Ecology and Conservation, University of Agricultural Sciences, GKVK, Bangalore, currently a team led by Prof. R Uma Shaankar is prospecting for indigenous sources of shikimic acid that can meet domestic and international market needs. Following novel approaches based on phylogenetic leads, they have screened over 240 plant species in the Western Ghats.

"We have completed screening about 240 species. Only 4 of the species yielded more than one percent of shikimic acid. Two of these species yield shikimic acid in excess of 4 percent and up to 7 percent. The results have enormous implications to exploit these resources for meeting the shikimic acid requirements, nationally and internationally," said Prof. Uma Shankar.

Camptothecin (CPT), a monoterpene pentacyclic indole alkaloid is an important anti-cancer compound found in several plant species. Based on its property to inhibit DNA topoisomerase I, several water-soluble anti-cancer drug formulations (e.g. Topotecan and Irinotecan) are currently being semi-synthesized from natural camptothecins. Currently the major source of

CPT is from Campotheca acuminata, a Chinese plant. The success of these drugs has propelled the demand for CPT worldwide. Among the plants reported to contain CPT, the highest concentration (about 0.3 percent on a dry weight basis) has been reported from Nothapodytes nimmoniana (Govindachari and Viswanathan, 1979), a plant available in the Western Ghats. With the rising demand for CPT, it is imperative that efforts are made to facilitate the sustainable supply of CPT without jeopardizing the natural populations of N. nimmoniana.

The School of Ecology and Conservation, with support from the Department of Biotechnology, has embarked on a program to identify alternate and high yielding sources of CPT from among the plant resources of the Western Ghats. The results of this work may have implications in developing sustainable models for the extraction of CPT.

"We have discovered two new plant sources for the production of CPT. These are very high yielding and could potentially replace the current major source of CPT, the Chinese plant. Obviously this finding can have profound economic implications. We have also isolated several strains of endophytic fungi from stem bark of individuals of Nothapodytes nimmoniana and have showed that these also produce CPT, though in smaller quantity. This finding is also potentially very interesting from the point of commercial applications. Using ecological niche models, we have for the first time also been able to model and predict the potential sites and populations that might accumulate higher levels of CPT. This finding has immense commercial implication for bioprospectors" said Prof. R Uma Shaanker.

Several industries have already evinced interest in the ongoing work and the possible scale-up that can make these findings commercially viable.

Therefore future programs of drug development from higher plants should include a careful evaluation of historical as well as current claims of the effectiveness of plants as drugs from alien cultures. Such information is rapidly disappearing as our own culture and ideas permeate the less developed countries of the world where there remains a heavy dependence on plants as sources of drugs.

"Industry collaboration is very useful for any research. It is the industry which needs to utilize these research findings and make it commercially available. In the US, 79 percent of the geneticists have industry tie-ups. Funding is very good in India but there is lack of good research. There are very few companies in India with a good R&D unit," Prof. R Uma Shaanker said.

Jahanara Parveen