J Nat Med (2008) 62:263–280
DOI 10.1007/s11418-008-0246-z

REVIEW

Plant-derived natural product research aimed at new drug discovery

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Received: 7 January 2008 / Accepted: 14 March 2008 / Published online: 22 April 2008

Abstract Many important bioactive compounds have been discovered from natural sources using bioactivity-directed fractionation and isolation (BDFl) [Balunas MJ, Kinghorn AD (2005) Drug discovery from medicinal plants. Life Sci 78:431–441]. Continuing discovery has also been facilitated by the recent development of new bioassay methods. These bioactive compounds are mostly plant secondary metabolites, and many naturally occurring pure compounds have become medicines, dietary supplements, and other useful commercial products. Active lead compounds can also be further modified to enhance the biological profiles and developed as clinical trial candidates. In this review, the authors will summarize research on many different useful compounds isolated or developed from plants with emphasis placed on those recently discovered by the authors' laboratories as antitumor and anti-HIV clinical trial candidates.

Keywords Bioactive plant-derived natural products · Drug discovery · Anticancer · Anti-HIV · Antimalaria

Introduction

Crude herbs have long been and continue to be the basis of many traditional medicines worldwide. In Asia, these therapies include traditional Chinese medicine (TCM), Japanese Chinese medicine (kampo), Korean Chinese medicine, jamu (Indonesia), and ayurvedic medicine (India), and in Europe, phytotherapy and homeopathy have found medicinal uses. In America, herbal therapies together with various other traditional remedies are generally classified as "alternative medicines." The combination of alternative medicine, mainly the aforementioned traditional and folk medicines used worldwide, with conventional medicine (Western medicine) is termed "integrative medicine."

Crude herbal drugs of TCM were formerly divided into three categories: upper, middle, and lower class medicines. Upper class medicines are usually not toxic, have moderate physiological effects, and are often used to maintain good health. Thus, they are sometimes called supplementary drugs. Both upper and middle class medicines are used as therapeutic drugs, but the latter medicines are more toxic than the former. Lower class medicines can contain very toxic substances, and must therefore be used with caution as medicines. TCM relies on close observation and unique principles [1] to generate herbal prescriptions that often contain herbs from all three categories. The centuries-long legacy of TCM provides rich information for modern research in drug discovery.

Anticancer and antitumor compounds

Both sample sources and bioassay screening systems are highly important to the development of novel, clinically useful anticancer agents.

Regarding screening methods, two bioassay types have mostly been used: cell-based and mechanism of action (MOA)-based. The initial cell-based assays mainly used L1210, P388 and KB cells in preliminary screening for

Antitumor Agents 263 and Anti-AIDS Agents 74.

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antitumor activity. To discover agents active against different types of cancer, screening against a panel of human cancer cell lines was implemented. Compounds that are found to be active agents in the in vitro studies are then tested for efficacy through in vivo xenograft studies. Recent developments of new MOA-based bioassay systems aimed at particular molecular targets have also revolutionized the discovery of potential drug candidates. Important anticancer drug targets include tubulin, DNA topoisomerases I and II (topo I and topo II), cyclin-dependent kinases (CDKs), growth and transcription factors, etc.

Regarding sample sources, higher plants have provided many effective, clinically useful anticancer drugs. These compounds include *Vinca* alkaloids, *Taxus* diterpenes, *Camptotheca* alkaloids, and *Podophyllum* lignans, as well as modified related compounds. Among the extensive reviews on research in this area [2–12], reviews describing the influential discoveries of taxol (tubulin-interactive) and camptothecin (topo I-interactive) by Wall and Wani illustrate how natural products have influenced the further development of natural product-derived and synthetic entities [13–15]. Our following discussion of the discovery and development of currently important antineoplastic compounds will be organized by plant species.

Because cancer terminology has often varied, Suffness and Douros [2] suggested the following definitions to avoid confusion. Cytotoxicity is used when compounds or extracts show activity against tumor cell lines. Antitumor or antineoplastic indicates that the materials are effective in vivo in experimental systems. Anticancer refers to compounds that are active clinically against human cancer.

From *Vinca* (*Catharanthus*) species (Fig. 1)

The *Vinca* alkaloids vinblastine (**A1**) and vincristine (**A2**) are well-known anticancer drugs. Their main clinical uses are to treat Hodgkin's lymphoma and acute childhood lymphoblastic leukemia, respectively. The target of *Vinca* alkaloids is tubulin, a protein needed for cell division, and their mechanism of action is inhibition of mitosis (the process of cell division).

Vinca rosea (also known as *Catharanthus roseus*) (Apocynaceae) is the original plant source of the *Vinca* alkaloids. This species has folkloric uses in Madagascar to inhibit milk secretion and as a hypotensive agent, astringent and emetic. Other *Vinca* species are used by the native people in the West Indian Islands to lower blood sugar levels.

Other drugs have been developed as synthetic analogs of vincristine and vinblastine to be active against other tumor types or have fewer side effects. For example, Burroughs Wellcome synthesized navelvine (vinorelbine) (**A3**), which is used to treat non-small cell lung and advanced breast cancers [16]. Structurally, **A3** has a smaller (eight-membered rather than nine-membered) C ring and a dehydrated D ring compared with **A1** [17]. Eldisine (vindesine) (**A4**), another structural analog, is used to treat acute lymphoblastic leukemia, breast cancer, and malignant melanoma.

In the new generation of receptor-specific targeted chemotherapy, EC145 (**A5**), which is a folic acid conjugate of desacetyl vinblastine monohydrazide, is undergoing Phase I anticancer clinical trials [18], and vinflunine (**A6**), a bifluorinated vinolrebine derivative, is in Phase II trials against bladder and kidney cancers [19, 20].

From *Taxus* species (Fig. 2)

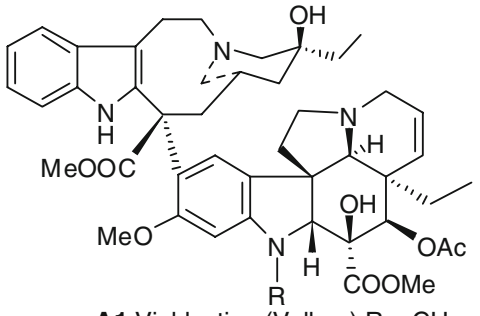
Chemotherapy of breast cancer was revolutionized by the discovery of taxol (paclitaxel) (**B1**), a taxane diterpene, by Wall and Wani from the bark of the Pacific yew tree *Taxus brevifolia* (Taxaceae) [21]. However, its antineoplastic potential could not be fully explored at first, as its source, the tree bark, was nonrenewable and severely limited its supply. An alternative renewable supply was found by the semi-synthesis of **B1** from 10-deacetylbaccatin III (**B2**), which is isolated from needles of the European yew tree. Various *Taxus* species have yielded around 400 taxoids. *Taxus* alkaloids were recently reviewed in the book *Taxus, genus Taxus*, edited by the authors of this review [22]. The biological activity and chemistry of taxoids from Japanese yew have also been reviewed [23].

B1 interacts with cellular tubulin to promote microtubule assembly and inhibit mitosis. It is now used extensively in patients with advanced and metastatic ovarian and breast tumors, particularly tumors that are refractory to standard chemotherapy. However, it is also active against brain, tongue, endometrial, and other cancers [24, 25]. The synthetic analog docetaxel (taxotere) (**B3**), also produced from the more readily available **B2**, is chiefly used against non-small cell lung cancers.

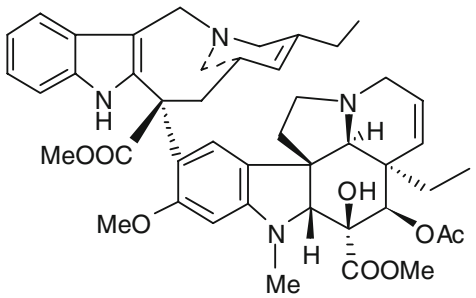
Other related antineoplastic taxane analogs have resulted from extensive structure–activity relationship (SAR) studies. For example, ortataxel (**B4**) is a promising orally administered taxoid now in Phase II clinical trials [26]. SAR studies of ring C-secotaxoids were recently published [27].

In effort to improve drug targeting or tissue distribution, taxoids have also been conjugated with various other compounds, including 3,17β-estradiol [28], various fatty acids [29], and a biodegradable polymer (poly-L-glutamic acid, paclitaxel polyglumex) [30, 31]. In the authors' laboratories, taxoids were conjugated with other anticancer agents, including epipodophyllotoxins (**B5**) [32] and camptothecin (**B6**) [33].

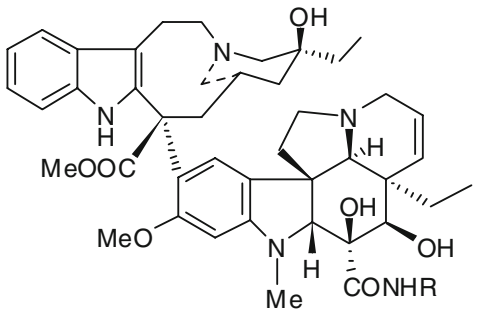
Recent overviews of various other aspects of taxoid development have been published. In one review, novel



A1 Vinblastine (Velban) R = CH_3
A2 Vincristine (Oncovin) R = CHO

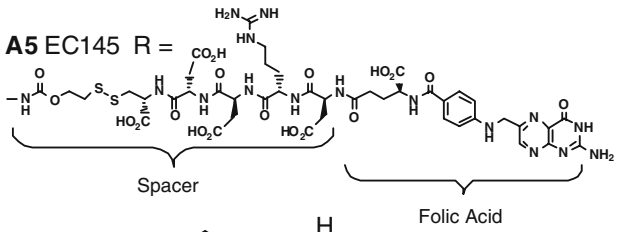


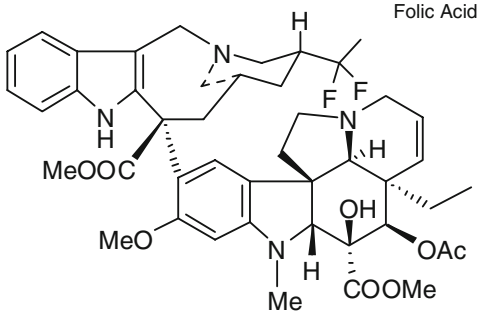
A3 Vinorelbine (Navelbine)



A4 Vindesine (Eldisine) R = H

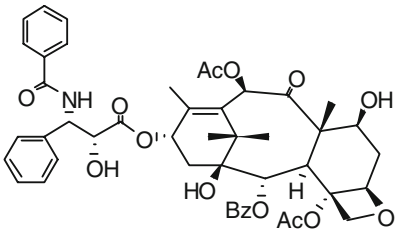
A5 EC145 R =



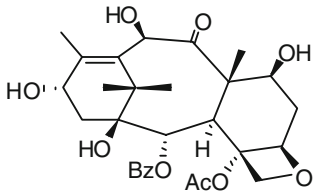


A6 Vinflunine

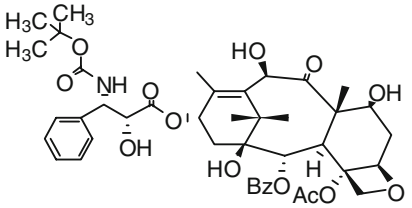
Fig. 1 Compounds from *Vinca* (*Catharanthus*) species



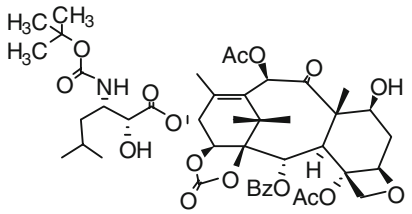
B1 Taxol (Paclitaxel)



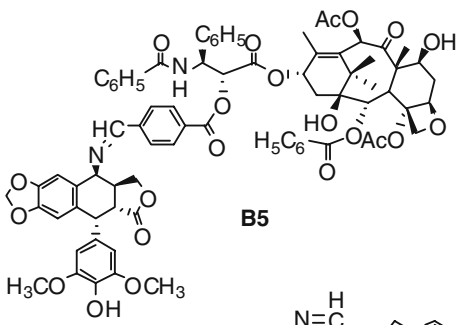
B2 10-Deacetylbaccatin III



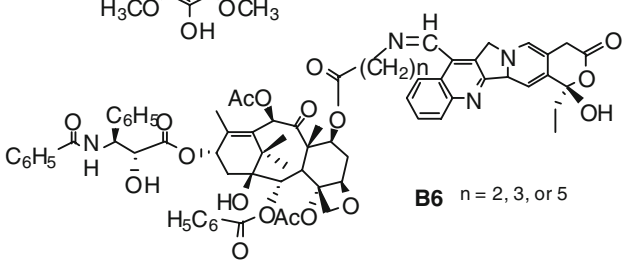
B3 Taxotere (Docetaxel)



B4 Ortataxel



B5



B6 n = 2, 3, or 5

Fig. 2 Compounds from *Taxus* species

taxane formulations, including many in clinical trials, have been studied to overcome solubility issues of **B1** and **B3** [34]. In another recent review, Kingston and Newman [35] state that **B3** is the first example of a "tunable" anticancer agent, and that it has activities beyond the known antitumor indications. An example is the use of paclitaxel-coated stents in cardiovascular therapies.

Other reports explore **B1** from the viewpoint of improved biochemical strategies and structure–activity relationships of taxoids as multidrug resistance modulators [36, 37]. Similarly, the synthesis and structure–activity relationships of taxuyunnanine C derivatives as multidrug-resistance modulators in MDR cancer cells have been reported [38].

From *Camptotheca* species (Fig. 3)

Camptothecin (CPT, **C1**) is a potent antitumor pentacyclic alkaloid isolated from Taiwanese or Chinese *Camptotheca acuminata* (Nyssaceae) [39, 40]. DNA topo I is its primary cellular target [41]. In China, the naturally occurring 10-hydroxycamtothecin (**C2**) is used to treat many cancers. This compound has a better therapeutic index than **C1**.

Because both natural products are poorly water soluble, semi-synthetic, more water-soluble analogs including topotecan (Hycamptin, **C3**) and irinotecan (Camptosar, **C4**) were developed. These two compounds are used primarily against advanced ovarian and metastatic colorectal cancers, respectively [42]. In work in the authors' laboratories, synthetic CPT analogs, such as **C5**, were found to be more active than **C1** against topo I [43], and two epipodophyllotoxin–camptothecin conjugates, **C6** and **C7**, inhibited both topo I and topo II [44]. The conjugates have also improved in vitro anticancer profiles [45] and are active against etoposide- and camptothecin-resistant KB cells (KB7D and KB/CPT 100, respectively). Combination therapy regimens have included CPT analogs as radiation sensitizers [45]. DB-67 (**C8**, a 7-silylcamptothecan or silatecan) [46] and rubitecan (**C9**, 9-nitrocamptotecin) [47] are new C1-analogs in anticancer clinical trials.

Several excellent reviews have discussed clinical applications of and perspectives on the camptothecins [48–50].

Recently, electrochemical studies of **C1** and its interaction with human serum albumin have been reported [51].

From *Podophyllum* species (Fig. 4)

Podophyllum (Berberidaceae) species, including the American *P. peltatum* L. (American mayapple) and Indian or Tibetan *P. emodi* Wall (syn. *P. hexansdrum* Royle), have long been used medicinally. In fact, podophyllin, a

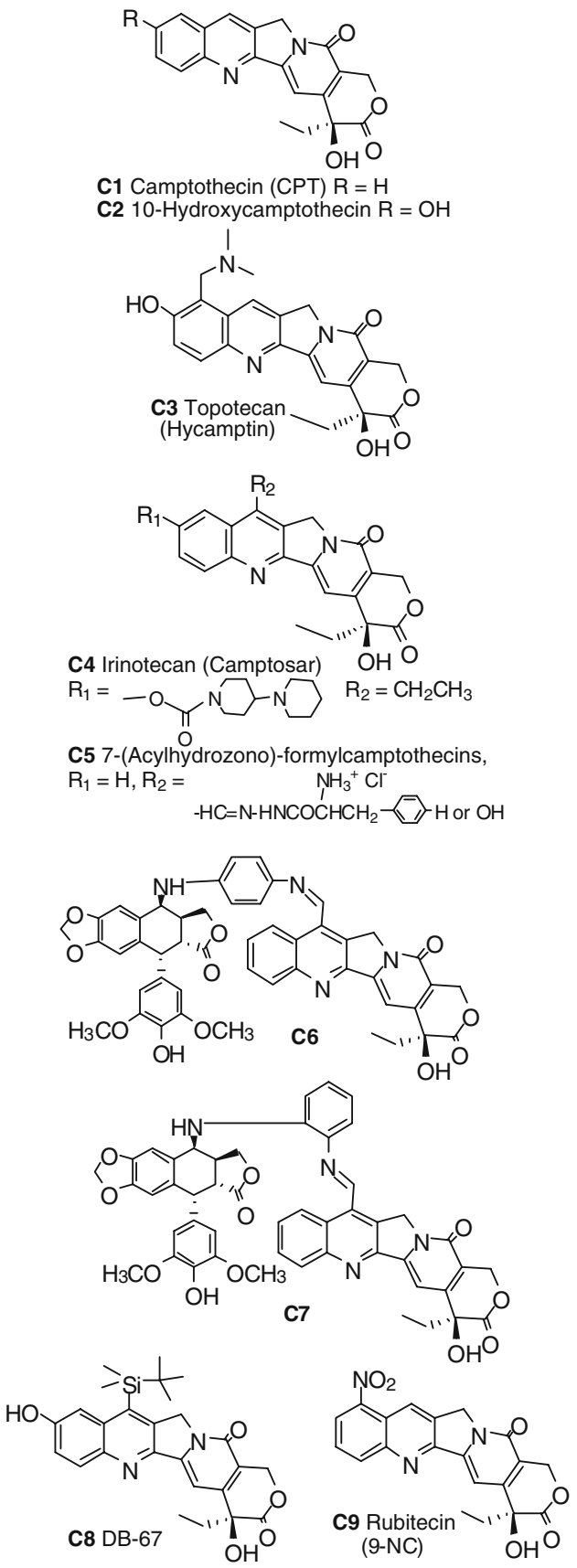
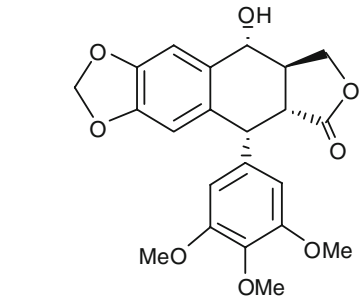


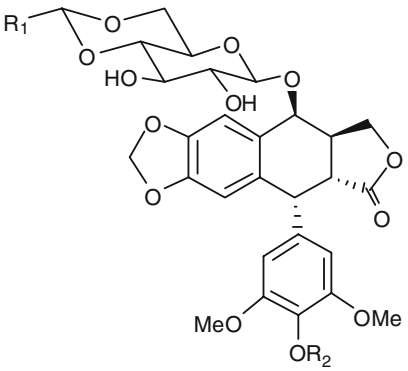
Fig. 3 Compounds from *Camptotheca* species

resin obtained from an alcoholic extract of *Podophyllum* rhizome and used to treat warts, was listed in the US Pharmacopoeia from 1820 to 1942. However, it was then removed due to undesirable toxicity [52].

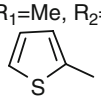
In 1880, podophyllotoxin (**D1**), an aryltetrainlactone cycloliganan with a flat, rigid five-ring skeleton, was isolated from *P. peltatum* rhizomes. Although it has antineoplastic activity, it is also extremely toxic, and thus, failed the NCI's Phase I antitumor drug clinical trials in the 1970s. However, chemical modification of **D1** led to the successful development of the clinically useful anticancer drugs etoposide (**D2**) and teniposide (**D3**). These compounds target cellular DNA topo II and are used to treat small cell lung and testicular cancers and lymphomas/leukemias. However, these compounds are poorly water soluble, which can lead to precipitation of the drug during intravenous administration. Accordingly, Etopopos (etoposide phosphate, **D4**) was developed as a clinically useful water-soluble phosphate ester of **D2**.



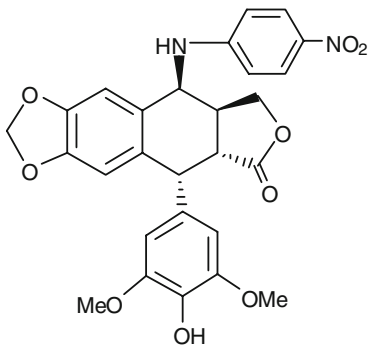
D1 Podophyllotoxin



D2 Etoposide, R_1=Me, R_2=H

D3 Teniposide, R_1 =  ,R_2 = H

D4 Etopophos, R_1 = Me, R_2 = PO_3H_2



D5 GL331

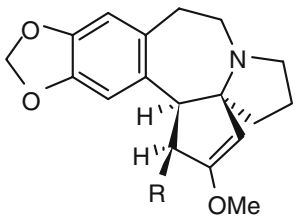
Fig. 4 Compounds from *Podophyllum* species

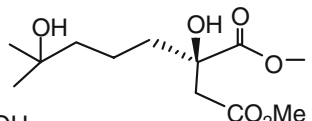
In addition to poor water solubility, limitations of **D2** include myelosuppression and drug resistance development. To improve the drug, SAR studies in the authors' laboratories led to several series of 4-alkylamino and 4-arylamino epipodophyllotoxin analogs, which showed increased inhibition of DNA topo II activity and increased cytotoxic acitivity in **D2**-resistant cell lines [53–55]. GL-331 (**D5**) [56], which contains a *p*-nitroanilino moiety at the position of **D2**, was chosen as a clinical trials candidate. **D5** is more water soluble, easier to manufacture, more active against in **D2**-resistant cell lines, and causes fewer side effects than **D2**. **D5** progressed to Phase IIa anticancer clinical trials (personal communications from Genelabs Technologies Inc. and F.V. Fossella, University of Texas M.D. Anderson Cancer Center). New computational strategies were applied in this rational design of improved **D2**-analogs [56, 57–59].

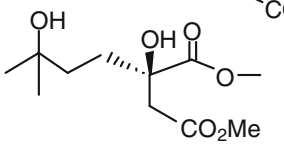
In 2004, Godaliza et al. [60] discussed the distribution, sources, application, and new cytotoxic derivatives of **D1**. Lee and Xiao [61] reviewed podophyllotoxins and related analogs, including **D5**, to demonstrate how plant natural products can be developed as successful preclinical drug candidates. Another review of **D1** has been published recently [62].

From *Cephalotaxus* species (Fig. 5)

In TCM, the bark of indigenous plants from the genus *Cephalotaxus* (Cephalotaxaceae) has long been used for



E1 Homoharringtonine R= 

E2 Harringtonine R= 

E3 Cephalotaxine, R = OH

Fig. 5 Compounds from *Cephalotaxus* species

various indications. Chinese investigators [63] discovered the antitumor properties of alkaloids from *C. fortunei* Hook., subsequent to Powell's [64–66] original isolation of the antitumor alkaloids homoharringtonine (**E1**) and harringtonine (**E2**). The Chinese evergreen tree *C. harringtonia* K. Koch var. *harringtonia* was also found to contain **E1** [67], and various *Cephalotaxus* species yielded other related active alkaloids [68, 69]. However, cephalotaxine (**E3**), the parent compound, does not show antitumor activity.

Although **E1** has reached Phase I/II clinical trials against myeloid leukemia in the US [70, 71], its severe side effects still remain problematic. Accordingly, the authors have continued to study new natural products from *Cephalotaxus* species and develop new analogs on the basis of SAR studies, as reviewed by Itokawa et al. [72].

From *Colchicum* species (Fig. 6)

The medicinal plant *Colchicum autumnale* L. (Liliaceae) contains the bioactive alkaloid colchicine (**F1**). **F1** and its close natural analog thiocolchicine (**F2**) (SCH_3 rather than OCH_3 at C-10) inhibit the polymerization of tubulin [73] and consequently inhibit mitosis. Both compounds show antileukemic activity, but are too toxic to use as anticancer agents, although **F1** is still used to treat gout and familial Mediterranean fever.

In SAR studies in the authors' laboratories, the C-7 acetamide group on ring B was replaced with various oxygen-containing groups [ketone (**F3**, thiocolchicone), hydroxy (**F4**), and ester (**F5**, **F6**)] [74]. These compounds were equally or more active in vitro than **F2**. In addition, colchinol-7-one thiomethyl ether or allo-ketone (**F7**), which has a six-membered ring C, was equipotent with the seven-membered-ring natural product **F1**. Three related ring-contracted colchicinoids (**F8–F10**) showed significant activity against drug-sensitive and -resistant KB cell lines [75].

Removing one or two of the methyl groups from the three ring A phenolic groups reduces tubulin/mitotic inhibition; thus, three methylated phenolic groups, as found in **F1–F10**, are needed for full potency. If all three methyl groups are removed, the resulting tri-demethylated colchicines and thiocolchicines (**F11–F14**) no longer interact with tubulin but instead inhibit DNA topo II [76]. They also are active in vitro against bone and breast cancers [77].

From *Salvia* species (*S. miltiorrhiza*) (Fig. 7)

In China, the roots and rhizome of *Salvia miltiorrhiza* (called Tanshen) have been widely used to treat cardiac and vascular disorders such as atherosclerosis or blood clotting abnormalities. Hemorrhage, dysmenorrhea, miscarriage,

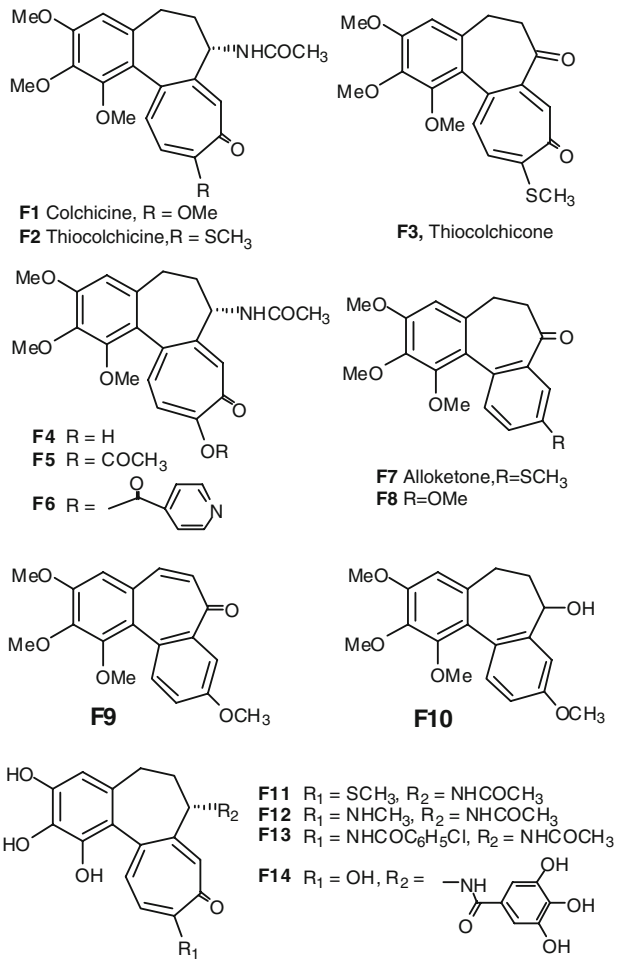


Fig. 6 Compounds from *Colchicum* species

swelling, inflammation, chronic hepatitis, and insomnia are also treated with Tanshen [78, 79]. Because this plant exhibits hypotensive effects, causes coronary artery vasodilation, and inhibits platelet aggregation, it should not be used in combination with warfarin. Clinically available preparations of a *S. miltiorrhiza*/*Dalbergia* mixture may show promise in the treatment of angina [80].

Salvia miltiorrhiza contains bioactive tanshinone diterpenoids, including tanshinone I (**G1**) and tanshinone IIA (**G2**) [81]. Sodium tanshinone sulfate (**G3**), a water-soluble derivative of **G2**, exhibits strong membrane-stabilizing effects on red blood corpuscles, and accordingly is used clinically to treat angina pectoris and myocardial infarction. *S. miltiorrhiza* also contains novel seco-abietane rearranged diterpenoids [82].

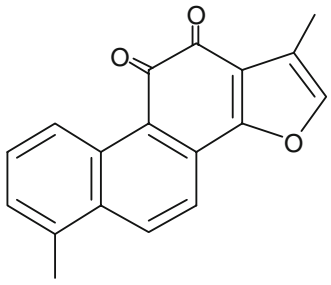
In addition to effects on the heart and blood vessels, *S. miltiorrhiza* shows cytotoxic activity, and strongly inhibits proliferation of liver cancer cells [83]. SAR studies with tanshinones have assayed effects against several human tumor cells, namely nasopharyngeal (KB), cervical (Hela), colon (colon-205), and laryngeal (Hep-2) [78, 79].

Salvia miltiorrhiza and Tanshen also contain neo-tanshinlactone (**G4**), a compound with a very unique and different structure compared with other compounds from this plant. In studies in the authors' laboratories, **G4** first showed unique specific activity against the MCF-7 breast cancer cell line, but insignificant activity against other cell lines in a tested panel. In additional studies, it was quite active against estrogen receptor positive (ER+) human breast cancer cell lines (MCF-7 and ZR-75-1), but inactive against ER negative (ER-) human breast cancer lines (MDA MB-231 and HS 587-T) [84]. Because more than 60% of breast cancer cases in postmenopausal women are ER+, this finding was quite significant. **G4** was 10-fold more potent and 20-fold more selective than the breast cancer drug tamoxifen against two ER+ cell lines. It was also potent against an ER− cell line that overexpresses HER2+, a key protein in regulating cell growth, which affects 25–30% of breast cancer patients [84]. Therefore, **G4** is an excellent candidate for further development toward anti-breast cancer clinical trials. More recent synthetic analog studies have ascertained certain structural features that are critical to the anticancer activity of this compound class and identified a compound (**G5**) with comparable or better anticancer activity [85].

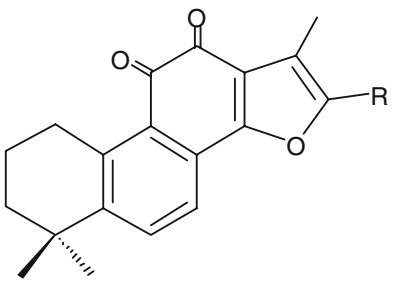
These new developments in the chemistry and biology of the bioactive constituents of Tanshen have recently been reviewed [86].

From *Brucea* species (Fig. 8)

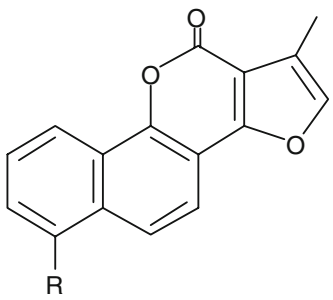
The tree *Brucea antidysenterica* (Simaroubaceae) is used in Ethiopia to treat cancer, and Kupchan et al. [87] identified the quassinoid bruceantin (**H1**) as the active principle. In the early 1970s, **H1** and related quassinoids



G1 Tanshinone I

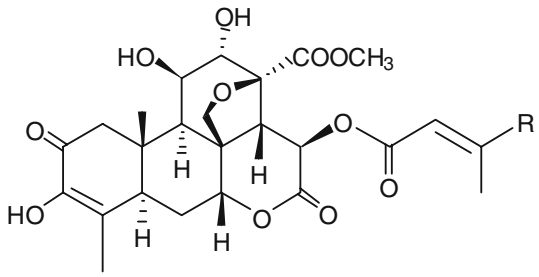


G2 Tanshinone II-A, R=H
G3 Sodiumtanshinone II-A sulfonate, R = SO_3Na

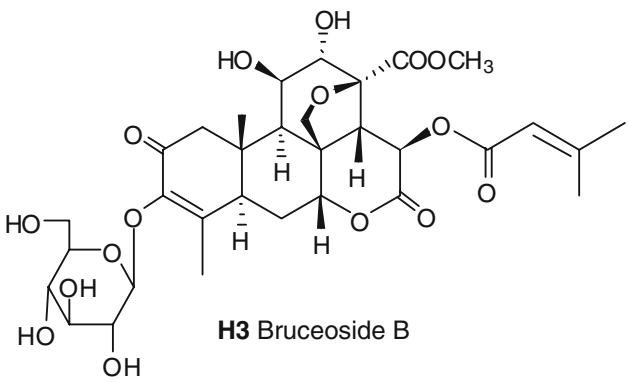


G4 Neo-tanshinlactone, R=CH_3
G5 R=CH_2CH_3

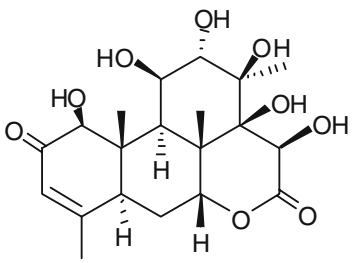
Fig. 7 Compounds from *Salvia* species



H1 Bruceantin, R = CH $(CH_3)_2$
H2 Brusatol, R = CH_3



H3 Bruceoside B



H4 Yadanziolide S

Fig. 8 Compounds from *Brucea* species

showed activity against various cancer cell types, particularly leukemic cells. However, in subsequent Phase I and II clinical trials, no objective tumor regressions were observed and clinical development was halted.

Recently, **H1** has been re-investigated in various leukemia, lymphoma, and myeloma cell lines, and also in animals where it induced regression in both early and advanced tumors. These new results indicate that **H1** still merits investigation for clinical efficacy against hematological malignancies [88].

Other quassinoids [e.g., brusatol (**H2**)] and quassinoid glycosides [e.g., bruceoside B (**H3**)] from *B. javanica* have been studied extensively for antitumor [89–92] and cancer chemopreventive [93] effects. A recent review of biologically active quassinoids discussed their potential for drug design [94].

In 2002, a new quassinoid, yadanziolide S (**H4**), and ten known compounds were isolated from the seeds of *B. javanica* [95]. Compound **H4** is tetracyclic rather than pentacyclic, and it is the first quassinoid isolated from this plant that does not have an additional oxygenated ring. All isolated compounds were tested for anticancer activity in human leukemia (HL-60) cell differentiation and in a mouse mammary model.

From *Euphorbia* species (Fig. 9)

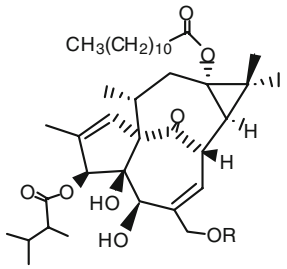
In China, the dried roots of *Euphorbia kansui* (Euphorbiaceae) are known as "kansui" and classified as a "lower class" medicine. This herbal remedy is used in China to treat ascites (abdominal fluid accumulation) and cancer.

Ingenol diterpenoids from this plant show various bioactivities. Kansuiphorins A–D (**I1**–**I4**) were isolated as cytotoxic principles by the authors' laboratories [96, 97]. **I1** and **I2** showed significant potency activity against P-388 leukemia in mice [98]. DBDI (**I5**), a related ingenol-type diterpene, uniquely suppressed mast cell activation, which is an inflammatory process. Thus, this compound might be used to treat allergic diseases [99]. In addition, two ingenols isolated from an immuno-enhancing *E. kansui* extract increased immune activity in a dose-dependent manner [100].

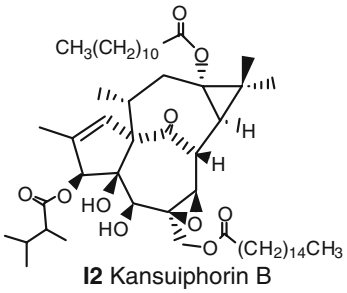
The species *E. ebracteolata* yielded three new cytotoxic diterpenoids, yuexiandajisus D–F (**I6**–**I8**) [101], with **I6** showing moderate cytotoxicity against HCT-8 and Bel-7402 cell lines [102]. *Euphorbia lagascae* is the source of the new macrocyclic lathyrane diterpenes latilagascens A–C (**I9**-**I11**), which inhibit replication of multidrug-resistant tumor cells [102].

From *Rubia* species (Fig. 10)

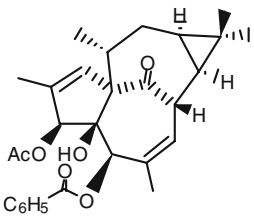
Rubiae Radix is a common Rubiaceous plant, found as *Rubia akane* in Japan, *R. cordifolia* in China and *R. tinctorum* in Europe. The former two show antineoplastic activity, but the latter does not. The cytotoxic active principles were named RAs named after *R. akane*. Sixteen RA series, from RA-I to RA-XVI, were isolated from *R. akane* and *R. cordifolia* [103–107].



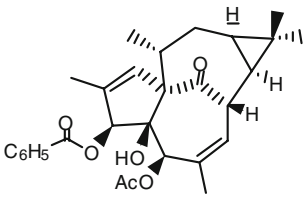
I1 Kansuiphorin A,R = $CO(CH_2)_{14}CH_3$
I5 DBDI, R = H



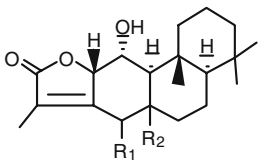
I2 Kansuiphorin B



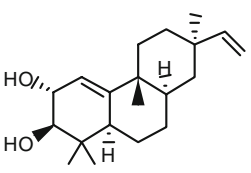
I3 Kansuiphorin C



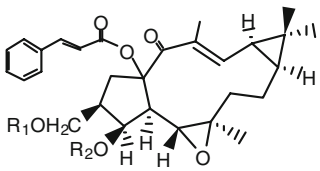
I4 Kansuiphorin D



I6 Yuexiandajisu D, R_1 = β-OH, R_2 = α-OH
I7 Yuexiandajisu E, R_1 = α-OH, R_2 = β-OH

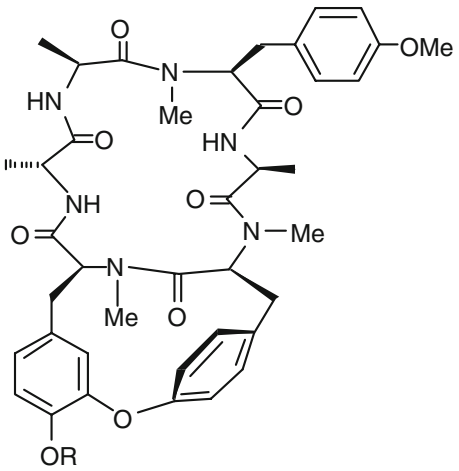


I8 Yuexiandajisu F

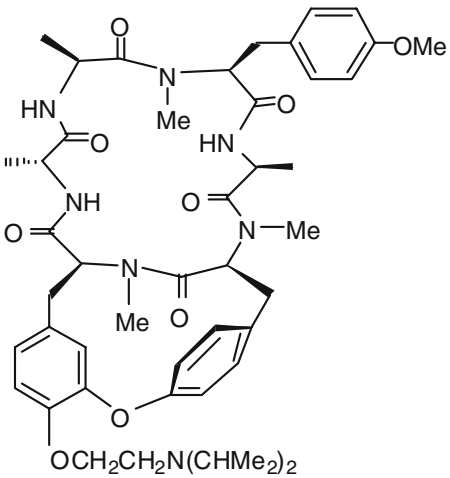


I9 R_1 = Ac, R_2 = H
I10 R_1 = R = H
I11 R_1 = R_2 = Ac

Fig. 9 Compounds from *Euphorbia* species



J1 RA-VII, R = Me
J2 RA-V, R = H



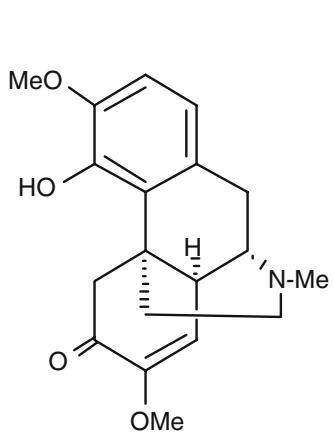
J3 TI-356

Fig. 10 Compounds from *Rubia* species

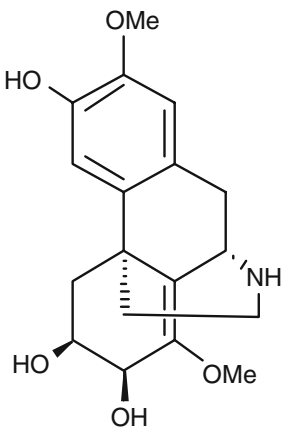
Among them, RA-VII (**J1**) showed the greatest potency against KB, P388 lymphocytic leukemia, and MM2 mammary carcinoma cells. RA-V (**J2**) possesses a reactive phenolic hydroxyl group on the Tyr-6 residue, and its modification has been extensively studied by introducing many different alkyl and acyl groups at this position. Analogs that had longer alkyl or acyl groups retained potent antitumor activity, with the *n*-hexyl derivatives showing the strongest in vitro activity [108–110]. In continuing modification studies [103–107], the synthetic TI-356 (**J-3**) was developed as a more potent compound [106, 107]. Hitotsuyanagi et al. also synthesized glycine-containing analogs of RA-VII [111–114].

From *Cocculus trilobus* (Fig. 11)

Cocculus trilobus DC. (Menispermaceae) is used as a diuretic, analgesic, and anti-inflammatory folkloric drug in East Asia. Cytotoxicity-guided isolation yielded sinococculine (**K1**) as an antitumor principle from the stems and rhizomes [115]. This compound is active in vitro against P388 leukemia, but is most likely a general cytotoxic rather a cell-specific agent [116]. Isosinococuline (**K2**), isolated from the same plant, also shows cytotoxic activity [117].



K1 Sinococuline



K2 Isosinococuline

Fig. 11 Compounds from *Cocculus trilobus*

From *Curcuma* (turmeric) species (Fig. 12)

Curcuma species (Zingiberaceae) have folkloric uses in India to treat biliary disorders, anorexia, cough, diabetic wounds, liver disorders, rheumatism, and sinusitis, and in China for abdominal pain and jaundice. Turmeric stimulates bile secretion in animals and has a protective effect on the liver.

However, this herb is most well known as a main ingredient of curry powder. It gives color and flavor to food and has aromatic, stimulant, and carminative properties. The yellow phenolic diarylheptanoid curcumin (**L1**) is the major pigment in the turmeric rhizome.

Pharmacologically, **L1** shows potent anti-oxidative and anti-inflammatory effects, cytotoxicity against tumor cells, and antitumor-promoting activity [118]. These effects and targets as well as possible roles for **L1** in cancer prevention and therapy have been recently reviewed [119, 120].

In the authors' laboratories, several synthetic curcumin analogs, including **L2**, showed potent antiandrogenic activities against PC-3 and DU-145 human prostate cancer cell lines [121], and subsequently showed anti-prostate cancer activity superior to that of hydroxyflutamide, the currently available and preferred anti-androgen for treating prostate cancer [122]. From additional anti-androgenic studies, dimethoxy-4-ethoxycarbonylethylenyl-curcumin (**L3**) has emerged as a promising prostate cancer drug candidate [123, 124]. This work on the design and

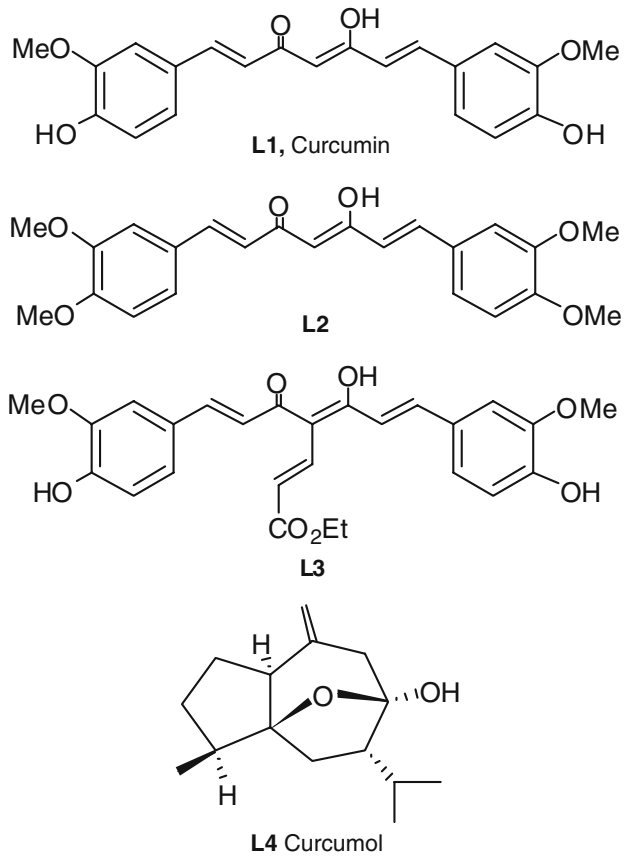


Fig. 12 Compounds from *Curcuma* (turmeric) species

development of curcumin analogs as prostate cancer agents has been reviewed recently [125].

In addition, curcumol (**L4**), a sesquiterpene obtained from *C. aromatica*, was effective against cervical cancer [4].

From *Maytenus* species (Fig. 13)

In South America, *Maytenus illicifolia* Mart ex Reiss. (Celastraceae), more commonly known as "Cangorosa," is used for its analgesic, antipyretic, antiseptic, and anticancer properties. In Paraguay, it is also used for birth control. *M. illicifolia* is the source of cytotoxic triterpenes, including pristimerin (**M1**) and isotingenone III (**M2**) [126], triterpene dimers dihydroisocangorosin A (**M3**) and cangorosin B (**M4**) [127, 128], and other new compounds [129].

Other *Maytenus* species have yielded compounds with various biological properties. The African plant *M. ovatus* (later renamed *M. serrata*) yielded the antileukemic maytansinoids [e.g., maytansine (**M5**)] [130, 131]. This compound progressed to Phase II clinical trials, but testing was suspended due neurotoxic side effects. *M. diversifolia* contains the related maytanprine (**M6**), which shows growth-inhibiting and apoptosis-inducing activities in

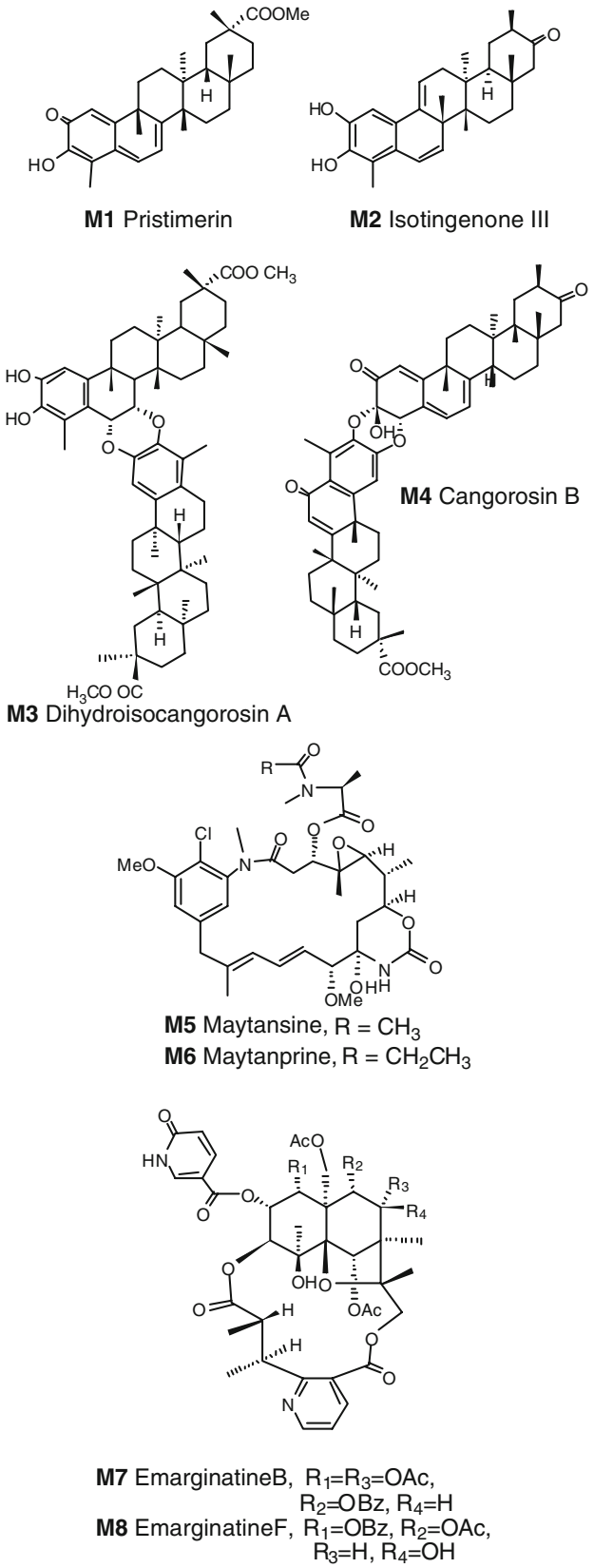


Fig. 13 Compounds from *Maytenus* species

K562 leukemia cells [132]. The authors also identified cytotoxic sesquiterpene pyridine alkaloids, including emargintines B (**M7**) and F (**M8**), from *M. emarginata* [133, 134]. Recently, *M. chuchuhuasca* yielded new triterpenes [135] and sesquiterpenes [136], and antitumor promoting sesquiterpenes were also isolated from *M. cuzooina* [137].

Anti-HIV compounds

The human immunodeficiency virus (HIV) is the causative agent of acquired immunodeficiency syndrome (AIDS), a degenerative disease of the immune system that results in life-threatening opportunistic infections and malignancies. Natural products with antiviral and immunomodulating effects are viewed as possible sources of new compounds to inhibit HIV and treat AIDS [138].

From *Lomatium suksdorfii* (coumarin derivatives) (Fig. 14)

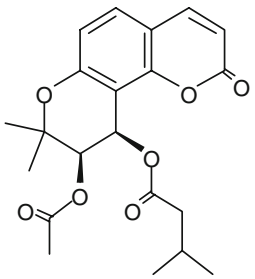
BDF1 of *Lomatium suksdorfii* (Apiaceae) yielded suksdorfin (**N1**), a dihydroseselin-type angular pyranocoumarin, as a lead anti-HIV natural product [139]. SAR studies then yielded the more potent lead compound 3′R,4′R-di-*O*-(−)-camphanoyl-(+)-*cis*-khellactone (DCK) (**N2**), which has two camphanoyl esters rather than the acetate and isovaleroyl esters found in **N1** [140]. Additional synthetic modification yielded 4-methyl DCK (**N3**) then 3-hydroxymethyl-4-methyl DCK (**N4**). **N4** has been selected as a clinical trial candidate [141].

Dihydropyrano[2,3-f]chromones are positional isomers of khellactones. The carbonyl is at position 4 in the former compound class, rather than at position 2 in the latter class. 3′R, 4′R-di-*O*-(−)-camphanoyl-2′,2′-dimethyldihydropyrano[2,3-f]chromone (DCP) (**N5**), and other DCP analogs are active against drug-resistant HIV strains, while DCK analogs are not. 2-Ethyl DCP (**N6**), with an ethyl group at the 2 position of DCP, is less cytotoxic, making it the most likely clinical trials candidate in the DCP series thus far [141, 142].

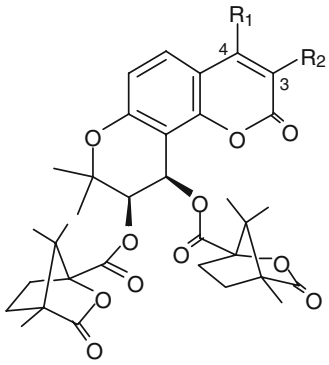
DCK and DCP compounds inhibit HIV reverse transcriptase (RT), but at a later step than that affected by AZT and other clinically approved RT inhibitors. The novel mechanism of action of DCK and DCP compounds (known as strand transfer inhibitors) in comparison to current drugs merits further investigation of their possible usefulness in the treatment of AIDS [143].

From *Syzigium claviflorum* (triterpene, betulinic acid derivatives) (Fig. 15)

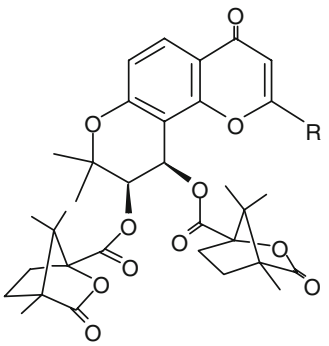
Syzigium claviflorum (Myrtaceae) is the plant source of two naturally occurring anti-HIV lupane triterpenes, betulinic



N1 Suksdorfin



N2 DCK,R_1=R_2=H
N3 4-MethylDCK,R_1=Me,R_2=H
N4 3-Hydroxymethyl-4-methylDCK,R_1=Me,R_2=CH_2OH



N5 DCP,R=H
N6 2-EthylDCP,R=CH_2CH_3

Fig. 14 Compounds from *Lomatium suksdorfii* (coumarin derivatives)

acid (**O1**) and platanic acid (**O2**) [144, 145]. SAR studies produced dimethyl succinyl betulinic acid (DSB, **O3**), which has successfully progressed to anti-AIDS clinical trials [146, 147]. To date, **O3** has completed seven clinical trials in over 300 patients (noninfected and infected).

O3 disrupts the late stage viral maturation processes of HIV, making it unlike any currently approved anti-AIDS drug. The viral core structure of new HIV particles produced from infected DSB-treated cells is defective and noninfectious [148]. **O3** is the first in a new class of anti-AIDS drugs with a novel target of viral maturation.

O3 was discovered in the author's Natural Products Research Laboratories (NPRL) [146]. It has been licensed and is being developed as a drug by Panacos

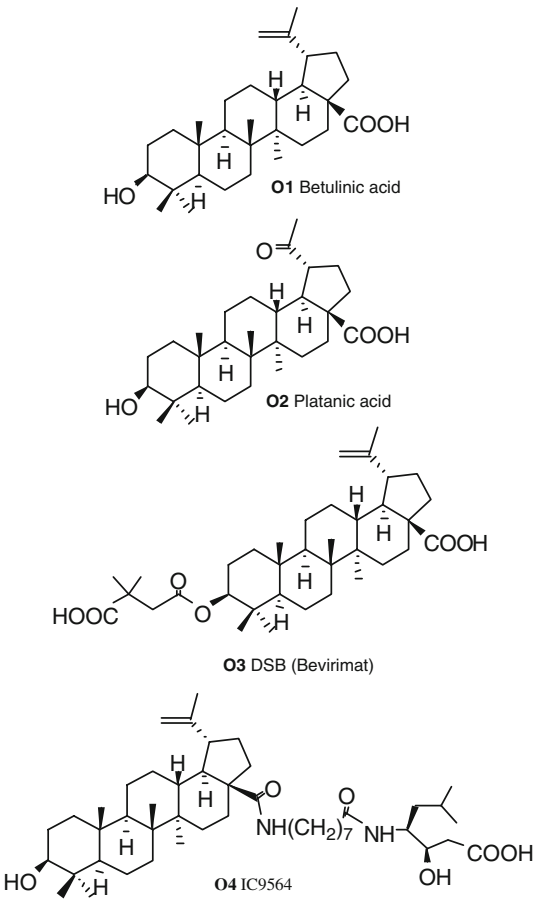


Fig. 15 Compounds from *Syzigium claviflorum* (triterpene derivatives)

Pharmaceuticals. It is the company's lead antiviral product and is now known as Bevirimat. Details on its clinical progress thus far are given below.

Two Phase I studies and a Phase I/II study of **O3** were completed during 2004. The drug was well tolerated and showed good anti-HIV levels in the body. It also showed activity in HIV-infected patients and significantly reduced viral blood levels (known as viral load) [information from the results of the Phase IIa study presented as an oral late breaker presentation at the 45th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, 16–19 Dec 2005, and from Triangle Business Journal 9 Sept 2005]. Based on these good results, **O3** was given Fast Track Status by the US Food and Drug Administration (FDA) in 2004. In a Phase IIa study, **O3** reduced viral load significantly (median reduction at a 200 mg dose was 91% decrease compared to placebo on day 11 after complete dosing) and showed antiviral potency with once-a-day oral dosing for 10 days in HIV-infected subjects not on other antiretroviral therapy. **O3** was well tolerated with only mild or moderate side effects without dose-limiting toxicity [information from the results of the Phase IIa study presented as an oral late breaker presentation at the 45th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, 16–19 Dec 2005, and from Triangle Business Journal 9 Sept 2005]. **O3** was also successfully administered in tablet form rather than by oral solution. When **O3** was administered together with the approved HIV drugs ritonavir and atazanavir, no significant adverse drug–drug interactions were seen, making it suitable for combination therapy (information provided by Panacos Inc.). Phase IIb clinical trials, which began in 2006, are still ongoing. An optimal dose of **O3** will be determined in these randomized, blinded, and placebo-controlled trials in HIV-infected patients failing current therapy (information provided by Panacos Inc.). Phase III clinical trials are targeted for 2007/2008, and will be performed with combination therapy in a total of 300–500 patients at commercial dose. The target for the New Drug Application (NDA) is 2008/2009 (information provided by Panacos Inc.). Panacos continues to mark **O3** as a leading new treatment for AIDS based on its excellent progress in clinical trials.

In summary, **O3** significantly reduced viral load, has a strong safety profile (with no evidence of organ toxicity or clinical intolerance), and shows no evidence of rapid resistance development, which is a primary cause of antiretroviral treatment failure [149, 150]. Recently, studies on DSB have been reviewed [151], together with IC9564 (**O4**), a new related active betulinic acid derivative [152].

Antimalarial compounds

From *Artemisia annua* (Qinghao, artemisinin derivatives) (Fig. 16)

The dried aerial parts of the herb *Artemisia annua* (Asteraceae) have been used in China for centuries to treat fever and malaria. The name of this Chinese prescription is Qinghau (sweet wormwood), and the active principle is artemisinin (**P1**) (Qing Hao Su) [153]. This clinically effective antimalarial compound rapidly kills *Plasmodium falciparum*, the malaria parasites, without being harming humans or animals [154, 155]. The novel endo-peroxide linkage in **P1** is needed for its antimalarial activity.

The synthetic derivatives artemether (**P2**) and arteether (**P3**) are widely used in malaria-prone regions, particularly India [156], and the World Health Organization lists artemether and sodium artesunate (a hemisuccinate derivative of dihydroartemisinin) (**P4**) in its Model List of Essential Medicines [157].

Other analogs, including ones from the authors' laboratory, have been synthesized [158]. OZ-277 (**P5**, also known as RBx11160) [159] has progressed to Phase II

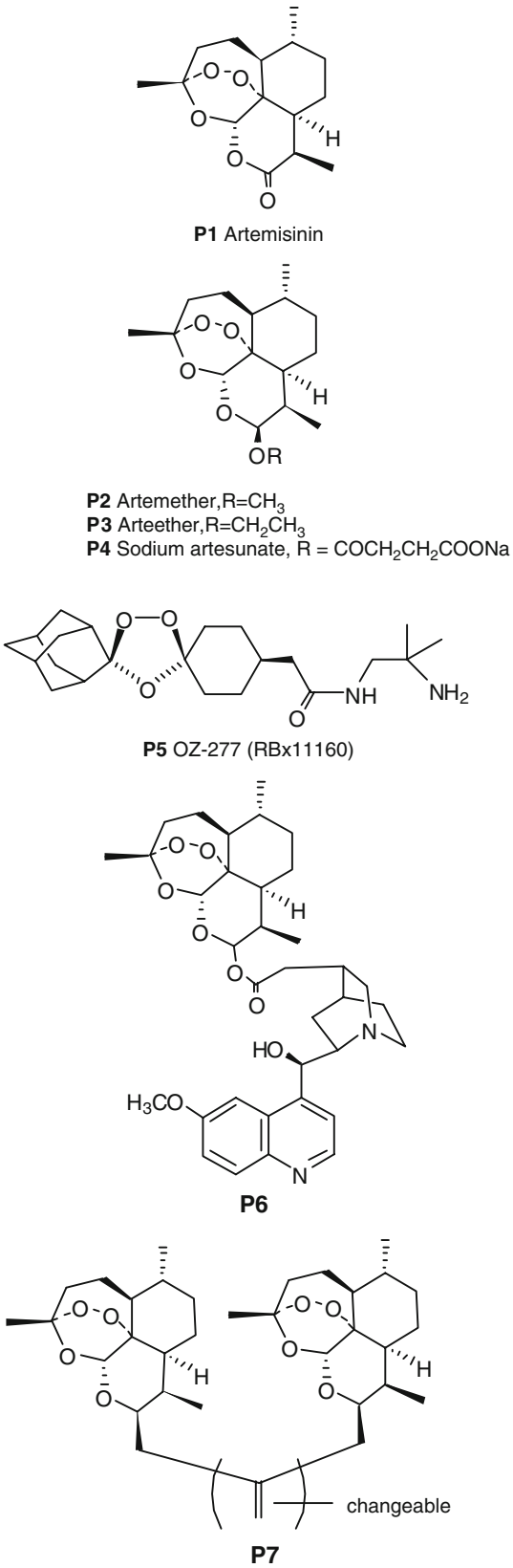


Fig. 16 Compounds from *Artemisia annua* (Qinghao, artemisinin derivatives)

clinical trials in India, Thailand, and Africa. Modification and pharmacological studies of this synthetic trioxolane are ongoing [160–162]. Moreover, a novel artemisinin–quinine hybrid (**P6**) was reported to have potent antimalarial activity [163]. Posner et al. [164] reported a new generation of trioxane dimers (**P7**), designed logically and prepared easily from the natural trioxane **P1**.

A recent review discusses artemisinin and related antimalarials [165].

Conclusion

As discussed in this review, plants are good sources for the discovery of potential medicines. Natural products and their analogs can be developed into useful drug candidates by the processes of highly efficient bioactivity-directed fractionation and isolation followed by analog synthesis through modern medicinal chemistry-based molecular modification. Continual improvements in bioassay technology coupled with the discovery of new biological targets will also benefit the drug discovery process. Thus, medicinal plants have long been appreciated for treating illness, and continue to be one of the best and most effective sources used to develop new plant-derived compounds as clinical candidates for new world-class medicines.

Acknowledgments We wish to thank Drs. K. Takeya and Y. Hitotsuyanagi of the Tokyo University of Pharmacy and Life Science, Dr. H. Morita of Hoshi Pharmaceutical University, Dr. O. Shirota of Tokushima Bunri University, and Dr. I. Takano of the Tokyo Metropolitan Institute of Public Health for their valuable contributions to some of this research. This investigation was supported by grants from the National Cancer Institute, NIH (CA-17625) and the National Institute of Allergy and Infectious Diseases, NIH (AI-33066), awarded to K.H. Lee.

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