Natural Product Triterpenoids and Their Semi-synthetic Derivatives with Potential Anticancer Activity*
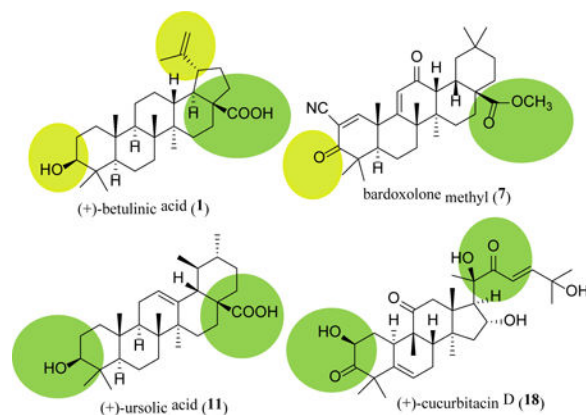
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Abstract

Triterpenoids are distributed widely in higher plants and are of interest because of their structural diversity and broad range of bioactivities. In particular, there is a very large literature on the propensity of a variety of triterpenoids to act as potential anticancer agents. In the present review, the anticancer potential is summarized for naturally occurring triterpenoids and their semi-synthetic derivatives, including examples of lupane-, oleanane-, ursane-, and cucurbitane-type pentacyclic triterpenoids, along with dammarane-type tetracyclic triterpenes including ginsenosides and their sapogenins and dichapetalins, which have been characterized as antitumor leads from higher plants. Preliminary structure-activity relationships and reported mechanisms of the antineoplastic-related activity are included. Prior studies for triterpenoids of plant origin are supportive of additional work being conducted on the more detailed biological and mechanistic evaluation for the progression of this type of natural products as possible cancer chemotherapeutic agents.

Graphical Abstract

(+)-betulinic acid (**1**)

bardoxolone methyl (**7**)

(+)-ursolic acid (**11**)

(+)-cucurbitacin D (**18**)

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* Dedicated to Professor Dr. Cosimo Pizza in recognition of his important contributions to natural product research on the occasion of his 70th birthday in 2019.

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Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

Plant-derived triterpenoids may mediate their potent antitumor activity through inhibition of NF-κB and STAT3 or induction of autophagy, indicating a promise for the development of new anticancer drugs from these compounds.

Keywords

natural products; triterpenoids; antitumor activity; synthetic modification; structure-activity relationships; mechanisms of anticancer activity

Introduction

Higher plants have afforded four major well-established classes of approved cancer chemotherapeutic drugs, inclusive of compounds based on bisindole and camptothecin alkaloids, taxane diterpenoids, and podophyllotoxin lignans, with the cephalotaxine alkaloid, omacetaxine mepesuccinate, having been introduced clinically for this purpose more recently [1, 2]. Natural products from all classes of terrestrial and marine micro- and macro-organisms continue to play a vital role in drug discovery, inclusive of the search of new oncological agents. Indeed, of a total of 175 small molecules approved as anticancer drugs in western medicine from 1940–2014, approximately 50% were either directly obtained from micro- and macro-organisms or derived synthetically from naturally occurring lead molecules [2, 3].

The triterpenoids are a large group of over 20,000 natural products derived from C_{30} precursors, with over 100 different carbon skeletons, which are typically 6–6–6–5 tetracyclic and 6–6–6–6–5– or 6–6–6–6–6 pentacyclic substances [4, 5]. The occurrence of triterpenoids in different types of organisms has been subjected to frequent review, with several hundred new compounds of this type described by investigators all over the world each year [6]. While neither naturally occurring nor semi-synthetic triterpenoids have current use as anticancer agents in western medicine, bardoxolone methyl, a synthetic oleanane-type triterpenoid, has reached clinical trial recently for the potential treatment of cancer [7].

Several investigators have reviewed specifically various classes of naturally occurring triterpenoids as potential anticancer agents [e.g., 5, 8–16]. The interest of the present authors on this same issue has been stimulated as a result of 2 long-standing collaborative multidisciplinary projects funded sequentially by the U.S. National Cancer Institute, in which numerous triterpenoids isolated from tropical plants collected in several continents were evaluated biologically [17, 18]. A significant initial observation made in this work was the specific inhibitory activity *in vitro* of the pentacyclic triterpenoid, (+)-betulinic acid (**1**) (Fig. 1), against 3 different cancer patient-derived melanoma cell lines [19]. As part of the same study, follow-up *in vivo* work showed significant inhibition of tumor growth when four-week old athymic nude mice inoculated with MEL-1 human melanoma cells were treated with compound **1** (5 mg/kg, once four days, i.p.) for 6 weeks, and neither tumor metastases nor structural abnormalities were observed in mice [19].

In the following portions of this review, our own recent experimental observations on biologically active plant-derived triterpenoids will be combined with descriptions of relevant work by other groups on triterpenoids having potential antineoplastic activity.

Lupane-type Triterpenoids

As part of a recent summary account, further preclinical studies were described in a book chapter that led eventually to the evaluation of (+)-betulinic acid (**1**) in phase I/II clinical trials to treat dysplastic melanocytic nevi. These clinical trials were conducted at the College of Medicine, University of Illinois at Chicago, Chicago, IL, USA, with the drug administered topically as a 20% ointment [20].

Following this development, there is presently quite a large contemporary body of literature on efforts to generate additional anticancer agents based on (+)-betulinic acid (**1**) and its close analogue, (+)-betulin (**2**) (Fig. 1), aimed at improving particularly both the antitumor efficacy and water solubility [e.g., 21–24]. It was realized in early work that the cytotoxic potency of (+)-betulinic acid (**1**) toward MEL-2 melanoma and KB human oral epidermoid carcinoma cells could be enhanced by altering the substituents at positions C-3, C-20, and C-28 [25]. As one synthetic approach, the inhibitory effects of (+)-betulin (**2**) were greatly enhanced on the proliferation of vincristine-resistant MCF-7 human breast cancer cells by introduction of a triphenylphosphonium cation conjugate at the C-28 position to produce 4-oxobutyltriphylphosphonium bromide betulin (**3**) (Fig. 1), which showed an IC_{50} value of 45 nM that was much lower than the positive controls, doxorubicin (IC_{50} 0.3 μM) and vinblastine (IC_{50} 9.2 μM) [26]. Another potent cytotoxic agent produced is the chimera derivative, betulastatin 3 [30-*N*-(Dap-Dil-Val-Dov)-betulin] (**4**, Fig. 1), which was prepared by bonding (+)-betulin (**2**, GI_{50} >10 μg/mL) to the Dov-Val-Dil-Dap unit of the anticancer compound, dolastatin 10, and showed a GI_{50} value of 0.04 μg/mL against DU-145 human prostate cancer cells [27].

Recently, an important approach that has been undertaken is production of the mPEG-betulinic acid conjugate, **5** (Fig. 1), a more water-soluble derivative of compound **1** that also augments the cytotoxic potency of the parent compound, (+)-betulinic acid (**1**) [28].

Oleanane-type Triterpenoids

(+)-Oleanolic acid (**6**) (Fig. 2) is a pentacyclic triterpenoid that exhibits promising antitumor efficacy and has been found to interact with multiple molecular targets [29]. It showed cytotoxic and anti-metastatic activities against A549 and H460 human non-small cell lung cancer cells by decreasing the expression of the angiogenic vascular endothelial growth factor (VEGF) and the development of melanoma-induced lung metastasis [30]. Also, it inhibited the proliferation of GBC-SD and NOZ human gallbladder cancer cells through the mitochondrial apoptosis pathway [31]. Tumor growth was suppressed significantly when 4 to 6-week-old athymic male nude mice inoculated with NOZ cells were treated with (+)-oleanolic acid (i.p., 75 or 150 mg/kg, once every two days) for 15 days, and no side effects were observed in the test mice used [31].

In addition, (+)-oleanolic acid (**6**) was found to inhibit mitomycin C-resistant HT-29 human colon cancer cell growth, which was proposed to be mediated through selective inhibition of human aldo-keto reductase [32]. It also inhibited HepG2 and SMC7721 hepatoma cell growth by suppression of the PI3K/Aκt1/mTOR signaling pathway and as a result of triggered reactive oxygen species (ROS)-dependent autophagy [33]. Interestingly, (+)-oleanolic acid (**6**) has been found to increase MDA-MB-231 human breast cancer cell migration and hence show promising properties for wound healing, an effect that was mediated by mitogen-activated protein kinases [34].

In a very recent study, (+)-oleanolic acid (**6**) was found to induce MG63 and Saos-2 human osteosarcoma cell apoptosis by targeting mitochondria in a Notch signaling-dependent manner [35]. By acting via a diverse range of cellular mechanisms, this endorses the potential of (+)-oleanolic acid for further development as an antitumor agent.

To improve on the solubility and therapeutic efficacy of (+)-oleanolic acid (**6**), a novel dosage form has been developed and evaluated, namely, (+)-oleanolic acid-encapsulated multivesicular liposomes (OA-MVLs). In a side-by-side comparison, this liposomal form of (+)-oleanolic acid showed an enhanced tumor growth inhibitory effect with respect to compound **6**, when male Kunming mice inoculated with murine hepatoma H22 cells were treated (i.p.) with (+)-oleanolic acid (**6**) or OA-MVLs (25, 50, or 100 mg/kg for each compound, once two days) for two weeks. The survival time of the tumor-bearing mice was increased by both treatments, and no body weight loss was observed in the OA-MVL treatment protocol, even at a high dose (100 mg/kg) [36].

As a result of structural modification at the C-3 and C-28 positions of (+)-oleanolic acid (**6**), the novel analogueCDDO-Me or RTA 402 (**7**) (Fig. 2) was synthesized [37]. This derivative inhibited potently production of nitric oxide induced by interferon-γ (IFN-γ) in mouse macrophages [37]. It also showed cytotoxicity against HepG2 human hepatoma and B16 2F10 mouse melanoma cells [38]. In addition, CDDO-Me (**7**) was found to redirect the activation profile of tumor-associated macrophages (TAMs), enhancers of tumor growth, development, and metastasis, from tumor-promoting to tumor-inhibiting, indicating a possible immunotherapeutic role in the treatment of cancer [39].

Increasingly, a number of investigations on CDDO-Me (**7**) have shown that this agent exhibited potent cytotoxicity toward various tumor cells to exert promising *in vivo* antitumor efficacy [40]. For example, it showed strong antiproliferative and proapoptotic activity against the MiaPaCa-2 and BxPC-3 human pancreatic ductal adenocarcinoma cell lines. Tumor growth was inhibited significantly when seven-week old Scid-Ncr female mice inoculated with MiaPaCa-2 cells were treated with CDDO-Me (**7**) (gavage, 7.5 mg/kg, daily, five days per week) for five weeks [41].

The antitumor efficacy of CDDO-Me (**7**) was found to be mediated by improving the immune response in cancer. Tumor growth was found to be inhibited significantly by CDDO-Me (**7**) when six- to eight-week old C57BL/6 female mice that were inoculated with EL-4 mouse thymoma cells and then vaccinated with dendritic cells transduced with full-

length survivin were treated with CDDO-Me (**7**) (oral chow, 150 mg/kg, daily, four days per week) for three weeks [42].

In a phase I clinical trial study, patients with locally advanced or metastatic pancreatic adenocarcinoma were treated with gemcitabine (i.v., weekly) and CDDO-Me (**7**, orally, daily), with immunology evaluated before and after the two-week treatment. Neither toxicity attributed to compound **7** nor significant change of the proportion of myeloid-derived suppressor cells (MDSC) mainly responsible for immune suppression in cancer were observed in the patients. Combined CDDO-Me and gemcitabine treatment resulted in a significant increase in the T-cell responses of the patients to tetanus toxoid and phytohemagglutinin, indicating the therapeutic promise of this triterpenoid derivative in enhancing cancer immunotherapy [42].

A further phase I study on CDDO-Me in patients with advanced solid tumors or lymphomas has been reported, with its MTD, DLTs, and appropriate dose for phase II studies established [7, 43]. However, this clinical trial on CDDO-Me was suspended due to some serious adverse events evident, indicating that further structural modification is required to decrease the side effects observed for this triterpenoid derivative (**7**), for future development of an effective anticancer agent [44].

The sweet-tasting oleanane-type triterpene glycoside glycyrrhizin (**8**) (Fig. 2) is used as an ingredient in the food and beverage industry and is the major active constituent of *Glycyrrhiza glabra* L. (licorice) (Fabaceae) [45]. This and two other *Glycyrrhiza* species are official sources of licorice in the *Chinese Pharmacopoeia*, with *G. glabra* demonstrated as having anti-inflammatory, antioxidant, antiviral, hepatotoxic, and neuroprotective propensities [46].

Among recent reports on the antitumor potential of glycyrrhizin (**8**), its cytotoxicity toward HepG2 and MHCC97-H hepatocellular carcinoma cells was found to be mediated by autophagy induced from the inhibition of Aκt/mTOR signaling [47]. It is worth mentioning that *Glycyrrhiza uralensis* Fisch. containing glycyrrhizin (**8**) is used as a component of PHY906, which is a long-established four-herb formula used in Chinese traditional medicine to treat a number of gastrointestinal conditions and to improve the therapeutic indices of a number of standard anticancer agents [48].

In a murine colon xenograft model, PHY906 enhanced significantly the antitumor activity and reduced the toxicity of irinotecan (CPT-11), when tumor-bearing mice were treated by CPT-11 (i.p., 360 mg/kg, daily) with (500 mg/kg, orally, twice a day) or without PHY906 for four consecutive days [49].

In a phase II study conducted in the United States using PHY906 with capecitabine as second-line therapy in patients with advanced pancreatic cancer, it was concluded that this combination may provide a safe and feasible salvage therapy for such patients after failure using gemcitabine [50].

As an additional example of a group of oleanane-type triterpenoids, compounds related to barrigenol represent a small group of olean-12-enes hydroxylated at the C-3, C-15, and/or

C-16, C-22 and/or C-21, and C-28 positions, which occur mainly in the plant families Apocynaceae, Lecythidaceae, Pittosporaceae, Sapindaceae, and Theaceae. In our continuing search for anticancer agents from tropical plants, a barrigenol-like triterpenoid, (+)-barringtogenol B (**9**) (Fig. 2), was isolated as a major cytotoxic component from an extract of the bark of *Cyrilla racemiflora* L. (Cyrillaceae), collected in Dominica [51]. This compound exhibited an IC_{50} value of 1.7 μM for HT-29 human colon cancer cells (the positive control, paclitaxel, showed an IC_{50} value of 0.8 nM) [51]. A preliminary structure-activity relationship (SAR) study showed that an angeloyl group attached at either C-21 or C-22 is necessary for barrigenol-like triterpenoids to mediate their cytotoxicity. The presence of a hydroxy group at the C-24 position enhances the cytotoxicity of some barrigenol-like triterpenoids, but introducing a hydroxy group at the C-15 position results in the potency being decreased [51].

Based on these SAR conclusions, xanthoceraside (**10**) (Fig. 2), a barrigenol-like triterpenoid isolated from the husks of *Xanthoceras sorbifolia* Bunge, with an angeloyl group substituted at C-21 and C-22, a hydroxy group connected at C-15, C-16, and C-28, and a tri-glycoside unit linked at the C-3 position, was found to be cytotoxic against A375.S2 human melanoma cells (IC_{50} 5.71 μM) but non-cytotoxic against normal peripheral blood mononuclear cells (PBMC), indicating a selective cytotoxicity for **10**. Mechanistic studies showed that xanthoceraside (**10**) induced A375.S2 cell apoptosis by activating caspase-3 and caspase-9 through the mitochondrial pathway that was induced by the downregulation of the IGF-1R/Raf/MEK/ERK cascade in A375.S2 cells [52]. These results indicate that the barrigenol-like triterpenoids may be worthy of further investigation for development as new anticancer agents.

Ursane-type Triterpenoids

There is an increasing interest in the potential antineoplastic propensities of the ursane-type triterpenoid, (+)-ursolic acid (**11**, Fig. 3) [e.g. 8, 10, 12, 15, 53], and a number of pertinent studies published in the last decade seem worthy of mention. (+)-Ursolic acid (**11**) suppressed the proliferation of androgen-independent DU145 and androgen-dependent LNCaP human prostate cancer cells through inhibition of NF-κB and signal transducer and activator of transcription-3 (STAT3) activation. Tumor growth was suppressed significantly when four-week old athymic BALB/c male nude mice inoculated with DU145 cells were treated with (+)-ursolic acid (i.p., 200 mg/kg, twice a week) for six weeks. No significant effects on body weight were observed in mice [53].

In both *in vitro* and *in vivo* studies, (+)-ursolic acid (**11**) inhibited the proliferation of R-HepG2 doxorubicin-resistant human hepatoma cells by inducing apoptosis through the caspase-independent apoptosis-inducing factor (AIF) signaling pathway [54]. Tumor growth was suppressed significantly, when four- to six-week old female nude mice inoculated with R-HepG2 cells were treated with (+)-ursolic acid (orally, 50 or 75 mg/kg, daily) for two weeks. No significant effects on the body weight, liver, heart, and spleen of mice were observed [54].

Interestingly, (+)-ursolic acid (**11**) has been found to inhibit the growth of SKOV3 sphere human ovarian cancer stem-like cells (CSCs). In an *in vivo* study, tumor growth was

inhibited significantly when five- to six-week old athymic BALB/*c-nu* female nude mice inoculated with SKOV3 sphere CSCs were treated with (+)-ursolic acid alone (i.p., 60 mg/kg, daily) or with (+)-ursolic acid (i.p., 60 mg/kg, daily) plus cisplatin (i.p., 2.5 mg/kg, daily) for two weeks [55].

In our collaborative work on tropical plants, *Syzygium corticosum* (Lour.) Merr. & L.M. Perry (Myrtaceae), collected in Vietnam, showed some promise in preliminary biological screening, and was thus subjected to activity-guided fractionation. Separation of the active extract from this species yielded a large amount of (+)-ursolic acid (**11**, with a yield of 0.2% w/w). This compound displayed a more potent NF-κB inhibitory activity (IC_{50} 31 nM) than the positive control rocaglamide (IC_{50} 70 nM). It also exhibited activity against MDA-MB-231 breast cancer cells (IC_{50} value of 5.9 μM) (the positive control, paclitaxel, showed an IC_{50} value of 17 nM) and was identified as the major cytotoxic principle of *S. corticosum* [56].

To characterize the functional groups necessary for mediation of its biological activity, two derivatives, (+)-uvaol (**12**) and (+)-3-*O*-(4-chlorobenzoyl)ursolic acid (**13**) (Fig, 3) were synthesized from (+)-ursolic acid (**11**). However, both semi-synthetic products (**12** and **13**) were found to be inactive, indicating the importance of the presence of both the C-3 hydroxy and C-28 carboxylic acid groups [56]. Following this observation, a preliminary structure-activity relationship (SAR) study using some semi-synthetic analogues indicated that the C-3 hydroxy and C-28 carboxylic acid groups and 19,20-dimethyl substitution are all essential for (+)-ursolic acid to mediate its cytotoxicity toward MDA-MB-231 breast cancer cells and NF-κB inhibitory activity [56].

Consistently, an earlier SAR study showed that the presence of a C-28 keto carbonyl group is important for pentacyclic triterpenes to inhibit mouse melanoma B16 2F2 cell growth by induction of cell differentiation [57]. Thus, the antiproliferative activity of (+)-ursolic acid (**11**) against all of A549 non-small cell lung, HeLa cervical, and MCF-7 breast human cancer cells was improved somewhat by modification at the C-28 position via esterification followed by amidation with amines. One of these semi-synthetic products, 3β-acetoxyursolic acid [1-(2-aminoethylamino)-1-oxo]ethyl ester (**14**) (Fig. 3), was found to exhibit discernible cytotoxicity, showing an IC_{50} value in the range 8–10 μM, while, the IC_{50} values of (+)-ursolic acid (**11**) were greater than 100 μM for all these three cancer cell lines used [58].

In addition, a series of novel pyrazole-fused (+)-ursolic acid derivatives was synthesized in a further structural modification of (+)-ursolic acid (**11**), by introduction of a pyrazole moiety at its C-2 and C-3 positions. Among these semi-synthetic derivatives, both a 2,3-*p*-pyrazol-1-yl-benzonitrile ursolic acid (**15**) (Fig. 3) and a 2,3–1-pyrazol-1-yl-cyclopropylmethyl ursolic acid (**16**) (Fig. 3) showed more potent cytotoxicity than either the other pyrazole-fused derivatives produced or the parent compound (**11**), toward a small panel of human cancer cell lines [59]. Surprisingly, compound **15** was found to induce HeLa human cervical cancer cell death through hyperstimulation of micropinocytosis, which can induce methuosis, a non-apoptotic type of cell death. This may provide a useful probe for the development of new cancer therapeutic agents to combat the multidrug resistance problem [59].

To improve on its water solubility for potential clinical applications, a carrier-free nanodrug by self-assembly of (+)-ursolic acid (**11**) has been developed, as a result of which the inhibitory effects on proliferation of A549 human lung cancer cells were found to be enhanced. Also, tumor growth was inhibited significantly, when six- to eight-week old BALB/*c-nu* female nude mice inoculated with A549 cells were treated with (+)-ursolic acid (**11**) or with (+)-ursolic acid-nanoparticles (i.p., 8 mg/kg, daily) for three weeks, and, in addition, the population of CD4$^+$ T-cells in the mice was increased. These results indicate that this (+)-ursolic acid-nanoparticle carrier-free nanodrug has the potential for use in cancer immunotherapy [60].

Mechanistically, (+)-ursolic acid (**11**) mediates its antitumor potential through inhibition of NF-κB activation induced by carcinogenic agents with targets at cyclooxygenase 2, matrix metalloproteinase 9, and cyclin D11 [61]. It also inhibits tumor growth through other promising mechanisms involving angiogenesis and metastasis [53]. In a phase I study to assess the multiple-dose tolerability, efficacy, and pharmacokinetics of a liposomal form of (+)-ursolic acid, patients with confirmed advanced solid tumors were administered with this drug candidate intravenously for 14 consecutive days of a 21-day treatment cycle. The (+)-ursolic acid liposome used was found to be safe and well-tolerated and showed improved potential for improving patient remission rates. Accordingly, a phase II study was recommended for this (+)-ursolic acid liposome drug candidate [62].

Cucurbitane-type Triterpenoids

Cucurbitacins are highly oxygenated cucurbitane-type tetracyclic triterpenoids that were identified initially from the plant family Cucurbitaceae and have been divided into twelve major structural categories [63]. Members of this group of natural products have been reported for their promising anticancer and anti-inflammatory activities [64], of which (+)-cucurbitacins B (**17**) and D (**18**) and (–)-cucurbitacins E (**19**) and I (**20**) have been investigated extensively for their cytotoxicity toward several human cancer cell lines (Fig. 4) [64, 65]. For example, (+)-cucurbitacin D (**18**) has been found to show potent cytotoxicity against a variety of human cancer cell lines, including human breast, central nervous system, colon, lung, oral epidermoid, and prostate cancer cells, with such activity mediated by induction of cell cycle arrest, mostly in the G2/M phase, and acting by modulating the JAK-STAT, Aκt-PKB, and MAPK pathways [63–65].

In a study conducted in our own laboratory, (+)-cucurbitacin D (**18**) was characterized as a major cytotoxic component against HT-29 human colon cancer cells from both the fruits and stem bark of *Elaeocarpus chinensis* (Gardner & Champ.) Hook.f. ex Benth. (syn.: *Friesia chinensis* Gardner & Champ.) (Elaeocarpaceae), collected in Vietnam, and showed an IC$_{50}$ value of 0.12 μM (the positive control, paclitaxel, showed an IC$_{50}$ value of 6 nM) [66].

Analysis of the structures of these potently cytotoxic triterpenoids, including (+)-cucurbitacins B (**17**) and D (**18**) and (–)-cucurbitacins E (**19**) and I (**20**), shows that they all contain a C-2 hydroxy group, a ketocarbonyl group at the C-3 and C-11 positions, a double bond at the C-1 and/or C-5 positions, 16α,20β-dihydroxy groups, a C-22 enone group, and a C-25 hydroxy or acetoxy group, indicating that these structural moieties could be important for a given cucurbitacin to mediate cancer cell-line cytotoxicity. This has been supported by

a study examining the chemical structures of 24 cucurbitacins and determining their resultant cytotoxicity against KB human oral epidermoid carcinoma cells, which showed that the presence of an α,β-unsaturated ketone and a C-25 acetoxy group, along with a free 16α-hydroxy group, are the most relevant structural features required for such activity [65].

An additional biological investigation showed that all of (+)-cucurbitacin D (**18**) and (−)-cucurbitacins E (**19**) and I (**20**) exhibited potent cytotoxicity against SW 1353 human chondrosarcoma cells, with the activity decreasing in the sequence **19**, **20**, and **18** [67]. This indicates that introduction of a C-1 enone group or replacement of C-25 hydroxy group with an acetoxy group could increase the cytotoxicity of (+)-cucurbitacin D (**18**) toward SW 1353 cells.

Consistent with these conclusions, (+)-cucurbitacin D (**18**) was found to exhibit around tenfold more cytotoxic potency than (+)-cucurbitacin F (**21**) (Fig. 4) against all of the A549 non-small cell lung cancer, HCT-15 colon cancer, SK-MEL-2 melanoma, SKOV3 ovarian cancer, and XF 498 human central nervous system (CNS) human cancer cell lines. Furthermore, saturation of C-23 double bond in (+)-23,24-dihydrocucurbitacin F (**22**) (Fig. 4) resulted in loss of activity (IC_{50} >50 μg/mL) against both KB human solid tumor and P-388 murine leukemia cells, when compared with (+)-cucurbitacin F (**21**), which showed activity toward KB and P-388 cells, with IC_{50} values of 0.074 and 0.04 μg/mL, respectively [68, 69].

The antineoplastic potential of all (+)-cucurbitacins B (**17**) and D (**18**) and (−)-cucurbitacins E (**19**) and I (**20**) have been reviewed previously [64, 65]. Briefly discussed below are an update of more recent studies on the anticancer potentials of the representative compound, (+)-cucurbitacin D (**18**).

(+)-Cucurbitacin D (**18**) has been found to suppress the proliferation of Hep3B human hepatoma cells [70], as well neurofibromatosis type 2 (*Nf2*)-deficient mouse Sch10545 schwannoma and telomerase-immortalized benign Ben-Men-1 human meningioma cells [71]. Also, this agent induced apoptosis in the doxorubicin-resistant human MCF7/ADR breast cancer cells through inhibiting STAT3 and NF-κB signaling [72], and its inhibitory effects toward human T cell leukemia cells were found to be associated with autophagy [73].

Interestingly, (+)-cucurbitacin D (**18**) was found to mediate cytotoxicity toward MCF-7 human breast cancer cells through disrupting interactions between heat shock protein 90 (Hsp90) and two co-chaperones, Cdc37 and p23 [74]. Tumor growth was inhibited significantly when six-week old female athymic nude mice inoculated with CaSki human cervical cancer cells were treated with (+)-cucurbitacin D (**18**) (injected intratumorally, 1 mg/kg, three times a week) for four weeks [75].

All of (+)-cucurbitacins B (**17**) and D (**18**) and (−)-cucurbitacins E (**19**) and I (**20**) are potently cytotoxic, and, in general, these triterpenoids are strong STAT3 inhibitors and thus show selective inhibitory activity toward the JAK/STAT pathway [64, 65]. STAT3 is a promising target for the discovery of new anticancer drugs, and thus cucurbitacins **17**–**20** may accordingly prove useful in the treatment of human cancer targeting STAT3.

Dammarane-type Triterpenoids I: Ginsenoside Sapogenins

In Chinese traditional medicine, the roots of *Panax ginseng* C.A. Meyer (ginseng) (Araliaceae), known locally as "renshen", are used as a complementary and alternative herbal supplement to support cancer chemotherapy [76]. The ginsenosides, containing mainly dammarane-type tetracyclic triterpene saponins, have been characterized as the major components of ginseng, and have attracted a great deal of attention owing to their promising bioactivities, including potential antitumor efficacy [77, 78]. As one of the major sapogenins of these ginsenosides, 20(*S*)-protopanaxadiol [20(*S*)-PPD, **23**] (Fig. 5) has been well documented for its potent antitumor activity, and is known mechanistically to induce tumor cell apoptosis and to suppress the NF-κB, JNK, and MAPK/ERK signaling pathways. It also exhibits antimetastasis and antiangiogenesis activities, as well as synergistic effects with existing anticancer drugs [78].

An *in vitro* study showed that 20(*S*)-PPD (**23**) exhibited only marginal activity toward a small panel of human cancer cell lines, with the IC_{50} values being in the range 20–80 μM [79]. In contrast, its growth inhibitory effect against MDA-MB-231 triple-negative human breast cancer cells was more highly evident (IC_{50} 5.9 μM), which was comparable to the potency determined for paclitaxel (IC_{50} 6.2 μM) [80]. This sapogenin (**23**) induced SF188 and U87MG human glioma cell apoptosis and autophagy through both caspase-dependent and -independent pathways [81], and it also inhibited Hep-2 human laryngeal carcinoma cell proliferation through apoptosis induction caused by down-regulation of the expression of the mTOR signaling pathway [82].

In an *in vivo* antitumor investigation, the sensitivity of radiotherapy to laryngeal carcinoma was found to be increased by 20(*S*)-PPD (**23**). When BALB/*c* female nude mice (18–22 g) bearing Hep-2 laryngeal tumors were treated with **23** (i.p., 20 mg/kg, once every two days), ionizing radiation (IR) (5 Gy), or **23** (i.p., 20 mg/kg, once every two days) plus IR (5 Gy) for two weeks, tumor growth was inhibited significantly in both the individual and combined treatments, and the combination (**23** plus IR) treatment caused more substantial decreases of tumor volume and weight [83].

In addition, an anti-colon tumor efficacy mediated through the TRAIL pathway was observed for 20(*S*)-PPD (**23**), when four-week old athymic female nude mice inoculated with HCT-116-luc human colon cancer cells were treated with **23** (i.p., 25 or 50 mg/kg, once two every days) for four weeks [84].

It is worthy of note that 20(*S*)-PPD (**23**) significantly enhanced the antitumor action of 5-flurouracil (5-FU), when four- to six-week old BALB/*c* female nude mice inoculated with HCT-116-luc human colon cancer cells were treated (i.p.) with 5-FU (30 mg/kg) or compound **23** (15 or 30 mg/kg) plus 5-FU (30 mg/kg) once a week for six weeks [85].

Also, 20(*S*)-PPD (**23**) delayed the castration-resistant regrowth of LNCaP prostate tumors after androgen-deprivation therapy and inhibited castration-resistant 22Rv1 prostate tumor growth with endogenous expression of AR-FL and AR-Vs, when male nude mice inoculated with LNCaP or 22Rv1 were treated with 20(*S*)-PPD (**23**) (gavage, 40 mg/kg, daily, six days per week) for four weeks [86]. A very recent investigation on the role of 20(*S*)-PPD (**23**) in

endometriosis (EMS) showed its anti-EMS activity, which was mediated possibly by control of estrogen-mediated autophagy regulation and improved natural killer (NK) cell cytotoxicity [87].

To increase its drug-like properties, nanosuspensions of 20(*S*)-PPD (**23**) have been prepared, and its oral bioavailability was found to be improved, when compared with the unmodified form of this compound [88]. An *in vivo* study showed that tumor growth was inhibited, when ICR mice inoculated with H22 murine sarcoma cells were treated with nanosuspensions of compound **23** (injected via the lateral tail vein, 20, 50, or 100 mg/kg, daily) for nine days [88].

To identify the structural requirements for the activity, a hydrogenated derivative, 20(*S*)-24,25-dihydroprotopanaxadiol [20(*S*)-2H-PPD (**24**), Fig. 5], was synthesized from 20(*S*)-PPD (**23**), and this synthetic analogue showed less potent cytotoxicity toward MDA-MB-231 human breast cancer cells than the parent compound, **23** [80]. However, an analogous compound, 20(*R*)-25-OH-PPD (**25**) (Fig. 5), isolated from the fruits of *Panax ginseng*, was found to show more potent cytotoxicity than 20(*S*)-PPD (**23**) toward a panel of human cancer cell lines. This cytotoxic sapogenin (**25**) was absorbed and distributed rapidly in the plasma and in the kidney, liver, spleen, and tumor tissues, after nude male mice bearing xenografts of human pancreatic tumors were treated (i.v. and oral) with this compound at doses of 10 and 20 mg/kg, respectively, indicating its relatively favorable pharmacokinetic properties [79, 89].

Interestingly, a methylated sapogenin, 20(*S*)-25-OCH$_3$-PPD (**26**) (Fig. 5), isolated from the leaves of *Panax notoginseng* (Birkill) F.H. Chen ex C.H. Chow showed cytotoxicity toward SW620 human colon cancer cells, with the IC$_{50}$ value being less than 5 μM. This sapogenin (**26**) induced LS174 and SW480 colon and A549 lung human cancer cell apoptosis by suppression of Wnt/β-catenin signaling [90], and it also inhibited t-HSC/Cl-6 murine hepatic stellate cell activation by inducing apoptosis and elevating the level of cellular glutathione, indicating that it exerts an antifibrosis effect on activated t-HSC/Cl-6 cells [91].

Both 20(*R*)-25-OH-PPD (**25**) and its close analogue, 20(*R*)-25-OCH$_3$-PPD were found to inhibit significantly the growth of human BGC-823, SGC-7901, and MKN-28 gastric cancer cells [92]. These two compounds also inhibited HPAC and PANC-1 human pancreatic cancer cell growth [93]. Pancreatic tumor growth was inhibited, when four- to six-week old male athymic nude *nu*/*nu* mice inoculated by Panc-1 cells were treated (i.p.) with both compounds separately (1, 5, or 10 mg/kg, daily, five days/week) for six weeks [93].

Mechanistically, 20(*R*)-25-OH-PPD (**25**) and 20(*R*)-25-OCH$_3$-PPD exhibited antipancreatic tumor efficacy partially through inhibition of the MDM2 oncogene and related pathways [93]. Mouse double minute 2 homolog (MDM2) protein is an important negative regulator of the p53 tumor suppressor and is regarded as a target for cancer chemotherapy. Thus, these two sapogenins show promise in terms of their potential anticancer activity targeting MDM2.

Importantly, 20(S)-25-OCH$_3$-PPD (**26**) was found to be tolerated at doses up to 600 mg/kg, and no mortality and treatment-related toxicity were observed in Sprague-Dawley rats, when the rats were treated orally with this compound (daily, 150, 300 and 600 mg/kg) for 92 consecutive days [94]. Also, the water solubility of 20(S)-25-OCH$_3$-PPD (**26**) was improved by synthetic derivatization reactions [95]. These support strongly the further development of 20(S)-25-OCH$_3$-PPD (**26**) as a new anticancer agent.

Both 20(S)-PPD (**23**) and 20(S)-protopanaxatriol [20(S)-PPT, **27**] (Fig. 5) are representative sapogenins of the ginsenosides, and these compounds were found to exhibit moderate cytotoxicity toward MDA-MB-231 human breast cancer cells. However, their hydrogenated derivatives, 20(S)-24,25-dihydroprotopanaxadiol [20(S)-2H-PPD (**24**)] and 20(S)-24,25-dihydroprotopanaxatriol [20(S)-2H-PPT (**28**)], were less potent than the parent compounds, **23** and **27**, respectively [80], indicating the functional importance of a C-24/25 double bond in these compounds. In addition, 20(S)-PPD (**23**) was more active than 20(S)-PPT (**27**) against MDA-MB-231 cells [80], showing that introducing an α-hydroxy group at the C-6 position results in the cytotoxic potency of 20(S)-PPD (**23**) being decreased. This was supported by the cytotoxicity observed for 20(R)-25-OH-PPD (**25**) and 20(R)-25-OH-PPT (**29**) toward a panel of human cancer cell lines, including breast, glioma, lung, pancreatic, and prostate cancer cells, for which **25** showed weak activity, with IC$_{50}$ values in the range 10–70 μM, but **29** did not (IC$_{50}$>100 μM) [79].

Dammarane-type Triterpenoids II: Ginsenosides

In analogous work, the antitumor potential has been investigated extensively for the PPD-type ginseng saponins, including the 20(S)-ginsenosides Rh$_2$ (G-Rh2, **30**) and Rg$_3$ (G-Rg3, **31**), and ginsenosides Rh$_3$ (G-Rh3, **32**), and Rk$_2$ (G-Rk2, **33**) (Fig. 6) [76, 78, 79, 96]. Of these, G-Rh2 (**30**) was up to ten-fold more active than G-Rg3 (**31**) toward a panel of human cancer cells [79], indicating that introducing an additional sugar unit in the C-3 saccharide moiety decreases the cytotoxic potency of G-Rh2 (**30**).

When 14 ginsenosides isolated from the steamed (heat-processed) leaves of *Panax ginseng* were evaluated for their cytotoxicity toward HL-60 human leukemia cells, G-Rh2 (**30**), G-Rh3 (**32**), and G-Rk2 (**33**) were found to be active, while **32** and **33** were the most potently active, showing IC$_{50}$ values of 0.8 and 0.9 μM, respectively [97], indicating that a double bond at the C-20(21) or C-20(22) position enhances the cytotoxicity of G-Rh2 (**30**).

The antineoplastic potential of various ginsenosides has been reviewed previously [78], and thus presented immediately below is an update of this topic, with G-Rh2 (**30**) being used as a representative example.

In recent studies, G-Rh2 (**30**) was found to significantly suppress cell proliferation, invasion, and migration in HEC1A human endometrial cancer cells [98], and it also decreased the viability of U87MG and A172 human glioma cells [99]. It induced ROS (reactive oxygen species)-mediated ER stress-dependent apoptosis in H1299 human lung cancer cells [100] and induced apoptosis in KG-1a human leukemia cells [101].

In an *in vivo* study, hepatoma growth was inhibited significantly, when 18–22 g female mice inoculated with H22 murine hepatoma cells were gavaged with G-Rh2 (**30**) (3 or 4 mg/kg, daily) for ten days [102]. A further study showed that hepatoma growth was inhibited significantly, and the serum IL-2 levels, TNF-α production, T lymphocytes, $CD4^+/CD8^+$ ratio, and NK cell levels of mice were increased, when seven- to eight-week old male Kunming mice inoculated with H22 cells were gavaged with G-Rh2 (**30**) (5 or 10 mg/kg, daily) for 15 days. This indicates that G-Rh2 mediates its antitumor activity partially through modulation of the immune system [103]. No obvious toxicity was observed in the mice used in these *in vivo* studies [102, 103].

Mechanistically, G-Rh2 (**30**) exhibits its potential antitumor activity through modulating the Aκt and Wnt/β-catenin signaling pathways [99, 101]. It targets EZH2 (the polycomb repressive complex 2 component enhancer of zeste homologue 2), a potent histone methyltransferase that catalyzes the trimethylation of histone 3 and lysine 27 [104], down-regulates the expression of the inhibitors of apoptosis (IAP), and synergizes with Annexin A2 inactivation to promote apoptosis [105]. Both EZH2 and Annexin A2 are over-expressed in liver cancer, and thus G-Rh2 (**30**) has been regarded as a promising candidate agent for targeted liver cancer therapy [105].

Interestingly, G-Rh2 (**30**) was found to mediate its antitumor efficacy by modulating the immune response [103, 106]. G-Rh2 (**30**) triggered $CD4^+$ and $CD8a^+$ T-lymphocyte infiltration in tumor tissues and increased T-lymphocyte cytotoxicity. An enhanced antitumor immunological response contributes to preventing the recurrence of cancer, and, thus, G-Rh2 (**30**) could serve as an adjuvant for use with existing cancer chemotherapeutic agents [106].

Dichapetalin-type Triterpenoids

A final group of triterpenoids selected for inclusion in this review are compounds of the dichapetalin-type. These compounds constitute a small group of 13,30-cyclodammarano[4,3]pyran derivatives, with the first member, (+)-dichapetalin A (**34**) (Fig. 7), being reported from *Dichapetalum madagascariense* Poir. (Dichapetalaceae) in 1995. In this reference, the authors reported a greater susceptibility of (+)-dichapetalin A (**34**) against the L1210 murine leukemia cell line (EC_{90} <0.0001 μg/ml) than against the KB human oral epidermoid carcinoma cell line [107]. This trend was noted also by Tuchinda et al., for their isolate (+)-acutissmatriterpene E (**35**) (Fig. 7) from *Phyllanthus acutissima* Miq. (Phyllanthaceae), which was more potently cytotoxic for the P-388 murine lymphocytic leukemia cell line (IC_{50} 0.005 μg/ml) than for the other human cancer cell lines evaluated, using ellipticine (IC_{50} 0.2 μg/mL toward P-388 cells) as the positive control [108].

The interest of our group in this class of compounds was stimulated by the isolation of several cytotoxic dichapetalins from the stem bark of *Dichapetalum gelonioides* (Roxb.) Engl. (Dichapetalaceae) collected in the Philippines, among which (+)-dichapetalin A (**34**) exhibited its most potent cytotoxic effects toward the SW626 human ovarian cancer cell line (IC_{50} 0.2 μg/ml). Also obtained in this study were the new (+)-dichapetalins I (**36**) and J (**37**)

(Fig. 7), which again demonstrated their most potent cytotoxic activity for SW626 cells (IC$_{50}$ 0.5 and 0.4 μg/ml, respectively) [109].

However, when tested in a follow-up *in vivo* hollow fiber assay, (+)-dichapetalin A (**34**) was inactive when tested in mice at doses of 1, 2, 4, and 6 mg/kg (i.p. administration) for four different types of human cancer cell lines, including SW626 cells [109]. In a more recent investigation by our group, a non-cytotoxic dichapetalin A analogue, (+)-songbodichapetalin (**38**) (Fig. 7), was isolated from the aerial parts of *Phyllanthus songboiensis* N. N. Thin (Phyllanthaceae) collected in Vietnam [110].

Analysis of the dichapetalin derivatives and their cytotoxic activity against cancer cell lines indicates that a methylenedioxy group connected at the C-3′ and C-4′ position is not required for this type of activity, but the presence of a hydroxy group at the C-22 position can enhance cytotoxicity. In addition, a primary C-26 hydroxy group seems to play a key role in determining the cytotoxic potency of the dichapetalin-type triterpenes [108, 110]. These preliminary SAR conclusions indicate that the antitumor potential of the dichapetalins could be improved by synthetic modification. Owing to their inherently potent cytotoxic potency for certain cancer cell lines, this group of cyclodammarane-type triterpene lactones seems worthy of additional *in vivo* antineoplastic testing and mechanism-of-action studies.

Conclusions

Plant-derived triterpenoids were frequently encountered along with more promising compounds in early anticancer screening campaigns. However, this type of natural products were deemed to be of insufficient promise for further development or more in-depth biological investigation, because of their general lack of potency in inhibiting the growth of the panels of murine and human cancer cell lines. Fortunately, over the last nearly 20 years, there has been an undeniable uptake of interest in the antitumor activities of triterpenoids, which have been supported by promising effects observed *in vivo* and by supportive mechanism-of-action investigations. For example, (+)-ursolic acid (**11**), a pentacyclic triterpenoid distributing widely in plants, modulates several important inflammation associated signaling pathways, including NF-κB, STAT3, and TRAIL signalings, and has reached cancer clinical trials [111]. Several triterpenoids decrease the expression of specificity protein (Sp) transcription factors in cancer cells. They also induce ROS, an important proteasome-independent pathway for downregulation of Sp transcription factors, and activate or deactivate nuclear receptors and G-protein coupled receptors, which contribute to their antitumorigenic activity [112]. In this regard, the recent progress made on plant triterpenoids as potential cancer chemotherapeutic agents is analogous to that made on sesquiterpene lactones of plant origin [113].

Isolation chemistry work on a given cytotoxic plant lead tends to afford a suite of structurally related active compounds and permits an initial evaluation of structure-cytotoxicity relationships, which in turn may guide the subsequent synthesis of more potent analogues of a bioactive compound. New techniques of formulation, such as the production of liposomes and nanoparticules of triterpenoids, have enabled both the resultant water solubility and bioavailability of the leading compounds to be enhanced. A range of

mechanistic effects on cancer cells have been shown for the triterpenoids, including inhibition of NF-κB and the induction of autophagy and/or the modulation of the human immune system. These mechanisms may contribute to limiting multidrug resistance, and thus, it may be confidently predicted that naturally occurring triterpenoids and their semi-synthetic derivatives will remain as promising leads for the development of new anticancer drugs in future years.

Acknowledgements

Abbreviations

AIF	apoptosis-inducing factor ()
CDDO-Me	methyl 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oate or bardoxolone methyl
Dap	dolaproine
Dil	dolaisoleuine
DLT	dose-limiting toxicities
Dov	N,N-dimethyl-L-valine
EMS	endometriosis
ER	endoplasmic reticulum
EZH2	the polycomb repressive complex 2 component enhancer of zeste homologue 2
G-Rh2	20(S)-ginsenoside Rh_2
G-Rg3	20(S)-ginsenoside Rg_3
G-Rh3	ginsenoside Rh_3
G-Rk2	ginsenoside Rk_2
GI$_{50}$	concentration that inhibits 50% cell growth
Hsp90	heat shock protein 90
IAP	inhibitors of apoptosis
ICR	Institute of Cancer Research
IFN-γ	interferon-γ
i.p.	intraperitoneal

i.v.	intravenous
JNK	c-Jun NH_2-terminal kinase
MAPK/ERK	mitogen-activated protein kinase/extracellular signal-regulated kinase
MDM2	mouse double minute 2 homolog
MDSC	myeloid-derived suppressor cells
MTD	maximum tolerated dose
NF-κB	nuclear factor kappa B
NK	natural killer
NOZ	NOZ human gallbladder cancer cell line
OA-MVL	oleanolic acid-encapsulated multivesicular liposome
PPD	protopanaxadiol
PPT	protopanaxatriol
ROS	reactive oxygen species
SAR	structure-activity relationship
STAT3	signal transducer and activator of transcription-3
TAM	tumor-associated macrophage
TNF-α	tumor necrosis factor-α
TRAIL	TNF-related apoptosis-inducing ligand
Val	L-valine
VEGF	vascular endothelial growth factor

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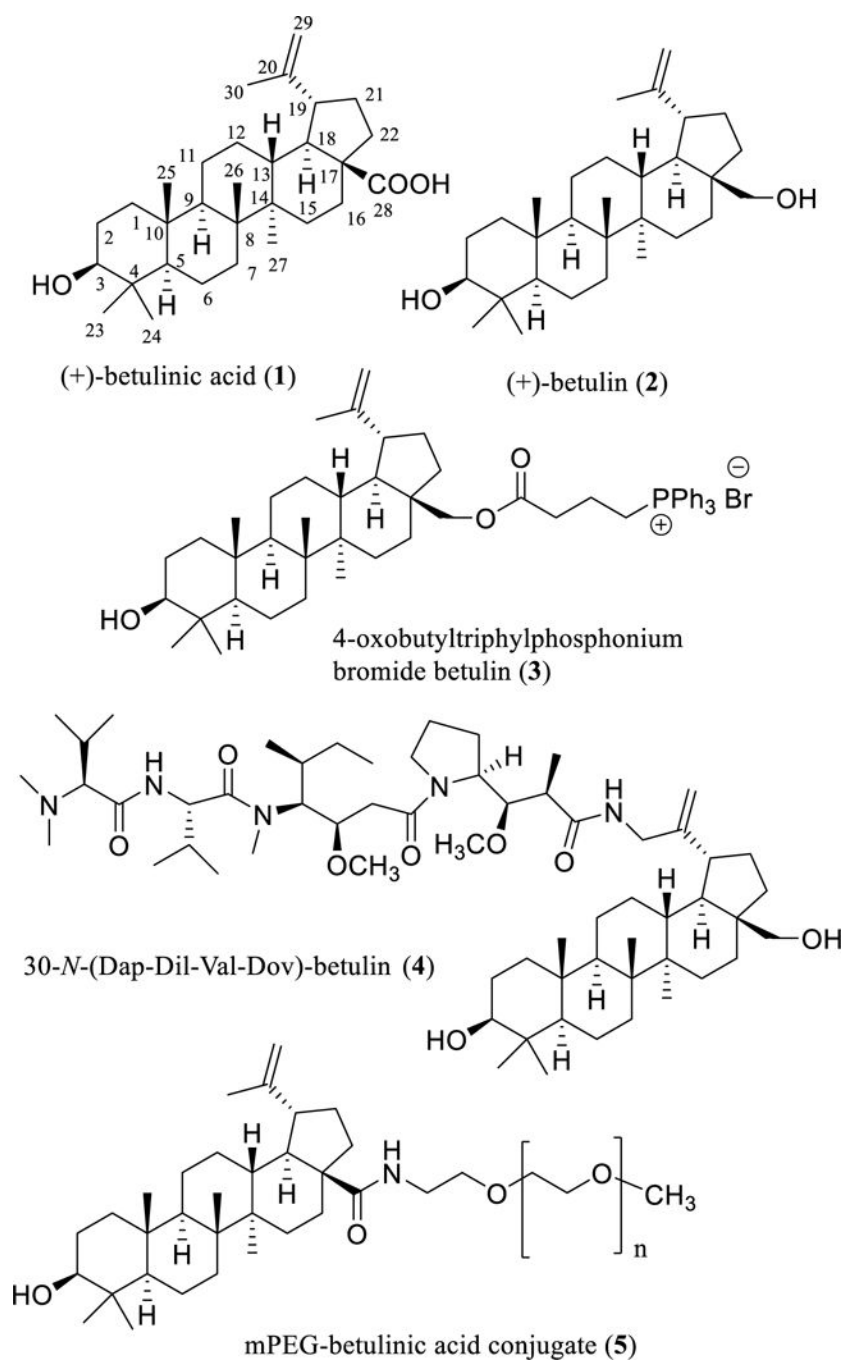
Fig. 1.
Structures of (+)-betulinic acid (**1**) and its natural and semi-synthetic derivatives (**2**–**5**) with potential anticancer activity (Dap: Dolaproine; Dil: Dolaisoleuine; Val: L-Valine; Dov: *N,N*-dimethyl-L-valine).
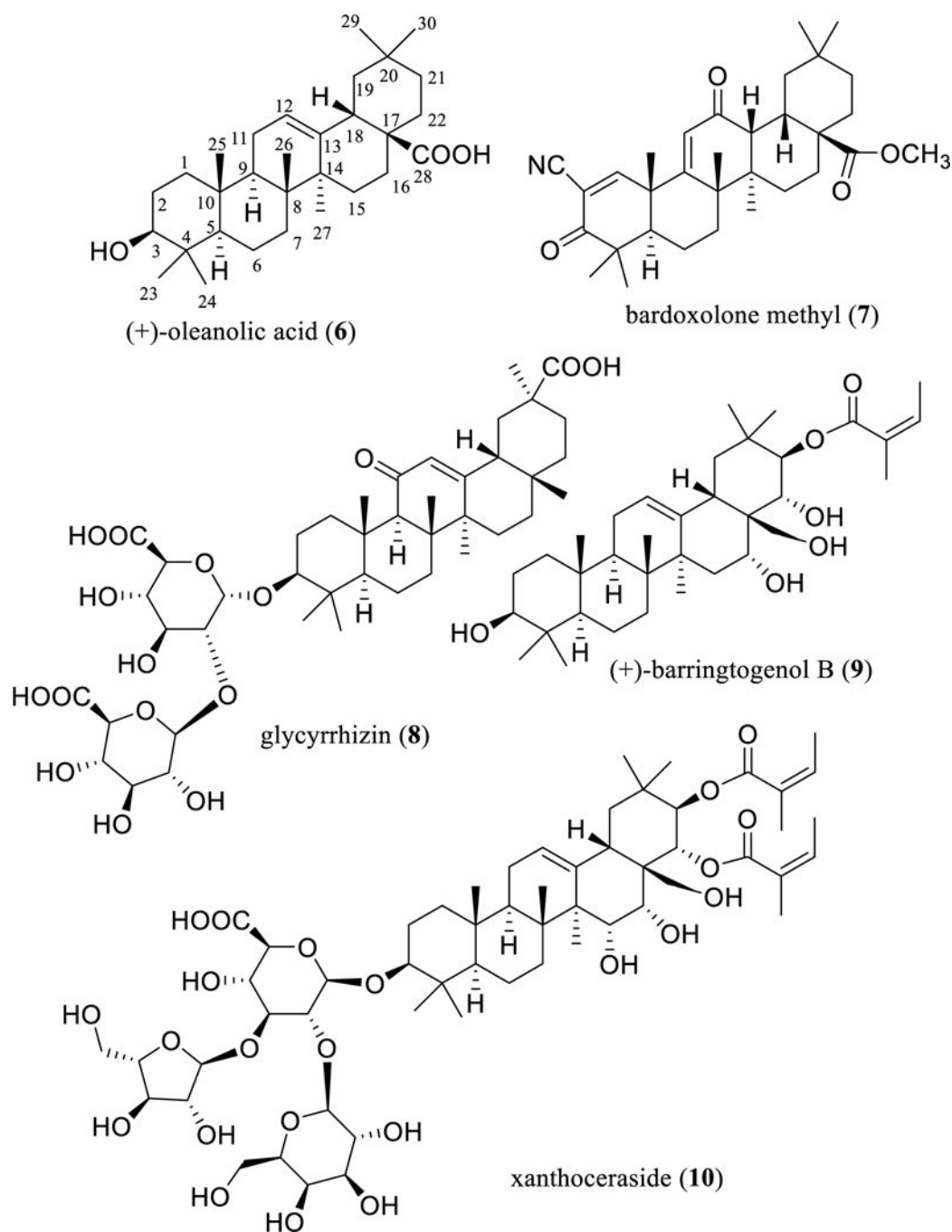
Fig. 2.
Structures of oleanane-type triterpenoids (**6** and **8**–**10**) and a semi-synthetic derivative (**7**) with potential anticancer activity.
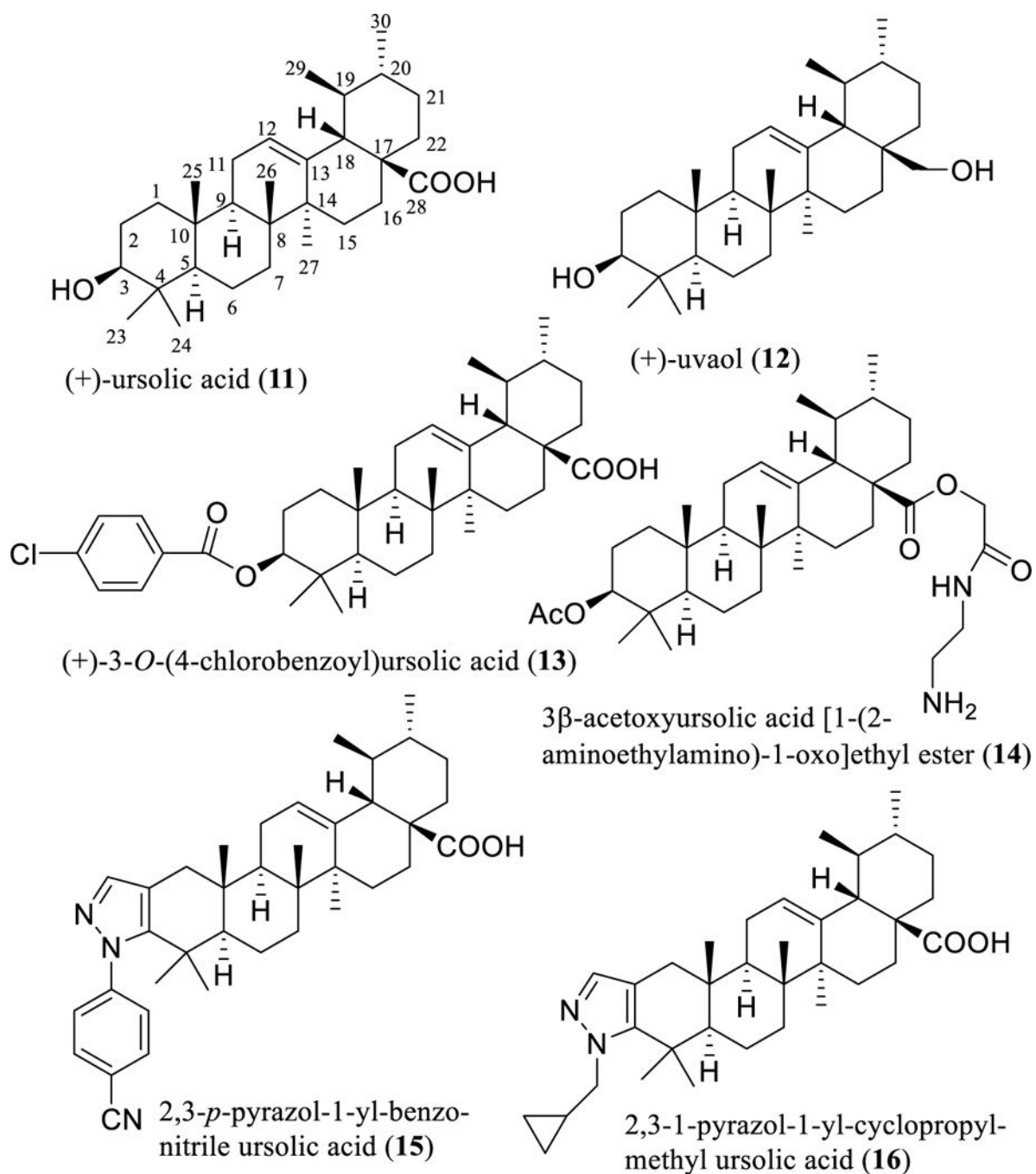
Fig. 3.
Structures of (+)-ursolic acid (**11**) and its semi-synthetic analogues (**12–16**) with potential anticancer activity.
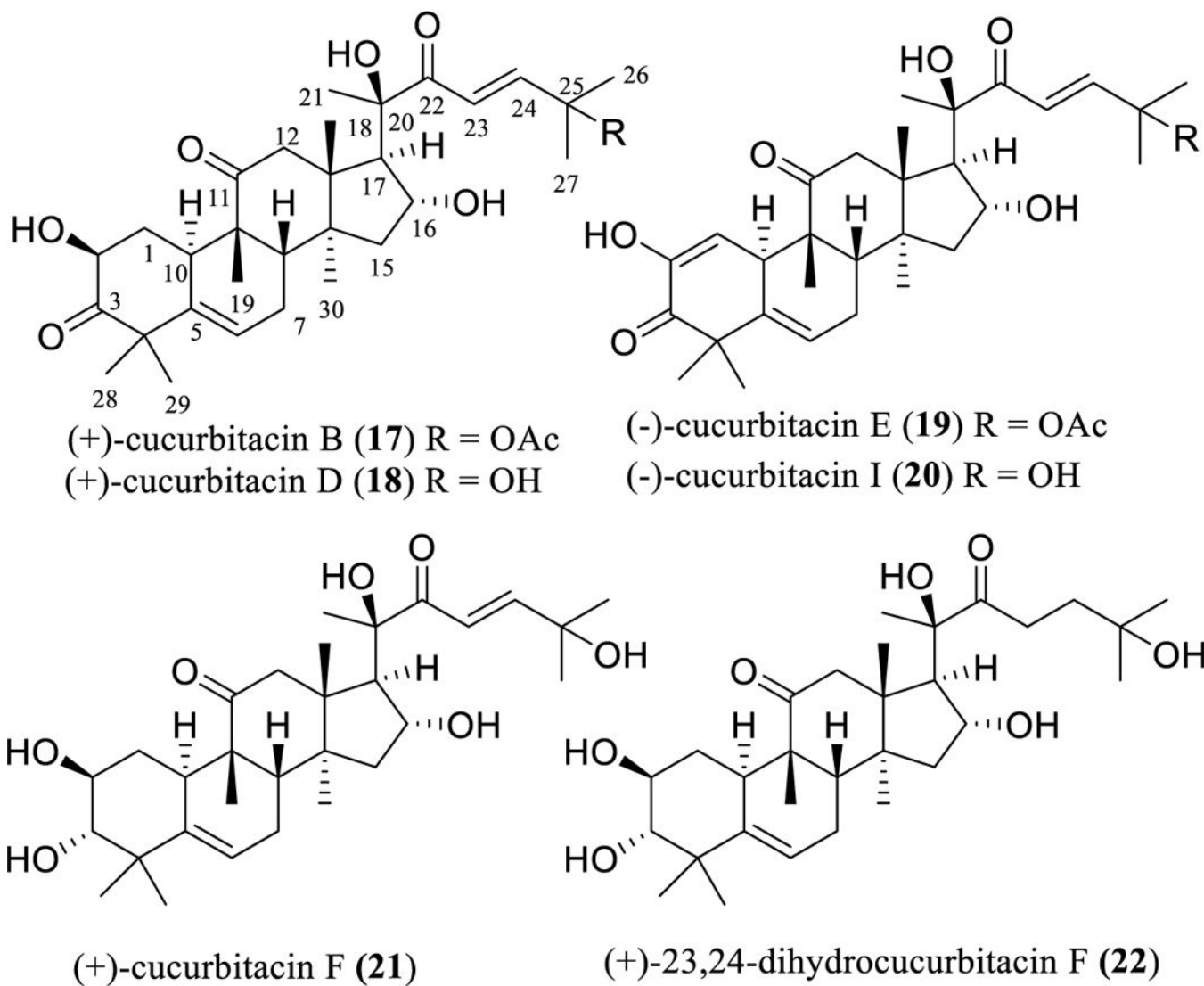
(+)-cucurbitacin B (**17**) R = OAc
(+)-cucurbitacin D (**18**) R = OH

(-)-cucurbitacin E (**19**) R = OAc
(-)-cucurbitacin I (**20**) R = OH

(+)-cucurbitacin F (**21**)

(+)-23,24-dihydrocucurbitacin F (**22**)

Fig. 4.
Structures of cucurbitacins (**17–21**) with potential anticancer activity and an inactive analogue (**22**).

20(S)-protopanaxadiol [20(S)-PPD, 23]

20(S)-24,25-dihydroprotopanaxadiol
[20(S)-2H-PPD (24)]: R = H

20(R)-25-OH-PPD (25): R = OH
20(S)-25-OCH₃-PPD (26): R = OCH₃

20(S)-protopanaxatriol [20(S)-PPT, 27]

20(S)-24,25-dihydroprotopanaxatriol
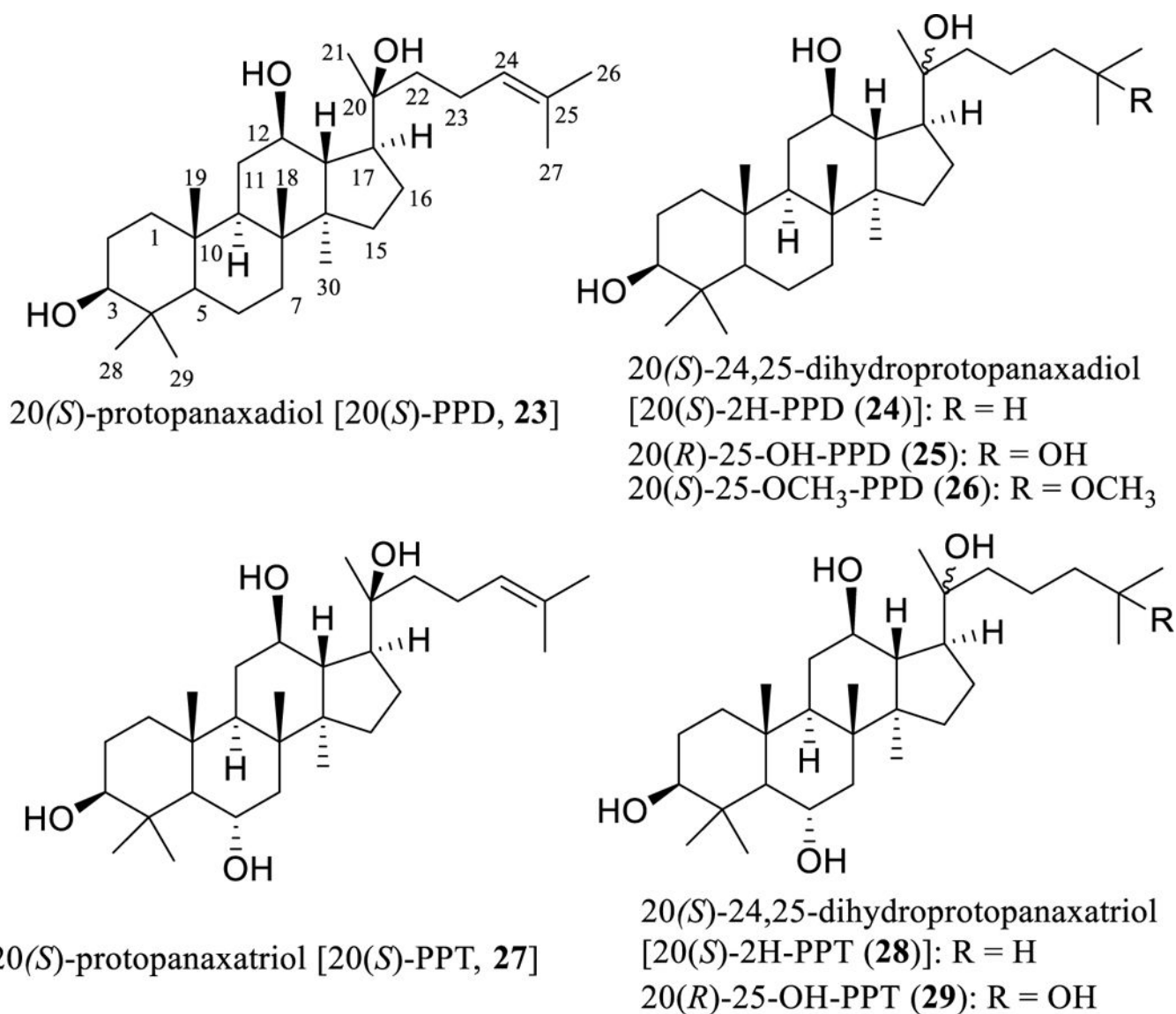[20(S)-2H-PPT (28)]: R = H

20(R)-25-OH-PPT (29): R = OH

Fig. 5.
Structures of dammarane-type triterpenoids (**23–29**) with potential anticancer activity.
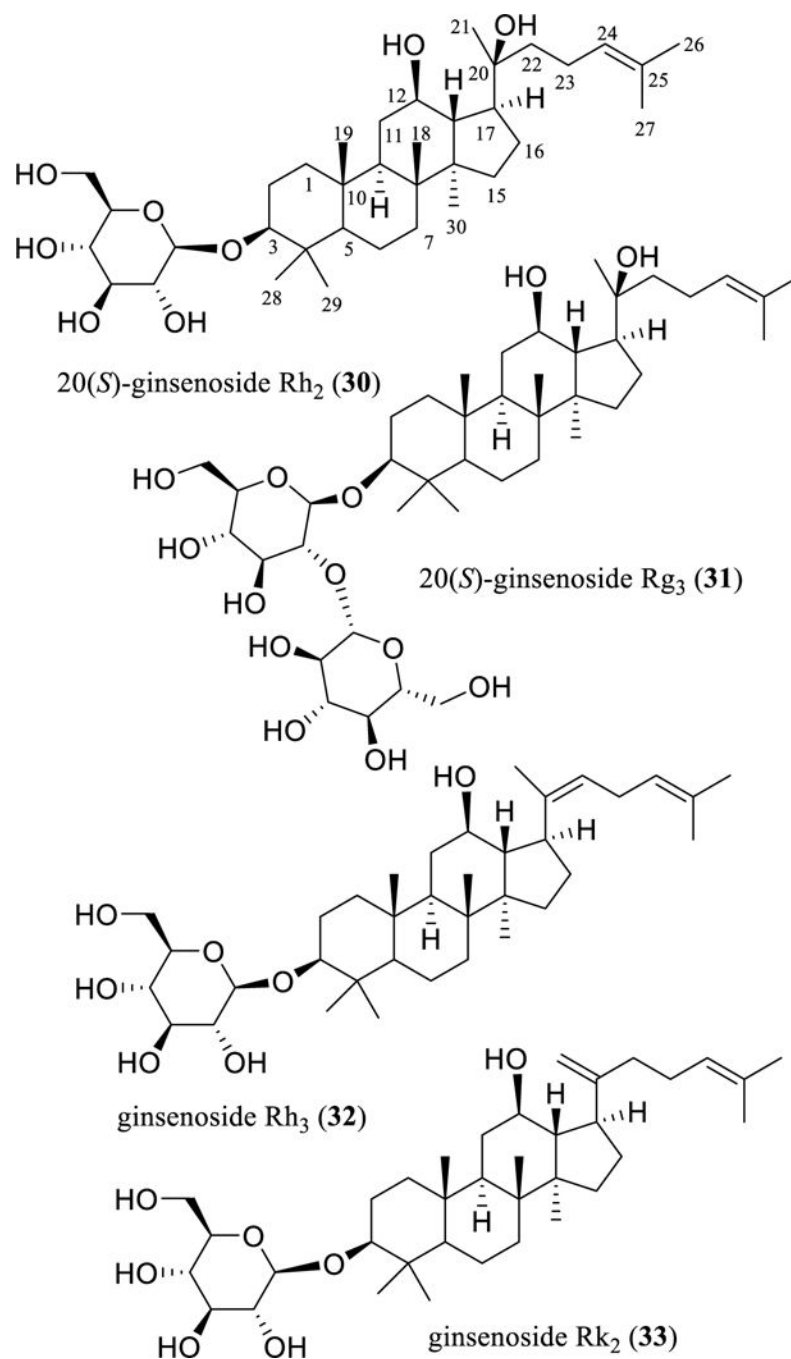
Fig. 6.
Structures of dammarane-type triterpenoid ginsenosides (**30**–**33**) with potential anticancer activity.
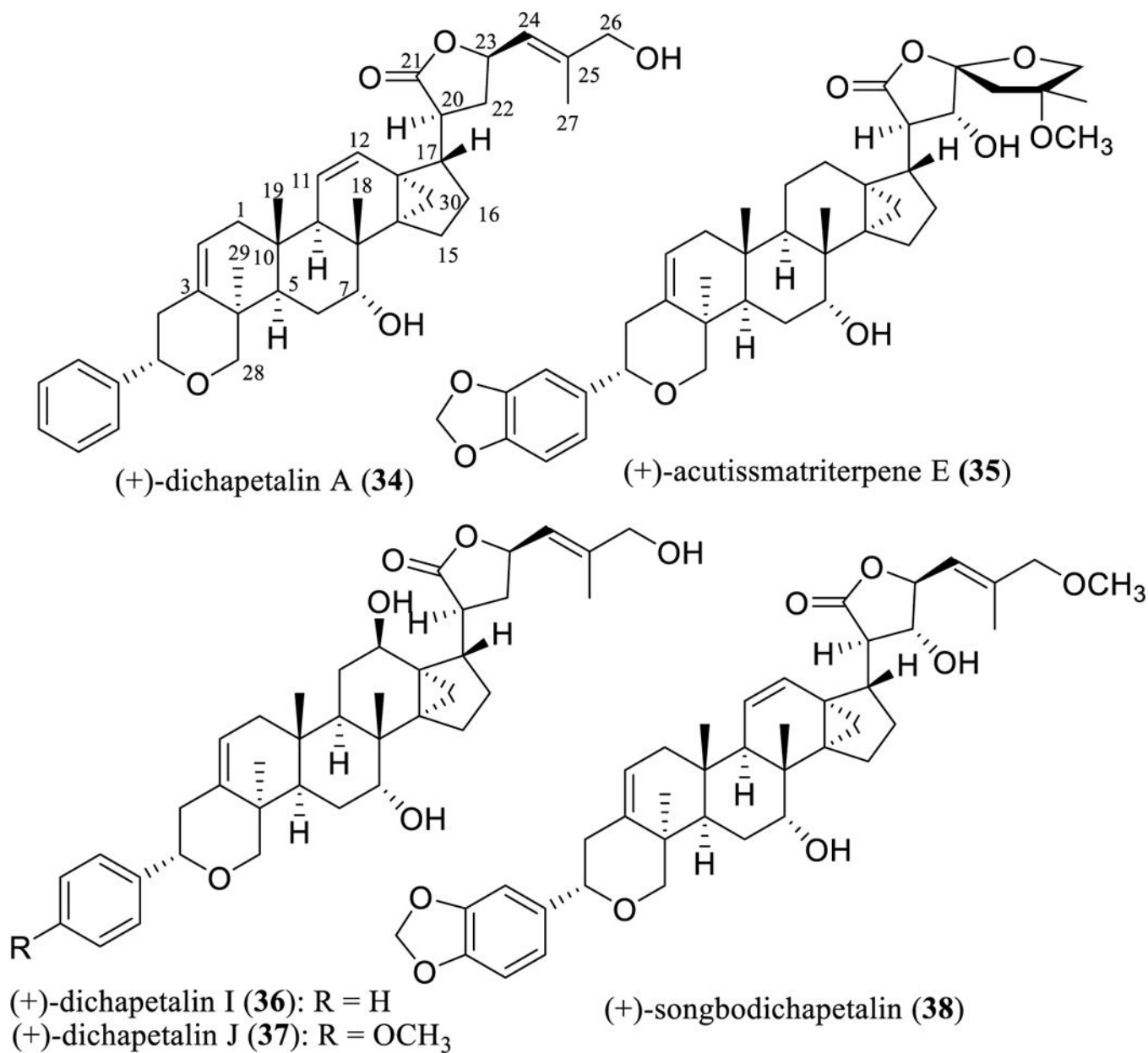
Fig. 7.
Structures of dichapetalin-type triterpenoids (**34–37**) with potential anticancer activity and their inactive analogue (**38**).