

Perspectives in Anticancer Plant Research

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Pharmacognosy, the science of medicinal plants, was born in the nineteenth century from rich traditions of plant remedy use in folk medicine and the historical clinical experience of officinal medicine. Numerous plant species have been reputed by ethnomedicines from around the globe to possess antitumor properties, alleviate symptoms of disease and improve conditions of cancer patients. Systematic study of medicinal plant anticancer properties began in the second half of the twentieth century with the development of stable cell lines. In the 1950th and 1960th, extensive screening of cytotoxic and antiproliferative properties was performed on a multitude of plant compounds in search of agents that could efficiently suppress cell growth. Mitotoxic alkaloids vincristine and vinorelbine, and several other plant compounds identified in these studies were introduced into clinical practice for the treatment of haematological and solid tumors. However, the overall outcome of this massive screening was largely disappointing. Only a fraction of 'anticancer' plants displayed high antiproliferative activity on tumor cells in culture, while activities of the vast majority of plant metabolites turned out to be low, as compared to those of chemically synthesized drugs.

It soon became evident that the initial view of 'anticancer' as 'antiproliferative' does not reflect complex interactions of plant metabolites with the mammalian organism. Many of the 'anticancer' plants are also employed in the treatment of non-cancerous diseases and possess established cholagogic, diuretic, adaptogenic and sedative properties. In some cases, striking discords were observed between the results of the cytotoxicity testing on cells in culture and antitumor action on laboratory animals [1]. A number of plant species (*Rhaponticum*, *Bergenia*, *Plantago*, *Eleutherococcus*, *Panax* and others) with demonstrated ability to reduce the growth of transplanted and chemically induced tumors in animal studies did not display significant cytotoxic activity on malignant cell lines in culture. Conflicting results, obtained with the use of different test systems, seemed to indicate some specificity displayed by phytotherapeutics against different tumor types. However, the degree of this specificity was not known. Other non-toxic plants (*Rhodiola*, *Aloe*, *Glycyrrhiza*, *Artemisia*) have been demonstrated to reduce toxicity and potentiate antitumor and antimetastatic activity of chemotherapeutics. With the development of modern biochemical and molecular approaches, evidence was collected on the ability of numerous plant compounds to induce apoptosis and to interfere with key components of regulatory machinery, which provided valuable insights into the mechanisms of suppression of tumor growth. However, limited knowledge is available so far on the biological activity of the majority of plant compounds.

The twentieth century was a time of massive identification and chemical investigation of plant secondary metabolites, which resulted in an impressive inventory of structurally defined compounds. In this century, the focus of medical plant research shifted from structural studies to elucidation of the mechanisms of action of biomolecules. Direct isolation and bioactivity-guided fractionation of plant extracts gave way to more powerful high-throughput and combinatorial chemistry techniques. Understanding of the function of the complex network of cell signal transduction pathways and the crucial role of deregulation of protein kinases in tumorigenesis opened new perspectives in anticancer plant research. In recent years, inhibitors of protein tyrosine kinases were found among all classes of plant secondary

metabolites, including phenylpropanoids, styrenes, anthraquinones, coumarins, terpenes, flavonoids and catechins [2]. Potent protein kinase inhibitory activity has been established for hypericin, emodin, curcumin, resveratrol, ellagic acid and some other well known components of the officinal and traditional medicinal plants. Undoubtedly, novel agents that could regulate the function of the cellular enzymes involved in cell signaling and apoptosis will be found among the diverse plant secondary metabolic compounds. These natural plant compounds may offer new promising base structures for rational design by enzymatic and chemical derivatization in the quest to develop more potent and selective drugs.

There is growing evidence that the human species could have adapted to plant secondary metabolic compounds during the millennia of evolutionary development on natural raw foods of the plant origin. Dietary exposure of the human population to plant metabolites decreased with the historical transition to cultured crops and with recently emergent food processing technologies. A notable correlation was observed between increased consumption of refined foods and the sharp rise in the incidence of malignancies and cardiovascular diseases during the twentieth century. Taking into account the long natural history of the human species, it is conceivable that plant secondary metabolites could be essential for regulatory tuning and stimulation of the immune system, liver detoxication or excretory function, and a lack of these compounds could contribute to the rise in disease rates. Experimental and clinical data suggest that common constituents of plant foods (i.e. flavonoids, isothiocyanates, phenolic and organic sulfur compounds) may act as natural cancer-preventing agents and adaptogens, and that development of cancers of the digestive tract is susceptible to modification by dietary factors [3,4]. In the years to come we expect to see more studies on the dietary factors affecting malignant growth that would provide a better link between the plant science and nutritional medicine. These perspectives carry a promise for the new pharmacognosy of the twenty first century, which has a potential to become a mature discipline based on the knowledge of specific mechanisms of action of plant bioactive compounds and their molecular targets that play causative functions in the development of disease.

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