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Perspective paper

Plants as a source of anti-cancer agents

Gordon M. Cragg *, David J. Newman

Natural Products Branch, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, P.O. Box B, Frederick, MD 21702-1201, USA

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Abstract

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

Keywords: Camptothecins; Combretastatins; Flavopiridol; Podophyllotoxins; Taxanes; Vinca alkaloids; Cell cycle target inhibitors

1. Introduction

Plants have a long history of use in the treatment of cancer (Hartwell, 1982). In his review, Hartwell lists more than 3000 plant species that have reportedly been used in the treatment of cancer, but in many instances, 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. Such symptoms would generally apply to skin, "tangible", or visible conditions, and may indeed sometimes correspond to a cancerous condition, but many of the claims for efficacy 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. Nevertheless, despite these observations, plants have played an important role as a source of effective anti-cancer agents, and 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 (Cragg et al., 2005; Newman et al., 2003).

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. As a result, the United States National Cancer Institute (NCI) initiated 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 (Cassady and Douros, 1980), 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 the development of new screening technologies led to the revival of collections of plants and other organisms in 1986, with a focus on the tropical and sub-tropical regions of the world. It is interesting to note, however that no new plant-derived clinical anti-cancer agents have, as yet, reached the stage of general use, but a number of agents are in preclinical development.

* Corresponding author. Tel.: +1 301 846 5387; fax: +1 301 846 6178.
E-mail address: cragg@mail.nih.gov (G.M. Cragg).

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2. Plant-derived anti-cancer agents in clinical use (Fig. 1)

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 (Gueritte and Fahy, 2005). While under investigation as a source of potential oral hypoglycemic agents, it was noted that extracts reduced white blood cell counts and caused bone marrow depression in rats, and subsequently they were found to be active against lymphocytic leukemia in mice. This led to the isolation of VLB and VCR as the active agents, so their discovery may

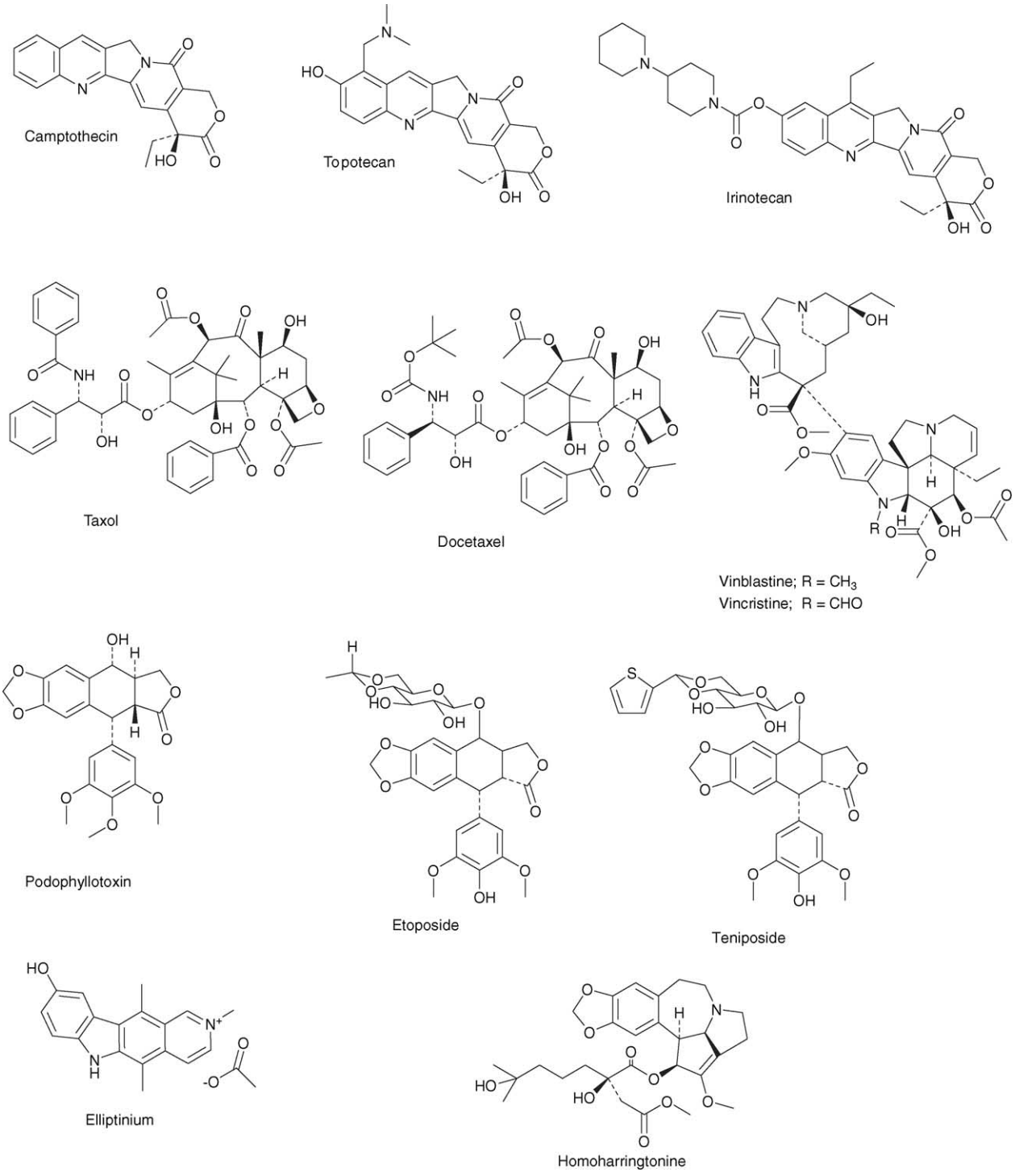

Fig. 1. Plant-derived anti-cancer agents in clinical use.

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 analogs 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, including leukemias, lymphomas, advanced testicular cancer, breast and lung cancers, and Kaposi's sarcoma.

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" (Lee and Xiao, 2005). The *Podophyllum* species (Podophyllaceae), *Podophyllum peltatum* Linnaeus (commonly known as the American mandrake or Mayapple), and *Podophyllum emodii* Wallich from the Indian subcontinent, have a long history of medicinal use, including the treatment of skin cancers and warts. 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 also isolated, and several of them were introduced into clinical trials, only to be dropped due to lack of efficacy and unacceptable toxicity. Extensive research 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.

A more recent addition to the armamentarium of plant-derived chemotherapeutic agents are the taxanes (Kingston, 2005). Paclitaxel (taxol®) initially was isolated from the bark the Pacific Yew, *Taxus brevifolia* Nutt. (Taxaceae), as part of a random collection program for the NCI by the U.S. Department of Agriculture (USDA). The use of various parts of *Taxus brevifolia* and other *Taxus* species (e.g., *Taxus canadensis* Marshall, *Taxus baccata* L.) by several Native American tribes for the treatment of some non-cancerous conditions has been reported, while the leaves of *Taxus baccata* are used in the traditional Asiatic Indian (Ayurvedic) medicine system, with one reported use in the treatment of "cancer" (Hartwell, 1982). 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, while docetaxel is primarily used in the treatment of breast cancer and NSCLC. Paclitaxel has also attracted attention in the potential treatment of multiple sclerosis, psoriasis and rheumatoid arthritis. In addition, 23 taxanes are in preclinical development as potential anti-cancer agents.

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) (Rahier et al., 2005). Camptothecin (as its sodium salt) was advanced to clinical trials by the NCI in the 1970s, but was dropped because of severe bladder toxicity, but extensive research led to the development of more effective derivatives, Topotecan and Irinotecan (CPT-11; Camptosar). Topotecan is used for the treatment of ovarian and small cell lung cancers, while Irinotecan is used for the treatment of colorectal cancers.

Other plant-derived agents in clinical use are homoharringtonine, isolated from the Chinese tree, *Cephalotaxus harringtonia* var. *drupacea* (Sieb and Zucc.) (Cephalotaxaceae) (Itokawa et al., 2005), 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.

3. Plant-derived anti-cancer agents in clinical development (Fig. 2)

Flavopiridol is totally synthetic, but the basis for its novel flavonoid structure is a natural product, rohitukine, isolated as the constituent responsible for anti-inflammatory and immunomodulatory activity from *Dysoxylum binectariferum* Hook. f. (Meliaceae), which is phylogenetically related to the Ayurvedic plant, *Dysoxylum malabaricum* Bedd., used for rheumatoid arthritis. Flavopiridol was one of the over 100 analogs synthesized during structure–activity studies, and was found to possess tyrosine kinase activity and potent growth inhibitory activity against a series of breast and lung carcinoma cell lines (Sausville et al., 1999). It also showed broad spectrum in vivo activity against human tumor xenografts in mice, which led to its selection for preclinical and clinical studies by the NCI in collaboration with the company, Hoechst. It is currently in 18 Phase I and Phase II clinical trials, either alone or in combination with other anti-cancer agents, against a broad range of tumors, including leukemias, lymphomas and solid tumors.

The combretastatins were isolated from the South African "bush willow", *Combretum caffrum* (Eckl. & Zeyh.) Kuntze (Combretaceae), collected in southern Africa in the 1970s as part of a random collection program for the NCI by the USDA, working in collaboration with the Botanical Research Institute of South Africa (Pinney et al., 2005). Species of the

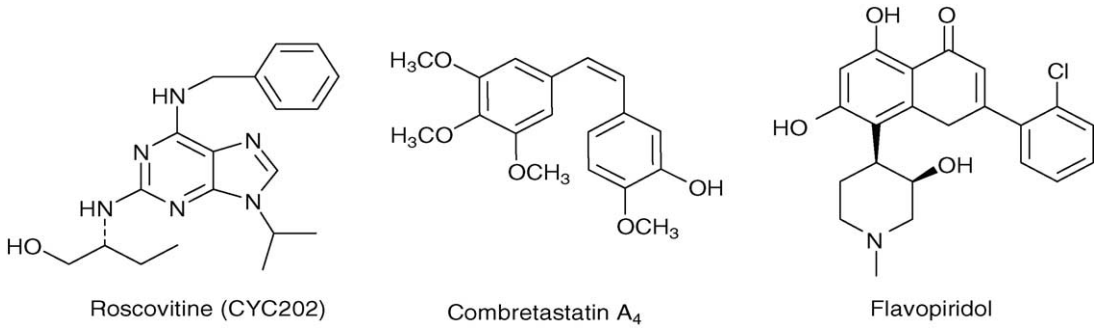

Fig. 2. Plant-derived anti-cancer agents in clinical development.

Combretum and *Terminalia* genera, both of which belong to the Combretaceae family, are used in African and Indian traditional medicine for the treatment of a variety of diseases, including hepatitis and malaria, and several *Terminalia* species have reportedly been used in the treatment of "cancer". The combretastatins are a family of stilbenes which act as anti-angiogenic agents, causing vascular shutdown in tumors and resulting in tumor necrosis. A water-soluble analog, combretastatin A4 phosphate (CA4), has shown promise in early clinical trials, and a number of combretastatin (CA4) mimics are being developed. Three are in clinical trials, while 11 are in preclinical development. This chemical class has served as a model for the synthesis of a host of analogs containing the essential trimethoxy aryl moiety (Fig. 2) linked to substituted aromatic moieties through a variety of two or three atom bridges including heterocyclic rings and sulfonamides, and provides an impressive display of the power of a relatively simple natural product structure to spawn a prolific output of medicinal and combinatorial chemistry (Li and Sham, 2002).

Another synthetic agent based on a natural product model is roscovitine which is derived from olomucine, originally isolated from the cotyledons of the radish, *Raphanus sativus* L. (Brassicaceae) (Meijer and Raymond, 2003). Olomucine was shown to inhibit cyclin-dependent kinases (Cdk), proteins which play a major role in cell cycle progression, and chemical modification resulted in the more potent inhibitor, roscovitine, which currently is in Phase II clinical trials in Europe. Further development of this series, following synthesis of a focused library via combinatorial chemistry techniques, has led to the purvalanols which were even more potent, and are in preclinical development (Chang et al., 1999).

4. Targeting natural products

A recurring liability of natural products, at least in the area of cancer chemotherapy, is that while often very potent, they have limited solubility in aqueous solvents and exhibit narrow therapeutic indices. These factors have resulted in the demise of a number of pure natural products, such as the plant-derived agents, bruceantin and maytansine, but an alternative approach to utilizing such agents is to investigate their potential as "warheads" attached to monoclonal antibodies specifically targeted to epitopes on tumors of interest (Sausville, 1997).

A promising case is that of maytansine. Maytansine (Fig. 3) was isolated in the early 1970s from the Ethiopian plant, *Maytenus serrata* (Hochst. Ex A. Rich.) Wilczek (Celastraceae), again collected for the NCI through the USDA random collection program (Cassady et al., 2004). Despite very low yields (2×10^{-5}% based on plant dry weight), its extreme potency in testing against cancer cell lines permitted the production of sufficient quantities to pursue preclinical and clinical development. Unfortunately, very promising activity in preclinical animal testing did not translate into significant efficacy in clinical trials, and it was dropped from further study in the early 1980s. Related compounds, the ansamitocins, were subsequently isolated from a microbial source, the Actinomycete, *Actinosynnema pretiosum*, and this posed the question as to whether the maytansines are actually plant products, or are produced through an association between a microbial symbiont and the plant; this is a topic of continuing study (Yu and Floss, 2005). The microbial source of closely related compounds has permitted the production of larger quantities of this class of compounds, and this factor, together with their extreme potency, has stimulated continued interest in pursuing their development. A derivative of maytansine, DM1, conjugated with a monoclonal antibody (mAb) targeting small cell lung cancer cells, is being developed as huN901-DM1 for the treatment of small-cell lung cancer, and another conjugate of DM1 to J591, a mAb targeting the prostate specific membrane antigen (PSMA), is in clinical trials against prostate cancer. A conjugate known as SB408075 or huC242-DM1 (also known as Cantuzumab Mertansine), produced by the coupling of DM1 to huC242, a mAb directed against the *muc*1 epitope expressed in a range of cancers, including pancreatric, biliary, colorectal, and gastric cancers, is currently in Phase I clinical trials in the USA.

Another case of considerable interest is that of thapsigargin (TG) (Fig. 3), isolated from the umbelliferous plant, *Thapsia garganica* L. (Apiaceae), collected on the Mediter-

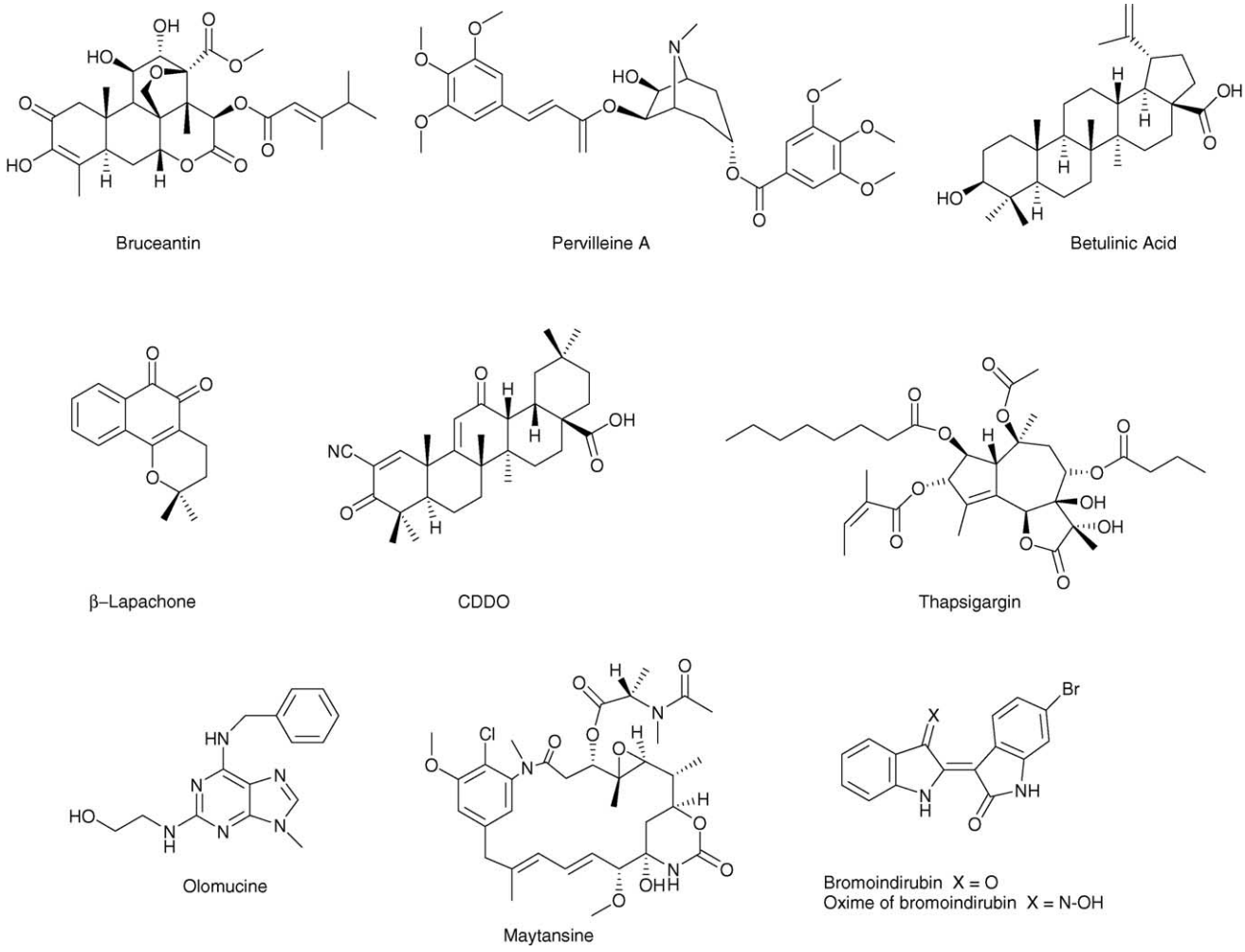

Fig. 3. Plant-derived anti-tumor agents in preclinical development.

ranean island of Ibiza (Denmeade et al., 2003). Thapsigargin induces apoptosis (cell death) in quiescent and proliferating prostate cancer cells, and while it does not show selectivity for prostate cancer cells, it has been conjugated to a small peptide carrier to produce a water-soluble prodrug which is specifically activated by prostate specific antigen (PSA) protease at metastatic prostate cancer sites. Treatment of animals bearing prostate cancer xenograft tumors demonstrated complete tumor growth inhibition without significant toxicity. Given that the prodrug is stable in human plasma, it holds promise as a treatment for human prostate cancer.

5. Plant-derived anti-tumor agents in preclinical development (Fig. 3)

A number of naturally derived agents have been entered into clinical trials and terminated due to lack of efficacy or unacceptable toxicity. The case of maytansine (Section 4) illustrates how the emergence of novel technologies can revive interest in these "old" agents. It is also worth remembering that the development of effective drugs, such as paclitaxel (taxol®) and the camptothecin derivatives, topotecan, and irinotecan (see Section 2), required 20–30 years of dedicated research and patience, and considerable resources, to ultimately prove their efficacy as clinical agents.

Another example of an "old" drug of the same vintage as taxol® and camptothecin having a possibility of revival is bruceantin which was first isolated from a tree, *Brucea antidysenterica* J.F. Mill. (Simaroubaceae), used in Ethiopia for the treatment of "cancer" (Cuendet and Pezzuto, 2004). As often happens, activity was observed in animal models bearing a range of tumors, but no objective responses were observed in clinical trials, and further development was terminated. Recent observations of significant activity against panels of leukemia, lymphoma and myeloma cell lines, as well as in animal models bearing early and advanced stages of the same cancers, has revived interest. This activity has been associated with the down-regulation of a key oncoprotein (c-MYC), and these data are being presented as strong evidence supporting the development of bruceantin as an agent for the treatment of hematological malignancies.

Betulinic acid, another plant-derived compound with a long history, is a lupane-type triterpene which has been isolated from many taxonomically diverse plant genera (Cichewitz and Kouzi, 2004). A major source is the birch tree, *Betula* spp. (Betulaceae), which is also a primary source of its C28 alcohol precursor, betulin, whose isolation was first reported in 1788. A variety of biological activities have been reported for betulinic acid, including anti-bacterial, anti-inflammatory and antimalarial, but the most important activities have been associated with inhibition of the replication of strains of the human immunodeficiency virus (HIV), and cytotoxicity against a range of cancer cell lines. Significant in vivo activity has been observed in animal models bearing human melanoma xenografts, and the NCI is assisting in the development of systemic and topical formulations of the agent for potential clinical trials.

The family of bis-indoles known generically as indirubins are the main constituents of Mu Lan (*Indigofera tinctoria* L.) (Leguminosae) a product from the Chinese Materia Medica used to treat chronic myelogenous leukemia. Indole-derived molecules are found in a large number of indigo-producing plants, and are also produced by bacteria and are found in gastropod mollusks, where they are the source of the purplish-red dye known from antiquity as "Tyrian Purple". They were the first human-used compounds identified as inhibitors of cyclin-dependent kinases (Cdks), key regulatory proteins in the cell cycle referred to in the discussion of olomucine and roscovitine in Section 3 above. Other substituted indirubins have been synthesized, and the 3′-monooxime and 5-bromo derivative (Fig. 3), show comparable activity to other known Cdk inhibitors, such as flavopiridol and roscovitine discussed earlier, and are candidates for preclinical development (Newman et al., 2002).

Triterpenoid acids, such as oleanolic and ursolic acid which are common plant constituents, are associated with weak anti-inflammatory and anti-tumor activities. Programs to synthesize new analogs having increased potencies have led to the synthesis of 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (CDDO) and its methyl ester, which exhibit potent in vitro and in vivo anti-tumor activity against a wide range of tumors, including breast carcinomas, leukemias, and pancreatic carcinomas (Couch et al., 2005). CDDO shows significant activity against epithelial ovarian carcinoma (EOC) cell lines, including lines which were resistant to clinically used agents such as cisplatin. Since EOC is the leading cause of death from gynecologic cancers, further evaluation of CDDO in the treatment of these cancers is being pursued (Melichar et al., 2004).

Species of the genus *Tabebuia* (Bignoniaceae) have a history of use in the Amazonian region for the treatment of several diseases, including syphilis, fevers, malaria, cutaneous infections, and stomach disorders. Claims for clinical efficacy in the treatment of cancers, starting in the 1960s, particularly in Brazil, led to widespread sales of the stem bark and trunk wood of *Tabebuia impetiginosa* (Mart. Ex DC.) Standl. (synonym *Tabebuia avellanedae* Lorentz ex Griseb.), *Tabebuia rosea* (Bertol.), and *Tabebuia serratifolia* (Vahl) Nicholson in health food stores under various names such as pau d'arco or lapacho. Numerous bioactive compounds have been isolated, but the naphthaquinones, particularly lapachol and β-lapachone, have received most attention. Lapachol showed significant in vivo anti-tumor activity in some early mouse models and was advanced to clinical trials by the NCI in the 1970s, but they were terminated due to unacceptable levels of toxicity (Suffness and Douros, 1980). The recent observation of significant activity by β-lapachone against a range of tumor cell lines, including breast, leukemia and prostate lines, and several multidrug resistant (MDR) lines, has stimulated renewed interest in this class of compounds (Ravelo et al., 2004), as has their potent inhibition of Cdc25 phosphatases, dephosphorylating enzymes that play a key role in cell cycle progression (Newman et al., 2002).

The resistance developed by many cancer patients to treatment with standard anti-cancer agents is a serious problem encountered in cancer chemotherapy, and may develop in a cell population through repeated exposure to treatment with a particular drug. This cell population may subsequently show broad cross-resistance to other anti-cancer agents even though it has never been exposed those agents, and this phenomenon is called multidrug resistance. MDR may be related to the presence of an MDR1gene encoding a protein (Pgp; P-glycoprotein) which effectively pumps the drugs out of the cell, thereby precluding their anti-tumor actions. Several compounds which reverse this effect in vitro in cell line studies (so-called MDR inhibitors) have been discovered, but their effectiveness in the clinic has been disappointing in many cases, so there is a continuing search for more effective MDR inhibitors. The pervilleines isolated from the Madagascar plant, *Erythroxylum pervillei* Baillon (Erythroxylaceae), have shown promising MDR activity both in vitro and in vivo, and pervilleine A is currently in preclinical development (Mi et al., 2003).

6. Cell cycle target inhibition and anti-cancer drug discovery

Up to the early 1990s, the discovery of novel anti-tumor agents from natural sources was largely based on testing for cytotoxic activity against cancer cell lines grown either in vitro or using in vivo models. Many of the naturally derived anti-cancer agents originally discovered using such assays, have been shown to exert their cytotoxic action through interaction with tubulin, and include agents, such as vinblastine, vincristine, colchicine, combretastatin and maytansine which promote the depolymerisation of tubulin, while, in the case of the taxanes, microtubules are "bundled" as a result of stabilization against depolymerization. The unique mechanism of taxol® promoted considerable interest in finding other chemotypes which act by similar mechanisms, and one such plant-derived chemotype is the jatrophane esters, in particular jatrophane 1, isolated from samples of the Corsican

and Sardinian plant, *Euphorbia semiperfoliata* Viv. (Euphorbiaceae); though reported as a cytotoxin earlier, its actual biological mechanism of action was not reported until recently (Miglietta et al., 2002). Other recently discovered taxol mimics include the microbial metabolites, the epothilones, and the marine invertebrate metabolites, discodermolide, eleutherobin, sarcodictyins and the laulimalides (Cragg et al., 2005; Cragg and Newman, 2004).

Other important examples are the camptothecin derivatives, topotecan and irinotecan, which exert their cytotoxic action through inhibition of topoisomerase I, a fundamental enzyme complex involved in DNA "winding and unwinding". Despite intensive research aimed at discovering other classes of compounds demonstrating topoisomerase I inhibitory activity, only a few novel chemotypes have been identified. These include the 2-aryl-quinoline derivatives (indenoquinolines), 3-aryl-isoquinoline derivatives (indenoisoquinolines), and the naphthyridines which can be traced to the protoberberine alkaloids, such as nitidine, isolated from *Zanthoxylum* and *Fagara* species (Rutaceae) (Cragg and Newman, 2004).

With the identification of an increasing number of molecular targets associated with particular cancers, high throughput screening of compounds against a range of such targets now forms the basis of anti-cancer drug discovery. Examples are the cyclin-dependent kinases, which, together with their cyclin partners, play a key role in the regulation of cell cycle progression, and inhibition of their activity delays or arrests progression at specific stages of the cell cycle (Newman et al., 2002). There are over 2000 kinases so far identified from genomic studies and all have a common site, the position where the ATP, that is, the source of the phosphate that is donated, is bound. The moderately anti-tumor active flavonoid, quercetin, is an early example of a natural product compound class that ultimately led to Cdk inhibitors. This flavanoid resembles an ATP-mimic where the planar bicyclic chromone ring system is an isostere of adenine. Quercetin exerts its anti-tumor effect through blocking cell cycle progression at the G0/G1 interface, consistent with Cdk inhibition, and a close analogue, myricetin, shows an IC_{50} close to 10 μM versus Cdk2. Flavopiridol (Fig. 2; Section 3) showed about a 100-fold more selectivity for Cdks compared to its activity for tyrosine kinases, and was the first compound identified by the NCI as a potential anti-tumor agent that subsequently was proven to be a relatively specific Cdk inhibitor. Other examples mentioned above include olomucine and roscovitine (Section 3), and the indirubins (Section 5).

7. Conclusions

Plants have been a prime source of highly effective conventional drugs for the treatment of many forms of cancer, and while the actual compounds isolated from the plant frequently may not serve as the drugs, they provide leads for the development of potential novel agents. As new technologies are developed, some of the agents which failed earlier clinical studies are now stimulating renewed interest. The ability to attach agents to carrier molecules directed to specific tumors, shows promise for effectively targeting highly cytotoxic natural products to the tumors while avoiding their toxic side effects on normal healthy tissues. With the rapid identification of new proteins having significant regulatory effects on tumor cell cycle progression, and their conversion into targets for high throughput screening, molecules isolated from plants and other natural organisms are proving to be an important source of novel inhibitors of the action of these key proteins, and have the potential for development into selective anti-cancer agents.

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