

**Advances in the antitumor activities and mechanisms of action of steroidal saponins**

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**[ABSTRACT]** The steroidal saponins are one of the saponin types that exist in an unbound state and have various pharmacological activities, such as anticancer, anti-inflammatory, antiviral, antibacterial and nerves-calming properties. Cancer is a growing health problem worldwide. Significant progress has been made to understand the antitumor effects of steroidal saponins in recent years. According to reported findings, steroidal saponins exert various antitumor activities, such as inhibiting proliferation, inducing apoptosis and autophagy, and regulating the tumor microenvironment, through multiple related signaling pathways. This article focuses on the advances in domestic and foreign studies on the antitumor activity and mechanism of actions of steroidal saponins in the last five years to provide a scientific basis and research ideas for further development and clinical application of steroidal saponins.

**[KEY WORDS]** Steroidal saponins; Tumor; Mechanism

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**Introduction**

Cancer is a growing, worldwide but not unified health problem. A mounting burden is derived from low- and middle-income countries as demographics change and risk factors transition, where the aftermaths of economic and behavioral globalization are joining the existing burden of infectious original cancers. Millions of people will be diagnosed with cancer each year for the predictable future [1]. Chemotherapy for cancer can prolong life by weeks or months and may provide palliation, either used alone or in combination with surgery or radiotherapy [2]. Recently, it has become possible to exploit basic information of chemotherapy to develop mechanism-based strategies for cancer prevention and treatment [3].

Various classes of recently discovered compounds have potent antitumor activity. Plants have provided an extensive reservoir of natural products used as a primary source of medicine throughout the history of civilization. Historical experiences with plants have led to discoveries of many pivotal drugs [4, 5]. The steroidal saponin compounds are widely distributed in traditional Chinese medicine (TCM) and mainly found in *Asparagus*, *rhizomes*, *Fritillaria*, *Liriope muscari*, etc. A variety of TCM treatment of cancer, like *Ophiopogon japonicas*, *Lilium*, and *Paris polyphylla*, are rich in steroidal saponins. Most of steroidal saponins contain a core structure of hexacyclic ABCDEF-ring system and the structures of compounds mentioned in this paper are shown in Fig. 1. Steroidal saponins have many excellent physiological and pharmacological activities, including antitumor, anti-inflammatory, antiviral, and antibacterial effects and a calming effect on nerves. Previous literature has also reviewed its immune regulation, blood sugar control, and blood pressure lowering activities. Steroidal saponins are popular especially for the prevention and treatment of tumors with low toxicity and high efficiency [6]. In vitro and in vivo studies have shown that steroidal saponin compounds possess a wide range of antitumor activities, such as inhibition of proliferation, induction of apoptosis and autophagy, and suppression of tumor invasion and metastasis [7-10].
In this brief review, we will mainly focus on the recent progress made in the investigations on antitumor activities of steroidal saponins and the underlying mechanisms of actions.

**Cytotoxicity of Steroidal Saponins in Cancer Cells**

Cell proliferation and apoptosis play major roles in maintaining homeostasis and deregulation of these processes is a hallmark of cancer.

Recent reports indicate that steroidal saponins can directly inhibit tumor growth both in vivo and in vitro.

**Effects of steroidal saponins on tumor cell cycle and related pathways**

Cancer cell proliferation is the basis of cancer development. Different from normal cells, cancer cells have faster mitosis and shorter cell cycle. In addition to block cell cycle, steroidal saponins can also regulate cancer cell proliferation through other related pathways.

**Effects of steroidal saponins on tumor cell cycle**

Total saponins from *Pulsatilla chinensis* (Bunge) Regel (*P. chinensis*), whose rhizoma has been used for thousands of years as a TCM herb, have demonstrated cytotoxic activity against the chronic myelogenous leukemia K562 cell line. Three compounds from the total saponins, 23-hydroxybe-tulinic acid (HBA), pulchinenoside A (PA), and anemoside B4 (AB4), are also cytotoxic, among which HBA is the most cytotoxic via blocking the cell cycle at the S phase. Glycosylation of HBA at C3 and C28 significantly weakens its cytotoxicity. In addition, total saponins and HBA could significantly disrupt the mitochondrial membrane potential and selectively upregulate the protein levels of Bax, cytochrome C,
and cleaved caspase3/9 and downregulate the levels of Bcl-2. Thus, total saponins from *P. chinensis* are expected to be candidate natural products for treating human chronic myelogenous leukemia. HBA might be one of the representative components responsible for the observed anticancer activity, which is further expected to be developed as an alternative drug for leukemia therapy.[11]

Three furostanol saponins derived from *Digitalis trojana*, 22-O-methylparvispinoside A/B and parvispinoside A, have cytotoxic activity in the human colon carcinoma HT29 cell line and the human breast cancer MCF-7 cell line. Among them, 22-O-methylparvispinoside B significantly changed the G2/M cell cycle phase in the HT-29 cell line at 10 μmol·L⁻¹.[12]

Diosgenin, a natural steroid saponin, has been reported to induce cancer cell cycle arrest. A recent study has shown that 5 μmol·L⁻¹ of diosgenin suppressed telomerase activity in the non-small cell lung cancer (NSCLC) A549 cell line,[13] and the growth suppressive effect of diosgenin has also been demonstrated in thryocytes, with an IC₅₀ of 35 μmol·L⁻¹ *in vitro* and at a dose of 20 or 100 mg·kg⁻¹ *in vivo*.[14, 15] Additionally, diosgenin also suppresses the proliferation of a Hepatocellular carcinoma (HCC) cell line via inhibiting STAT3 signaling pathway[16]. One steroidal saponin with diosgenin and tetrasaccharide moieties has the strongest inhibitory effect on human nasopharyngeal carcinoma epithelial (CNE) cells, with an IC₅₀ of 1.50 ± 0.14 μmol·L⁻¹, through inducing cell cycle arrest.[17]

SBF-1, a synthetic steroid glycoside, shows significant anticancer activity against melanoma cells. In the mouse melanoma B16BL6 cell line, SBF-1 induces cell cycle arrest through reducing the expression of various cell cycle related proteins. Moreover, SBF-1 inhibits the activity of 3-phosphoinositide dependent protein kinase 1 (PDK1) and hence downregulates phosphorylation of Akt. PDK1 only interacts with Akt3 isoform and SBF-1 almost completely blocks this interaction. In addition, SBF-1 reduces expression of integrin-α7 and adhesion to fibronectin, which is decreased by knockdown of Akt. Furthermore, SBF-1 suppresses the growth of melanoma xenografts and inhibits the phosphorylation of Akt *in vivo*. In a mouse model of spontaneous metastasis, SBF-1 inhibits melanoma metastasis into draining popliteal lymph nodes at very low doses of 1 and 3 μg·kg⁻¹[18].

**Effects of steroidal saponins on other cancer cell proliferation pathways**

Asterosaponin 1, a novel cytostatic agent isolated from starfish, shows proliferation inhibition of A549 cell line[20].

Rhzima paridis, the root of both *Paris polyphylla* Smith var. chinensis (Franch.) Hara and *Paris polyphylla* Smith var. yunnanensis (Franch.) Hand Mazz, mainly contains steroidal saponins with the general designation of Paris saponins (PS), whose anticancer activity has been widely explored. PS shows a significant growth inhibition in the mouse cervical cancer U14 cell line *in vitro*. In *vivo*, PS prolongs the survival of mice, increases the serum IFN-γ level and reduces the serum IL-4 level, suggesting that PS may exert its anti-cancer activity by enhancing the immune system of tumor-bearing mice.[21] Additionally, in a rat model of esophageal cancer established by sustained subcutaneous injection of N-nitrosomethylbenzylamine (NMBA) for 10 weeks, daily administration of PS from the first injection of NMBA significantly inhibited the growth, vitality, invasion, and migration of the esophageal cancer EC9706 cell line and the KYSE150 cell line in a dose-dependent manner. Flow cytometry revealed that esophageal cancer cell cycle G2/M arrest was induced by PS. In addition, the expression of COX-2 and cyclin D1 in esophageal cancer cells and rat esophageal tissues are also significantly suppressed by PS[22]. In another rat model of diethylstilbestrol (DEN) induced hepatoma, PS inhibited liver cancer and alleviated liver injury via suppressing formation of malondialdehyde (MDA) and nitric oxide (NO) and increasing production of superoxide dismutases (SOD) in liver tissues and upregulating GST-α/μ/π in DEN-induced rats[23]. PS also showed anticancer activity in a mouse model of urethane-induced lung carcinogenesis. Mechanisms deemed effective might involve the inhibitions of oxidative stress and inflammation and the activation of apoptosis via suppression of the EGFR/P13K/Akt signaling pathway[24].

PS-I inhibits the growth of the human NSCLC PC9ZD cell line through altering cell cycle via enhancing the G2/M phase. The rates of the G2/M phase were approximately 100%, 150%, and 200% compared to the control group in PS-I treated groups with concentrations of 1, 2 and 4 μg·mL⁻¹, respectively[25]. Moreover, PS-I enhances the sensitivities of the human NSCLC H1299, H460, and H446 cell lines to camptothecin (CPT) and 10-hydroxycamptothecin (HCPT). PS-I greatly upregulates the inhibition of cancer cell proliferation induced by CPT/HCPT through the mitochondrial pathway involving caspase 3/9 activation and cytochrome C release. Furthermore, PS-I strengthens the inhibition of the p38 MAPK, Akt, and ERK signaling pathways mediated by CPT/HCPT[26]. Because an EGFR mutation is commonly accompanied by the treatment of NSCLC, four PS compounds (PS-I/II/VI/VII) are demonstrated to inhibit the proliferation and induce apoptosis in EGFR-TKIs-resistant PC9ZD cancer cells through downregulation of P13K, p-Akt, and Bcl-2 and upregulation of Bax and caspase 3/9, suggesting that these four saponins could be developed as systemic
treatment strategies for EGFR-resistant lung cancer\[27\].

Bufalin, derived from the parotid and skin venom glands of toads, is a key bioactive component of *Venenum bufonis* and has been reported to reverse resistance to reversible and irreversible EGFR-TKIs induced by exogenous HGF through inducing death signaling and inhibiting the Met/PI3K/Akt pathway\[28\].

Polyphlyllin I, isolated from *Rhizoma Paridis* Chonglou, has been shown to inhibit proliferation of the human ovarian cancer HO-8910PM cell line through activating the JNK signaling pathway\[29\].

Steroidal saponin from *Trillium tschonoskii* (TTS) is shown to be a potential treatment for hepatocellular carcinoma (HCC). Studies have shown that TTS could significantly reverse multidrug resistance (MDR) and enhance chemosensitization in HCC cells. *In vitro*, TTS significantly increases the sensitivity of R-HepG2 to anticancer drugs, and *in vivo*, TTS induces R-HepG2 sensitization to doxorubicin and dose-dependently reduces xenograft tumor formation of R-HepG2 cells through inhibiting cancer cell proliferation in mice\[30\].

Sprengerinin C (SC), a novel component derived from *Ophiopogon japonicus* (L.f.) Ker-Gawl, promotes the death of different types of cancer cells, including the HCC HepG-2 cell line and the BEL7402 cell line, with IC\textsubscript{50} values being 3.07 and 8.13 \(\mu\)mol\(\cdot\)L\(^{-1}\) respectively, and the human uterine carcinoma HeLa cell line, with an IC\textsubscript{50} being 1.74 \(\mu\)mol\(\cdot\)L\(^{-1}\)\[31\].

*Fagonia indica*, a small spiny shrub, whose aqueous decoction of aerial parts is popularly used against various skin lesions, is pivotal in folk medicine for its multiple traditional pharmacological activities. The cytotoxic activity of the saponin glycoside is strong in the human breast cancer MDA-MB-468 cell line and the human colon adenocarcinoma Caco-2 cell line\[32\].

Steroidal saponins from *Dioscorea zingiberensis* Wright (DZW) have displayed cytotoxic activity against cancer cells. Seven steroidal saponins were isolated and identified from the rhizomes of DZW: diosgenin, trillin, diosgenin diglucoside, deltonin, zingiberensis saponin (ZS), protodeltonin, and parvilloside. All the seven compounds inhibit the proliferation of a panel of established murine and human cancer cell lines *in vitro*; among them, ZS has the maximal cytotoxic effect, even equivalent to doxorubicin on the murine colon carcinoma cell line C26\[33\].

Trinervuloside B, a new steroidal saponin isolated from *Smilax trinervula*, shows cytotoxicity in the human gastric cancer SGC-7901 cell line and the human colon carcinoma HCT-116 cell line with IC\textsubscript{50} values being 8.1 and 5.5 \(\mu\)mol\(\cdot\)L\(^{-1}\), respectively\[34\].

Chinese crude drug “tong-guan-teng” which mainly contains C21 steroidal glycosides, is effective for lung cancer. A recent clinical study has discovered that a combination of tong-guan-teng extract with chemotherapy significantly improves the effective rate (ER) and quality of life improvement rate (QOLIR) of advanced NSCLC patients, which provides a new strategy for the treatment of lung cancer\[35\].

**Effects of steroidal saponins on cancer cell apoptosis and related pathways**

Apoptosis is the process of autonomous cell death, during which a series of intracellular events decommission the unwanted or dangerous cells\[36\]. It is necessary to focus modern anticancer drug discovery on novel therapeutic agents capable of apoptosis regulation because many tumor promoters inhibit cell death\[37\]. Apoptosis is mainly mediated by two pathways: an extrinsic (death-receptor) pathway and an intrinsic (mitochondrial) pathway. Recently, steroidal saponins have been accepted for their clinical use in the treatment of cancer by inducing apoptosis via these pathways.

**Effects of steroidal saponins on extrinsic apoptosis pathway**

Diosgenin has been reported to selectively induce apoptosis in insulin-like growth factor-1 (IGF-1) pretreated primary human thyrocytes through Fas-related and mitochondrial apoptotic pathways; in the former, it inhibits FLIP and activated caspase-8, and in the latter, it enhances the production of ROS and cleaved caspase-9 and regulates the balance of Bax/Bcl-2\[38\]. Furthermore, diosgenin interferes with cancer cell growth and metastasis through three different groups of MAPKs, namely, ERKs, JNKs, and p38 MAPKs. Kim et al. have demonstrated that diosgenin at 40 \(\mu\)mol\(\cdot\)L\(^{-1}\) strongly generates ROS to induce apoptosis in the HepG2 cell line through activation of ASK1, a critical upstream signal molecule for JNK/p38 MAPK activation\[39\]. In contrast, JNK signaling pathway is significantly suppressed by diosgenin at 20 \(\mu\)mol\(\cdot\)L\(^{-1}\) in squamous cell carcinoma and human prostate cancer cells\[40\,41\]. Previous studies have demonstrated the inhibitory effects of diosgenin on NF-xB and STAT3 contributing to the induction of apoptosis\[42\]. Additionally, diosgenin upregulates the expression and activity of 5-lipoxygenase (5-LOX) and COX-2 in the HT-29 cell line and the HCT-116 cell line, which further leads to apoptosis\[43\]. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), a member of the tumor necrosis factor (TNF) cytokine family, selectively induces apoptosis in cancer cells with no effect on normal cells Diosgenin elevates the sensitization of the HT-29 cell line to TRAIL, as the cell line has a strong resistance to TRAIL-induced apoptosis. The mechanisms underlying this result may involve the overexpression of functional TRAIL receptor DR5 and an increase in COX-2 expression\[44\].

Diosgenyl saponins have a variety of biological functions. Recent research has found a new type of diosgenyl saponin that might induce apoptosis in an OSCC cell line through both extrinsic and intrinsic pathways This finding provides a research foundation for the development of new types of diosgenyl saponin derivatives into anti-oral cancer agents against OSCC\[45\]. Moreover, a newly synthesized diosgenyl saponin (diosgenyl saponin N), diosgenyl-\(\alpha\)-L-rhamnopyranosyl-(1→2)-[\(\beta\)-D-xylpyranosyl-(1→4)]-\(\alpha\)-L-arabinopyranoside, selectively induces apoptosis via the extrinsic pathway in estrogen re-
receptor (ER)-positive MCF-7 cells compared with ER-negative MCF-10A and MDA-MB-231 cells, as ER-α is a pivotal therapeutic target in the treatment of breast cancer. This finding indicates that this new saponin may be more effective in clinical application [46].

Bufadienolide, the main category of biologically active compounds in the traditional Chinese medicine ChanSu, sensitizes death receptor TRAIL through the suppression of the STAT3/Mcl-1 pathway [47]. Arenobufagin, a type of bufadienolide, is a natural substance extracted from toad venom. It has been shown to enhance apoptosis and autophagy in HepG2 human hepatocellular carcinoma cells through inhibiting the PI3K/Akt/mTOR signaling pathway [48].

Aspafilioside B, a steroidal saponin derived from Asparagus filicinus, has been shown to induce the apoptosis in an HCC cell line in vitro and in vivo. The mechanism may be through upregulation of H-Ras and N-Ras, which causes phosphorylation of c-Raf and activation of ERK and p38, consequently inducing G2 phase arrest and apoptosis [49].

Bufalin has been shown to reverse HGF-induced EGFR-TKIs resistance via blocking the Met/PI3K/Akt signaling pathway in an EGFR mutant lung cancer cell line [50]. Moreover, bufalin also increases apoptosis in SW620 human colon cancer cells by inhibiting the JAK/STAT3 signaling pathway [51] and has been reported to be a sensitizer of death receptor-induced apoptosis via the STAT1-dependent signaling pathway in HeLa cells [52].

Periplocin, a natural product derived from Cortex periplocae, can induce apoptosis in SW480 human colon carcinoma cells via the β-catenin/TCF signaling pathway both in vitro and in vivo [53]. Periplocin also induces apoptosis in a variety of human lung cancer cell lines (A549, SPCA-1, H1975, NCI-H446, NCI-H460, NCI-H292, and NCI-H69) through the Akt and ERK signaling pathways in vitro and in vivo [54].

Effects of steroidal saponins on intrinsic apoptosis pathway

Dioscin, a natural product, shows a variety of pharmacological activities, including lipid-lowering, anti-cancer, and hepatoprotective effects. In C6 glioma cells, dioscin significantly increases Ca2+ release and ROS generation. ROS generation causes mitochondrial damage, including structural diversification, mitochondrial permeability transition enhancement and mitochondrial membrane potential weakening, which leads to a further release of cytochrome C and increased activities of caspase-3/9. Additionally, oxygen stress induces S-phase arrest and DNA damage by regulating the expression of DNA Topo I, p53, CDK2, and cyclin A. Simultaneously, dioscin decreases the protein expression of Bcl-2 and Bcl-xl and increases Bax, Bak, Bid and cleaved poly (ADP-ribose) polymerase [55]. In human breast cancer cell lines MDA-MB-231, MDA-MB-453, and T47D, dioscin induces cell death via the apoptosis inducing factor (AIF) signaling pathway [56]. In the HL-60 cell line, dioscin dose-dependently induces apoptosis through externalization of phosphatidylserine and cleavage of lamin A/C and PARP-1 [57].

Trillium tschonoskii steroidal saponins (TTS) induces apoptosis in HT-29 cells partly by triggering a mitochondrial-mediated apoptotic pathway and inhibiting the MAPK pathway [58].

Solamine, one of the steroid alkaloids belonging to the Solanaceae family, is mainly found in the plant nightshade (Solanum nigrum L.) and the tuber of potato (Solanum tuberosum L.). Solanine can inhibit cancer cell growth through caspase-3 dependent mitochondrial apoptosis both in pancreatic cancer cells and a nude mouse model Mechanistically, solanine triggers the opening of the mitochondrial membrane permeability transition pore (MPTP) through downregulating the Bcl-2/Bax ratio, and initiates release of cytochrome c and Smac, thus processing the caspase-3 zymogen into an activated form. Additionally, cancer metastasis related proteins-MMP-2/9, is also inhibited in the cells treated with solanine, suggesting that solanine may be efficacious for the treatment of pancreatic cancer [59].

OSW-1, a natural compound derived from the bulbs of Ornithogalum saundersiae, induces a mitochondrial-associated apoptotic pathway in the HCC Hep3B cell line. OSW-1 affects the gene expression of multiple signaling pathways in Hep3B cells, involving the WNT, MAPK, VEGF, and p53 signaling pathways [60]. In addition, OSW-1 induces calcium-dependent apoptosis in human pancreatic cancer cells and leukemia cells via inhibiting the sodium-calcium exchanger 1 on the plasma membrane, which leads to a further increase in cytosolic Ca2+ and a decrease in cytosolic Na+. The elevated cytosolic Ca2+ give rise to a mitochondrial calcium overload and thus causes the loss of mitochondrial membrane potential, release of cytochrome c, and activation of caspase-3. Moreover, OSW-1 triggers a Ca2+-dependent cleavage of endoplasmic reticulum (ER) chaperone molecular GRP78, which has been known to facilitate cell survival and drug resistance [61]. Similar to these findings, a new cytostatic agent found in starfish, asterosaponin 1, causes apoptosis in A549 cells through an ER stress-associated pathway Asterosaponin 1 could increase cytosolic Ca2+ levels and enhance the expression of the ER molecular chaperones GRP78 and GRP94 in a time- and dose-dependent manner. Co-incubation of A549 cells with asterosaponin 1 increases the expression and activity of three known essential ER-associated apoptotic molecules: CHOP, caspase-4, and JNK2 [20].

Polyphyllin I induces apoptosis in the HO-8910PM cell line via downregulating PIK3C2B, caspase 9 and Wnt5A and upregulation of the expression levels of activated caspase 9, c-Jun, and p-c-Jun [29].

RCE-4, the main active component of Reineckia carnea (Andr.) Kunth., which has been used in the treatment of a variety of diseases in folk remedies, has been found in several plants of the Liliaceae family. When incubated with the human cervical cancer cell line CaSki, RCE-4 induces mitochondrial-mediated apoptosis via initiation of decrease in the mitochondrial membrane potential and triggering release of
cytochrome c\cite{62}. In HeLa cells, RCE-4 promotes apoptosis via suppressing phosphorylation of the PI3K/Akt/mTOR signaling pathway and decreasing the transcription of IL-1β and IL-6\cite{60}.

Zingiberensis saponin (ZS), a steroidal saponin isolated from Dioscorea zingiberensis Wright (DZW), could induce apoptosis by activating caspase-3/9 and specifically cleaving the proteolytic domain of poly (ADP-ribose) polymerase in the murine colon carcinoma cell line C26, which is similar to doxorubicin\cite{63}.

Effects of steroidal saponins on other apoptosis pathways

Sergio Lopez has detected the anticancer activity of saponins from the edible part of wild asparagus (triguerro Hueter) Tajar, HT, landrace), a valuable ingredient of the Mediterranean diet that contains 10–100 times higher steroidal saponins than the commercial hybrids. Three furostan-type steroids make up 90% of the total saponins, and their excellent stability has been demonstrated by in vitro digestion. They induce apoptosis in the HCT-116 cell line via blocking the activation of the ERK/Akt/mTOR signaling pathway and arresting G0/G1 cell cycle by disrupting cyclin D expression\cite{64}.

Paris saponins (PS), the representative components of Rheizoma Parisidis, have been reported to induce apoptosis in cancer cells. PS has been reported to induce apoptosis in esophageal cancer cells, and the mechanism of action might be related to its interference of the cell cycle and the COX-2 signaling pathway, as PS could dose-dependently decrease the release of prostaglandin E2, a downstream molecule of COX-2\cite{22}. Moreover, PS induces apoptosis in A549 cells\cite{65}, and also significantly promotes apoptosis in SW480 colorectal cancer cells through regulating the IL-6/JAK-STAT3 apoptosis molecular pathway\cite{66-67}. PS-I and PS-II, the characterized compounds, have selective anticanicancer activity in liver, breast, and prostate cancer cells, and their anticanicancer effects are exerted by induction of cell cycle G2/M arrest and apoptosis via multiple targets in HepG2 cells\cite{66,67}. Additionally, PS-I significantly induces apoptosis in a variety of NSCLC cell lines through a multi-regulatory process involving G2/M arrest and regulation of the expression of Bax, Bcl-2 and caspase-3 combined with hyperthermia at 43 °C. Simultaneously, PS-I induces apoptosis in an analogous manner in gefitinib-resistant PC9ZD cells, and PS-I also decreases glucose uptake in nude mice bearing xenografts\cite{69}. PS-II displays cytotoxicity to SKOV3 cells\cite{66}. PS-VII induces apoptosis in the human cervical cancer HeLa cell line, with an IC50 value of 2.62 ± 0.11 μmol L⁻¹. The mechanism may be activation of intrinsic apoptotic pathways by increasing the expression of caspase-3/9 and Bax while decreasing that of Bcl-2\cite{70}. Furthermore, PS-VII could disrupt the MAPK and AKT pathways by suppressing phosphorylation of MEK1/2, ERK1/2 and GSK-3β\cite{71}. Additionally, PS-VII could dose-dependently induce apoptosis and modulate drug resistance in the adriamycin-resistant human breast cancer MCF-7/ADR cell line\cite{72}.

Sprengerin C (SC) induces apoptosis in HepG-2/ BEL7402 cells through p53-mediated G2/M-phase arrest and an NADPH oxidase/reactive oxygen species-dependent caspase apoptosis pathway\cite{73}.

Timosaponin AIII (TAAII) is isolated from the Chinese medicinal herb Anemarrhena asphodeloides Bunge. TAAII induces caspase-dependent apoptosis in HCC through inhibition of XIAP expression in vitro, and in vivo, intraperitoneal injection of TAAII (7.5 mg kg⁻¹) suppressed tumor growth in mice through activating cancer cell apoptosis\cite{74}.

Saponin glycoside isolated from Fagonia indica can induce apoptosis. In MCF-7 cells expressing no caspase-3, saponin glycoside at > 100 μmol L⁻¹ could cause necrosis through cell lysis, as demonstrated in sheep red blood cells. In MDA-MB-468 and Caco-2 cells, which express caspase-3, the saponin glycoside induces apoptosis through PARP and caspase-3 cleavage, which has been confirmed by the reversal of growth inhibition when co-cultured with the pan-caspase inhibitor Z-VAD-FMK. Moreover, saponin glycoside (12.5 μmol L⁻¹) is non-toxic to HUVEC or U937 cells in a DNA ladder assay, showing certain selectivity between malignant and normal cells\cite{72}.

Macrostemonoside A (MSS.A), which is an active steroidal saponin identified from Allium macrostemon Bung, could dose-dependently induce apoptosis in human colorectal cancer SW480 cells via inducing ROS production and inhibiting tumor growth in a carcinogenic xenograft model\cite{75}.

Ophiopogon B (OP-B) is a bioactive component derived from Radix Ophiopogon Japonicus. In SGC-7901 gastric cancer cells, OP-B exerts dose-dependent anti-proliferative effects. A study of the mechanism shows that OP-B-induced apoptosis is associated with an increased generation of ROS and a loss of MMP\cite{76}.

Autophagy regulation of Steroidal Saponins in Cancer Cells

Autophagy is a tightly-regulated cellular self-digestion process through which cellular components are targeted to lysosomes for degradation. Key functions of autophagy are providing energy and metabolic precursors under starvation, alleviating stress by removal of damaged proteins and organelles, which are deleterious for cell survival\cite{77}.

TAIII has been reported to induce autophagy in AMPKa/mTOR-dependent and p53-independent pathways in HCC cells, and XIAP suppression is also involved TAAII triggers the XIAP lysosomal degradation, promoting the ubiquitination of XIAPs. TAAII-treated cells switch to necrotic death when autophagy is blocked. Given the above evidence, it is worth considering the development of TAAII as a novel anticancer agent based on autophagy\cite{74}.

Paris polyphylla steroidal saponins (PPSS) decreases the percentage of viable A549 cells via both apoptosis and autophagy; the former is due to cleavage of PARP and activation
of caspase-8 and caspase-3, and the latter is confirmed by the conversion of LC3 I to LC3 II and the upregulation of Beclin 1 [79].

OP-B, commonly used in the treatment of pulmonary disease in traditional Chinese medicine, suppresses the growth of the NSCLC cell lines NCI-H157 and NCI-H460, which is attributed to the induction of autophagy by OP-B through inhibition of the PI3K/Akt signaling pathway [79]. In A549 cells, OP-B induces cell cycle arrest in S and G2/M phases via suppressing the phosphorylation of histone H3 and the expression of Myt1, which induces autophagy. In a xenograft model, OP-B significantly inhibits cancer cell proliferation [80].

Spicatoside A, isolated from the tubers of Lirioppe platyphylla, inhibits the growth of HCT116 in vivo. HCT116 cells treated with spicatoside A in vitro induces autophagy through suppressing the PI3K/Akt/mTOR and upregulating p53 levels. Continued exposure to spicatoside A leads to apoptosis in HCT116 via accumulation of PARP and the release of cytochrome C. In the switch from autophagy to apoptosis, cleavage of beclin1 by activated caspase plays a key role [81].

**Effects of Steroidal Saponins on Tumor Metastasis**

Cancer metastasis is a multistep cell-biological process involving dissemination and migration of cancer cells, angiogenesis of cancer, regulation of tumor microenvironment and epithelial-mesenchymal transition, etc. Recent advances indicate that steroidal saponins have implications on the steps of the cascade which appear amenable to therapy of cancer metastasis.

**Effects of steroidal saponins on cancer cell adhesion, invasion and migration**

Abnormal cell migration and invasion is a hallmark feature of metastatic cells in cancer [82]. The migration process of cancer cells requires appropriate remodeling of the actin cytoskeleton [83]. Cdc42 is a key member of the Rho family of small GTPases that regulate the rearrangement of the actin cytoskeleton [84]. Recently, He et al. have found that 5 μmol·L⁻¹ of diosgenin significantly suppresses actin polymerization and Vav2 phosphorylation and reduces Cdc42 activation in the MDA-MB-231 cell line, which might explain the anti-metastatic effect of diosgenin [85]. Additionally, diosgenin inhibits the invasion and migration of PC-3 cell lines by reducing the mRNA levels and enzyme activity of MMP-2 and MMP-9 [86].

Polyphyllin I has been reported to suppress the metastasis of the human ovarian cancer cell line HO-8910PM. When cancer cells are incubated with polyphyllin I, 123 genes are differentially expressed. These genes participate in multiple signal transduction pathways, involving apoptosis, proliferation, and metastasis. Among them, PIK3C2B, caspase 9 and Wnt5A are downregulated and c-Jun is upregulated in dose- and time-dependent manners [29].

As cancer metastasis is an energy consuming process, metabolic alterations in Lewis pulmonary adenoma mice treated with PS and cisplatin are detected. The results suggest that PS might suppress metastasis via inhibiting cancer cellular metabolism through regulating the p53/mTOR-ε-Myc-HIF-1α network [87]. Additional, PS-VII suppresses the invasion and migration of the U2OS osteosarcoma cell line through inhibiting MMP-2/9 production via suppressing the phosphorylation of p38 MAPKs [88].

Ophiopogon-D (OP-D), a steroidal saponin isolated from *Ophiopogon japonicas*, suppresses cancer cell invasion and adhesion via inhibition of the expression and secretion of MMP-9 but not MMP-2 OP-D also inhibits the phosphorylation of p38, indicating its inhibition of the MAPK pathway [89]. DT-13, a saponin monomer also derived from *Ophiopogon japonicas*, exhibits anticanter activity in several cancer cell lines. First, DT-13 could inhibit the adhesion and migration of human breast cancer cells under hypoxia through targeting various elements. DT-13 reduces the increased levels of HIF-1α, p-ERK1/2 and p-Akt induced by hypoxia, suppressed the excretion of VEGF, reduced the levels of p-VEGFR2 and p-Akt, and then inhibited migration and invasion [90].

Second, DT-13 could inhibit the adhesion and invasion of MDA-MB-435 cells via decreasing the phosphorylation of p38 and the expression and excretion of MMP-2/9 [91]. Meanwhile, the *in vivo* anticancer efficacy of DT-13 is also evaluated by orthotopic implantation of MDA-MB-435 cells into nude mice. The results show that DT-13 significantly inhibits MDA-MB-435 cell lung metastasis and slightly restricted tumor growth [92]. In addition, DT-13 could inhibit A549 proliferation, adhesion to HUVECs and fibronectin, and invasion through the extracellular matrix by suppressing the expression of MMP-2 and MMP-9 [93]. Moreover, DT-13 could also inhibit gastric cancer cell migration [94].

Bufalin suppressed the proliferation, migration, adhesion and invasion of the human hepatoma cell lines HCCLM3 and HepG2. Bufalin could significantly suppress the nuclear translocation of β-catenin, decrease the levels of p-AKT, p-GSK3β, and MMP-2/9 and increase the levels of GSK3β and E-cadherin [95].

Cucurbitacin E, a compound from the climbing stem of *Cucumis melo L.*, exhibited anti-metastatic activities in the MDA-MB-231 and 4T1 human breast cancer cells *via* suppression of the Src/FAK/Rac1/MMP pathway [96].

Timosaponin AIII suppresses the invasion and migration of A549 cells through the upregulation of MMP-2/9 via inhibition of the ERK1/2, Src/FAK and β-catenin signaling pathways [97].

**Effects of steroidal saponins on angiogenesis**

Angiogenesis is critical for cancer invasiveness and metastasis, which is dependent on the direct action of angiogenic factors, such as VEGF and integrin [98].

Discogenin has been reported to abolish the expression of VEGF in the human prostate cancer cell line PC-3 in a dose-dependent manner [86]. Moreover, in breast cancer cells, prostate cancer cells and squamous cell carcinoma, discogenin suppresses tumorigenesis by disrupting the PI3K/Akt/mTOR signaling pathway [86, 99].
In VEGF-treated HUVECs, SC dose-dependently restricts the elevated levels of MMP-2/9 and PECAM-1, which is also supported by an in vivo nude mouse xenograft model of human hepatocellular carcinoma[79].

PS-II significantly suppresses the growth, motility and tubule formation of VEGF-stimulated HUVECs in a dose- and time-dependent manner through blocking the activation of VEGFR2, which was indispensable for the VEGF-induced phosphorylation of several intracellular pro-angiogenic kinases, such as ERK, Src, focal adhesion and AKT kinase[100].

Terrestrosin D, isolated from *Tribulus terrestris L.*, suppresses VEGF secretion and angiogenesis in a PC-3 cell line and xenograft cancer cells. Moreover, Terrestrosin D induces apoptosis in the PC-3 cell line via a caspase non-dependent pathway and inhibited tumor growth in a PC-3 xenograft mouse model[101].

In a chicken chorioallantoic membrane (CAM) model, DT-13 significantly decreases the density of vessels, suggesting that DT-13 may have anti-angiogenic activity in vivo[100].

Cucurbitacin B suppresses tubulogenesis in HUVECs and blocks angiogenesis in CAM assay through inhibiting activity of VEGFR2[102].

**Effects of steroidal saponins on tumor microenvironment**

Drug resistance is one of the main reasons for the scant efficacy of chemotherapy in the treatment of gastric cancer. HIF-1α, a key transcriptional factor during hypoxia, participates in drug resistance. In a recent study, the hypoxia-mimic (cobalt chloride) sensitive gastric cell line BGC-823 was established, and the efficacy of diosgenin, which has certain anticancer activity in a hypoxic microenvironment, was explored. Results have demonstrated diosgenin might be a potent candidate for inhibiting the survival and invasion of BGC-823 cells treated with cobalt chloride Additionally, diosgenin can display better efficacy when combined with HIF-1α specific short hairpin RNA (shRNA). The anti-invasion efficacy of diosgenin may be associated with E-cadherin, integrin α5, and integrin β6. The above results indicate that diosgenin is expected to be a candidate compound for the control of gastric cancer cells under hypoxic conditions, especially with the lower level of HIF-1α[103].

**Effects of steroidal saponins on epithelial-mesenchymal transition**

OSW-1 is able to regulate a variety of miRNAs, which are related to cancer proliferation, differentiation, apoptosis, cell adhesion, migration, polarity and EMT, including miR-299, miR-1908, miR-125b, miR-187a, miR-1275, hagv-1-mir-H6-3p, miR-181, miR-210, miR-483, miR-126, and miR-208 When used simultaneously with doxorubicin, OSW-1 upregulates miR-141, miR-142, miR-200c, and miR-1275, compared with doxorubicin alone Additionally, the expression of miR-142-3P had an approximate 58 fold-change compared to its expression with other treatments[104].

Chang *et al.* have reported that diosgenin inhibits the HGF- induced upregulation of vimentin and MDM2 in prostate cancer cells, while the expression of E-cadherin is not affected[105]. Similarly, diosgenin at 10 μmol·L⁻¹ markedly inhibits the high glucose-induced increase in α-smooth muscle actin (α-SMA) and decrease in E-cadherin in HK-2 cells, suggesting that diosgenin antagonizes high glucose-induced renal tubular fibrosis through the EMT pathway[106].

**Discussion and Conclusion**

In this article, we have overviewed the recent progress for steroidal saponins in a variety of cancer models in vitro and in vivo. Different studies from multiple aspects indicate that steroidal saponins are a group of compounds with potential anticancer activity for various types of cancers, including lung cancer, breast carcinoma, osteosarcoma, colon carcinoma, leukemia, erythroleukemia, laryngeal carcinoma, and prostate cancers. Table 1 shows the sources and potential targets of various steroidal saponins mentioned in this paper. Most steroidal saponins are easily extracted from TCM and have been used clinically for thousands of years, and therefore, they may be safe chemotherapeutic candidates for cancer treatment. Steroidal saponins mainly exert anticancer activity via their regulation of PI3K/Akt and MAPK signaling pathways, and the schematic representation of potential molecular mechanisms is shown in Fig. 2. Nevertheless, the clearer mechanisms of action and anticancer targets of steroidal saponins need future investigations.

Steroidal saponins also have a unique advantage in the field of anticancer treatment. Compared with ordinary chemotherapy drugs, steroidal saponins have better selectivity and less drug resistance. On the one hand, steroidal saponins possess greater sensitivity to EGFR, estrogen receptor, and HIF1α etc; on the other hand, steroidal saponins behave high activity in drug-resistant cancer cell lines; for instance, PS-I shows anticancer activity to gefitinib-resistant PC9ZD cell line and PS-VII to adriamycin-resistant MCF-7 cell line and so on[27]. Additionally, most steroidal saponins can enhance sensitivity of current clinical chemotherapy drugs to specific cancer cell line; for instance, combination therapy with “tong-guan-teng” extract and chemotherapy drugs significantly improve life quality of NSCLC patients[105]. Given that, steroidal saponins provide more choices for cancer chemotherapy. However, preclinical and clinical trials are needed to investigate the anticancer effects of steroidal saponins used either alone or in combination with current standard drugs to verify their further usefulness as novel potent anticancer agents.

Steroidal saponins have diverse and complex structures, apart from anticancer activity, they possess many other pharmacological activities, such as antibacterial, cardiovascular protection, and free radical scavenging effects. At present, the steroidal saponins are mostly extracted from TCM with cumbersome preparation process and low yield. Therefore, the synthesis and structural optimization of steroidal saponins are also one of the important research directions.

In conclusion, steroidal saponins show anticancer activities, but the underlying mechanisms of action remain to be fully elucidated. The determination of specific targets of steroidal
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<td>K562</td>
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<td><em>Digitalis trojana</em></td>
<td>HT29, MCF-7</td>
<td>G2/M cell cycle phase</td>
<td>[12]</td>
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<td>22-O-methylparvispin oxide B</td>
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<td>HT29, MCF-7</td>
<td>Cytotoxic, G2/M cell cycle phase</td>
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<td>a synthetic steroidal glycoside</td>
<td>B16BL6</td>
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<td><em>Radix Ophiopogon Japonicus</em></td>
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Continued
steroidal saponins is required to further validate their applications in the prevention and treatment of human diseases. Further in vivo evaluation and drug development of these steroidal saponins are of current interest. Based on the successful identification of anticancer drug candidates from steroidal saponins, we have reasons to expect further successes in this research area in the future.

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