PLANTS AS A SOURCE OF ANTI-CANCER AGENTS

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Contents

Summary

Plant-derived compounds have played an important role in the development of several clinically useful anti-cancer agents. These include vinblastine, vincristine, the camptothecin derivatives, topotecan and irinotecan, etoposide, derived from epipodophyllotoxin, and paclitaxel (taxol®). Several promising new agents are in clinical development based on selective activity against cancer-related molecular targets, including flavopiridol and combretastin A4 phosphate, and some agents which failed in earlier clinical studies are stimulating renewed interest.

1. Introduction

Plants have a long history of use in the treatment of cancer. Hartwell, in his review of plants used against cancer, lists more than 3000 plant species that have reportedly been used in the treatment of cancer. In many instances, however, the “cancer” is undefined, or reference is made to conditions such as “hard swellings”, abscesses, calluses, corns, warts, polyps, or tumors, to name a few. These symptoms would generally apply to skin, “tangible”, or visible conditions, and may indeed sometimes correspond to a cancerous condition. Many of the claims for efficacy in the treatment of cancer, however, should be viewed with some skepticism because cancer, as a specific disease entity, is likely to be poorly defined in terms of folklore and traditional medicine. This is in contrast to other plant-based therapies used in traditional medicine for the treatment of afflictions such as malaria and pain, which are more easily defined, and where the diseases are often prevalent in the regions where traditional medicine systems are extensively used. However, despite these observations, it is significant that over 60% of currently used anti-cancer agents are derived in one way or another from natural

sources, including plants, marine organisms and micro-organisms. Indeed, molecules derived from natural sources (so-called natural products)**,** including plants, marine organisms and micro-organisms, have played, and continue to play, a dominant role in the discovery of leads for the development of conventional drugs for the treatment of most human diseases.

While in past years, cancer has been regarded mainly as a group of diseases afflicting the more developed countries, the incidence of various forms of cancer is now rapidly rising worldwide. Reference to the World Health Organization database on cancer incidence and mortality [http://www.who.int/cancer/resources/incidences/en/] indicates substantial numbers of cases of major cancers in less developed countries (see Table 1).

Cancer Type	**Number of cases in the year 2000***		
	Total	**More developed countries**	**Less developed countries**
All (except skin)	5,317,905	2,503,772	2,814,132
Breast	1,050,346	579,285	471,063
Colon/Rectum	498,574	318,694	180,059
Kidney	118,255	79,090	39,158
Leukemia	144,321	58,416	85,912
Liver	398,364	73,270	325,108
Lung	901,746	470,836	430,919
Melanoma	65,177	50,608	14,571
Oral Cavity	169,524	59,959	109,553
Ovary	192,379	91,307	101,060
Prostate	542,990	415,568	127,419
Stomach	558,458	208,282	350,176

* Numbers apply to all ages and males only, except for breast and ovary. The total numbers often do not correspond to the sums of the more and less developed countries

Table 1. The number of cases in more developed/less developed countries as of the year 2000

The search for anti-cancer agents from plant sources started in earnest in the 1950s with the discovery and development of the vinca alkaloids, vinblastine and vincristine, and the isolation of the cytotoxic podophyllotoxins (see Section 2). These discoveries prompted the United States National Cancer Institute (NCI) to initiate an extensive plant collection program in 1960, focused mainly in temperate regions. This led to the discovery of many novel chemotypes showing a range of cytotoxic activities, including the taxanes and camptothecins, but their development into clinically active agents spanned a period of some 30 years, from the early 1960s to the 1990s. This plant collection program was terminated in 1982, but with the development of new screening technologies, the NCI revived the collections of plants and other organisms in 1986. This time the focus was on the tropical and sub-tropical regions of the world, but it is interesting to note that no new plant-derived clinical anti-cancer agents have, as yet,

reached the stage of general use. However, as described in Sections 3 to 5, a number of agents are in preclinical development.

2. Plant-Derived Anti-Cancer Agents in Clinical Use

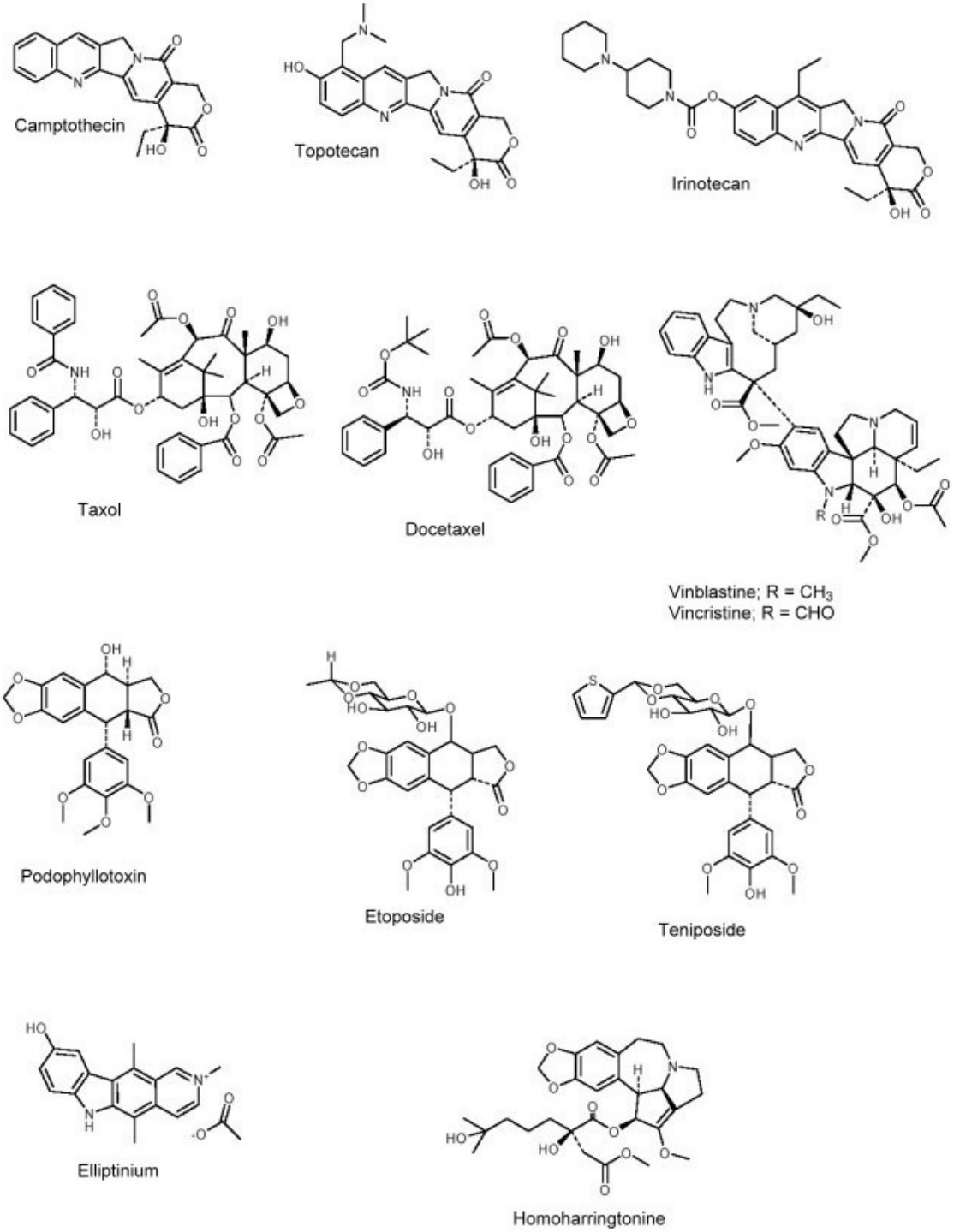

Figure 1. Plant-derived anti-cancer agents in clinical use.

The first agents to advance into clinical use were the so-called vinca alkaloids, vinblastine (VLB) and vincristine (VCR), isolated from the Madagascar periwinkle,

Catharanthus roseus G. Don. (Apocynaceae), which was used by various cultures for the treatment of diabetes. These drugs were first discovered during an investigation of the plant as a source of potential oral hypoglycemic agents. While research investigators could not confirm this activity, it was noted that extracts reduced white blood cell counts and caused bone marrow depression in rats, and subsequently it was found that the treatment of mice bearing a transplantable lymphocytic leukemia caused significant life extension. This led to the isolation of VLB and VCR as the active agents, so their discovery may be indirectly attributed to the observation of an unrelated medicinal use of the source plant. It is interesting to note that though the plant was originally endemic to Madagascar, the samples used in the discovery of VLB and VCR were collected in Jamaica and the Philippines. More recent semi-synthetic analogues of these agents are vinorelbine (VRLB) and vindesine (VDS). These agents are primarily used in combination with other cancer chemotherapeutic drugs for the treatment of a variety of cancers. VLB is used for the treatment of leukemias, lymphomas, advanced testicular cancer, breast and lung cancers, and Kaposi's sarcoma, and VCR, in addition to the treatment of lymphomas, also shows efficacy against leukemias, particularly acute lymphocytic leukemia in childhood. VRLB has shown activity against non-small-cell lung cancer and advanced breast cancer. Of over 2069 anti-cancer clinical trials recorded by the NCI as being in progress as of July 2004, over 160 are drug combinations including these agents against a range of cancers.

The two clinically-active agents, etoposide (VM 26) and teniposide (VP 16-213), which are semi-synthetic derivatives of the natural product, epipodophyllotoxin (an isomer of podophyllotoxin), may be considered as being more closely linked to a plant originally used for the treatment of "cancer". The *Podophyllum* species (Podophyllaceae), *P. peltatum* Linnaeus (commonly known as the American mandrake or Mayapple), and *P. emodii* Wallich from the Indian subcontinent, have a long history of medicinal use, including the treatment of skin cancers and warts. *P. peltatum* was used by the Penobscot Native Americans of Maine for the treatment of "cancer", and interest was promoted by the observation in the 1940s that venereal warts could be cured by topical application of an alcohol extract of the dried roots (called podophyllin). The major active constituent, podophyllotoxin, was first isolated in 1880, but its correct structure was only reported in the 1950s. Many closely related podophyllotoxin-like lignans were isolated during this period, and several of them were introduced into clinical trials, only to be dropped due to lack of efficacy and unacceptable toxicity. Extensive research at Sandoz Laboratories in Switzerland in the 1960s and 1970s led to the development of etoposide and teniposide as clinically effective agents which are used in the treatment of lymphomas and bronchial and testicular cancers. Of 2069 anti-cancer clinical trials recorded by the NCI as being in progress as of July 2004, over 150 are drug combinations including etoposide against a range of cancers. A more recent addition to the armamentarium of plant-derived chemotherapeutic agents is the class of molecules called taxanes. Paclitaxel (taxol®) initially was isolated from the bark of *Taxus brevifolia* Nutt. (Taxaceae), collected in Washington State as part of a random collection program by the U.S. Department of Agriculture (USDA) for the National Cancer Institute (NCI). The use of various parts of *T. brevifolia* and other *Taxus* species (e.g. *T. canadensis* Marshall, *T. baccata* L.) by several Native American tribes for the treatment of some non-cancerous conditions has been reported, while the leaves of *T. baccata* are used in the traditional Asiatic Indian (Ayurvedic) medicine system, with

one reported use in the treatment of "cancer". Paclitaxel, along with several key precursors (the baccatins), occurs in the leaves of various *Taxus* species, and the ready semi-synthetic conversion of the relatively abundant baccatins to paclitaxel, as well as active paclitaxel analogs, such as docetaxel (Taxotere®), has provided a major, renewable natural source of this important class of drugs. Paclitaxel is used in the treatment of breast, ovarian and non-small-cell lung cancer (NSCLC), and has also shown efficacy against Kaposi sarcoma. Paclitaxel has also attracted attention in the potential treatment of multiple sclerosis, psoriasis and rheumatoid arthritis. Docetaxel is primarily used in the treatment of breast cancer and NSCLC. The importance of this class of anti-cancer agents may be judged from the fact that 12 and 23 taxane analogs are in clinical and preclinical development, respectively. In addition, of 2069 cancer clinical trials recorded by the NCI as being in progress as of July 2004, 248 or close to 12% are listed as involving taxane-derived drugs, including 134 with paclitaxel (Taxol®), 105 with docetaxel (Taxotere®), and 10 with miscellaneous taxanes, either as single agents or in combination with other anti-cancer agents. In addition, 23 taxanes are in preclinical development.

Another important addition to the anti-cancer drug armamentarium is the class of clinically-active agents derived from camptothecin, which is isolated from the Chinese ornamental tree, *Camptotheca acuminata* Decne (Nyssaceae), known in China as the tree of joy. Camptothecin was discovered from extracts of plants originally collected by the U. S. Department of Agriculture as a possible source of steroidal precursors for the production of cortisone. The extract of *C. acuminata* was the only one of 1000 of these plant extracts tested for anti-tumor activity which showed efficacy, and camptothecin was isolated as the active constituent. Camptothecin (as its sodium salt) was advanced to clinical trials by the NCI in the 1970s, but was dropped because of severe bladder toxicity. However, extensive research was performed by several pharmaceutical companies in a search for more effective camptothecin derivatives, and Topotecan (Hycamtin®), developed by SmithKline Beecham (now Glaxo SmithKline), and Irinotecan (CPT-11; Camptosar®), originally developed by the Japanese company, Yakult Honsha, are now in clinical use. Topotecan is used for the treatment of ovarian and small-cell lung cancers, while Irinotecan is used for the treatment of colorectal cancers. Of the 2069 cancer clinical trials recorded by the NCI as being in progress, as of July 2004, 94 or approximately 4.5% are listed as involving camptothecin-derived drugs, including 64 with irinotecan (CPT-11), 26 with topotecan, and 4 with other miscellaneous analogues, either as single agents or in combination with other anti-cancer agents. In addition, 15 other camptothecin derivatives are in preclinical development. Other plant-derived agents in clinical use are homoharringtonine, isolated from the Chinese tree, *Cephalotaxus harringtonia* var. *drupacea* (Sieb and Zucc.) (Cephalotaxaceae), and elliptinium, a derivative of ellipticine, isolated from species of several genera of the Apocynaceae family, including *Bleekeria vitensis* A. C. Sm., a Fijian medicinal plant with reputed anti-cancer properties. A racemic mixture of harringtonine and homoharringtonine (HHT) has been used successfully in China for the treatment of acute myelogenous leukemia and chronic myelogenous leukemia. Purified HHT has shown efficacy against various leukemias, including some resistant to standard treatment, and has been reported to produce complete hematologic remission (CHR) in patients with late chronic phase chronic myelogenous leukemia (CML). Elliptinium is marketed in France for the treatment of breast cancer.

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Biographical Sketches

Gordon Cragg was born in Cape Town, South Africa, and obtained his undergraduate training in chemistry at Rhodes University before proceeding to Oxford University where he obtained his D. Phil. in organic chemistry in 1963. After two years of postdoctoral research in natural products chemistry at the University of California, Los Angeles, he returned to South Africa to join the Council for Scientific and Industrial Research. In 1966, he was appointed to the staff of the Department of Chemistry at the University of South Africa, and transferred to the University of Cape Town in 1972. In 1979, he returned to the United States to join the Cancer Research Institute at Arizona State University, working with Professor G. Robert Pettit on the isolation of potential anti-cancer agents from plant and marine invertebrate sources. In 1985, he moved to the National Cancer Institute in Bethesda, Maryland, and was appointed Chief of the Natural Products Branch in 1989. His major interests lie in the discovery of novel natural product agents for the treatment of cancer and AIDS. He has been awarded the National Institutes of Health Merit Awards for his contributions to the development of the drug, taxol (1991), leadership in establishing international collaborative research in biodiversity and natural products discovery (2004), and contributions to developing and teaching NIH technology transfer training courses (2004). From 1998 to 1999 he served as President of the American Society of Pharmacognosy, and was elected to Honorary Membership of the Society in 2003. He has established collaborations between the National Cancer Institute and organizations in many countries promoting drug discovery from their natural resources. He has published over 100 papers related to these interests.

David Newman was born in Grays, Essex, UK. Initially he trained as a chemical analyst (Grad. RIC), followed by an M.Sc. in Organic Chemistry (University of Liverpool), and then after time in the UK chemical industry, he obtained a D.Phil. in Microbial Chemistry from the University of Sussex in 1968. Following two years of postdoctoral studies on the structure of electron transport proteins at the University of Georgia, USA, he worked for Smith Kline and French in Philadelphia, Pennsylvania, as a biological chemist predominately in the area of antibiotic discovery. During this time period, he obtained an MS in Information Sciences in 1977 from Drexel University, Philadelphia. He has worked for a number of US-based pharmaceutical companies in natural products-based discovery programs in anti-infective and cancer treatments, and joined the Natural Products Branch of the NCI in 1991. He is responsible for the marine and microbial collection programs of the NCI, and in concert with Gordon Cragg, for the NCI's Open and Active Repository programs. In 2003 he was awarded the NIH Merit Award for his contributions to the development of potential anti-cancer agents from marine and microbial sources. His scientific interests are in the discovery and history of novel natural products as drug leads in the anti-infective and cancer areas, and in the application of information technologies to drug discovery. In conjunction with Gordon Cragg, he has established collaborations between the National Cancer Institute and organizations in many countries promoting drug discovery from their natural resources. He has published over 60 papers, presented over 60 abstracts, holds 17 patents that are related to these interests, is both a UK Chartered Chemist and a UK Chartered Biologist and is also an adjunct full professor at the Center of Marine Biotechnology, University of Maryland.