Triterpenoids as reversal agents for anticancer drug resistance treatment

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Overexpression of ATP-binding cassette (ABC) transporters in cancer cells results in multidrug resistance (MDR), which is one of the major obstacles in the treatment of cancer patients. None of the strategies to overcome MDR has been successfully applied in the clinic until now. Plenty of evidence shows that some triterpenoids function as reversal agents of MDR for anticancer drug resistance treatment. Here, we review the latest findings of reversing cancer MDR with triterpenoids. Findings are summarized showing that triterpenoids are MDR modulators and potential chemosensitizers. Finally, we contemplate future prospects of modulating MDR in the clinic.

Introduction
Resistance to chemotherapy is a major impediment to effective cancer treatment that has been intensively studied for the past three decades. The primary effect of anticancer drugs is to inhibit activities of target molecules, thereby triggering various cellular signal transduction pathways, leading to cell death or cell cycle arrest. These secondary effects result in apoptosis or other types of cell death including autophagy, mitotic, catastrophe, necrosis and senescence. Therefore, modifications of these genes and pathways can mediate anticancer drug resistance [1]. Drug resistance mechanisms can affect a single drug or target multiple drugs simultaneously. In the case of multidrug resistance (MDR), tumor cells possess intrinsic or acquired crossresistance to a variety of structurally and mechanistically unrelated drugs, impacting the effective treatment of cancer [2]. Although the molecular mechanisms can be diverse, such as mismatch DNA repair enzymes, upregulation of oncogenes or involving mutations of tumor suppressor genes, one of the most extensively studied mechanisms for pleiotropic MDR involves cellular drug efflux transporters.

ATP-binding cassette (ABC) transporters are a super family, with 48 different transporter proteins having been identified in humans so far. Among these transporters, P-glycoprotein (P-gp/ABCB1), multidrug-resistance protein 1 (MRP1/ABCC1) and, more recently, breast-cancer-resistance protein (BCRP/ABCG2) efflux drugs to reduce the accumulation and decrease intracellular retention of cytotoxic agents below therapeutic thresholds in MDR cancer cells, thereby limiting cancer kill [3]. A second mechanism for MDR involving these transporters could be the intracellular redistribution of cytotoxic agents away from the site of action. In this case, although the total cellular drug concentration is not reduced, an alteration of intracellular drug distribution limits exposure of the target organelle to the drug [4]. Accordingly, inhibition of ABC transporters could enhance the chemosensitivity of cancer treatment.

Triterpenoids are structurally diverse organic compounds, characterized by a basic backbone modified in multiple ways that enables the formation of more than 20,000 known members. Triterpenoids are synthesized from isopentenyl pyrophosphate through the 30-carbon intermediate squalene. Triterpenoids are widespread in nature, and can be found in, for example, fungi, ferns, single cotyledon and dicotyledonous plants, animals and marine organisms. Several triterpenoids, such as ursolic and
oleanic acid, betulinic acid, celestrol and lupeol, possess anti-oxidative and anti-inflammatory, anti-diabetic properties, and have been suggested to be potentially promising anticancer agents [5]. In addition, to improve anticancer activity, some synthetic triterpenoid derivatives have been synthesized, including cyanon-3,12-dioxooleana-1,9 (11)-dien-28-oic (CDDO), its methyl ester bardoxolone methyl (CDDO-Me) and imidazolide (CDDO-Im) derivatives, and they are presently under evaluation in Phase I studies [6].

In this review, we first discuss the chemical reactivity of triterpenoids and their anticarcinogenic mechanisms. Then, we focus on the interactions of them with some ABC transporters and explore their MDR reversal effects.

**Chemical properties of triterpenoids**

Triterpenoids are metabolites of isopentenyl pyrophosphate oligomers and comprise the largest group of natural products from plants, with over 20,000 known members. Triterpenoid carbon frameworks are cyclized by members of the oxidosqualene cyclase family. Oxidosqualene cyclases convert oxidosqualene to one or more cyclic triterpene alcohols with up to six carbocyclic rings [7]. The structural regions are heterogeneous, although the minor parts are acyclic, bicyclic and tricyclic triterpenoids; the two major types of oxidosqualene cyclases are tetracyclic and pentacyclic triterpenoids [7]. Tetracyclic triterpenoids include dammaranes, lanostanes, cycloartanes, cucurbitanes, tirucallanes and meliacanes, whereas pentacyclic triterpenoids include oleananes, ursanes, lupanes and friedelanes. The chemical classifications and core structures of triterpenoids are shown in Fig. 1. Triterpenoids exist in free form or combined with sugar into glycosides, and the latter are referred to as triterpenoid saponins. Saponins can be chemically categorized as comprising an aglycone linked to one or more sugar chains [8]. There are two groups of saponins: one containing a steroidal aglycone and the other containing a triterpenoid aglycone. Triterpenoid saponins can be synthesized from the attachment of hydrophilic monosaccharides or oligosaccharides to a hydrophobic sapogenin backbone. The common sugars attached to sapogenin are glucose, xylose, arabinose, rhamnose, galactose, glucuronic acid, acetyl and acetyl amino sugar, and so on. Squalene is considered the common precursor for biosynthesis of steroid and triterpenoid systems [9].

Free triterpene compounds can dissolve in petroleum ether, ethyl ether, chloroform, methanol, ethanol and other organic solvents, but can be insoluble in water [10]. Triterpenoid saponins are easy to dissolve in hot water, dilute alcohol, hot methanol and hot ethanol, whereas they are hardly soluble in acetone, ether, petroleum ether and polar organic solvents. The solubility of saponins in butyl alcohol mixed with water or amyl alcohol is much better, so the n-butyl alcohol is often used as the solvent to extract and separate saponins in experimental research [8]. Most triterpenoids can interact with strong acid (sulfuric acid, phosphoric acid or perchloric acid), medium acid (trichloroacetic acid) or Lewis acid (zinc chloride, aluminum trichloride, antimony trichloride) in anhydrous conditions, producing the color change

![Triterpenoid Structures](https://example.com/triterpenoid_structures.png)

**FIGURE 1**

The chemical classifications and core structures of triterpenoids. Based on the chemical structures, triterpenoids are mainly classified into tetracyclic triterpenoids and pentacyclic triterpenoids. Tetracyclic triterpenoids include dammaranes, lanostanes, cycloartanes, cucurbitanes, tirucallanes and meliacanes, whereas pentacyclic triterpenoids include oleananes, ursanes, lupanes and friedelanes.
or fluorescence, such as the Liebermann–Burchard reaction, Kahldenberg reaction, Rosen–Heimer reaction, and so on [10]. In addition, the saponins can connect with cholesterol in the cytomembrane to generate insoluble molecular compounds to destroy red blood cells. But not all saponins elicit a hemolysis effect; on the contrary, some saponins even have the capacity to be antihemolytic. Like ginseng, total saponins possess no hemolytic phenomena but, after subextraction, type B and C ginsenoside saponins do have significant hemolytic effects, whereas type A can resist hemolysis [8]. At present, the pharmacokinetics of triterpenoids have not been fully characterized, although several studies have been carried out in animals. Triterpenoids from the diet are believed to pass through the small intestine, be hydrolyzed to aglycone by enterobacteria in the ecum and colon and absorbed into epithelial cells via lipophilicity-dependent simple diffusion [11].

Anticancer properties of triterpenoids
Triterpenoids have attracted much attention as potential anticancer agents. Numerous reports on the chemopreventive and antigenotoxic effects of triterpenoids have been published. Triterpenoids are highly multifunctional and the antitumor activity of these compounds is measured by their ability to block nuclear factor (NF)-κB activation, induce apoptosis, inhibit signal transducer and cell proliferation, suppress angiogenesis, cause mitochondrial dysfunction and modulate MDR genes and proteins [12]. Various cellular receptors have been reported to be involved in the anticancer activities of triterpenoids, including an aryl hydrocarbon receptor, the androgen receptor and members of the vascular endothelial growth factor (VEGF) protein family [5]. Promoting apoptosis is another crucial tumor-suppression mechanism, with respect to which the triterpenoids are multi-targeted. For example, triterpenoids trigger apoptosis by down-regulating Bcl-2 and up-regulating caspase-3 [13]. Triterpenoids can also enhance tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL)-induced apoptosis and induce apoptosis through mitochondrial pathway activation [14]. In addition, a recent study shows a novel pathway by reducing telomerase hTERT gene expression to inhibit telomere end-transferase activity to induce apoptosis [15]. Recently, the antitumor properties of the celestrol methylester pristimerin, a natural triterpenoid isolated from Celastrus and Maytenus spp., have been reported, showing that this compound was more potent than celestrol in inhibiting NF-κB and proteasome activity and in inducing myeloma cell apoptosis in vitro and in vivo [16]. Studies carried out on cutaneous T cell lymphoma cells indicate that avicins, like other triterpenoids, inhibit phosphorylation of signal transducer and activator of transcription (STAT)3, and these observations have been confirmed in a large number of cancer cell lines, showing also that the inhibitory effects of avicins on STAT3 phosphorylation are dependent on inhibition of janus kinase (Jak)1 and Jak2 phosphorylation and activation of protein phosphatase-1 [17]. Allantus excelsa chloroform extract-1 (AECHL-1), a tereoisomeric cyclic triterpenoid that mediates growth suppression and has been linked to S-G2/M arrest, apoptosis induction and microtubule disruption [18]. In many studies, the influence of CDDO and its derivatives on growth inhibition in different solid tumors and leukemias was shown [19]. The mechanism of this action is independent of p53 status, whereas recruitment of proteins involved in the cell cycle, such as cyclin D1, p21, p27, proliferating cell nuclear antigen (PCNA), cavelin and Myc, seems to be important [20]. The latest studies on CDDO and its derivatives show that oleanane triterpenoid CDDO-Me inhibits Akt activity without affecting phosphoinositide-dependent kinase-1 (PKD1) kinase or protein phosphatase 2A (PP2A) activity in cancer cells [21]. In addition, Gao et al. reported that reactive oxygen species (ROS) have a vital role in the antiproliferative and apoptosis-inducing activity of CDDO-Me in ovarian cancer cells [22].

Triterpenoids as chemosensitizers of the multipump category
Triterpenoids showed growth-inhibitory activity on drug-sensitive and MDR cells. Betulinic, oleanolic and pomolic acids demonstrated cytotoxicity in MDR and sensitive leukemia cell lines [23]. Fifteen cycloartanes, isolated from Euphodinia spp., reversed MDR and induced apoptosis in L5178Y mouse lymphoma cells, including its MDR subline [24]. New A-ring- and/or C-ring-modified methyl oleanolate derivatives showed cytotoxic activity in KB, MCF-7 and HeLa cell lines [25]. In addition, triterpenoids at a noncytotoxic concentration enhanced the effect of chemotherapeutic drug on MDR cells. Data have shown that triterpenoids interacted directly or indirectly with transporter proteins to inhibit drug efflux mediated by either MDR1 or MR1 or BCRP [26–29]. Sipholane triterpenoids along with their semisynthetic derivatives were evaluated for their cytotoxicity and effect on human epidermoid carcinoma cells KB-3-1 and their resistant counterpart KB-C2 cells reversing Pgp-mediated MDR to colchicines [26]. The tested drugs include cancer chemotherapeutics colchicine, vinblastine, vincristine and paclitaxel, using the fluorescent substrate rhodamine-123. In one study, siphonol A was found to be the most potent, and it increased the sensitivity of resistant KB-C2 cells by 16 times toward colchicines [30]. In addition, accumulation and efflux studies with the P-gp substrate paclitaxel demonstrated that siphonol A dose-dependently increased the intracellular accumulation of paclitaxel by directly inhibiting P-gp-mediated drug efflux [30]. The interactions of triterpenoids with ABC transporters as well as their chemical structures are summarized in Table 1 and Fig. 2.

Mechanisms of triterpenoids reversing MDR
Interactions between triterpenoids and P-gp
P-gp (ABC1), encoded by the human MDR1 gene, was the first human ABC drug transporter identified [31] and today it is one of the best characterized multidrug efflux pumps. Plenty studies demonstrated that triterpenoids can efficiently inhibit its activity in many MDR cell lines with different mechanisms, including direct interaction with the P-gp active site, stimulating the activity of the P-gp ATPase or inhibiting the photoaffinity to drugs [30]. A study by Yoshida et al. showed that triterpenoids are capable of decreasing P-gp expression in a dose-dependent manner [32]. Earlier studies revealed that the expression of P-gp involves the Wnt/β-catenin signaling pathway [33] and HSF1-DNA-binding activity [34]. Triterpenoids reverse MDR partly through down-regulating P-gp expression and inhibiting the P-gp structure-related drug-efflux activity, and the latter is of more significance.

It is known that a biologically active P-gp consists of two homologous halves, each with one transmembrane domain
TABLE 1

<table>
<thead>
<tr>
<th>Triterpenoids</th>
<th>Compounds (increased accumulation)</th>
<th>Involved transporters</th>
<th>Cell lines</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cucurbitacin I</td>
<td>[3H]-Digoxin</td>
<td>P-gp</td>
<td>LLC-GA5-COL150</td>
<td>[50]</td>
</tr>
<tr>
<td>Cycloartane</td>
<td>Colchicine, rhodamine-123</td>
<td>P-gp</td>
<td>L5178 Y/Adr</td>
<td>[24]</td>
</tr>
<tr>
<td>Dehydrotumulosic acid</td>
<td>Vincristine, rhodamine-123</td>
<td>P-gp</td>
<td>K BV200</td>
<td>[43]</td>
</tr>
<tr>
<td>Ginsenoside Rg(3)</td>
<td>Vinblastine, rhodamine-123</td>
<td>P-gp</td>
<td>K BV20C</td>
<td>[33]</td>
</tr>
<tr>
<td>20(S)-Ginsenoside Rh2</td>
<td>Adriamycin</td>
<td>P-gp</td>
<td>MCF-7/Adr</td>
<td>[60]</td>
</tr>
<tr>
<td>Sipholenol A</td>
<td>Colchicine, rhodamine-123, paclitaxel, vinblastine</td>
<td>P-gp</td>
<td>KB-C2/KBV1</td>
<td>[30]</td>
</tr>
<tr>
<td>Ursolic acid</td>
<td>Daunorubicin, rhodamine-123</td>
<td>P-gp</td>
<td>KB-C2/KBV1</td>
<td>[29]</td>
</tr>
<tr>
<td>Oleanolic acid</td>
<td>Rhodamine-123, colchicine</td>
<td>MRP1</td>
<td>Ma104</td>
<td>[27]</td>
</tr>
<tr>
<td>Glycyrrhetic acid</td>
<td>E2,17βG</td>
<td>BCRP</td>
<td>LLC-PK1</td>
<td>[28]</td>
</tr>
</tbody>
</table>

Abbreviations: ABC transporters, ATP-binding cassette transporter; BCRP, breast-cancer-resistance protein; MRP1, multidrug-resistance protein 1; P-gp, P-glycoprotein.

(TMD) containing six transmembrane helices and one nucleotide-binding domain (NBD), with helices 4, 5 and 6 in the N-terminal half and helices 10, 11 and 12 in the C-terminal half to form the transport substrate site(s) [35]. TMDs form the substrate-binding sites and/or substrate-translocation pathways through the membrane to the efflux substrates, whereas NBDs are located in the interior of the cytoplasm, participating in ATP binding and hydrolysis and acting as ‘engines’ [36]. Inhibition of either one can cause malfunction of P-gp. Competitive inhibitors act as substrates for P-gp and have similar or greater affinity compared with cytotoxic agents to active drug-binding sites of P-gp, by contrast noncompetitive inhibitors usually bind to a different region to induce a conformational change of P-gp via a crosslinking pattern [37].

It is reported that structurally diverse P-gp substrates (phenazine, doxorubicin, cephalaxin, ampicillin, quinidine and penicillin G) interact with membrane lipids, and are found predominantly within the membrane interface region [38]. Many triterpenoids are P-gp substrates. Abraham et al. reported that three siphone triterpenoids that are established P-gp substrates interacted with the drug-binding site and increased the intracellular

**FIGURE 2**
Chemical structures of triterpenoids discussed in Table 1. The chemical structures of cucurbitacin I, cycloartane, dehydrotumulosic acid, ginsenoside Rg(3), 20(S)-ginsenoside Rh2, sipholenol A, ursolic acid, oleanolic acid and glycyrrhetic acid are shown.
accumulation of [3H]-paclitaxel by directly inhibiting P-gp-mediated drug efflux, stimulating the activity of P-gp ATPase and inhibiting the photoaffinity labeling of the transporter with [125I]-iodoarylazidoprazosin [39]. To develop more potent P-gp inhibitors, more sipholane triterpenoids and their semisynthetic derivatives were isolated, synthesized and examined for their activities against P-gp [26,40]. SAR analysis showed that the P-gp-inhibiting activities of sipholanol A were decreased with substitutions at C-28 involving aldehyde or hydroxy groups and with substitutions at C-16 involving ketone or carbonyl groups [26,40]. Other researchers have also reported that some triterpenoids, such as ginsenoside (contained in Ginseng Radix) [41], kugaucin J (a known triterpenoid from BMLE, bitter melon leaf extract) [42], triterpenoids isolated from Portia cocos [43] and rosemary phytochemical triterpenoids [29], can be P-gp substrates or inhibitors acting in similar manner. Recently, it was reported that BBA (23-O-(1,4’-Bipiperidine-1-carbonyl) betulinalic acid), a novel 23-hydroxybetulinic acid derivative, potently reverses ABCB1-mediated drug resistance in vitro and in vivo [44]. In addition, some triterpenoids perhaps possess a drug–drug synergistic effect to MDR cell lines and their counterparts. For example, Yun-Hong Huang et al. reported that, at subcytotoxic concentration, asiaticoside shows a synergistic effect with vincristine in KB, KBV-200, MCF-7 and MCF-7/ADM cell lines. In all four cell lines the apoptosis rates, Bcl-2 phosphorylation levels and activated caspase-3 protein were much higher in asiaticoside plus vincristine groups than in vincristine or asiaticoside groups [45].

Other than the above mentioned triterpenoids, there are a lot of other reversal agents for P-gp reported, including first-generation inhibitors (verapamil, quinidine, cyclosporine A), second-generation inhibitors [PSC833 (valspodar), VX710 (bircodar)] and third-generation inhibitors [R101933 (janiquidar), OC144093 (ONT093), LY335979 (zosuquidar), GF120918 (elacridar) and XR9576 (tariquidar)] [46]. Unfortunately, most of these inhibitors were ineffective in clinical trials owing to their unfavorable side effects or toxic pharmacokinetic interactions or simply because the magnitude of improvement in therapeutic outcome of these inhibitors with conventional chemotherapeutic agents was either nonsignificant or inconclusive [46]. Recently, inhibitors from natural sources have sometimes been referred to as fourth-generation inhibitors [47]. In fact, compounds from natural products including triterpenoids provide one of the most diverse and novel chemical scaffolds suitable for the development of new inhibitors and, most importantly, they are usually low in toxicity and are well tolerated in the human body [47]. For example, sipholane triterpenoids including sipholenol A, sipholenol L, sipholenone E and siphonellinol D are less toxic but show slightly weaker reversal effects than verapamil [30,39]. Therefore, triterpenoids are now more and more attractive to scientists for screening and developing nontoxic, potent and selective P-gp inhibitors, and probably have the potential to be more successful than many inhibitors already developed.

Interactions between triterpenoids and MRP1
In 1992, MRP1 was the first member of the MRP family (MRP1–9) to be identified [3,48]. Unlike other ABC transporters, the unique membrane-spanning domain, known as the additional TM0 domain structure, can give MRP1 a specialized function for leukotriene C4 transportation involved in immunoresponse sensitivity [49]. In contrast to P-gp, MRP1 acts as a glutathione-S-conjugate efflux pump (GS-X pump). Glutathione (GSH) participates in an MRP1-mediated efflux. GSH favors binding with substrates by inducing conformational change in MRP1 [50]. Thus, the depletion of GSH impairs the function of MRP1 and can lead to MDR reversion. A recent study demonstrated that cucurbitacin I, a tetracyclic triterpenoid, was capable of enhancing doxorubicin-antitumor activity. Cucurbitacin I had the capacity to reduce GSH synthesis to stimulate MRP-mediated GSH transport by increasing the affinity of MRP1 for GSH [51]. A study on the interaction between oleanolic acid and ABC transporters demonstrated that OA did not alter P-gp activity but inhibited the activity of MRP1 protein without downregulation of protein expression, suggesting that oleanolic acid is a substrate for MRP1 [27]. Most studies on the interaction between triterpenoids and ABC transporters mainly focus on the best well-known: P-gp, thus the exact mechanisms by which triterpenoids inhibit MRP1-mediated efflux remain unknown. But it is hypothesized that the potential mechanisms of triterpenoids to inhibit MRP1-mediated efflux include: (i) decreasing intracellular concentrations of GSH which is necessary for MRP1 efflux [52]; (ii) acting as substrates to compete toward other substrates [27]; (iii) direct or indirect binding with MRP1 at ATP-binding sites or other binding sites [53]; (iv) modulating MRP expression, and so on.

Interactions between triterpenoids and BCRP
BCRP, also known as BRCP1, ABCG2 or AbCP, was initially isolated in mitoxantrone-selected MDR cell lines expressing neither P-gp nor MRP [54]. BCRP is a half-transporter of ABC transporters, thought to require a dimer or a multimer for efficient transmembrane substrate translocation [55]. Yoshida et al. reported that glycyrrhetic acid can potently inhibit BCRP-mediated membrane transport and might interact with their substrates in BCRP-overexpressing LLC-PK1 cells [28]. Whether triterpenoids are substrates of BCRP or whether they can inhibit the expression of BCRP are still questions to be solved. The mechanisms by which triterpenoids interact with BCRP to modulate MDR need further investigation.

Concluding remarks
Active efflux of cytotoxic agents by ABC transporters is the most common mechanism of MDR. P-gp, MRP1 and BCRP have been shown to confer resistance to several anticancer agents. Tremendous efforts have been made to discover and synthesize inhibitors or modulators to these proteins. Therefore, potent and nontoxic inhibitors remain to be identified for clinical use in MDR reversal. Triterpenoids are predominantly found in various plants including seaweeds as well as in wax-like coatings of various fruits and medicinal herbs, thus have the advantage of low toxicity. Furthermore, in a pharmacokinetic Phase I study in cancer patients, some triterpenoids and their derivatives were well tolerated [6,56,57].

When it comes to the anticancer mechanisms, triterpenoids are multitargeted agents [8]. The schematic diagram of triterpenoids targeting multiple pathways and reversing MDR through ABC transporters is shown in Fig. 3. They can act as transporter inhibitors or modulators [26,30], and have been associated with apoptosis [13,14], cell signaling or other antitumor mechanisms [58,59]. What is more, triterpenoids co-administered with cytotoxic agents can enhance their anticancer effect on MDR carcinoma cells [15,60].
The schematic diagram of triterpenoids targeting multiple pathways and reversing multidrug resistance (MDR) through ATP-binding cassette (ABC) transporters.

Triterpenoids work as reversal agents for MDR by directly inhibiting the pump activities of P-gp and MRP1, therefore result in the increase of the intracellular accumulation of anticancer drugs and the death of cancer cells. The mechanisms interacting with BCRP to reverse MDR need further study. In *in vitro* studies some triterpenoids exhibit a concentration-dependent action on P-gp and this can be enhanced when co-administrated with chemotherapy drugs, thus chemotherapy and triterpenoid combination therapy is becoming an effective strategy to overcome MDR in cancer treatment, but further *in vivo* or clinical studies are needed to define the appropriate and safe dose.

**Conflicts of interest**
The authors have no conflicts of interest to declare.

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