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# Discovery of new anticancer agents from higher plants

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## 1. ABSTRACT

Small organic molecules derived from higher plants have been one of the mainstays of cancer chemotherapy for approximately the past half a century. In the present review, selected single chemical entity natural products of plant origin and their semi-synthetic derivatives currently in clinical trials are featured as examples of new cancer chemotherapeutic drug candidates. Several more recently isolated compounds obtained from plants showing promising *in vivo* biological activity are also discussed in terms of their potential as anticancer agents, with many of these obtained from species that grow in tropical regions. Since extracts of only a relatively small proportion of the ca. 300,000 higher plants on earth have been screened biologically to date, bioactive compounds from plants should play an important role in future anticancer drug discovery efforts.

## 2. INTRODUCTION

Natural products are generally defined as small-molecule secondary metabolites that originate from marine organisms, microorganisms, and plants. They occur as distinctive chemical types in taxonomically different organisms, for which they serve multiple biological functions related to organism survival. These naturally derived substances exhibit considerable structural diversity, and tend to adopt the preferred conformation and necessary steric complexity to exert varied activities in biological test systems. When compared with synthetic organic compounds as a whole, natural product molecules typically have more chiral centers, less hetero atoms, less heavy atoms, and more varied ring systems. Overall, natural products are generally regarded as possessing "drug-like" pharmacological qualities and "biologically friendly" molecular properties (1-3). These attributes make natural

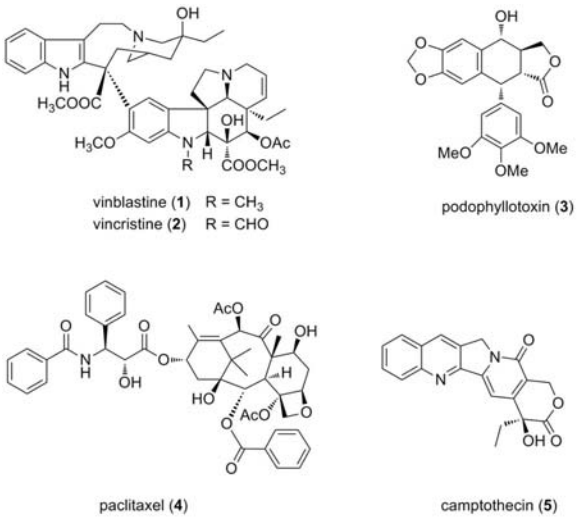



**Figure 1.** Structures of plant-derived compounds used as cancer chemotherapeutic agents.

products an invaluable resource of chemical diversity and hence they have acted as excellent lead compounds for optimization by synthetic organic chemistry methods in anticancer agent discovery.

Natural products have proved to be very useful in anticancer chemotherapy drug development over last five decades, particularly those derived from terrestrial microbes and higher plants. An important review of the anticancer drugs introduced to the market in North America, western Europe, and Japan since the 1940s has indicated that some 47% of a total of the 155 anticancer drugs approved up to 2006 were either natural products or directly derived from natural product lead compounds by semi-synthesis (4). However, a reduced emphasis on natural products in terms of new drug development has become evident by large pharmaceutical companies during approximately the last 20 years (5-7). One of the major reasons underlying this decline is that the pharmaceutical industry has largely changed its strategy of drug discovery to the rapid high-throughput screening of molecular target-based pure compound chemical libraries, which have been generated particularly using combinatorial chemistry. Also, it is considered too time-consuming and labor-intensive to perform bioassay-guided isolation of natural products from crude extracts. Moreover, there is a tendency when screening natural product samples to rediscover bioactive compounds of already known structure. However, in recent years, new technologies have been developed to enhance natural product drug discovery in an industrial setting, including streamlined screening procedures and enhanced organism sourcing mechanisms (5-7). These changes actually bode well for the additional inclusion of natural product samples in anticancer drug discovery in the future. Indeed, several new anticancer agents of natural origin have been introduced to the market recently (8), and there is a promising pipeline of natural products in oncology-related clinical trials from various types of organisms (9-11).

The approved plant-derived oncology cancer chemotherapeutic agents used clinically in the United States may be structurally classified into four major groups: the vinca alkaloids, the epipodophyllotoxin lignans, the taxane diterpenoids, and the camptothecin quinoline alkaloid derivatives (Figure 1). The discoveries of the five antineoplastic lead compounds: vinblastine (vincaleukoblastine, **1**) (12, 13), vincristine (leurocristine, **2**) (13, 14), podophyllotoxin (**3**) (15) paclitaxel (taxol, **4**) (16), and camptothecin (**5**) (17), represent significant contributions to natural products isolation accomplished by pioneering natural product chemists, and these have all led subsequently to considerable advances in cancer chemotherapy. These compounds have been found to act on two important biochemical targets, tubulin and topoisomerase. According to our present knowledge, vinca alkaloids and taxanes both target cellular microtubulin, but they lead to cancer cell death through different specific mechanisms. Thus, vinca alkaloids such as vinblastine and vincristine bind to the microtubulin "vinca domain" site in the β-subunit, and disrupt the assembly of microtubules in mitosis (18), while paclitaxel acts as a microtubule stabilizer, by binding to the taxane site, and, as a result, interfering with the normal breakdown of microtubules during cell division (18, 19). Camptothecin and its clinically used analogues, irinotecan and topotecan, arrest the cell cycle at the S-phase by inhibiting the activity of topoisomerase I, leading to the inhibition of DNA replication and transcription (20, 21). Podophyllotoxin binds to tubulin and interferes with the formation of spindles in mitosis (22). In contrast, the two clinically used derivatives of podophyllotoxin, etoposide, and teniposide are topoisomerase II inhibitors, which arrest the cell cycle in the metaphase by stabilizing the covalent DNA-enzyme cleavable complex, and inducing topoisomerase II-mediated DNA breakage (22). Since there is already much published information on the above-mentioned four classes of plant-derived anticancer compounds (e.g., 23-25), these agents will not be further discussed in the present review.

Much of the progress in discovering and developing natural product drugs for the oncology market has been made by pharmaceutical and biotechnology companies. There has also been a long-standing commitment to this same end by the U.S. National Cancer Institute (NCI). Through the use of extramural and intramural funding mechanisms, the NCI has focused on the extensive collection and biological screening of extracts from plants and other organisms for their potential anticancer activity. The NCI has also played an important role in terms of antineoplastic drug development (26-29). During the period 1960 to 2004, some 174,000 plant samples were collected, including many from tropical regions, and these were screened through a systematic combination of *in vitro* and *in vivo* screens (25-27). In this process, extracts of small-scale plant samples were subjected to a standard solvent extraction protocol. Initially, the extracts were evaluated against a three cell-line panel, inclusive of MCF-7 breast, NCI-H460 lung, and SF-268 CNS cancer cells, with active samples then tested against a 60-cell line panel derived from leukemia and eight solid tumors including breast cancer, CNS tumor, colon cancer, non-small cell lung cancer, postage cancer, renal cell cancer and ovarian cancer (25-27). Compounds of interest are then

evaluated in the *in vivo* hollow fiber assay, a rapid and economic murine model developed at NCI in order to prioritize candidate compounds for possible further *in vivo* testing. In this assay, human cancer cells are grown within fibers that are implanted at subcutaneous or intraperitoneal sites in immunodeficient mice (30, 31). Further *in vivo* evaluation in murine xenograft systems is conducted for compounds deemed active in the *in vivo* hollow fiber assay (25-27).

In the following paragraphs of this review, a number of selected plant-derived antineoplastic single chemical entities currently under clinical trials as oncology drug candidates, and several promising lead compounds purified from plants, will be discussed in term of their plant origin, modes of action, as well as their potential use as anticancer agents.

## 3. SELECTED ANTINEOPLASTIC PLANT-DERIVED SINGLE CHEMICAL ENTITIES IN CLINICAL TRIALS

A relatively large number of chemical entities of plant origin are currently in clinical trials (9-11). However, a considerable percentage of the plant-derived oncology drug candidates in clinical trials are based on paclitaxel [ABI-007, DHA-paclitaxel, paclitaxel poliglumex, RPR-116278A, XRP9881 (RPR109881A)], camptothecin [9-aminocamptothecin, exatecan mesylate, oral topotecan (hycamptin), rubitecan (9-nitrocamptothecin, Orathecin™)], vinblastine and vincristine (vinflunine ditartrate, vinorelbine, anhydrovinblastine, vincristine sulfate TCS), and epipodophyllotoxin (NK-611 and tafluposide 105) (9-11). Members of these already established classes of candidate drugs will not be discussed in this section, with compounds of other structural types referred to instead. In this manner, it is hoped to better emphasize the overall structural diversity of promising chemical entities from plants as potential cancer chemotherapeutic agents (Figure 2).

Betulinic acid (**6**), a pentacyclic triterpenoid with a lupane skeleton, is widespread in the plant kingdom. This compound was purified as the active principle from *Ziziphus mauritiana* Lam. (Rhamnaceae), collected in Zimbabwe, using the bioassay-guided fractionation in earlier work by our group when at the University of Illinois at Chicago (32). In this investigation, betulinic acid was found to show *in vivo* selective growth inhibitory activity in athymic mice bearing human melanoma xenografts (32). This triterpenoid has been shown also to exhibit cytotoxicity against neuroectodermal and brain tumor cells (33). It induces apoptosis through regulation of the intrinsic pathway by changing mitochondrial membrane potential and activation of p38 MAPK and SAP/JNK by initiating ROS (reactive oxygen species) generation (34). This compound can be semi-synthesized by oxidation of betulin (**7**), a more abundant naturally occurring analogue (35). A betulinic acid-containing ointment is undergoing Phase I/II clinical evaluation for the treatment of dysplastic nevi with moderate to severe dysplasia (36).

Combretastatin A1 (**8**) and combretastatin A4 (**9**) are representative of several *cis*-stilbenes from *Combretum caffrum* Kuntze (Combretaceae), a shrub from South Africa, that were isolated in the 1980s by Pettit and colleagues at Arizona State University (37, 38). Substances in the combretastatin class are antineoplastic agents that also act as tubulin-binding and vascular disrupting agents (VDAs), and cause morphological changes within endothelial cells, which can lead to rapid and selective vascular collapse in solid tumors and result in the shutdown of the nutrient supply for malignant cells (39, 40). Combretastatin A4 phosphate (**10**, CA4P) is a phosphate prodrug of combretastatin A4 (**9**), which inhibits the polymerization of tubulin by binding on tubulin at the cochicine-site with highly affinity, and leads to the failure of microtubule formation (41). CA4P (**10**), both alone, and in combination with conventional oncological agents, is currently in several Phase I/II clinical trials for the treatment of anaplastic thyroid carcinoma and other advanced solid tumors in the United States (42, 43). AVE8062 (AC7700, **11**), a propanamide derivative of compound **9**, exhibits even an more potent antitumor effect than CA4P by inducing an irreversible blockage of tumor blood flow, and is now in Phase I clinical studies in Europe and the United States (44, 45). CA1P (Oxi4503, 12), a bisphosphate prodrug of combretastatin A1 (12) also reported to be more potent than CA4P (**10**), is undergoing Phase I anticancer clinical trials in the U.K. (45).

Curcumin (**13**) is a phenolic diarylheptanoid isolated from turmeric, the roots of *Curcuma longa* L. (Zingiberaceae). Turmeric is a common spice widely consumed in many Asian countries, and has a long history of use in the traditional medicinal systems of India and China as a remedy for the treatment of ailments such as arthritis, digestive disorders, gallbladder and liver problems, and eye and skin infections (46, 47). The types of biological activities attributed to curcumin cover a wide range, and include antioxidant, anti-inflammatory, antimicrobial, immunomodulatory, and potential cancer chemopreventive effects (46, 47). Curcumin can induce apoptosis and inhibits the proliferation of a wide variety of malignant cells. The mechanisms underlying the activities exhibited by curcumin are complex, and involve the regulation of combined signaling pathways at multiple levels by acting on various targets. These include the modulation of gene transcription factors (NFκB, p53, AP-1), growth factors and their receptors (PDGF, EGF, VEGF), cell surface adhesion molecules (E-cadherin, β-cadenin), and protein kinases (CDKs, EGFR, PKC, p38 MAPK) (46, 47). Clinical studies of curcumin alone or in combination with other chemotherapeutic agents have been carried out in the United States and Israel for patients with colorectal and pancreatic cancers (48).

Flavopiridol (alvocidib, **14**) is a semisynthetic substance derived from rohitukine (**15**), an *N*-methylpiperidine alkaloid isolated initially from *Amoora rohituka* (Roxb.) Wight & Arn. (Meliaceae), and then identified as an anti-inflammatory and immunomodulatory agent from the stem bark of a native plant from India, *Dysoxylum binectariferum* Hiern (Meliaceae) (49, 50). Flavopiridol was found to exhibit cytotoxity for a wide range of cancer cell lines and has demonstrated *in vivo*

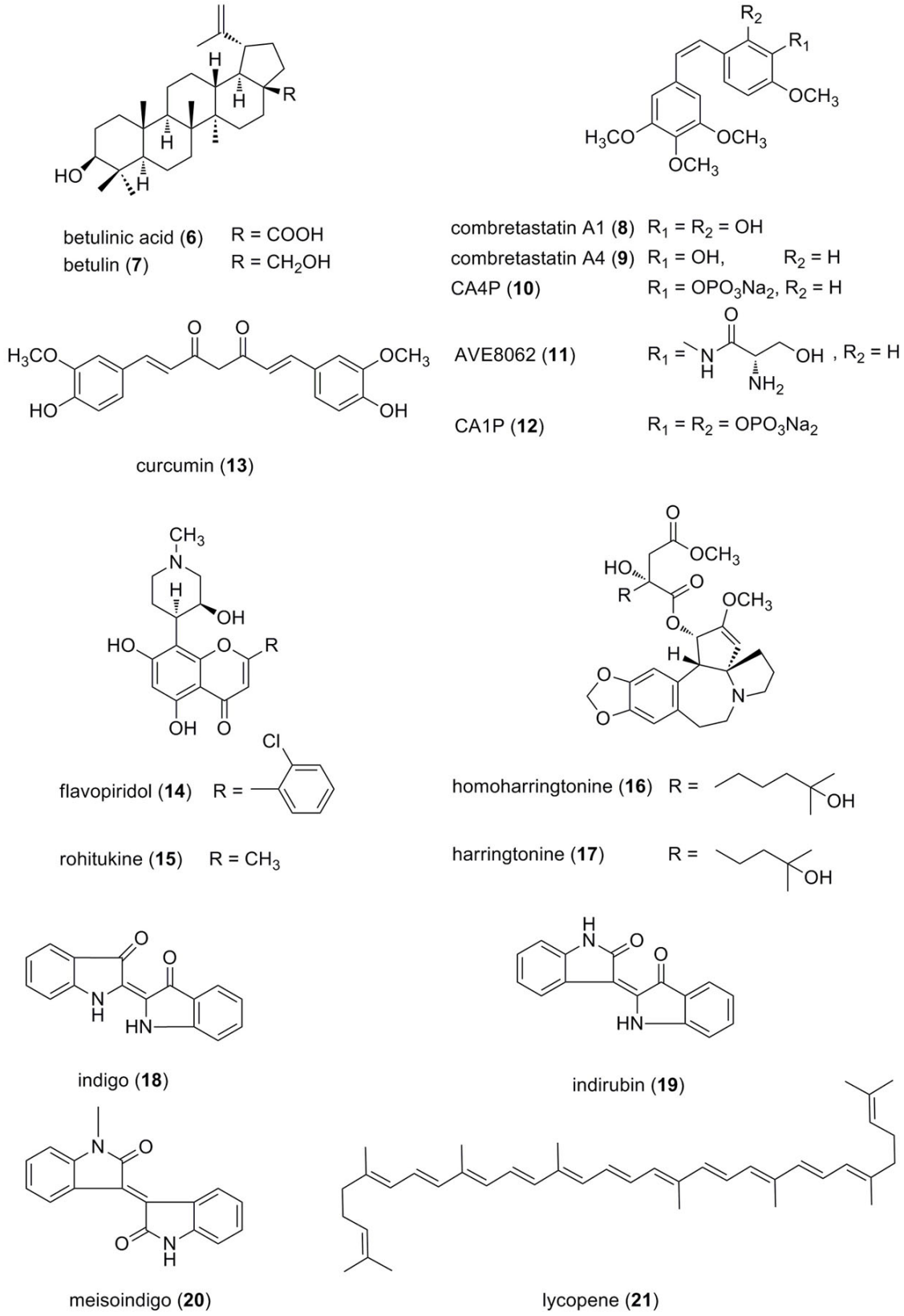



**Figure 2.** Structures of selected chemical entities of plant origin in oncologyclinical trials.
activity against prostate cancer, head and neck cancer, hematopoietic neoplasia, leukemia, and lymphoma

xenograft murine models (51, 52). Mechanistic studies revealed that flavopiridol inhibits the activity of cyclin-dependent kinases (CDKs) by competing with ATP at their nucleotide binding sites, and causes cell cycle arrest at either the $G_1$ or $G_1$/M phases. Further studies indicated that flavopiridol also exhibits apoptosis induction, and anti-angiogenic and antiproliferative effects, by interacting at multiple other targets besides CDK (53, 54). Flavopiridol is the first cyclin-dependent kinase inhibitor in clinical trials for the treatment of patients with non-Hodgkin's lymphoma, renal, prostate, colon and gastric cancers (53-56).

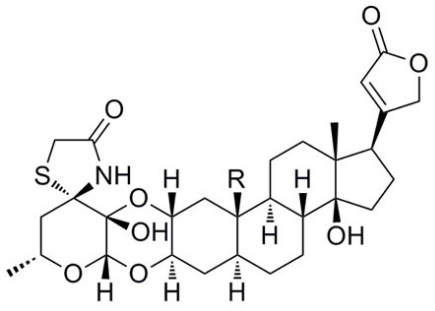
Homoharringtonine (**16**, HHT), a cephalotaxine alkaloid ester, along with its analogue harringtonine (**17**), was first isolated in the early 1970s from the bark of *Cephalotaxus harringtonia* (Knight ex J. Forbes) K. Koch (Cephalotaxaceae), an evergreen tree native to East Asia, by Powell, Weisleder, and Smith at the United States Department of Agriculture facility at Peoria, Illinois (57). The only structural difference between these two alkaloids is that homoharringtonine possesses an additional methylene group in the ester side-chain when compared to harringtonine. Homoharringtonine (**16**) may be obtained also from several other *Cephalotaxus* species. The mechanism of action of compounds 16 and 17 is unusual, and they promote apoptosis and inhibit protein synthesis at the ribosomal level (58, 59). Clinical studies of a mixture of homoharringtonine (**16**) and harringtonine (**17**) were initiated in 1970s by the Chinese Academy of Medical Sciences, for use in the treatment of acute myeloid leukemia (AML) and chronic myeloid leukemia (CML). Homoharringtonine (**16**) has entered various Phase II/III clinical trials for patients with CML in the United States and in Europe (58-60). A semi-synthetic version of homoharringtonine (sHHT), also known as omacetaxine mepesuccinate and prepared by esterification of the parent compound cephalotaxine obtained from the leaves of a *Cephalotaxus* species, is undergoing a clinical trial for the treatment of CML in patients with imatinib resistance and intolerance (61).

Indigo (**18**) and indirubin (**19**) are two *bis*-indole alkaloids obtained from the blue dye "Indigo Naturalis", which is also known as "Qing Dai" in the People's Republic of China. "Qing Dai" is a traditional Chinese medicinal herbal formula with antibacterial, anti-inflammatory, febrifuge, and hemostatic effects. It is composed of the dried residue derived from the leaves and/or stems of several plants that produce a dark blue dye, including *Baphicacanthus cusia* (Nees) Bremek. (Acanthaceae), *Indigofera suffruticosa* Mill. (Fabaceae), *Indigofera tinctoria* L. (Fabaceae), *Isatis tinctoria* L. (Brassicaceae), and *Polygonum tinctorium* Ait. (Polygonaceae) (62, 63). A mechanistic study has demonstrated that indirubin (19) exerts its antileukemic effect by competing with ATP for binding to the catalytic subunit of cyclin-dependent kinase (CDK), leading to the inhibition of this enzyme. The crystallized structure of a CDK2/indirubin analogue complex indicated an interaction with an ATP binding site via hydrogen bonds to key amino acids (64). Meisoindigo (1-methylisoindigo, **20**) is a derivative developed to improve the solubility in water and other pharmaceutical properties of indirubin. This compound showed significant activities against cancer cells through a multi-targeting profile including inhibition of DNA biosynthesis and assembly of microtubules, induction of cell differentiation, and down-regulation of c-myb gene expression (64, 65). Meisoindigo (**20**) has been subjected to clinical trial in the People's Republic of China for chronic myelogenous leukemia (CML) (66).

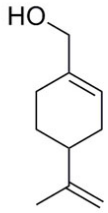
Lycopene (**21**), a well-known red pigment based on a β-carotene skeleton, is distributed widely in fruits and vegetables, and is especially abundant in tomatoes (*Solanum lycopersicum* L.; Solanaceae) and processed tomato products (67). The 40-carbon aliphatic chain of the molecule of lycopene contains thirteen *trans*- double bonds, with eleven of these being conjugated. Besides its antioxidant and anti-inflammatory activities, lycopene also exhibits anticarcinogenic peoperties in both *in vitro* and *in vivo* models (68, 69). Mechanism-of-action studies have indicated that lycopene exerts its anticancer and chemoprevention activities through the activation of the electrophile/antioxidant response element (EpRE/ARE) transcription system, inducing the expression of phase II detoxifying enzymes, and arresting the cell cycle at the $G_0/G_1$ phase by regulating cyclin D1 and the PI3K/Akt pathway (69). Lycopene has entered Phase II clinical trials in the United States for the prevention and treatment of prostate cancer (70).

2"-Oxovoruscharin (**22**), a cardenolide with a rare dihydrothiazole ring in its molecule, was isolated from a tropical evergreen shrub, *Calotropis procera* (Aiton) W.T. Aiton (Asclepiadaceae), and was demonstrated to have potent *in vitro* antitumor and $Na^+/K^+$-ATPase inhibitory activities (71). UNBS1450 (**23**), derived from 2"-oxovoruscharin by reducing the formyl group in the molecule to a hydroxymethyl group, exhibited an improved *in vitro* cytotoxicity profile activity when compared with the parent compound (72). A mechanistic investigation demonstrated that UNBS1450 induces the disruption of the actin cytoskeleton to affect multiple signaling pathways by binding to the sodium pump, and leads to non-apoptotic cell death (73). UNBS1450 has entered Phase I clinical studies in Europe for patients with solid tumors and lymphomas (74).

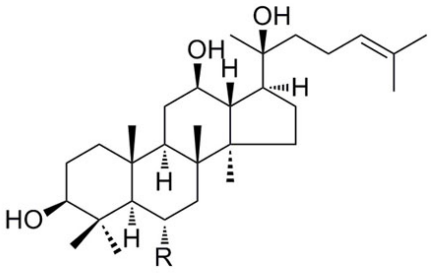
Perillyl alcohol (POH, **24**), is a monoterpenoid with a monocyclic carbon skeleton that is found in the essential oils in a number of plants such as lavender (*Lavendula* x *intermedia*; Lamiaceae) and cherries [*Prunus avium* (L.) L. (Rosaceae)] (75). Preclinical studies have indicated that perillyl alcohol exhibits cytotoxicity for cancer cell lines derived from lung cancer, pancreatic cancer, prostate cancer, breast cancer and leukemia, and also showed *in vivo* inhibitory effects against UVB-induced skin carcinogenesis and DMBA-induced murine melanoma models (76, 77). Mechanistically, perillyl alcohol induces cell cycle arrest at the $G_0/G_1$ phase, by modulating the protein levels of cyclin-dependent kinases and



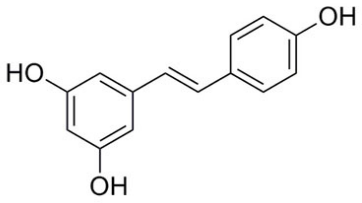
2''-oxovoruscharin (**22**) R = CHO
UNBS1450 (**23**) R = $CH_2OH$



perillyl alcohol (**24**)



protopanaxadiol (**25**) R = H
protopanaxatriol (**26**) R = OH



resveratrol (**27**)

**Figure 3.** Structures of selected compounds derived from plants with potential anticancer activity.

cyclin-dependent kinase inhibitors (78). Perillyl alcohol is undergoing Phase I/II clinical trials in patients with breast cancer, ovarian cancer and glioblastoma multiform (79).

Protopanaxadiol [**25**; 20*S*-protopanaxadiol (PPD)] and protopanaxatriol [**26**; 20*S*-protopanaxatriol (PPT)] are two dammarane-type triterpenoids prepared by the hydrolysis of certain saponins obtained from Asian ginseng (*Panax ginseng* C.A. Mey.; Araliaceae) and related species (80). Protopanaxadiol induces cancer cell apoptosis and inhibits proliferation through targeting the Wnt/ β-catenin signaling pathway, down-regulating AKt activity, and inhibiting the effects of P-glycoprotein (P-gp) (81-83). Protopanaxadiol and protopanaxatriol are reported to have immunomodulating activity (84). A mixture of protopanaxadiol (**25**) and protopanaxatriol (**26**) (Pandimex$^{TM}$) has been approved conditionally in mainland China for the treatment of advanced cancers of the breast, colon-rectum, lung, and pancreas, and is ongoing a Phase I clinical trial in the United States for advanced lung, gastric, breast, and pancreatic cancers in combination with paclitaxel or alone (85, 86).

Resveratrol (**27**, 3,5,4'-trihydroxy-*trans*-stilbene) is a phenolic compound found in several dietary items, such as grapes (*Vitis vinifera* L.; Vitaceae), white mulberries (*Morus alba* L.; Moraceae), and peanuts (*Arachis hypogaea* L.; Fabaceae). This compound is also considered as a major constituent responsible for the cardioprotective activity of red wine (87, 88). Intensive studies have revealed that resveratrol possesses antioxidant, anti-inflammatory, and anticarcinogenetic activities, and can prevent and slow a wide range of illnesses, including age-related diseases, cancer, cardiovascular problems, diabetes, and ischemic injuries (87-89). Resveratrol inhibits the growth of cancer cells and induces apoptosis by acting at multiple cellular targets, including activation of p53, inhibiting cycloxygenase and cytochrome P450 enzymes, and activating AMP-activated kinase (AMPK) (87-89). Resveratrol has been also reported to show sensitization effects on drug-resistant tumor cells and to result in a synergistic cytotoxicity when combined with established anticancer therapies (90). This compound is now undergoing Phase I/II clinical trials for the prevention and treatment of colon cancer in the United States (91).

## 4. SOME PLANT-DERIVED COMPOUNDS WITH POTENTIAL ANTICANCER ACTIVITY (Figure 3)

A series of anthracenone *C*-glycosides,

alvaradoins E-N, was isolated from the leaves of *Alvaradoa haitiensis* Urb. (Picramniaceae), by Mansukh Wani and colleagues at Research Triangle Institute in North Carolina (92). Among these compounds, alvaradoin E (**28**), and its 10(*R*) isomer, alvaradoin F (**29**), were found to be the most potent cytotoxic agents against the KB cell line, exhibiting $IC_{50}$ values of 0.050 and 0.065 μM, respectively (92). Alvaradoins E and F were also evaluated in *in vivo* hollow fiber assay using KB, LNCaP, and Col2 cells, and both demonstrated significant inhibitory activity at the intraperitoneal site, while being less active when administered subcutaneously (93). In an *in vivo* P388 murine lymphocytic leukemia model study, alvaradoin E exhibited discernible activity (92). This compound was studied further for its mechanism of action. After treatment of LNCaP human prostate cancer cells with alvaradoin E, early signs of apoptosis including chromatin condensation and dose-dependent membrane depolarization were noticed. A significant decrease in cell viability accompanied by an increase in DNA breakage was observed using HL-60 leukemia cells (93).

Quassinoids are highly oxygenated degraded triterpenoid derivatives typically with a bitter taste, which are found in many species in the family Simaroubaceae. As the major active principles of these plants, quassinoids have been documented with a wide spectrum of biological activities, including anti-HIV, antimalarial, antiparasitic, antitumor, and insecticidal effects (94). Bruceantin (**30**), a quassinoid with potent cytotoxicity, was brought to clinical trials as an anticancer candidate by the U. S. NCI in the 1980s, but was eventually dropped because of a lack of demonstrated efficacy (95). Very recently, a new antitumor quassinoid, 2′-(*R*)-*O*-acetylglaucarubinone (**31**) was isolated by Usami *et al.* from the bark of *Odyendyea gabonensis* (Pierre) Engler (96). Compound **31** exhibited potent cytotoxicity against a small panel of human cancer cell lines, including prostate (DU145), lung (A549), and oral epidermoid carcinoma (KB) cells, with $ED_{50}$ values around 0.05 μg/mL in each case. This compound was further evaluated using multiple breast cancer and ovarian cancer cell lines. Compound 31 demonstrated strong inhibitory effects against several ER- or/and PR-negative cell lines, suggesting that neither the estrogen receptor (ER) nor the progesterone receptor (PR) is the major target of this compound. Moreover, the HER2-overexpressing ER/PR-negative SKBR3 cell line was hypersensitive to this quassinoid, which implied that the HER2 signaling pathway might be involved in mediating its cytotoxicity (96). The *in vivo* mammary epithelial proliferation inhibitory activity of compound 31 was evaluated using a *Brca1/p53*-deficient mouse model. The mammary duct branching points were reduced to 32% after a daily intraperitoneal injection of 0.1/mg of compound 31 for one week, and the reduction effect on such branching was even more significant than observes for the control compounds, bruceantin (**30**) and paclitaxel (96). Further mechanism studies of action on this promising antineoplastic agent are being carried out.

More than 30 species in the family Amaryllidaceae have been documented as having a history of use as folk medicines for the treatment of tumors. Two isocarbostyril alkaloids, narciclasine (**32**) and pancratistatin (**33**), first isolated from bulbs of a *Narcissus* species (97) and from *Hymenocallis littoralis* Salisb. (formerly known as *Pancratium littorale* Jacq.) (98), respectively, are two of the most promising antineoplastic compounds from this plant family, and are effective and selective anticancer agents with the potential for clinical development. These two compounds exhibited *in vivo* growth inhibitory activity, in turn, in M5076 sarcoma (99) and P388 lymphocytic leukemia models (98). A study has indicated that normal human fibroblasts were nearly 250-fold less sensitive to narciclasine than MCF-7 cells and PC-3 cells (100). Pancratistatin selectively induced apoptosis of leukemia cells from patients with minimal affect on normal peripheral blood mononuclear cells (101), and induced apoptosis specifically in breast cancer cells in comparison to non-cancerous cells (102). Pyridinum narciclasine (**34**) and sodium pancratistatin 3,4-*O*-cyclic phosphate (**35**) are prodrugs of narciclasine and pancratistatin, respectively, which have been produced to improve the water solubility of these two compounds (99, 103). Compound **35** was shown to retain the potency of cancer cell line inhibition when compared to the parent compound (**33**), and has been selected for preclinical development (103).

Tanshinone I (**36**), tanshinone IIA (**37**), and cryptotanshinone (**38**), are three major diterpene quinone derivatives isolated from the rhizomes of *Salvia miltiorrhiza* Bunge (Lamiaceae), which is known as "Tanshen" in traditional Chinese medicine and used as a herbal remedy with multiple therapeutic effects (104). These three tanshinone derivatives exhibited significant *in vitro* cytotoxicity against several human carcinoma cell lines (104). Tanshinone I (**36**) was found to inhibit the growth and invasion of breast cancer cells both *in vitro* and *in vivo* through regulation of adhesion molecules including ICAM-1 and VCAM-1 (105), and induce apoptosis of leukemia cells by interfering with the mitochondrial transmembrane potential ($\Delta\Psi$m), increasing the expression of Bax, as well as activating caspase-3 (106). Tanshinone IIA (**37**) has been reported to inhibit the growth of cervical cancer cells through disrupting the assembly of microtubules, and induces $G_2$/M phase arrest and apoptosis (107). This compound (**37**) can also inhibit invasion and metastasis of hepatocellular carcinoma (HCC) cells both *in vitro* and *in vivo*, by suppressing the expression of the metalloproteinases, MMP2 and MMP9 and interfering with the NFκB signaling pathway (108). Cryptotanshione (**38**) was reported to induce cell-cycle arrest at the $G_1$-$G_0$ phase, which was accompanied by the inhibition of cyclin D1 expression, retinoblastoma (Rb) protein phosphorylation, and of the rapamycin (mTOR) signaling pathway (109). Compound 38 can sensitize DU-345 breast cancer cells by suppressing the expression of the apoptosis inhibitory protein, Bcl-2 (110). Neo-tanshinlactone (**39**) is a new lead antineoplastic compound isolated from *S. miltiorrhiza* by Dr. Kuo-Hsiung Lee's research group at the University of North Carolina (111). Unlike the tanshinones, neo-tanshinlactone (**39**) possesses a lactone feature rather than an *ortho*-quinone moiety in ring C. This compound exhibited selectivity against two estrogen receptor-positive ($ER^+$) breast cancer cell lines, MCF-7 and ZR-75-1, with $ED_{50}$

values, in turn, of 0.6 and 0.3 μg/mL (111). Compound **40**, a synthetic analogue of neo-tanshinlactone (**39**), was found to inhibit the growth of the estrogen-dependent breast cancer cells, ZR-75-1, in an *in vivo* xenograft model (112). These investigations suggest that neo-tanshinlactone (**39**) and its derivatives might be promising candidates for the treatment of hormone-dependent breast cancers.

Silvestrol (**41**), and its 5'''*S* epimer, episilvestrol (**42**), were isolated by Kinghorn *et al.* from the tropical plant *Aglaia foveolata* Pannell (Meliaceae), with the structure and absolute configuration elucidated using single-crystal X-ray crystallography analysis (113). Silvestrol has also been documented as an antineoplastic constituent of *Aglaia leptantha*, collected in Sarawak, Malaysia, but with the stereochemistry of the 1,4-dioxanyloxy ring undetermined (114). This "flavagline" derivative was found to possess potent cytotoxicity for a small panel of human cancer cell lines and exhibited activity in both *in vivo* hollow fiber and P-388 lymphocytic leukemia assays (113). The total synthesis of silvestrol (**41**) has been accomplished by two independent groups (115-117). Preliminary mechanistic studies conducted by Dr. Steven Swanson and co-workers at the University of Illinois at Chicago showed that in LNCaP human prostate cancer cells, silvestrol produces a p53-independent cell-cycle blockage at the G2/M check-point, and induces apoptosis through the regulation of caspases-2, -9 and -10 but not caspases-3 and -7 (118, 119). Additional investigation at The Ohio State University Medical Center, in the laboratory of Dr. Michael Grever, demonstrated that silvestrol exhibited B-cell selective activity and showed efficacy in both chronic lymphocytic leukemia and acute lymphocytic leukemia models (120). Silvestrol can lead an early reduction in Mcl-1 expression in chronic lymphocytic leukemia cells (120), and inhibits the translation of malignancy-related mRNA by regulating initiation factor elF4A (121). The compound demonstrated synergy with other agents using acute mylegenous leukemia cells (122) and modulated sensitivity to doxorubicin in a pre-clinical mouse lymphoma model (123). Further preclinical evaluation of silvestrol (**41**) as a potential antileukemic agent is ongoing.

## 5. CONCLUSION

Although cancer is one of the most pressing heath concerns worldwide, the success rate in oncology new drug development is more than three times less than that for cardiovascular diseases (124). Cancer drug discovery is difficult because of many inherent obstacles such as tumor heterogeneity (124). Chemotherapy is an important option in modern cancer treatment, and plant-derived chemotherapeutic agents have contributed greatly to the progress of oncology chemotherapy development and to clinical practice. From the examples of antineoplastic candidates described in this review, it is evident that small molecules of plant origin continue to be valuable as sources of potential lead compounds in anticancer drug discovery. According one recent estimate, more than 85% of higher plants have not been evaluated systematically for the presence of bioactive principles (125). There are more than 60 compounds from plant sources in the pipeline as potential anticancer agents (9-11). Innovations in the multidisciplinary investigative methods offer great promise for plant-derived drug discovery and development. These include new techniques related to compound isolation and structure elucidation, enhanced high-throughput biological screening procedures using novel biological targets, and continuing improvements in synthetic chemistry to make the optimization of the lead compounds more efficient. Therefore, there remains great potential to explore the plant kingdom for new antineoplastic lead compound by using novel targets and newly developed technologies, so a promising future for anticancer drug development based on these agents can be predicted.

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