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Invited Mini Review

The continuing search for antitumor agents from higher plants

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ABSTRACT

Plant secondary metabolites and their semi-synthetic derivatives continue to play an important role in anticancer drug therapy. In this short review, selected single chemical entity antineoplastic agents from higher plants that are currently in clinical trials as cancer chemotherapy drug candidates are described. These compounds are representative of a wide structural diversity. In addition, the approaches taken toward the discovery of anticancer agents from tropical plants in the laboratory of the authors are summarized. The successful clinical utilization of cancer chemotherapeutic agents from higher plants has been evident for about half a century, and, when considered with the promising pipeline of new plant-derived compounds now in clinical trials, this augurs well for the continuation of drug discovery research efforts to elucidate additional candidate substances of this type.

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1. Introduction

Cancer is one of the leading causes of death in both developed countries and developing countries and is therefore of worldwide concern. According to global cancer statistics released by the American Cancer Society, the total number of deaths from cancer in 2007 was 7.6 million, or about 20,000 deaths each day, with 38% in developed countries and 62% in developing countries. By 2050, 27 million new cancer cases and 17.5 million cancer deaths are projected to occur in the world (American Cancer Society, 2007). Accordingly, much effort has been made to develop various approaches to reduce the threat caused by cancer. Chemotherapy is an important option in modern cancer treatment, and many clinically available anticancer drugs, of synthetic or natural product origin, are currently used to treat some types of leukemias, lymphomas and solid tumors (Chabner et al., 2005; DeVita et al., 2008). A recent analysis of the anticancer drug market in North America, Europe, and Japan during the period 1981–2006 revealed that 47.1% of a total of 155 clinically approved anticancer drugs were either unmodified natural products or their semi-synthetic derivatives, or synthesized molecules based on natural product compound pharmacophores (Newman and Cragg, 2007). Natural products, characterized as small-molecule secondary metabolites that originate from terrestrial and marine plants, microorganisms and animals, tend to present more structurally diverse "drug-like" and "biologically friendly" molecular qualities than pure synthetic compounds at random, and are an important source of novel lead structures for the synthetic and combinatorial chemistry aspects of anticancer drug discovery (Bindseil et al., 2001; Firn and Jones, 2003; Vuorelaa et al., 2004). Despite certain technical limitations inherent in the investigation of the small-molecule organic constituents of organisms using modern drug discovery platforms, improvements in automated high-throughput bioactivity screening techniques and technologies applied in the processes of compound analysis, purification, and structural identification have significantly speeded up the natural product bioassay-guided fractionation procedure (Koehn and Carter, 2005; Potterat and Hamburger, 2006; Anonymous, 2007). The application of biotech-

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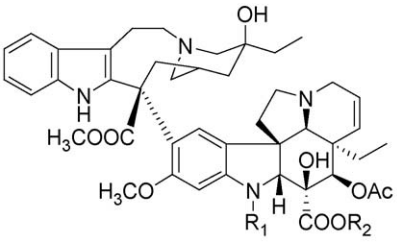
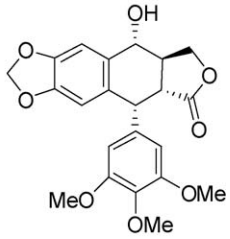
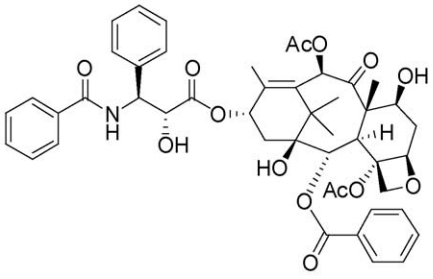
nological methods has allowed selected natural product metabolites to be produced in a relatively controlled manner, and to be less limited by sourcing problems caused by environmental, seasonal and geographical effects (Fischbach and Walsh, 2006). It has been concluded recently that natural products from all types or organisms offer an "unlimited" resource for future drug discovery (Li and Vederas, 2009).



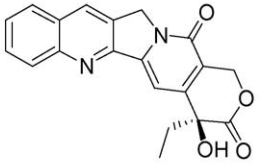
vinblastine (**1**) $R_1 = CH_3$ $R_2 = CH_3$
vincristine (**2**) $R_1 = CHO$ $R_2 = CH_3$



podophyllotoxin (**3**)



paclitaxel (**4**)



camptothecin (**5**)

For millennia, terrestrial plants have been used as a prominent source of medicines, and their early use in this regard in Ancient Egypt, India, China, and the Arab world has been documented (Sneader, 2005). In a volume summarizing a series of review articles that appeared previously in the journal *Lloydia* by the late Dr. Jonathan L. Hartwell, then at the U.S. National Cancer Institute, more than 3000 plant species were described with evidence of previous use for treating cancer (Hartwell, 1982). However, it must be pointed out that cancer is not easy to be diagnosed in a reliable manner like certain other diseases such as skin infections and gastrointestinal disturbances, so claims of efficacy in treating cancer by plants used in traditional medicine should be treated with some skepticism (Cragg et al., 2009). Despite this reservation, there are now four major structural classes of plant-derived compounds used in western medicine as single chemical entity compounds, namely, the vinca alkaloids (vinblastine, vincristine, vinorelbine), the epipodophyllotoxin lignans (etoposide, teniposide, etoposide phosphate), the taxane diterpenoids (paclitaxel, docetaxel), and the camptothecin quinoline alkaloid derivatives (toptotecan, irinotecan), as listed in order of their introduction to established oncology therapy in the United States (Chabner et al., 2005; DeVita et al., 2008). Since a detailed treatment of these four classes of plant-derived agents has appeared in the literature recently (Cragg et al., 2005), these compounds will not be further discussed in the present review. However, it should be noted that the contributions of pioneering natural product chemists in North American academic, governmental, industrial, and private research institutions were instrumental in the isolation and/or structure elucidation of the key lead compounds vinblastine (**1**) (Noble et al., 1958; Svoboda et al., 1959; Neuss et al., 1962), vincristine (**2**) (Svoboda, 1961; Neuss et al., 1962), podophyllotoxin (**3**) (Hartwell and Schrecker, 1951), paclitaxel (originally taxol, **4**) (Wani et al., 1971), and camptothecin (**5**) (Wall et al., 1966). The antineoplastic activities of these five lead compounds were discovered through systematic laboratory studies, rather than relying on ethnomedical observations on their respective plant of origin (Fabricant and Farnsworth, 2001).

In the following sections of this short review, we will provide a brief overview of a number of plant-derived substances currently under clinical trial as antineoplastic drug candidates. Approaches taken towards the discovery of anticancer agents from tropical plants, as carried out in the laboratory of the authors, will be described, prior to some concluding remarks. It must be considered that, in the last 50 years, most new drugs of natural origin have been obtained from soil microorganisms, terrestrial fungi, and higher plants (Kinghorn, 2008). However, there is now a sizeable pipeline of about 25 potential anticancer drugs of marine origin presently in clinical trials, and the first of these, ecteinascidin (trabectidin) is used clinically to treat soft tissue sarcoma in Europe (Sashidhara et al., 2009). Therefore, a central question to be posed is whether or not it is desirable to continue to search for potential new anticancer compounds from terrestrial higher plants specifically, or if it would be preferable to de-emphasize this work in order to concentrate available research resources on natural products derived from other types of organisms for this purpose, such as those of marine origin.

2. Selected plant-derived antineoplastic agents in clinical trials

Natural products continue to be an invaluable resource of anticancer drug discovery in recent years, by considering the comparatively large number of chemical entities of natural origin currently under clinical trial (Corson and Crews, 2007; Butler, 2008; Harvey, 2008; Saklani and Kutty, 2008; Sashidhara et al., 2009). In the paragraphs below, plant-derived oncology drug candidates, now in clinical trials, will be considered specifically. Presently, a large number of derivatives of paclitaxel and camptothecin are in clinical trials to treat various types of cancer,