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Plants as a source of anti-cancer and anti-HIV agents

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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, and paclitaxel (Taxol®). Several promising new agents are in clinical development based on selective activity against cancer-related molecular targets, including flavopiridol and Combretastatin A4 phosphate. Recently, plants have yielded several agents showing anti-AIDS activity, and one of these, (+)-calanolide A, is in clinical development.

Key words: AIDS, cancer, drugs, HIV, plant products

Introduction

Over the ages, humans have relied on nature for their basic needs for the production of foodstuffs, shelters, clothing, means of transportation, fertilisers, flavours and fragrances, and not least, medicines. Plants have formed the basis of sophisticated traditional medicine systems that have been in existence for thousands of years in countries, such as China (Chang & But, 1986) and India (Kapoor, 1990). These plant-based systems continue to play an essential role in health care; it has been estimated by the World Health Organisation that approximately 80% of the world's inhabitants rely mainly on traditional medicines for their primary health care, while plant products also play an important role in the health care systems of the remaining 20% of the population mainly residing in developed countries (Farnsworth *et al*., 1985). Well-known examples of plant-derived medicinal agents include the antimalarial drug quinine, obtained from the bark of *Cinchona officinalis*, the analgesics, codeine and morphine from *Papaver somniferum*, the antihypertensive reserpine from *Rauwolfia serpentina*, and the cardiac glycoside, digoxin from *Digitalis purpurea* (Kinghorn, 1994).

Plant-Derived Anti-Cancer Agents in Development and Clinical Use

Over 60% of currently used anticancer agents are derived in one way or another from natural sources (Cragg *et al*., 1997). Plants have a long history of use in the treatment of cancer (Hartwell, 1982), though many of the claims for the efficacy of such treatment should be viewed with some scepticism because cancer, as a specific disease entity, is likely to be poorly defined in terms of folklore and traditional medicine (Cragg *et al*., 1994). The first agents to advance into clinical use were the so-called vinca alkaloids, vinblastine and vincristine (Fig. 1; A), isolated from the Madagascar periwinkle, *Catharanthus roseus,* 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 hypoglycaemic agents; therefore, their discovery may be indirectly attributed to the observation of an unrelated medicinal use of the source plant (Cragg *et al*., 1994). More recent semi-synthetic analogues of these agents are vinorelbine and vindesine (Newman *et al*., 2000). The two clinically-active agents, etoposide and teniposide, which are semi-synthetic derivatives of the natural product epipodophyllotoxin (Fig. 1; B), may be considered as being more closely linked to a plant originally used for the treatment of "cancer". Epipodophyllotoxin is an isomer of podophyllotoxin which was isolated as the active anti-tumour agent from the roots of various species of the genus *Podophyllum*. These plants possess a long history of medicinal use by early American and Asian cultures, including the treatment of skin cancers and warts (Cragg *et al*., 1994).

More recent additions to the armamentarium of plant-derived chemotherapeutic agents are the taxanes and camptothecins. Paclitaxel (Fig. 1; C) (Kingston, 2001) initially was isolated from the bark of *Taxus brevifolia*, collected in Washington State as part of a random collection programme by the US Department of Agriculture for the National Cancer Institute [NCI] (Cragg *et al*., 1993*a*). The use of various parts of *T. brevifolia* and other *Taxus* species (e.g. *canadensis, baccata*) by several Native

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American tribes for the treatment of some non-cancerous conditions has been reported (Hartwell, 1982), while the leaves of *T. baccata* are used in the traditional Asiatic Indian (Ayurvedic) medicine system (Kapoor, 1990), 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 (Cortes & Pazdur, 1995), has provided a major, renewable natural source of this important class of drugs. Likewise, the clinically-active agents, topotecan (hycamptamine), irinotecan (CPT-11; CAMPTOSAR) and 9-aminocamptothecin, are semi-synthetically derived from camptothecin (Fig. 1; D), isolated from the Chinese ornamental tree, *Camptotheca acuminata* (Potmeisel & Pinedo, 1995). Camptothecin (as its sodium salt) was advanced to clinical trials by NCI in the 1970s, but was dropped because of severe bladder toxicity.

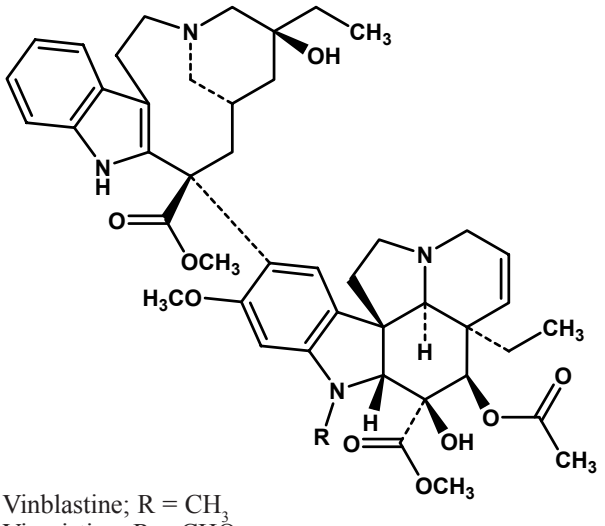
Other examples of plant-derived agents currently in investigational use are homoharringtonine, isolated from the Chinese tree, *Cephalotaxus harringtonia* var. *drupacea* (Sieb and Zucc.), and elliptinium, a derivative of ellipticine, isolated from species of several genera of the *Apocynaceae* family, including *Bleekeria vitensis*, a Fijian medicinal plant with reputed anticancer properties (Cragg *et al*., 1994). Homoharringtonine has shown efficacy against various leukemias, while elliptinium is marketed in France for the treatment of breast cancer (Cragg *et al*., 1993*b*). The flavone, flavopiridol (Fig. 2; 1), is totally synthetic, but the basis for its novel structure is a natural product, rohitukine, isolated from *Dysoxylum binectariferum*. It is currently in Phase II clinical trials against a broad range of tumours (Christian *et al*., 1997). While flavopiridol alone is probably not a viable treatment, use of the compound in conjunction with other agents such as paclitaxel and cisplatin has led to partial and complete remissions in a number of Phase I patients, leading to Phase II studies in patients with a variety of paclitaxel-resistant tumors (Kaubisch & Schwartz, 2000). Similar trials are currently underway in many centers as can be seen by a search of the NCI web-based clinical trials database (http://www.cancer.gov/search/clinical_trials).

The combretastatins, derived from *Combretum caffrum,* are a family of stilbenes which act as anti-angiogenic agents, causing vascular shutdown in tumours and resulting in tumour necrosis (Holwell *et al*., 2002). A water-soluble analogue, combretastatin A-4 phosphate, has shown promise in early clinical trials. A number of other plant-derived agents were entered into clinical trials and were terminated due to lack of efficacy or unacceptable toxicity. Some examples are acronycine, bruceantin, maytansine and thalicarpine (Cragg *et al*., 1993*a*). Others in various stages of pre-clinical development are betulin, which exhibits selective activity against melanoma cell lines (Pisha *et al*., 1995), and thapsigargin analogues which have shown promising *in vivo* activity when conjugated to a hexapeptide targeting prostate cancers (Jakobsen *et al*., 2001). Both these drugs are in development through the NCI Rapid Access to Intervention Development (RAID) program, which assists academic investigators in the pre-clinical development of agents showing promising anti-tumour activity (http://dtp.nci.nih.gov/docs/raid/raid_index.html).

Plant-Derived Cell Cycle Target Inhibitors
(Newman *et al.,* 2002)

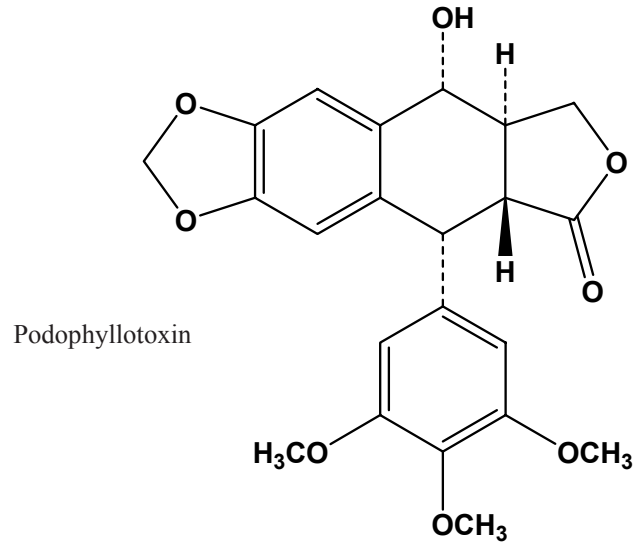
Up to the early 1990s, the discovery of novel anti-tumour agents from natural sources was largely based on testing for cytotoxic activity against cancer cell lines grown either *in vitro* or using *in vivo* models. Many of the naturally derived anti-cancer agents originally discovered using such assays have been shown to exert their cytotoxic action through interaction with tubulin. Thus agents such as vinblastine, vincristine, colchicine, combretastatin and maytansine promote the depolymerisation of tubulin (Rowinsky & Donehower, 1996), while, in the case of the taxanes, microtubules are "bundled" as a result of stabilisation against depolymerisation (Rowinsky, 1997). The search for more effective tubulin-interactive agents continues, and recently discovered taxol mimics include the microbial metabolites, the epothilones, and the marine invertebrate metabolites, discodermolide, eleutherobin, sarcodictyins and the laulimalides (He

Fig. 1A. Vinblastine/Vincristine

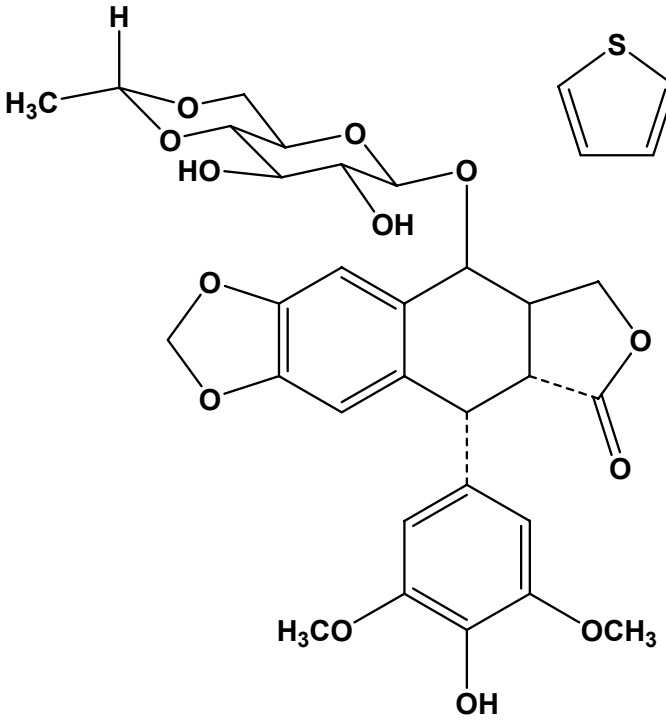


Vinblastine; R = CH_3
Vincristine; R = CHO

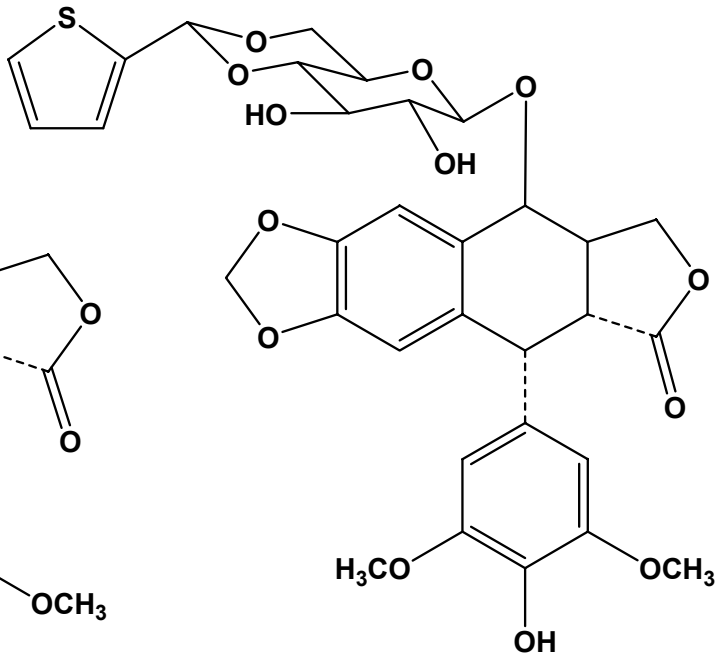
Fig. 1B. Podophyllotoxin and Derivatives



Podophyllotoxin



Etoposide



Teniposide

et al., 2001). 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".

With the identification of an increasing number of molecular targets associated with particular cancers, anti-cancer drug discovery is now based on high throughput screening of compounds against a range of such targets. Cyclin-dependent kinases (CDKs), together with their cyclin partners, play a

Fig. 1C. Paclitaxel (Taxol®)

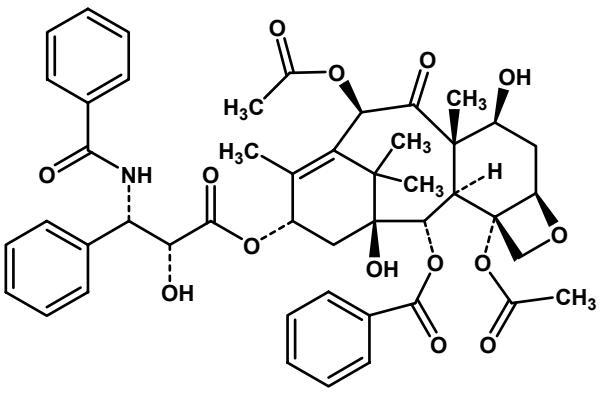


Fig. 1D. Camptothecin Derivatives

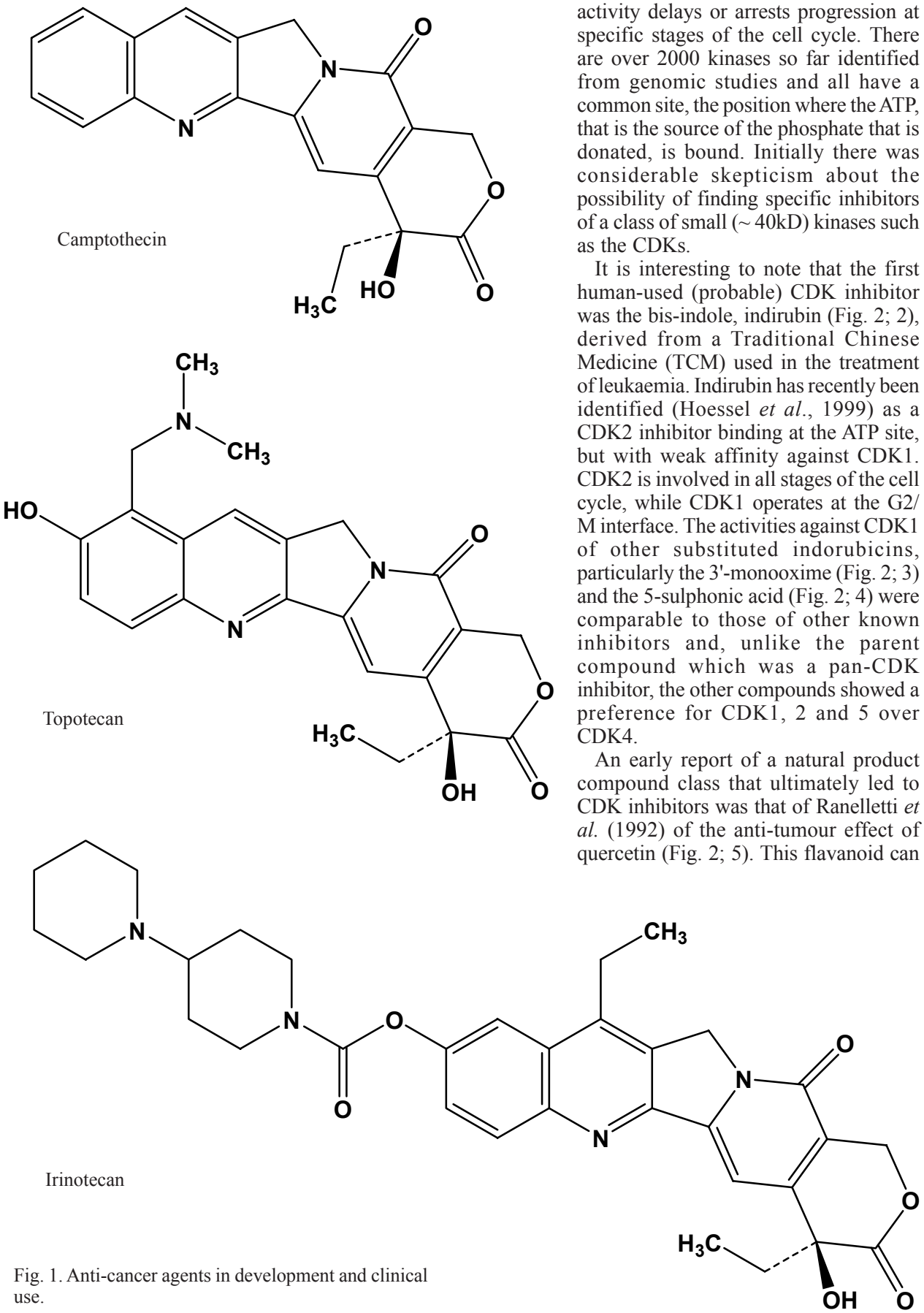


Fig. 1. Anti-cancer agents in development and clinical use.

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. 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. Initially there was considerable skepticism about the possibility of finding specific inhibitors of a class of small (~ 40kD) kinases such as the CDKs.

It is interesting to note that the first human-used (probable) CDK inhibitor was the bis-indole, indirubin (Fig. 2; 2), derived from a Traditional Chinese Medicine (TCM) used in the treatment of leukaemia. Indirubin has recently been identified (Hoessel *et al*., 1999) as a CDK2 inhibitor binding at the ATP site, but with weak affinity against CDK1. CDK2 is involved in all stages of the cell cycle, while CDK1 operates at the G2/M interface. The activities against CDK1 of other substituted indorubicins, particularly the 3'-monooxime (Fig. 2; 3) and the 5-sulphonic acid (Fig. 2; 4) were comparable to those of other known inhibitors and, unlike the parent compound which was a pan-CDK inhibitor, the other compounds showed a preference for CDK1, 2 and 5 over CDK4.

An early report of a natural product compound class that ultimately led to CDK inhibitors was that of Ranelletti *et al.* (1992) of the anti-tumour effect of quercetin (Fig. 2; 5). This flavanoid can

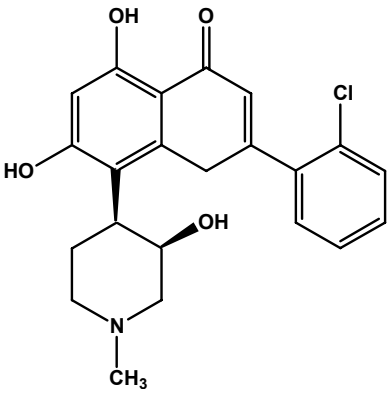
be thought of as an ATP-mimic where the planar bicyclic chromone ring system is an isostere of adenine. Quercetin was shown to exert its anti-tumour effect through blocking cell cycle progression at the G0/G1 interface, consistent with CDK inhibition; however, a close analogue, myricetin (Fig. 2; 6), shows an IC_{50} close to 10 μM versus CDK2 (Walker, 1998). Flavopiridol (Fig. 2; 1) showed about a 100 fold more selectivity for CDKs compared to its activity for tyrosine kinases (Sielecki *et al*., 2000), and was the first compound identified by the NCI as a potential anti-tumour agent that subsequently was proven to be a relatively specific CDK inhibitor (Losiewicz *et al*., 1994).

Plant-Derived Anti-HIV Agents

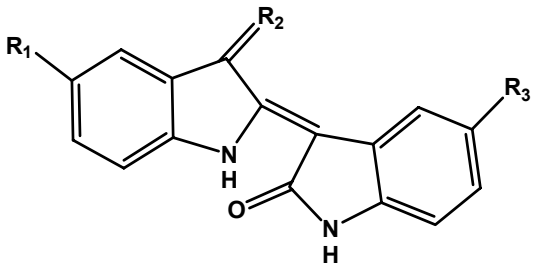
From 1987 to 1996, the NCI tested over 30 000 plant extracts in an *in vitro* cell-based anti-HIV screen which determined the degree of HIV-1 replication in treated infected lymphoblastic cells versus that in treated uninfected control cells. Several natural products have shown *in vitro* activity (http://www.niaid.nih.gov/daids/dtpdb/natprod.htm), and four of these have advanced into pre-clinical development.

Michellamine B (Fig. 3; 7) was isolated as the main *in vitro* active agent from the leaves of the liana, *Ancistrocladus korupensis*, collected in the Korup region of southwest Cameroon (Boyd *et al*., 1994). Continuous infusion studies in dogs indicated that *in vivo* effective anti-HIV concentrations could only be achieved close to toxic dose levels. Thus, despite *in vitro* activity against an impressive range of HIV-1 and HIV-2 strains, the difference between the toxic dose level and the anticipated level required for effective antiviral activity was small, and NCI decided to discontinue further studies aimed at clinical development. However, the discovery of novel antimalarial agents, the korupensamines, from the same species (Hallock *et al*., 1994), adds further promise for this species.

An extract of the leaves and twigs of the tree, *Calophyllum lanigerum*, collected in Sarawak, Malaysia in 1987, yielded (+)-calanolide A (Fig. 3; 8) which showed significant anti-HIV activity (Kashman *et al.,* 1992). Efforts to relocate the original tree failed, and collections of other specimens of the same species gave only trace amounts of calanolide A. A detailed survey of *C. lanigerum* and related species discovered that latex of *Calophyllum teysmanii* yielded extracts with significant anti-HIV activity. The active constituent was found to be (-)-calanolide B (Fig. 3; 9), which was isolated in yields of 20% to 30%. While (-)-calanolide B is slightly less active than (+)-calanolide A, it has the advantage of being readily available from the latex which is tapped in a sustainable manner by making small slash wounds in the bark of mature trees without causing any harm to the trees. The calanolides were licensed by NCI/NIH to Medichem Research, Inc., which, as required by the NCI Letter of Collection (Mays *et al.,* 1997), negotiated an agreement with the Sarawak State Government. The drugs are being developed by Sarawak Medichem Pharmaceuticals, a joint venture company formed between the Sarawak State Government and Medichem Research, Inc. (+)-Calanolide A (which has been synthesised by



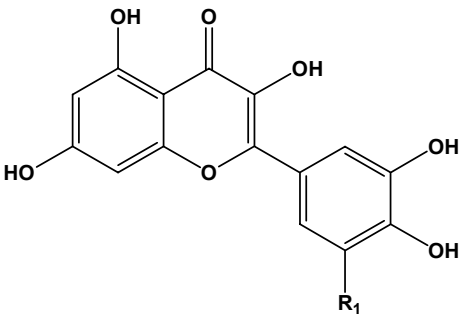
1 Flavopiridol



2 Indirubin
R1 = H R2 = O R3 = H

3 Indirubin-3'-monooxime
R1 = H R2 = N-OH R3 = H

4 Indirubin-5-sulphonic acid
R1 = H R2 = O R3 = SO_3H

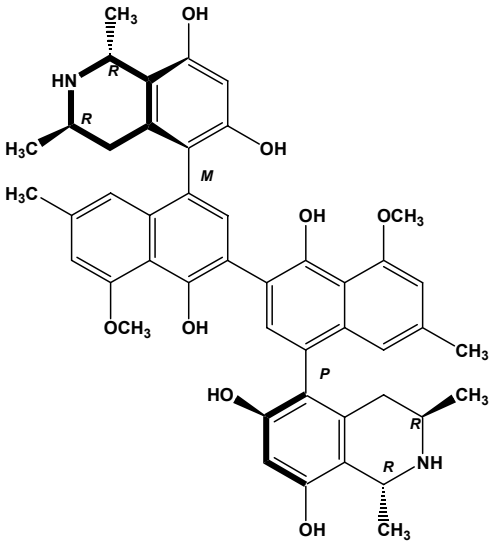


5 Quercetin R_1 = H
6 Myricetin R_1 = OH

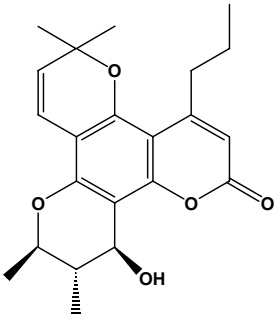
Fig. 2. Potential anti-cancer leads.

Medichem chemists) is currently in Phase II clinical trials, while (-)-calanolide B is in pre-clinical development. The development of the calanolides has been reviewed as a "Benefit-Sharing Case Study" for the Executive Secretary of the Convention on Biological Diversity by staff of the Royal Botanic Gardens, Kew (ten Kate and Wells, http://www.biodiv.org/programmes/socio-eco/benefit/case-studies.asp

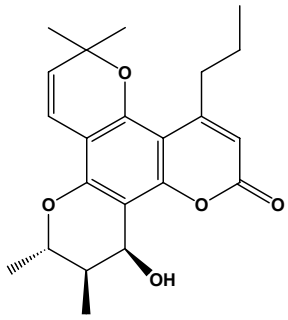
Prostratin (Fig. 3; 10) was isolated as the active constituent from an extract of the wood of the tree, *Homalanthus nutans* (Gustafson *et al*., 1992). The plant was identified by Dr Paul Cox as being used for the treatment of yellow fever (subsequently identified as hepatitis) based on interviews with traditional healers in Samoa conducted under terms of a covenant negotiated with the chiefs and orators in the village of Falealupo, and with the concurrence of the Samoan Prime Minister and members of parliament (Cox, 2001). Subsequent studies determined that prostratin is a potent activator of HIV expression in latently infected T-cell lines (Gulakowski *et al*., 1997), and its potential value in HIV therapy lies more in its possible utility as a viral activator rather than as an anti-HIV agent. The further development of prostratin is being undertaken by the AIDS ReSearch Alliance of America (ARA) (supported by the NCI and the National Institute for Allergy and Infectious Diseases) which has negotiated an agreement with the government of Samoa allowing for benchmark payments to the government of Samoa, the village and the families of the healers. In addition, ARA will endeavor to obtain prostratin from Samoan plant sources as long as it can be produced in a cost-effective manner, and will strive to ensure that the drug will be distributed at minimal profit in developing nations where use of the drug is approved.



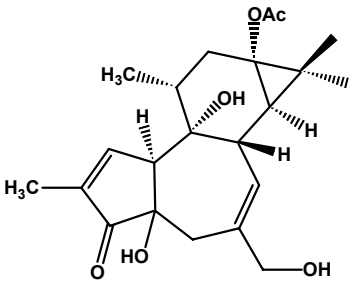
7 Michellamine B



8 (+) - Calanolide A



9 (-) - Calanolide B



10 Prostratin

Fig. 3. Potential anti-HIV leads.

Extracts of the "smokebush", *Conospermum incurvum*, collected in Western Australia, yielded conocurvone as the active agent (Decosterd *et al*., 1993). Conocurvone was licensed to the Australian company, AMRAD, which negotiated an agreement with the State government of Western Australia, but further development of the natural product and synthetic analogues has recently been terminated.

References

Boyd M R, Hallock Y F, Cardellina II J H, Manfredi K P, Blunt J W, McMahon J B, Buckheit Jr R W, Bringmann G, Schaffer M, Cragg G M, Thomas D W, Jato J G. 1994. Anti-HIV michellamines from *Ancistrocladus korupensis. Journal of Medicinal Chemistry* **37**:1740-1745.

Chang H M, But P H. 1986. *Pharmacology and Applications of Chinese Materia Medica,* Vols 1 and 2. Singapore: World Scientific Publishing. 1320 pp.

Christian M C, Pluda J M, Ho T C, Arbuck S G, Murgo A J, Sausville E A. 1997. Promising new agents under development by the Division of Cancer Treatment, Diagnosis, and Centers of the National Cancer Institute. *Seminars in Oncology* **24**:219-240.

Cortes J E, Pazdur R. 1995. Docetaxel. *Journal of Clinical Oncology* **13**:2643-2655.

Cox P A. 2001. Ensuring equitable benefits: the Falealupo Covenant and the anti-HIV drug Prostratin from a Samoan medicinal plant. *Pharmaceutical Biology* **39**:33-40 (Supplement).

Cragg G M, Newman D J, Snader K M. 1997. Natural products in drug discovery and development. *Journal of Natural Products* **60**:52-60.

Cragg G M, Schepartz S A, Suffness M, Grever M R. 1993*a*. The taxol supply crisis. New NCI policies for handling the

large-scale production of novel natural product anticancer and anti-HIV agents. *Journal of Natural Products* **56**:1657-1668.

Cragg G M, Boyd M R, Cardellina II J H, Newman D J, Snader K M, McCloud T G. 1994. Ethnobotany and drug discovery: the experience of the US National Cancer Institute. In *Ethnobotany and the Search for New Drugs. Ciba Foundation Symposium 185,* pp. 178-196. Eds D J Chadwick, J Marsh. Chichester, UK: Wiley & Sons.

Cragg G M, Boyd M R, Cardellina II J H, Grever M R, Schepartz S A, Snader K M, Suffness M. 1993*b*. Role of plants in the National Cancer Institute drug discovery and development program. In *Human Medicinal Agents from Plants. American Chemical Society Symposium Series 534,* pp. 80-95. Eds A D Kinghorn and M F Balandrin. Washington, DC: American Chemical Society.

Decosterd L A, Parsons I C, Gustafson K R, Cardellina J H II, McMahon J B, Cragg G M, Murata Y, Pannell L K, Steiner J R, Clardy J, Boyd M R. 1993. Structure, absolute stereochemistry, and synthesis of conocurvone, a potent, novel HIV-inhibitory naphthoquinone trimer from a *Conospermum* sp. *Journal of the American Chemical Society* **115**:6673-6679.

Farnsworth N R, Akerele O, Bingel A S, Soejarto D D, Guo Z. 1985. Medicinal plants in therapy. *Bulletin of the World Health Organization* **63**:965-981.

Gulakowski R J, McMahon J B, Buckheit Jr R W, Gustafson K R, Boyd M R. 1997. Antireplicative and anticytopathic activities of prostratin, a non-tumor promoting phorbol ester, against human immunodeficiency virus (HIV). *Antiviral Research* **33**:87-97.

Gustafson K R, Cardellina II J H, McMahon J B, Gulakowski R J, Ishitoya J, Szallasi Z, Lewin N E, Blumberg P M, Weislow O S, Beutler J A, Buckheit Jr R W, Cragg G M, Cox P A, Bader J P, Boyd M R. 1992. A non-promoting phorbol from the Samoan medicinal plant *Homalanthus nutans* inhibits cell killing by HIV-1. *Journal of Medicinal Chemistry* **35**:1978-1986.

Hallock Y F, Manfredi K P, Blunt J W, Cardellina II J H, Schaffer M, Gulden K P, Bringmann G, Lee A Y, Clardy J, Francois G, Boyd M R. 1994. Korupensamines A-D, novel antimalarial alkaloids from *Ancistrocladus korupensis*. *Journal of Organic Chemistry* **59**:6349-6355.

Hartwell J L. 1982. *Plants Used Against Cancer*. Lawrence, MA: Quarterman. 438 pp.

He L, Orr G A, Horwitz S B. 2001. Novel molecules that interact with microtubules and have functional activity similar to Taxol (TM). *Drug Discovery Today* **6**:1153-1164.

Hoessel R, Leclerc S, Endicott J A, Nobel M E M, Lawrie A, Tunnah P, Leost M, Damiens E, Marie D, Marko D, Niederburger E, Tang W, Eisenbrand G, Meijer L. 1999. Indirubin, the active constituent of a Chinese antileukaemia medicine, inhibits cyclin-dependent kinases. *Nature Cell Biology* **1**:60-67.

Holwell S E, Cooper P A, Grosios K, Lippert III J W, Pettit G R, Shnyder S D, Bibby M C. 2002. Combretastatin A-1 phosphate, a novel tubulin-binding agent with *in vivo* anti-vascular effects in experimental tumors. *Anticancer Research* **22**:707-712.

Jakobsen C M, Denmeade S R, Isaacs J T, Gady A, Olsen C E, Christensen S B. 2001. Design, synthesis, and pharmacological evaluation of thapsigargin analogues for targeting apoptosis to prostatic cancer cells. *Journal of Medicinal Chemistry* **44**:4696-4703.

Kapoor L D. 1990. *CRC Handbook of Ayurvedic Medicinal Plants*. Boca Raton, Florida: CRC Press. 416 pp.

Kashman Y, Gustafson K R, Fuller R W, Cardellina II J H, McMahon J B, Currens M J, Buckheit R W, Hughes S H, Cragg G M, Boyd M R. 1992. The calanolides, a novel HIV-inhibitory class of coumarin derivatives from the tropical rainforest tree, *Calophyllum lanigerum*. *Journal of Medicinal Chemistry* **35**:2735-2743.

Kaubisch A, Schwartz G K. 2000. Cyclin-dependent kinase and protein kinase C inhibitors: A novel class of antineoplastic agents in clinical development. *Cancer Journal* **6**:192-212.

Kinghorn A D. 1994. The discovery of drugs from higher plants. In *The Discovery of Natural Products with Therapeutic Potential*, pp. 81-108. Ed. V P Gullo. Boston: Butterworth-Heinemann.

Kingston D G I. 2001. Taxol, a molecule for all seasons. *Chemical Communications,* pp. 867-880.

Losiewicz M D, Carlson B A, Kaur G, Sausville E A, Worland P J. 1994. Potent Inhibition of CDC2 Kinase Activity by the Flavanoid, L86-8275. *Biochemical and Biophysical Research Communications* **201**:589-595.

Mays T D, Mazan K D, Cragg G M, Boyd M R. 1997. Triangular Privity - a working paradigm for the equitable sharing of benefits from biodiversity research and development. In *Global Genetic Resources: Access, Ownership and Intellectual Property Rights*, pp. 279-298. Eds K E Hoagland and A Y Rossman. Washington, DC: Association of Systematics Collections.

Newman D J, Cragg G M, Snader, K M. 2000. The influence of natural products upon drug discovery. *Natural Products Reports* **17**:215-234.

Newman D J, Cragg G M, Holbeck S, Sausville E A. 2002. Natural products and derivatives as leads to cell cycle pathway targets in cancer chemotherapy. *Current Cancer Drug Targets* **2**:279-308.

Pisha E, Chai H, Lee I-S, Chagweder T E, Farnsworth N R, Cordell G A, Beecher C W W, Fong H H S, Kinghorn A D, Brown D M, Wani M C, Wall M E, Hieken T J, Das Gupta T K, Pezzuto J M. 1995. Discovery of betulinic acid as a selective inhibitor of human melanoma that functions by induction of apoptosis. *Nature Medicine* **1**:1046-1051.

Potmeisel M, Pinedo H. 1995. *Camptothecins: New Anticancer Agents.* Boca Raton, Florida: CRC Press. 149 pp.

Ranelleti F O, Ricci R, Larocca L M, Maggiano N, Capelli A, Scamibia G, Benedett-Panici P, Mancuso S, Rumi C, Plantelli M. 1992. Growth inhibitory effect of quercetin and presence of type-II estrogen-binding sites in human colon-cancer cell lines and primary colorectal tumors. *International Journal of Cancer* **50**:486-492.

Rowinsky E K. 1997. The development and clinical utility of the taxane class of antimicrotubule chemotherapy agents. *Annual Review of Medicine* **48**:353-374.

Rowinsky E K, Donehower R C. 1996. Antimicrotubule agents. In *Cancer Chemotherapy and Biotherapy*, pp. 263-296. Eds B A Chabner and D L Longo. Lippincott-Raven.

Sielecki T, Boylan J F, Benfield P A, Trainor G L. 2000. Cyclin-dependent kinase inhibitors: Useful targets in cell cycle regulation. *Journal of Medicinal Chemistry* **43**:1-18.

Walker D H. 1998. Small-molecule inhibitors of cyclin-dependent kinases: molecular tools and potential therapeutics. *Current Topics in Microbial Immunology* **227**:149-165.