

Steroidal saponins: Natural compounds with the potential to reverse tumor drug resistance (Review)

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Abstract. Steroidal saponins are a type of natural product that have been widely used in Chinese herbal medicine, with a variety of pharmacological activities, such as antitumor, anti-inflammatory and anti-bacterial effects. Cancer has become a growing global health problem, and drug therapy is currently the most important clinical antitumor treatment. However, drug resistance is a major obstacle to the effectiveness of chemotherapy, resulting in >90% of deaths of patients with cancer receiving conventional chemotherapy. It has been found that steroidal saponins may exert an effect on the reversal of drug resistance in tumor cells by regulating apoptosis, autophagy, epithelial-mesenchymal transition and drug efflux through multiple related signaling pathways. The present study reviews the role and mechanism of steroidal saponins in the treatment of tumor drug resistance, aiming to provide a scientific basis and research ideas for the future development and clinical application of natural steroidal saponins.

2. Mechanisms of drug resistance in cancer chemotherapy
3. Mechanisms of steroidal saponins in reversing tumor drug resistance
4. Conclusion and prospects

1. Introduction

As the second leading cause of death worldwide, cancer is a major cause of premature mortality and shortened life expectancy with the growth and aging of the global population (1). It was estimated that the global incidence of cancer and its mortality rate would approach 19.3 million cases and 10 million deaths in 2020, and that these rates would increase to 30.2 and 16.3 million by 2040, respectively (2). Traditionally, the approaches for cancer treatment mainly include surgical resection, chemotherapy and radiotherapy. In recent years, although innovative treatment strategies, such as gene therapy and immunotherapy, have gradually become supplementary and alternative treatments for patients with cancer, chemotherapy remains the sole therapeutic approach for numerous patients. However, in addition to side effects, such as severe nausea and vomiting (3), varying degrees of drug resistance are gradually developed in tumor cells after a period of treatment with chemotherapy, which is less than ideal. For a long time, the drug resistance of tumors has been the principal cause of the failure of chemotherapy and of tumor recurrence (4), accounting for >90% of deaths of patients with cancer (5). Therefore, solving the challenge of drug resistance in tumor cells has become a key step in cancer treatment.

Notably, natural products (NPs), such as Chinese herbs and their extract preparations, have long been widely used to treat various diseases, and they remain an important repository for the exploration and identification of novel drugs. NPs have been used as alternatives to a number of chemically synthesized drugs due to their high efficiency and low toxicity. Studies have shown that NPs exert obvious antitumor effects, and their combination

Contents

1. Introduction

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with chemotherapy can reduce the dosage and toxic side effects of chemotherapy, and improve drug efficacy (6,7).

Naturally occurring steroidal saponins are a type of natural saponin mainly derived from a variety of monocotyledonous angiosperms, such as Agavaceae, Dioscoreaceae, Liliaceae, Alliaceae and Dracaenaceae (8). According to different molecular backbone structures, steroidal saponins are commonly classified into various types, of which spirostanol-type steroidal saponins and furostanol-type steroidal saponins are the most widely distributed. The spirostanol steroidal saponins are the main type with an ABCDEF six-ring structural chemical backbone formed by a steroidal aglycone and a C27 spirostane skeleton (9). By contrast, the furostanol steroidal saponins have an ABCDE pentacyclic ring with a sixth open ring (Fig. 1). On account of the attachment to different glycoside backbones and different numbers of sugar chains, steroidal saponins have a wide range of functional and pharmacological activities, such as anti-inflammatory (10,11), anti-bacterial (12), antitumor (13-16), immunomodulatory (17), anti-angiogenesis (18), lipid and glucose metabolism-regulating (19,20) and anti-Alzheimer's disease (21) effects. Over the last few years, numerous studies have shown that steroidal saponins exhibit a wide range of antitumor activities, and their anti-drug resistance activity has also attracted wide attention for further exploration, either as a monotherapy or when administered as a drug-drug combination in diverse tumor models (22-25). The present study provides a review on the mechanism of drug resistance in cancer chemotherapy, and the action of >10 steroidal saponins (Fig. 2) in reversing drug resistance in tumors.

2. Mechanisms of drug resistance in cancer chemotherapy

The resistance of tumors can be confined to a specific drug or can extend to multiple drugs with independent modes of action, which is known as multidrug resistance (MDR) (26). According to the chronological order in which tumor drug resistance arises, drug resistance can be divided into primary resistance and acquired resistance (27,28). Primary drug resistance means that tumor cells have an inherent resistance to a particular antitumor drug before they are exposed to it (29). Notably, the mechanisms underlying primary drug resistance may be related to certain innate genetic mutations in tumor cells, tumor heterogeneity or activation of intrinsic resistance pathways, such as the function of interferon signaling pathways and immune-evasive oncogenic signaling pathways (30-33). Acquired drug resistance, on the other hand, is induced by chemotherapeutic drugs; that is, tumor cells become progressively less sensitive to the drugs during the employment of chemotherapy and ultimately establish resistance (28). Mostly, the development of acquired drug resistance is due to changes in the tumor microenvironment, mutations in oncogenes (34), such as Kirsten rat sarcoma viral oncogene homolog (*KRAS*) and human epidermal growth factor receptor (EGFR)-2 (*HER2*), and mutations in drug molecular targets, such as EGFR (35,36). However, in cancer cells, a new 'driver mutation' may occur at a different site of the proto-oncogene or in a different proto-oncogene, which can activate a different oncogenic pathway, and allow the tumor to bypass the effects of the therapy; for instance, in non-small cell lung cancer

(NSCLC) driven by the *KRAS*^{G12C} mutation, the *KRAS*^{Y96D} mutation confers resistance to *KRAS*^{G12C}-selective inhibitors in cancer cells (37); NSCLC driven by *EGFR* gene mutation can reactivate the rat sarcoma (RAS)/mitogen-activated protein kinase (MAPK) signaling pathway and mediate drug resistance through mutations in *KRAS*, the human MAPK kinase 1 or neuroblastoma-RAS genes after treatment with EGFR inhibitors (38).

At present, it has been confirmed that the mechanisms of drug resistance in tumors mainly include the following: The induction of apoptosis, autophagy and hypoxia, upregulation of the ATP-binding cassette (ABC) transporter family, epithelial-mesenchymal transition (EMT), tumor stem cell regulation, microRNA regulation, epigenetic regulation and enhanced DNA damage repair ability (4,5,27,39,40). Furthermore, pump resistance and non-pump resistance mechanisms have been described (41); of note, drug inactivation and degradation, anti-apoptotic effects and antioxidant defense, and DNA repair, replication and biosynthesis are considered as non-pump resistance mechanisms, whereas the pump resistance mechanisms mainly include upregulation of the ABC transporter family.

Apoptosis evasion-mediated drug resistance. Apoptosis is a type of programmed cell death, which can maintain normal cellular functioning and embryonic development by promoting cell death induced by multiple stimuli. Apoptosis can be induced by death receptor-dependent exogenous and mitochondria-dependent endogenous apoptotic pathways, and the process principally consists of alterations in mitochondrial outer membrane permeability, and the activation of a series of cysteinyl aspartate specific proteinase (caspase) and catabolic hydrolase (42). A prospective cohort study indicated that the apoptosis index, Ki-67 index and the ratio between the two, could serve as auxiliary assessments for the efficacy and prognosis of chemotherapy in patients with gastric cancer undergoing perioperative chemotherapy and radical gastrectomy (43). Furthermore, the avoidance of apoptosis is one of the hallmarks of chemotherapy resistance (44). The key to the occurrence of endogenous apoptosis lies in the balance between pro-apoptotic and pro-survival protein regulators (e.g., Bax and Bcl-2) (45). Notably, the upregulation of pro-survival proteins, such as Bcl-extra large and myeloid cell leukemia 1, has been suggested as one of the main reasons for the survival and drug resistance of various tumor cells (46). In addition, Bcl-2 can disrupt apoptotic signaling and ultimately inhibit the activation of caspases and apoptosis by preventing the release of cytochrome *c* from mitochondria (47).

Autophagy-mediated drug resistance. Autophagy is a highly conserved intracellular catabolic process that occurs to degrade and eliminate misfolded proteins and damaged organelles, which is essential for maintaining metabolic homeostasis and energy balance. The process of autophagy mainly includes three stages: Phagocytic bubble assembly, autophagy formation and autophagy lysosome degradation (48). Depending on how it happens, autophagy has been mainly classified into three modes: Macroautophagy, microautophagy and chaperone-mediated autophagy (49). Autophagic cell death serves an important role in the action of antineoplastic drug therapy.

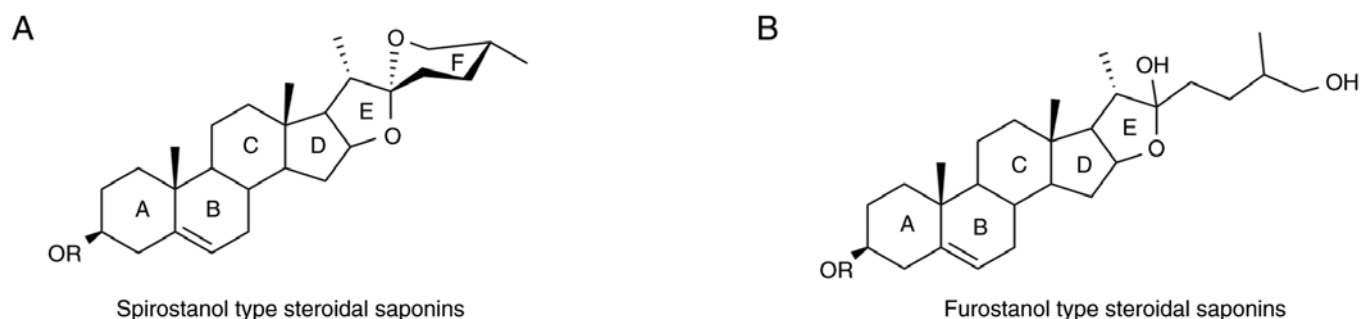


Figure 1. Structural chemical backbone of (A) Spirostanol-type and (B) Furostanol-type steroidal saponins.

However, during tumorigenesis and progression, autophagy has dual effects: In the early stage of tumor development, excessive autophagy induces autophagic cell death; by contrast, in cells in the middle and late stages, an increased level of autophagy promotes tumor survival and malignancy (50). Mammalian target of rapamycin (mTOR) kinase is an essential regulator of autophagy, which can be activated by the phosphatidylinositol-3 kinase (PI3K)/protein kinase B (AKT)/mTOR pathway to inhibit autophagy, and can also promote autophagy through the negative regulation of the AMPK/mTOR pathway (51). Several studies have shown that the inhibition of autophagy can significantly enhance the sensitivity of tumor cells to chemotherapeutic agents and reverse drug resistance (52-54).

EMT-mediated drug resistance. EMT is a process of change in which tumor cells lose epithelial characteristics and acquire a mesenchymal phenotype (55). The intrinsic mechanism is primarily associated with the specific loss of the epithelial marker E-cadherin and cell polarity, and the acquisition of the mesenchymal marker N-cadherin by tumor cells, including the activation of transcription factors such as Twist and Snail, and the expression of vimentin proteins (56). It has been shown that the occurrence of EMT might be related to a variety of tumor events, including tumorigenesis, deterioration, migration, invasion, acquisition of tumor stemness and drug resistance (57-59). EMT is a key step in inducing the formation of cancer stem cells (CSCs). The signaling pathways that activate EMT exhibit similarities with those that drive CSCs, such as the Wnt, Hedgehog and Notch pathways. Once EMT occurs, tumor cells will exhibit characteristics similar to those of CSCs, such as increased efflux of intracellular drugs and enhanced anti-apoptotic effects (60,61), thereby facilitating the survival and drug resistance of tumor cells.

ABC transporter protein family-mediated drug resistance. The phenotype of drug resistance in tumor cells is usually associated with the upregulation of members of the ABC transporter protein family, especially P-glycoprotein (P-gp) encoded by the *ABCB1* gene (62), MDR-related protein 1 (MRP1) encoded by the *ABCC1* gene and breast cancer resistance protein (BCRP) encoded by the *ABCG2* gene (63). These transporter proteins act as drug efflux pumps to catalyze the efflux of chemotherapeutic agents, thus contributing to the decreased levels of intracellular drug concentrations, and therefore attenuating the antitumor effects of drug therapy. It has been reported that the upregulation of P-gp, MRP1 and BCRP may give rise to poor

clinical response and drug resistance in a variety of cancer types, such as human ovarian cancer, colon cancer, NSCLC and pancreatic cancer (64,65).

The mechanisms of drug resistance arising in tumor cells are complex, and there may be multiple mechanisms that intersect on one pathway to jointly mediate drug resistance in tumors. For example, the PI3K/AKT/mTOR signaling pathway, also referred to as the PAM axis, which is one of the most vital pathways regulating the basic physiological functions of cells, has a complex cascade that has an important role in the regulation of cell growth, differentiation, apoptosis, proliferation and metastasis (66). In general physiological and pathological processes, the PI3K/AKT/mTOR pathway works by transmitting signals from the upstream regulatory proteins, such as phosphatase and tensin homologue, PI3K and receptor tyrosine kinases, to a number of downstream effectors, such as mTOR, glycogen synthase kinase-3 β , forkhead box O and mouse double minute 2 proteins (67). However, the hyperactivation and alteration of this pathway are often associated with the survival, proliferation, invasion and migration of tumor cells, further influencing the outcome of targeted therapy in human cancer (68). Due to PI3K being a primary drug target for cancer therapy, the development of more optimized PI3K inhibitors has consistently been a direction in the field of anticancer drug development. However, the rapidly accelerated fibrosarcoma (RAF)/MAPK kinase (MEK)/extracellular signal-regulated kinase (ERK) signaling pathway is another pathway that exerts a similar function to the PI3K/AKT/mTOR pathway (69), and a cross-inhibitory pattern exists between these two pathways, which exerts negative regulation on each other's activity. Therefore, when one pathway is chemically blocked, it releases the cross-inhibition and effectively activates the other pathway to synergistically mediate cell survival (Fig. 3) (67,70). Consequently, the complex crosstalk between signaling pathways is strongly associated with the refractoriness of tumors; however, a study has shown that the development of drugs targeting these crosstalk-pathway regulatory factors offers a new strategy for solving this problem (71).

3. Mechanisms of steroidal saponins in reversing tumor drug resistance

Multiple pathways to induce apoptosis. Timosaponin AIII (TS-AIII) (Fig. 2A) is a steroidal saponin obtained from the rhizome of *Anemarrhena asphodeloides* (AA). For more than

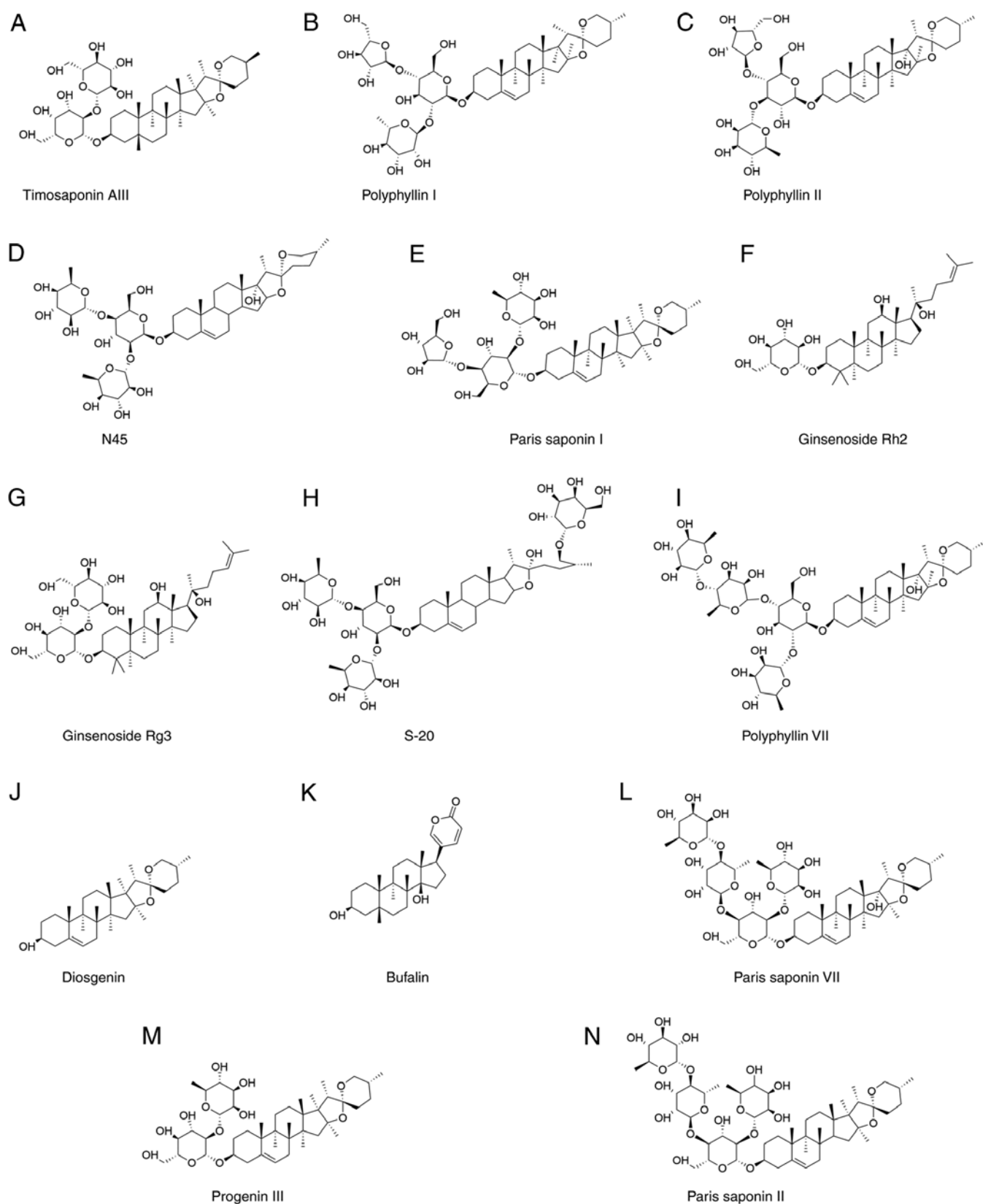


Figure 2. Chemical structures of (A) Timosaponin AIII, (B) Polyphyllin I, (C) Polyphyllin II, (D) N45, (E) Paris saponin I, (F) Ginsenoside Rh2, (G) Ginsenoside Rg3, (H) S-20, (I) Polyphyllin VII, (J) Diosgenin, (K) Bufalin, (L) Paris saponin VII, (M) Progenin III and (N) Paris saponin II mentioned in the text.

a decade, studies on the anticancer effects of TS-AIII have been reported, and it has been shown that TS-AIII exerts its anticancer effects in a variety of tumor cells mainly by inducing apoptosis and cell cycle arrest through multiple

pathways (72). In terms of antitumor drug resistance, related studies have shown that either TS-AIII or AA treatment could significantly inhibit growth and promote cell cycle arrest in PANC-1 and BxPC-3 cells (pancreatic cancer cells with

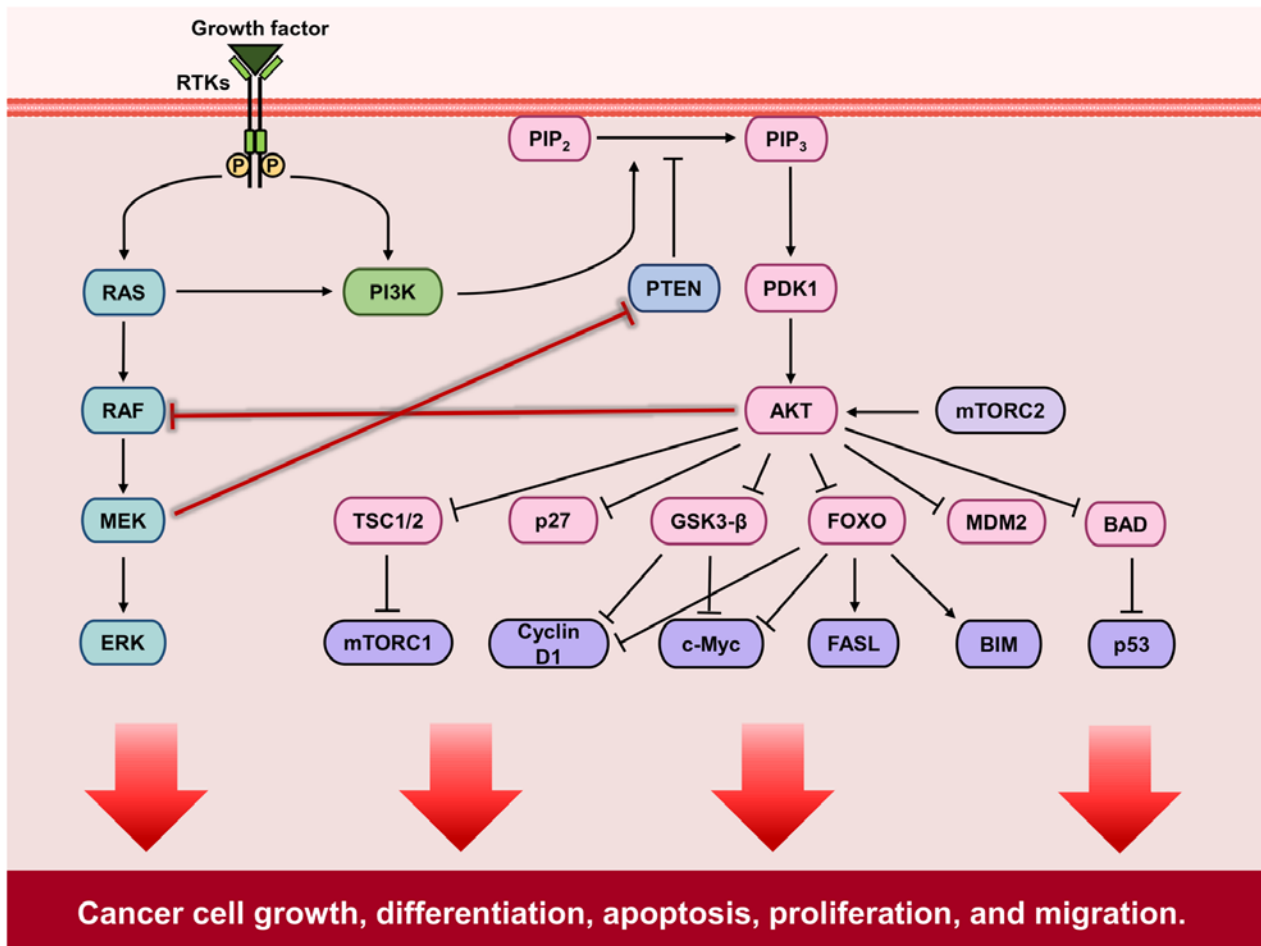


Figure 3. Cross-inhibition between the PI3K/AKT/mTOR and RAF/MEK/ERK pathways. AKT negatively regulates ERK activation by phosphorylating and inactivating RAF, while MEK suppresses the PI3K signaling pathway by promoting the membrane localization of PTEN, thereby achieving the negative regulation between the two pathways. PI3K, phosphatidylinositol-3 kinase; AKT, protein kinase B; mTOR, mammalian target of rapamycin; RAF, rapidly accelerated fibrosarcoma; MEK, mitogen-activated protein kinase kinase; ERK, extracellular signal-regulated kinase; PTEN, phosphatase and tensin homologue.

varying degrees of resistance to gemcitabine). Furthermore, when used separately in combination with gemcitabine, both TS-AIII and AA induced caspase-dependent apoptosis of pancreatic cancer cells more than gemcitabine alone. The underlying mechanism may be related to the regulation of the activity of PI3K/AKT pathway proteins involved in the cell cycle and proliferation (73). Another study demonstrated that TS-AIII could inhibit cell growth and induce apoptosis in paclitaxel-resistant tumor cells (A549/Taxol and A2780/Taxol) by suppressing activation of the PI3K/AKT/mTOR and RAS/RAF/MEK/ERK signaling pathways, resulting in a more stable antitumor effect (74).

As one of the 'vulnerable' species designated by the International Union for Conservation of Nature Red List, *Paris polyphylla* is an important medicinal plant in the traditional system of medicine, and steroidal saponins are one of the main bioactive chemical components of this plant (75). Polyphyllin I (PP-I) (Fig. 2B) and PP-II (Fig. 2C) isolated from the rhizome of *Paris polyphylla*, have been proven to have an obvious effect on reversing tumor drug resistance. In a previous study (76), the overexpression of the long noncoding RNA metastasis-associated lung adenocarcinoma transcript-1 (MALAT1) increased signal transducer and

activator of transcription 3 (STAT3) expression in NSCLC cells, leading to gefitinib resistance in the lung cancer cells, whereas PP-I downregulated the expression of MALAT1, inhibiting the phosphorylation of STAT3 and finally leading to the apoptosis of NSCLC cells. Similarly, PP-II triggered apoptosis to strengthen the sensitivity of PC-9/ZD cell lines to gefitinib by downregulating the protein levels of PI3K, AKT and mTOR, and upregulating the levels of Bax, caspase-9 and caspase-3 (77).

N45 (Fig. 2D), a steroidal saponin once known as saponin 9 is derived from the rhizome of *Paris vietnamensis* (Takht.). Liu *et al* (78) showed that N45 exhibited significant cytotoxic effects on glioblastoma cells with IC₅₀ values of 3.14 μ M in U251 cells and 2.97 μ M in U87MG cells. The same group proved that N45 could induce mitochondrial apoptosis to inhibit the proliferation of temozolomide-resistant glioblastoma cells (U87R) by increasing the Bax/Bcl-2 ratio, and the levels of cytochrome *c* and cleaved caspase. The underlying molecular mechanism included the reactive oxygen species (ROS)-mediated inactivation of the PI3K/AKT pathway, which resulted in downregulated expression of the nuclear factor- κ B (NF- κ B) p65 and O6-methylguanine-DNA methyltransferase (79).

Similarly, by triggering the apoptotic pathway, steroidal saponins can work synergistically with chemotherapy drugs to enhance the sensitivity of tumors to chemotherapy. Paris saponin I (PS-I) (Fig. 2E), isolated from *Paris polyphylla*, has been reported to induce apoptosis by regulating the expression of Bcl-2, Bax and caspase-3 proteins, and by promoting G₂/M phase cell cycle arrest by activating P21^{waf1/cip1} when combined with cisplatin, thereby improving the sensitivity of gastric cancer cell lines to cisplatin (80). In lung cancer cell lines, PS-I similarly acted as a chemosensitizer of camptothecin (CPT)/10-hydroxycamptothecin (HCPT), which synergistically inhibited cell proliferation and induced apoptosis by improving activation of the p38 MAPK/caspase signaling pathway in H1299 cells, as well as by inhibiting activation of the AKT and ERK pathways in H460 and H446 cells (81). Combination treatment with ginsenoside Rh2 (Fig. 2F) and cisplatin has been shown to potentially overcome the tolerance of NSCLC cells to cisplatin by promoting apoptosis and inhibiting cisplatin-induced phosphorylation of EGFR, PI3K and AKT, thus suppressing the production of superoxide, the expression of programmed death-ligand 1 and autophagy (82).

Inhibition/induction of autophagy. According to *in vitro* and *in vivo* research, autophagy induced by doxorubicin in hepatocellular carcinoma cells promoted tumor cell survival. By contrast, the 20(S)-ginsenoside Rg3 (G-Rg3), a stereoisomer of G-Rg3 (Fig. 2G), which was isolated from steamed *Panax ginseng* C.A. Meyer, was shown to suppress the late stage of autophagy by inhibiting the maturation, fusion or degradation stages, thus exhibiting a positive effect on doxorubicin-induced hepatocellular carcinoma cell death. The potential mechanism of this effect was partly relevant to regulation of the C/EBP homologous protein (CHOP) transcription factor at the genomic level (83). Besides, the combination of G-Rg3 and paclitaxel was able to promote cytotoxicity and apoptosis of triple-negative breast cancer cell lines by interrupting the NF- κ B signaling pathway, thus downregulating the protein levels of NF- κ B, p65 and Bcl-2, and upregulating the levels of Bax and caspase-3 (84). An earlier study also showed that G-Rg3 could enhance the antitumor effects of radiation therapy on NSCLC cells by targeting and regulating the NF- κ B protein and its regulatory gene products (85).

In addition, a series of findings made by Wang's research team with regard to black nightshade (*Solanum nigrum* L.) found that the promotion of autophagy could significantly inhibit the proliferation of drug-resistant tumor cells. *Solanum nigrum* L. is a plant belonging to the Solanaceae family that commonly grows in Africa and Southeast Asia, and has been widely used as a vegetable, fruit and source of various therapeutic medicines for a number of years (86). Wang *et al.* (87) found that S-20 (Fig. 2H), a novel component isolated from the berries of black nightshade, induced both autophagy and caspase-dependent apoptosis to overcome the Adriamycin resistance of K562 cells (K562/ADR); however, upon the addition of inhibitors to these two pathways, it was discovered that autophagic death was the primary pathway through which S-20 exerted its anti-drug resistance effect, rather than apoptosis. The mechanism of action was associated with the activation of ERK, which further suppressed

the expression of BCRP and P-gp proteins (87). By contrast, in a subsequent study, this research group reported that the total saponins from the berries of *Solanum nigrum* exerted anti-drug resistance activity by significantly downregulating the phosphorylation level of mTOR kinase in K562/ADR cells and xenograft tumors, inducing autophagy in K562/ADR cells and inhibiting the expression of drug resistance proteins (88). Furthermore, the synergistic combination of the total saponins of *Solanum nigrum* and Adriamycin could induce apoptosis through the intrinsic and extrinsic pathways, and activate autophagy by downregulating the PI3K/AKT/mTOR signaling pathway and upregulating the MAPK signaling pathway, thereby significantly enhancing the antitumor resistance activity in K562/ADR cells (89).

Inhibition of EMT. PP-I has been demonstrated to resensitize HCC827-ER cells to erlotinib and to enhance antitumor activity by reversing the EMT process through inhibitory effects on the activation of the IL-6-mediated signaling pathway and the phosphorylation of STAT3 protein, thereby decreasing the levels of vimentin and increasing those of E-cadherin (90). Furthermore, PP-I combined with polyphyllin VII (PP-VII) (Fig. 2I) could inhibit the invasion and metastasis of cisplatin-resistant NSCLC cells (A549/DDP) by upregulating levels of the epithelial marker E-cadherin, and downregulating those of the mesenchymal markers vimentin and α -smooth muscle actin. Meanwhile, the combination also induced apoptosis and autophagy to promote A549/DDP cell death via upregulation of p53 expression and inhibition of the cancerous inhibitor of protein phosphatase 2A/AKT/mTOR signaling axis (91).

A study on the inhibitory effects of diosgenin (DG) (Fig. 2J) on breast cancer stem cells (bCSCs) showed that DG induced apoptosis by activating caspase-3/7 and releasing ROS. Further investigation identified that, in sFRP4-OE cells, a model of bCSCs that overexpressed Wnt antagonists, DG treatment significantly increased the expression of E-cadherin, decreased N-cadherin and β -catenin proteins, and downregulated the expression of the pro-invasive genes *Twist* and *Snail*, thus inhibiting EMT and suppressing the invasiveness of bCSCs, probably via the Wnt/ β -catenin pathway (92).

Reduction of drug efflux. In human chronic myelogenous leukemia Adriamycin-resistant cells (K562/ADM), TS-AIII exhibited the ability to downregulate overexpressed P-gp and MRP1 in a dose-dependent manner, further improving the retention of Adriamycin in the cells, and the underlying mechanism may be related to the PI3K/AKT signaling pathway in this process (93). Bufalin (Fig. 2K), an extract of the natural Chinese herbal medicine *Venenum bufonis*, has been reported to prevent Adriamycin outflow by inhibiting nuclear factor erythroid 2-related factor 2 and weakening the expression of the downstream target genes, including heme oxygenase-1 and P-gp, thus reversing the drug resistance of K562/A02 cells (94).

Trillium tschonoskii Maxim (TTM) is a folk medicine that originated from Liliaceae in China. TTM has long been known as 'Yan Ling Cao' and is used to treat traumatic brain injury and headaches (95). Previous studies showed that the steroidal saponin of *Trillium tschonoskii* (TTS) could downregulate the expression of P-gp in R-HepG2 (a cell line in which the

sensitivity to doxorubicin was much lower than that of parental cells) in a dose-dependent manner at both the transcriptome and protein levels (96). Moreover, TTS treatment enhanced the cytotoxic effect of doxorubicin on primary tumors both *in vitro* and *in vivo*. Paris saponin VII (PS-VII) (Fig. 2L) derived from the roots of TTM has been reported to reduce Adriamycin transmembrane outflow in Adriamycin-resistant breast cancer cells by inhibiting the expression and function of P-gp at a low dose (97). Another study demonstrated that PS-VII significantly enhanced the sensitivity of HepG2 cells to Adriamycin via inhibition of the PI3K/AKT/MAPK signaling pathway, thus decreasing the expression of P-gp, MRP1 and BCRP proteins, increasing the intracellular accumulation of Adriamycin and also inducing cell apoptosis (98). Additionally, co-incubation of H1975 cells with PP-VII and gefitinib enhanced the anti-proliferative effect of gefitinib by upregulating p21 protein expression, and downregulating the expression levels of cyclin-dependent kinase (CDK)2, CDK4, Cyclin E and Cyclin D1, leading to a cellular G₁-phase block (99).

Low cytotoxic concentrations of total saponins from *Paris forrestii* inhibited ERK phosphorylation through the MAPK signaling pathway, thereby reducing expression of MDR1 mRNA and P-gp protein, ultimately reversing drug resistance in Adriamycin-resistant human breast cancer cells (MCF-7/ADM) (100).

Shenmai injection (SMI) is derived from the famous Chinese patent medicine known as Shenmai San, which has been clinically used for the treatment of cardiovascular and cerebrovascular diseases. A previous study demonstrated that SMI could inhibit the function and expression of P-gp through the MAPK/NF- κ B signaling pathway, and further potentiate the sensitivity of breast cancer cells to chemotherapeutic drugs (101). Moreover, *Panax ginseng* and *Ophiopogon japonicus*, as the primary components of SMI (102), have been proven to be rich in steroidal saponins (103,104). Based on the aforementioned facts, the present review indicates the potential possibility to further investigate the effects of SMI components on the reversal of tumor drug resistance.

4. Conclusion and prospects

In conclusion, naturally occurring steroidal saponins have emerged as promising agents in the reversal of drug resistance in multiple types of cancer (Table I), with evidence suggesting their potential to induce apoptosis, modulate apoptosis and autophagy, inhibit EMT and block drug efflux mediated by the ABC transporter protein family (Fig. 4). Moreover, combination treatment with existing chemotherapeutic agents has been reported to enhance efficacy and overcome the challenges of drug resistance. Existing research has provided preliminary evidence that steroidal saponins have notable therapeutic potential in reversing tumor drug resistance. However, the current research is still in its infancy, with limitations in understanding the mechanisms of action, the potential direct targets based on their molecular backbone structures and the potential side effects of steroidal saponins. Furthermore, most studies lack *in vivo* experimental and clinical trial evidence.

Based on the aforementioned studies, it may be indicated that multiple pathways could simultaneously mediate the

reversal of drug resistance. For example, the total saponins of *Solanum nigrum* have been shown to induce both autophagy and apoptosis in human chronic myeloid leukemia (89), and PS-VII not only inhibits the expression of the ABC transporter family-related proteins, but also induces apoptosis (98). Progenin III (Fig. 2M) is another steroidal saponin isolated from the fruits of the Arecaceae tree, *Raphia vinifera* P. An *in vitro* experimental study demonstrated that progeny III exhibited favorable antiproliferative activity against 18 human and animal cancer cell lines, including those with a drug resistance phenotype, such as the P-gp-overexpressing subline CEM/ADR5000 cells from CCRF-CEM human T-lymphoblast leukemia cells. Of note, progenin III significantly induced the apoptosis of CCRF-CEM cells, the mechanism of which may be related to the activation of caspase-3/7, the alteration of mitochondrial membrane potential, the increased generation of ROS, as well as the induction of autophagy and necroptosis (105). A previous study has demonstrated that the promoters of ABC transporter genes contain binding sites for EMT transcription factors, and the overexpression of these EMT transcription factors can increase the expression of ABC transporters in breast cancer cells, thereby leading to stronger drug resistance (106). Therefore, it is also an effective choice for drug resistance mediated by multiple pathways to exploit multi-target drug inhibitors.

A large number of studies have shown that the level, distribution and oxidative metabolism of tumor cell lipids can affect the drug resistance characteristics of tumor cells by regulating drug efflux transporters, drug permeability through membranes and intracellular death mechanisms (107-110). However, due to the wide variety of tumor cell lipids, rapid changes in their composition and large individual differences, there is difficulty in developing plasma membrane-targeted drugs. Although the relevant studies have achieved preliminary results, their feasibility, specificity and safety still need to be explored by in-depth studies (111-113). An experimental study *in vivo* showed that Rhizoma Paridis saponins, a NP of *Paris polyphylla*, when used in combination with sorafenib for hepatocellular carcinoma, was able to overcome sorafenib intolerance. The underlying mechanism may be based on the PI3K/AKT/mTOR pathway to protect against mitochondrial damage, inhibit anaerobic glycolysis and suppress lipid synthesis (114). In addition, a study showed that various natural compounds exert their pharmacological activities by targeting endoplasmic reticulum (ER) stress, with the inositol requiring enzyme 1 (IRE1)/c-Jun N-terminal kinase (JNK) and eukaryotic translation initiation factor 2 α /CHOP pathways acting as two important signaling pathways (115). Paris saponin II (Fig. 2N) combined with cisplatin could significantly enhance the cytotoxicity of cisplatin to lung cancer cells by inducing cytoplasmic vacuolization and paraptosis, based on the upregulation of ER stress-related proteins, including IRE1 α , caspase-12, splicing of X-box binding protein 1 and CHOP, through the activation of the JNK pathway (116). A recent study also confirmed that PP-I induced ferroptosis via the ERK/DNA methyltransferase 1/acetyl-coenzyme A synthetase long-chain family member 4 axis in castration-resistant prostate cancer cells (117). These findings may bring novel ideas to the future research of steroidal saponins reversing drug resistance.

Table I. Summary of related potential mechanisms of reversing tumor drug resistance by steroidal saponins.

Compounds/ extracts (Fig.)	Source	Chemotherapeutic drugs/cell models	Cancer types	Related potential mechanisms	(Refs.)
Timosaponin AIII (Fig. 2A)	Rhizome of <i>Anemarrhena asphodeloides</i>	Gemcitabine Taxol Adriamycin	Pancreatic cancer Lung cancer, ovarian carcinoma Chronic myeloid leukemia	Timosaponin AIII induces caspase-dependent apoptosis by regulation of the PI3K/AKT signaling pathway. Timosaponin AIII inhibits cell growth and induces apoptosis by suppressing the PI3K/AKT/mTOR and RAS/RAF/MEK/ERK signaling pathways. Timosaponin AIII downregulates P-gp and MRP1 levels through the PI3K/AKT signaling pathway in a dose-dependent manner to improve the retention of ADM in cells.	(73) (74) (93)
Polyphyllin I (Fig. 2B)	Rhizome of <i>Paris polychylla</i>	Gefitinib	Lung cancer	Polyphyllin I induces apoptosis by downregulating the expression of MALAT1 and inhibiting the phosphorylation of STAT3.	(76)
Polyphyllin II (Fig. 2C)	Rhizome of <i>Paris polychylla</i>	Erlotinib	Lung cancer	Polyphyllin I inhibits the activation of the IL-6-mediated signaling pathway and the phosphorylation of STAT3 protein to decrease the vimentin level and increase the E-cadherin level in HCC827-ER cells.	(90)
N45 (Fig. 2D)	Rhizome of <i>Paris vietnamensis</i> (Takht.)	Temozolomide	Glioblastoma	Polyphyllin II triggers apoptosis to strengthen the sensitivity of PC-9/ZD cell lines to gefitinib by downregulating the PI3K/AKT/mTOR pathway. N45 induces mitochondrial apoptosis to inhibit the proliferation of U87R cells by the ROS-mediated inactivation of the PI3K/AKT pathway.	(77) (79)
Paris saponin I (Fig. 2E)	<i>Paris polychylla</i>	Cisplatin	Gastric cancer	Paris saponin I combined with cisplatin induces apoptosis and G ₂ /M phase cell cycle arrest by the activation of P21 ^{waf1/cip1} .	(80)
Ginsenoside Rh2 (Fig. 2F)	Ginseng	Camptothecin/ 10-hydroxycamptothecin Cisplatin	Lung cancer Lung cancer	Paris saponin I combined with CPT/HCPT induces apoptosis separately by activating the p38 MAPK/caspase signaling pathway and inhibiting the AKT and ERK pathways in different cell lines. Ginsenoside Rh2 combined with cisplatin promotes apoptosis, but suppresses the production of superoxide, the expression of PD-L1 and autophagy by inhibiting cisplatin-induced phosphorylation of EGFR, PI3K and AKT.	(81) (82)
20(S)-ginsenoside Rg3 (Fig. 2G)	Steamed <i>Panax ginseng</i> C.A. Meyer	Doxorubicin	Hepatocellular carcinoma	20(S)-ginsenoside Rg3 suppresses the late stage of autophagy by regulating the CHOP transcription factor at the genomic level.	(83)

Table I. Continued.

Compounds/ extracts (Fig.)	Source	Chemotherapeutic drugs/cell models	Cancer types	Related potential mechanisms	(Refs.)
Ginsenoside Rg3 (Fig. 2G)	<i>Panax ginseng</i> C.A. Meyer	Paclitaxel	Triple-negative breast cancer	Ginsenoside Rg3 combined with paclitaxel induces apoptosis and decreases the protein levels of NF- κ B p65 by interrupting the NF- κ B signaling pathway.	(84)
S-20 (Fig. 2H)	<i>Solanum nigrum</i> L.	Adriamycin	Chronic myeloid leukemia	S-20 induces autophagic death by the activation of ERK to inhibit the expression of BCRP and P-gp.	(87)
Total saponins	<i>Solanum nigrum</i> L.	Adriamycin	Chronic myeloid leukemia	Total saponins of <i>S. nigrum</i> induce autophagy by significantly downregulating the phosphorylation level of mTOR kinase <i>in vitro</i> and <i>in vivo</i> to exert anti-drug resistance activity.	(88)
Polyphyllin I (Fig. 2B) + polyphyllin VII (Fig. 2I)	Rhizome of <i>Paris polyphylla</i>	Cisplatin	Lung cancer	Polyphyllin I combined with polyphyllin VII inhibits invasion and metastasis by upregulating E-cadherin and downregulating vimentin and α -SMA levels, and induces apoptosis and autophagy by upregulating p53 expression and inhibiting the CIP2A/AKT/mTOR pathway.	(91)
Diosgenin (Fig. 2J)	Fenugreek, <i>Rhizoma polygonati</i> , <i>Smilax china</i> , <i>Dioscorea villosa</i> , <i>Trigonella foenum-graecum</i> , and <i>Dioscorea</i> rhizome.	sFRP4-OE bCSCs	Breast cancer	Diosgenin inhibits the expression of twist, snail, E-cadherin and N-cadherin by regulating the Wnt/ β -catenin pathway to suppress the invasiveness of bCSCs.	(92)
Bufalin (Fig. 2K)	<i>Venenum Bufonis</i>	Adriamycin	Chronic myeloid leukemia	Bufalin inhibits Nrf2 and decreases the expression of HO-1 and P-gp to prevent Adriamycin outflowing.	(94)
Paris saponin VII (Fig. 2L)	<i>Trillium tschonoskii</i> Maxim	Adriamycin	Breast cancer	Paris saponin VII inhibits the expression and function of P-gp in a low dose manner to prevent Adriamycin outflowing.	(97)
		Adriamycin	Hepatocellular carcinoma	Paris saponin VII induces apoptosis and decreases the expression of P-gp, MRP1 and BCRP by inhibiting the PI3K/AKT/MAPK signaling pathway.	(98)
Polyphyllin VII (Fig. 2I)	Rhizome of <i>Paris polyphylla</i>	Gefitinib	Lung cancer	Polyphyllin VII combined with gefitinib induces G ₁ phase block in H1975 cells by upregulating p21 protein level and downregulating the expression of CDK2, CDK4, Cyclin E and Cyclin D1.	(99)
Total saponins from <i>Paris forrestii</i>	<i>Paris forrestii</i> (Takht.) H. Li	Adriamycin	Breast cancer	Total saponins from <i>Paris forrestii</i> inhibit the expression of MDR1 and P-gp through the MAPK/ERK signaling pathway.	(100)

Table I. Continued.

Compounds/ extracts (Fig.)	Source	Chemotherapeutic drugs/cell models	Cancer types	Related potential mechanisms	(Refs.)
Progenin III (Fig. 2M)	Areca-ceae tree, <i>Raphia vinifera</i> P.	CEM/ADR5000 cells	Leukemia	Progenin III induces apoptosis in CCRF-CEM cells by the activation of caspase3/7, the alteration of mitochondrial membrane potential, the increased generation of ROS, and the induction of autophagy and necroptosis.	(105)
Rhizoma Paridis saponins	<i>Paris polyphylla</i>	Sorafenib	Hepatocellular carcinoma	Rhizoma paridis saponins combined with sorafenib in H22 mice model protects against mitochondrial damage, inhibits anaerobic glycolysis and suppresses lipid synthesis through the PI3K/AKT/mTOR pathway.	(114)
Paris saponin II (Fig. 2N)	<i>Paris polyphylla</i> var. <i>yunnanensis</i> (Fr.) Hand. Mazz. (Melanthiaceae)	Cisplatin	Lung cancer	Paris saponin II combined with cisplatin induces cytoplasmic vacuolization and paraptosis by upregulating ER stress-related proteins including IRE1 α , caspase 12, XBP1 and CHOP through the activation of the JNK pathway.	(116)

PI3K, phosphatidylinositol-3 kinase; AKT, protein kinase B; mTOR, mammalian target of rapamycin; RAS, rat sarcoma; RAF, rapidly accelerated fibrosarcoma; MEK, MAPK kinase; ERK, extracellular signal-regulated kinase; P-gp, P-glycoprotein; MRP1, MDR-related protein 1; ADM, Adriamycin; MALAT1, metastasis-associated lung adenocarcinoma transcript-1; STAT3, signal transducer and activator of transcription 3; IL-6, interleukin 6; HCC827-ER cells, EGFR-mutant non-small cell lung cancer HCC827 cells; PC-9/ZD cell lines, the gefitinib-resistant non-small cell lung cancer cells; ROS, reactive oxygen species; CPT, camptothecin; HCPT, 10-hydroxycamptothecin; MAPK, mitogen-activated protein kinase; Caspase, cysteinyl aspartate specific proteinase; PD-L1, programmed death-ligand 1; EGFR, epidermal growth factor receptor; CHOP, C/EBP homologous protein; NF- κ B, nuclear factor- κ B; BCRP, breast cancer resistance protein; α -SMA, α -smooth muscle actin; CIP2A, cancerous inhibitor of protein phosphatase 2A; BCSC, breast cancer stem cell; Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase-1; CDK2/4, cyclin-dependent kinase 2/4; CCRF-CEM, the human T-lymphoblast leukemia cells; ER, endoplasmic reticulum; IRE1 α , inositol requiring enzyme 1 α ; XBP1, X-box binding protein 1; JNK, c-Jun N-terminal kinase.

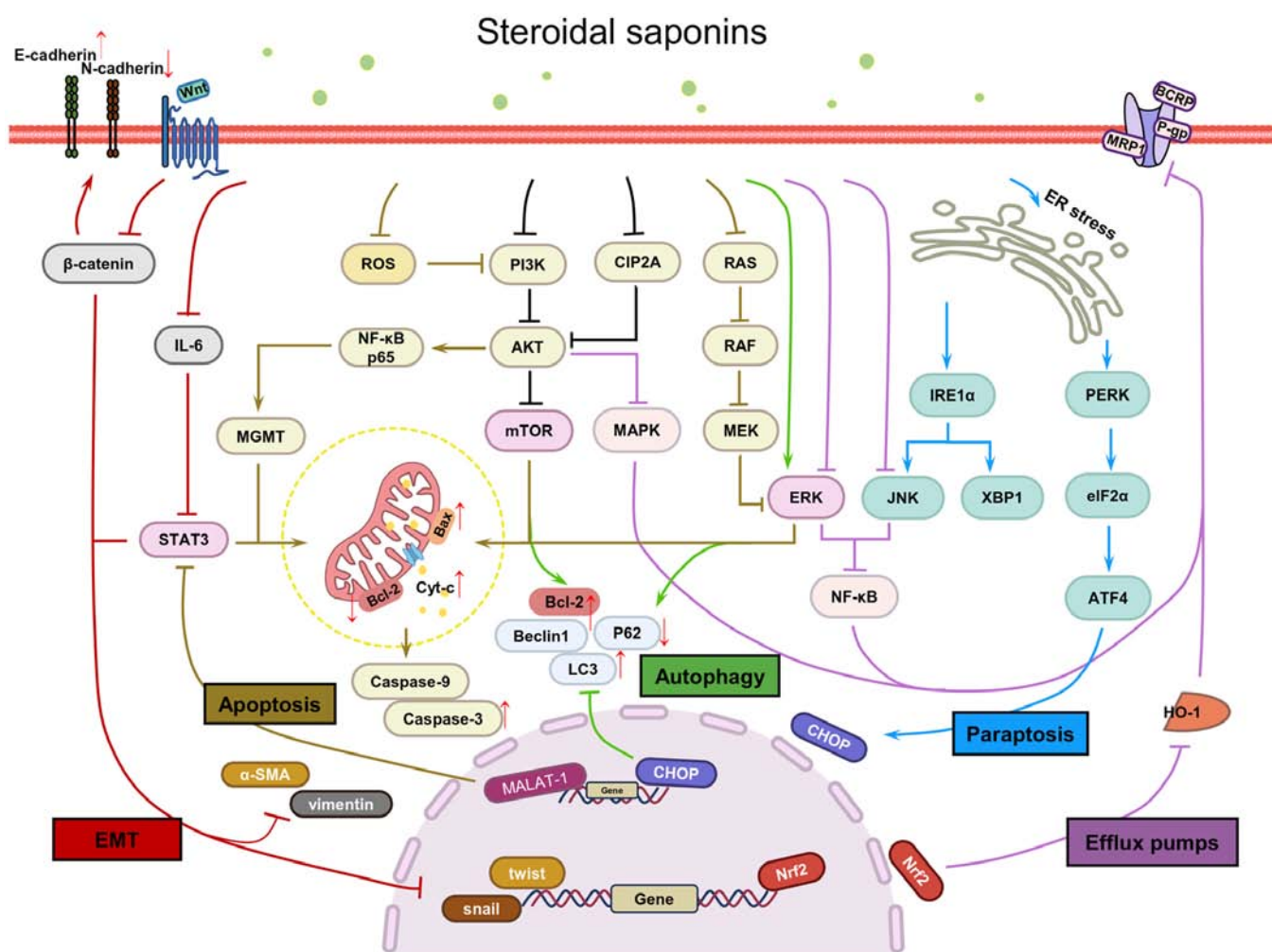


Figure 4. Schematic representation of the potential molecular mechanisms for the reversal of multidrug resistance in tumors by steroidal saponins. IL-6, interleukin 6; STAT3, signal transducer and activator of transcription 3; α -SMA, α -smooth muscle actin; MALAT1, metastasis-associated lung adenocarcinoma transcript-1; ROS, reactive oxygen species; NF- κ B, nuclear factor- κ B; MGMT, O6-methylguanine-DNA methyltransferase; Cyt-c, cytochrome c; Caspase-9/3, cysteinyl aspartate specific proteinase-9/3; PI3K, phosphatidylinositol-3 kinase; AKT, protein kinase B; mTOR, mammalian target of rapamycin; P62, protein sequestosome 1; LC3, microtubule-associated protein 1 light chain 3; CHOP, C/EBP homologous protein; CIP2A, cancerous inhibitor of protein phosphatase 2A; MAPK, mitogen-activated protein kinase; RAS, rat sarcoma; RAF, rapidly accelerated fibrosarcoma; MEK, MAPK kinase; ERK, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; IRE1 α , inositol requiring enzyme 1 α ; XBP1, X-box binding protein 1; ER, endoplasmic reticulum; PERK, protein kinase RNA-like ER kinase; eIF2 α , eukaryotic translation initiation factor 2 α ; ATF4, activating transcription factor 4; Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase-1; BCRP, breast cancer resistance protein; P-gp, P-glycoprotein; MRP1, MDR-related protein 1.

Steroidal saponins are widely found in the natural world, with a wide range of sources and varieties. However, the tedious preparation and extraction processes of NPs remain a problem in need of resolution, and the resulting low yield may make it difficult to meet the requirements of future widespread commercialization. Moreover, the water solubility of natural drugs is poor, resulting in a low drug efficacy. Hence, the synthesis and structural optimization of steroidal saponins is an important research direction. Notably, researchers have focused their attention on technical areas, and have made headway in *in vitro* synthesis and biotransformation (118-120). The application of nanocarriers has achieved initial success. Dendrosomal nano solanine could overcome drug resistance in human chronic myelogenous leukemia cells by attenuating the PI3K/AKT/mTOR signaling pathway and inhibiting the expression of telomerase reverse transcriptase to exert a stronger antitumor effect (121).

As newer steroidal saponins are discovered (122,123), their potential must be explored, and future studies should focus

on verifying the efficacy and safety of steroidal saponins in reversing tumor drug resistance, combined with *in vivo* and *in vitro* experiments, and further elucidating their potential targets and mechanisms. Steroidal saponins may be promising candidates for cancer treatment and for the reversal of drug resistance.

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Availability of data and materials

Not applicable.

Authors' contributions

JY conceived the idea of the study and provided overall supervision for the project. AC and HL collected materials and wrote the manuscript. XL, MZ and BX helped with literature screening and manuscript writing. BW provided constructive guidance and revised the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

- Brustugun OT, Moller B and Helland A: Years of life lost as a measure of cancer burden on a national level. *Br J Cancer* 111: 1014-1020, 2014.
- Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 71: 209-249, 2021.
- Hofman M, Morrow GR, Roscoe JA, Hickok JT, Mustian KM, Moore DF, Wade JL and Fitch TR: Cancer patients' expectations of experiencing treatment-related side effects: A university of Rochester cancer center-community clinical oncology program study of 938 patients from community practices. *Cancer* 101: 851-857, 2004.
- Wu Q, Yang Z, Nie Y, Shi Y and Fan D: Multi-drug resistance in cancer chemotherapeutics: Mechanisms and lab approaches. *Cancer Lett* 347: 159-166, 2014.
- Bukowski K, Kciuk M and Kontek R: Mechanisms of multidrug resistance in cancer chemotherapy. *Int J Mol Sci* 21: 9248, 2020.
- Awad MG, Ali RA, Abd El-Monem DD, El-Magd MAJM and Toxicology C: Graviola leaves extract enhances the anticancer effect of cisplatin on various cancer cell lines. *Mol Cell* 16: 385-399, 2020.
- Zhu X, Na X, Zeng Y, Xu Y, Chai D, Yang H, Miao J, Zhang Y, Yang F, Wang Y and Zhou Y: Polyphyllin I combined with doxorubicin shows chemosensitization effect in vivo and reduces immunotoxicity of doxorubicin. *Mol Cell Toxicol* 18: 359-369, 2022.
- Sahu NP, Banerjee S, Mondal NB and Mandal D: Steroidal saponins. *Fortschr Chem Org Naturst* 89: 45-141, 2008.
- Sparg SG, Light SE and van Staden J: Biological activities and distribution of plant saponins. *J Ethnopharmacol* 94: 219-243, 2004.
- Li M, Luo H, Huang Z, Qi J and Yu B: Screening and identification of Anti-inflammatory compounds from erdong gao via Multiple-target-cell extraction coupled with HPLC-Q-TOF-MS/MS and their Structure-activity relationship. *Molecules* 28: 295, 2022.
- Passos FRS, Araújo-Filho HG, Monteiro BS, Shanmugam S, Araújo AAS, Almeida JRGS, Thangaraj P, Júnior LJQ and Quintans JSS: Anti-inflammatory and modulatory effects of steroidal saponins and sapogenins on cytokines: A review of pre-clinical research. *Phytomedicine* 96: 153842, 2022.
- Qin XJ, Sun DJ, Ni W, Yan H, Chen CX, Cheng YC, He L and Liu HY: Steroidal saponins with antimicrobial activity from stems and leaves of *Paris polyphylla* var. *yunnanensis*. *Steroids* 77: 1242-1248, 2012.
- Pang X, Wan LF, Yang J, Bai PY, Zhang J, Chen XJ, Yan XL and Ma BP: Steroidal saponins from *Trillium tschonoskii* rhizome repress cancer stemness and proliferation of intrahepatic cholangiocarcinoma. *Bioorg Chem* 121: 105679, 2022.
- Xiang YC, Peng P, Liu XW, Jin X, Shen J, Zhang T, Zhang L, Wan F, Ren YL, Yu QQ, *et al*: Paris saponin VII, a Hippo pathway activator, induces autophagy and exhibits therapeutic potential against human breast cancer cells. *Acta Pharmacol Sin* 43: 1568-1580, 2022.
- Chien HJ, Liu CJ, Ying TH, Wu PJ, Wang JW, Ting YH, Hsieh YH and Wang SC: Timosaponin AIII inhibits migration and invasion abilities in human cervical cancer cells through inactivation of p38 MAPK-Mediated uPA expression in vitro and in vivo. *Cancers (Basel)* 15: 37, 2022.
- Yang J, Cao L, Li Y, Liu H, Zhang M, Ma H, Wang B, Yuan X and Liu Q: Gracillin isolated from *reineckia carnea* induces apoptosis of A549 cells via the mitochondrial pathway. *Drug Des Devel Ther* 15: 233-243, 2021.
- Yu J, Deng H and Xu Z: Targeting macrophage priming by polyphyllin VII triggers anti-tumor immunity via STING-governed cytotoxic T-cell infiltration in lung cancer. *Sci Rep* 10: 21360, 2020.
- Zeng KW, Song FJ, Li N, Dong X, Jiang Y and Tu PF: ASC, a bioactive steroidal saponin from *Ophiopogon japonicus*, inhibits angiogenesis through interruption of Src tyrosine kinase-dependent matrix metalloproteinase pathway. *Basic Clin Pharmacol Toxicol* 116: 115-123, 2015.
- Zhang H, Xu J, Wang M, Xia X, Dai R and Zhao Y: Steroidal saponins and sapogenins from fenugreek and their inhibitory activity against α -glucosidase. *Steroids* 161: 108690, 2020.
- Li W, Ji L, Tian J, Tang W, Shan X, Zhao P, Chen H, Zhang C, Xu M, Lu R and Guo W: Ophiopogonin D alleviates diabetic myocardial injuries by regulating mitochondrial dynamics. *J Ethnopharmacol* 271: 113853, 2021.
- Li X, Huang L, Kong L, Su Y, Zhou H, Ji P, Sun R, Wang C, Li W and Li W: Ginsenoside Rg1 alleviates learning and memory impairments and A β disposition through inhibiting NLRP1 inflammasome and autophagy dysfunction in APP/PS1 mice. *Mol Med Rep* 27: 6, 2023.
- Bai C, Yang X, Zou K, He H, Wang J, Qin H, Yu X, Liu C, Zheng J, Cheng F and Chen J: Anti-proliferative effect of RCE-4 from *Reineckia carnea* on human cervical cancer HeLa cells by inhibiting the PI3K/Akt/mTOR signaling pathway and NF- κ B activation. *Naunyn Schmiedebergs Arch Pharmacol* 389: 573-584, 2016.
- Chen L, Cheng CS, Gao H, Zhan L, Wang F, Qu C, Li Y, Wang P, Chen H, Meng Z, *et al*: Natural compound methyl protodioscin suppresses proliferation and inhibits glycolysis in pancreatic cancer. *Evid Based Complement Alternat Med* 2018: 7343090, 2018.
- Zhao YZ, Zhang YY, Han H, Fan RP, Hu Y, Zhong L, Kou JP and Yu BY: Advances in the antitumor activities and mechanisms of action of steroidal saponins. *Chin J Nat Med* 16: 732-748, 2018.
- Auyeung KK, Law PC and Ko JK: Combined therapeutic effects of vinblastine and Astragalus saponins in human colon cancer cells and tumor xenograft via inhibition of tumor growth and proangiogenic factors. *Nutr Cancer* 66: 662-674, 2014.
- Gillet JP and Gottesman MM: Mechanisms of multidrug resistance in cancer. *Methods Mol Biol* 596: 47-76, 2010.
- Wang X, Zhang H and Chen X: Drug resistance and combating drug resistance in cancer. *Cancer Drug Resist* 2: 141-160, 2019.
- Bungaro M, Buttiglieri C and Tucci M: Overcoming the mechanisms of primary and acquired resistance to new generation hormonal therapies in advanced prostate cancer: Focus on androgen receptor independent pathways. *Cancer Drug Resist* 3: 726-741, 2020.
- Yuan R, Hou Y, Sun W, Yu J, Liu X, Niu Y, Lu JJ and Chen X: Natural products to prevent drug resistance in cancer chemotherapy: A review. *Ann NY Acad Sci* 1401: 19-27, 2017.
- Vasan N, Baselga J and Hyman DM: A view on drug resistance in cancer. *Nature* 575: 299-309, 2019.

31. Gonçalves AC, Richiandone E, Jorge J, Polónia B, Xavier CPR, Salaroglio IC, Riganti C, Vasconcelos MH, Corbet C and Sarmiento-Ribeiro AB: Impact of cancer metabolism on therapy Resistance-clinical implications. *Drug Resist Updat* 59: 100797, 2021.
32. Kalbasi A and Ribas A: Tumour-intrinsic resistance to immune checkpoint blockade. *Nat Rev Immunol* 20: 25-39, 2020.
33. Cucolo L, Chen Q, Qiu J, Yu Y, Klapholz M, Budinich KA, Zhang Z, Shao Y, Brodsky IE, Jordan MS, *et al*: The interferon-stimulated gene RIPK1 regulates cancer cell intrinsic and extrinsic resistance to immune checkpoint blockade. *Immunity* 55: 671-685.e10, 2022.
34. Sun Y, Li X, Cheng H, Wang S, Zhou D, Ding J and Ma F: Drug resistance and new therapies in gallbladder cancer. *Drug Discov Ther* 17: 220-229, 2023.
35. Jaromi L, Csongei V, Vesel M, Abdelwahab EMM, Soltani A, Torok Z, Smuk G, Sarosi V and Pongracz JE: KRAS and EGFR mutations differentially alter ABC drug transporter expression in Cisplatin-resistant non-small cell lung cancer. *Int J Mol Sci* 22: 5384, 2021.
36. Arcila ME, Chaft JE, Nafa K, Roy-Chowdhuri S, Lau C, Zaidinski M, Paik PK, Zakowski MF, Kris MG and Ladanyi M: Prevalence, clinicopathologic associations, and molecular spectrum of ERBB2 (HER2) tyrosine kinase mutations in lung adenocarcinomas. *Clin Cancer Res* 18: 4910-4918, 2012.
37. Tanaka N, Lin JJ, Li C, Ryan MB, Zhang J, Kiedrowski LA, Michel AG, Syed MU, Fella KA, Sakhi M, *et al*: Clinical acquired resistance to KRAS(G12C) inhibition through a novel KRAS Switch-II pocket mutation and polyclonal alterations converging on RAS-MAPK reactivation. *Cancer Dis* 11: 1913-1922, 2021.
38. Cooper AJ, Sequist LV and Lin JJ: Third-generation EGFR and ALK inhibitors: Mechanisms of resistance and management. *Nat Rev Clin Oncol* 19: 499-514, 2022.
39. Jie G, Yijiang J, Ayijiang, Ye L and Yuji W: Research progress of tumor multi-resistance mechanism and reversal of resistance. *Modern Oncol* 30: 3991-3995, 2022.
40. Pastushenko I and Blanpain C: EMT transition states during tumor progression and metastasis. *Trends Cell Biol* 29: 212-226, 2019.
41. Minko T, Rodriguez-Rodriguez L and Pozharov V: Nanotechnology approaches for personalized treatment of multidrug resistant cancers. *Advanced drug delivery reviews* 65: 1880-1895, 2013.
42. Mariño G, Niso-Santano M, Baehrecke EH and Kroemer G: Self-consumption: The interplay of autophagy and apoptosis. *Nat Rev Mol Cell Biol* 15: 81-94, 2014.
43. Wu A, Jia Y, Dong B, Tang L, Liu Y, Du H, Yuan P, Dong P and Ji J: Apoptosis and KI 67 index correlate with preoperative chemotherapy efficacy and better predict the survival of gastric cancer patients with combined therapy. *Cancer Chemother Pharmacol* 73: 885-893, 2014.
44. Ferrari P, Scatena C, Ghilli M, Bargagna I, Lorenzini G and Nicolini A: Molecular mechanisms, biomarkers and emerging therapies for chemotherapy resistant TNBC. *Int J Mol Sci* 23: 1665, 2022.
45. Plati J, Bucur O and Khosravi-Far R: Dysregulation of apoptotic signaling in cancer: Molecular mechanisms and therapeutic opportunities. *J Cell Biochem* 104: 1124-1149, 2008.
46. Kaloni D, Diepstraten ST, Strasser A and Kelly GL: BCL-2 protein family: Attractive targets for cancer therapy. *Apoptosis* 28: 20-38, 2023.
47. Nicholson DW: From bench to clinic with Apoptosis-based therapeutic agents. *Nature* 407: 810-816, 2000.
48. Li YJ, Lei YH, Yao N, Wang CR, Hu N, Ye WC, Zhang DM and Chen ZS: Autophagy and multidrug resistance in cancer. *Chi J Cancer* 36: 52, 2017.
49. Chiang HL, Terlecky SR, Plant CP and Dice JF: A role for a 70-kilodalton heat shock protein in lysosomal degradation of intracellular proteins. *Science* 246: 382-385, 1989.
50. Poillet-Perez L and White E: Role of tumor and host autophagy in cancer metabolism. *Genes Dev* 33: 610-619, 2019.
51. Hardie DG: AMPK: Positive and negative regulation, and its role in whole-body energy homeostasis. *Curr Opin Cell Biol* 33: 1-7, 2015.
52. Nguyen HG, Yang JC, Kung HJ, Shi XB, Tilki D, Lara PN Jr, DeVere White RW, Gao AC and Evans CP: Targeting autophagy overcomes Enzalutamide resistance in castration-resistant prostate cancer cells and improves therapeutic response in a xenograft model. *Oncogene* 33: 4521-4530, 2014.
53. Chen K and Shi W: Autophagy regulates resistance of non-small cell lung cancer cells to paclitaxel. *Tumour Biol* 37: 10539-10544, 2016.
54. Liu J, Deng X, Sun X, Dong J and Huang J: Inhibition of autophagy enhances timosaponin AIII-induced lung cancer cell apoptosis and anti-tumor effect in vitro and in vivo. *Life Sci* 257: 118040, 2020.
55. Brabletz T, Kalluri R, Nieto MA and Weinberg RA: EMT in cancer. *Nat Rev Cancer* 18: 128-134, 2018.
56. Mashouri L, Yousefi H, Aref AR, Ahadi AM, Molaei F and Alahari SK: Exosomes: Composition, biogenesis, and mechanisms in cancer metastasis and drug resistance. *Mol Cancer* 18: 75, 2019.
57. Nieto MA, Huang RY, Jackson RA and Thiery JP: EMT: 2016. *Cell* 166: 21-45, 2016.
58. De Craene B and Berx G: Regulatory networks defining EMT during cancer initiation and progression. *Nat Rev Cancer* 13: 97-110, 2013.
59. Shibue T and Weinberg RA: EMT, CSCs, and drug resistance: The mechanistic link and clinical implications. *Nat Rev Clin Oncol* 14: 611-629, 2017.
60. Duan H, Liu Y, Gao Z and Huang W: Recent advances in drug delivery systems for targeting cancer stem cells. *Acta Pharm Sin B* 11: 55-70, 2021.
61. Du B and Shim JS: Targeting Epithelial-Mesenchymal transition (EMT) to overcome drug resistance in cancer. *Molecules* 21: 965, 2016.
62. Yan LL, Zhang YJ, Gao WY, Man SL and Wang Y: In vitro and in vivo anticancer activity of steroid saponins of *Paris polyphylla* var. *yunnanensis*. *Exp Oncol* 31: 27-32, 2009.
63. Dean M, Rzhetsky A and Allikmets R: The human ATP-binding cassette (ABC) transporter superfamily. *Genome Res* 11: 1156-1166, 2001.
64. Wu CP, Hsiao SH, Huang YH, Hung LC, Yu YJ, Chang YT, Hung TH and Wu YS: Sitravatinib sensitizes ABCB1- and ABCG2-Overexpressing Multidrug-resistant cancer cells to chemotherapeutic drugs. *Cancers* 12: 195, 2020.
65. Gu J, Huang W, Wang X, Zhang J, Tao T, Zheng Y, Liu S, Yang J, Chen ZS, Cai CY, *et al*: Hsa-miR-3178/RhoB/PI3K/Akt, a novel signaling pathway regulates ABC transporters to reverse gemcitabine resistance in pancreatic cancer. *Mol Cancer* 21: 112, 2022.
66. Luo Q, Du R, Liu W, Huang G, Dong Z and Li X: PI3K/Akt/mTOR signaling pathway: Role in esophageal squamous cell carcinoma, regulatory mechanisms and opportunities for targeted therapy. *Front Oncol* 12: 852383, 2022.
67. Ersahin T, Tuncbag N and Cetin-Atalay R: The PI3K/AKT/mTOR interactive pathway. *Mol Biosyst* 11: 1946-1954, 2015.
68. Xu F, Na L, Li Y and Chen L: Roles of the PI3K/AKT/mTOR signalling pathways in neurodegenerative diseases and tumours. *Cell Biosci* 10: 54, 2020.
69. Asati V, Mahapatra DK and Bharti SK: PI3K/Akt/mTOR and Ras/Raf/MEK/ERK signaling pathways inhibitors as anticancer agents: Structural and pharmacological perspectives. *Eur J Med Chem* 109: 314-341, 2016.
70. Mendoza MC, Er EE and Blenis J: The Ras-ERK and PI3K-mTOR pathways: Cross-talk and compensation. *Trends Biochem Sci* 36: 320-328, 2011.
71. Shafei MA, Forshaw T, Davis J, Flemban A, Qualtrough D, Dean S, Perks C, Dong M, Newman R and Conway ME: BCATC modulates crosstalk between the PI3K/Akt and the Ras/ERK pathway regulating proliferation in triple negative breast cancer. *Oncotarget* 11: 1971-1987, 2020.
72. Lin Y, Zhao WR, Shi WT, Zhang J, Zhang KY, Ding Q, Chen XL, Tang JY and Zhou ZY: Pharmacological activity, pharmacokinetics, and toxicity of Timosaponin AIII, a natural product isolated from *Anemarrhena asphodeloides* Bunge: A review. *Front Pharmacol* 11: 764, 2020.
73. MarElia CB, Sharp AE, Shemwell TA, Clare Zhang Y and Burkhardt BR: *Anemarrhena asphodeloides* Bunge and its constituent timosaponin-AIII induce cell cycle arrest and apoptosis in pancreatic cancer cells. *FEBS Open Bio* 8: 1155-1166, 2018.
74. Song XY, Han FY, Chen JJ, Wang W, Zhang Y, Yao GD and Song SJ: Timosaponin AIII, a steroidal saponin, exhibits anti-tumor effect on taxol-resistant cells in vitro and in vivo. *Steroids* 146: 57-64, 2019.
75. Thapa CB, Paudel MR, Bhattarai HD, Pant KK, Devkota HP, Adhikari YP and Pant B: Bioactive secondary metabolites in *Paris polyphylla* Sm. and their biological activities: A review. *Heliyon* 8: e08982, 2022.
76. Yang Q, Chen W, Xu Y, Lv X, Zhang M and Jiang H: Polyphyllin I modulates MALAT1/STAT3 signaling to induce apoptosis in gefitinib-resistant non-small cell lung cancer. *Toxicol Appl Pharmacol* 356: 1-7, 2018.

77. Zheng R, Jiang H, Li J, Liu X and Xu H: Polyphyllin II restores sensitization of the resistance of PC-9/ZD Cells to gefitinib by a negative regulation of the PI3K/Akt/mTOR signaling pathway. *Curr Cancer Drug Targets* 17: 376-385, 2017.
78. Liu Y, Wang M, Liu K, Qiu P, Zhang S, Lu Y, Tang N and Tang H: New steroidal saponins from the rhizomes of *Paris vietnamensis* and their cytotoxicity. *Molecules* 23: 588, 2018.
79. Zhang S, Lu Y, Li H, Ji Y, Fang F, Tang H and Qiu P: A steroidal saponin from *Paris vietnamensis* (Takht.) reverses temozolomide resistance in glioblastoma cells via inducing apoptosis through ROS/PI3K/Akt pathway. *Biosci Trends* 14: 123-133, 2020.
80. Song S, Du L, Jiang H, Zhu X, Li J and Xu J: Paris Saponin I sensitizes gastric cancer cell lines to cisplatin via cell cycle arrest and apoptosis. *Med Sci Monit* 22: 3798-3803, 2016.
81. Liu Z, Zheng Q, Chen W, Wu M, Pan G, Yang K, Li X, Man S, Teng Y, Yu P and Gao W: Chemosensitizing effect of Paris Saponin I on Camptothecin and 10-hydroxycamptothecin in lung cancer cells via p38 MAPK, ERK, and Akt signaling pathways. *Eur J Med Chem* 125: 760-769, 2017.
82. Chen Y, Zhang Y, Song W, Zhang Y, Dong X and Tan M: Ginsenoside Rh2 improves the cisplatin Anti-tumor effect in lung adenocarcinoma A549 cells via superoxide and PD-L1. *Anticancer Agents Med Chem* 20: 495-503, 2020.
83. Kim DG, Jung KH, Lee DG, Yoon JH, Choi KS, Kwon SW, Shen HM, Morgan MJ, Hong SS and Kim YS: 20(S)-Ginsenoside Rg3 is a novel inhibitor of autophagy and sensitizes hepatocellular carcinoma to doxorubicin. *Oncotarget* 5: 4438-4451, 2014.
84. Yuan Z, Jiang H, Zhu X, Liu X and Li J: Ginsenoside Rg3 promotes cytotoxicity of Paclitaxel through inhibiting NF- κ B signaling and regulating Bax/Bcl-2 expression on triple-negative breast cancer. *Biomed Pharmacother* 89: 227-232, 2017.
85. Wang L, Li X, Song YM, Wang B, Zhang FR, Yang R, Wang HQ and Zhang GJ: Ginsenoside Rg3 sensitizes human non-small cell lung cancer cells to γ -radiation by targeting the nuclear factor- κ B pathway. *Mol Med Rep* 12: 609-614, 2015.
86. Chhon S, Jeon J, Kim J and Park SU: Accumulation of anthocyanins through overexpression of AtPAP1 in *Solanum nigrum* lin. (Black Nightshade). *Biomolecules* 10: 277, 2020.
87. Wang Y, Xu J, Wang Y, Xiang L and He X: S-20, a steroidal saponin from the berries of black nightshade, exerts anti-multidrug resistance activity in K562/ADR cells through autophagic cell death and ERK activation. *Food Funct* 13: 2200-2215, 2022.
88. Wang Y, Wang S, Xu J, Wang Y, Xiang L and He X: Total steroidal saponins from black nightshade (*Solanum nigrum* L.) overcome tumor multidrug resistance by inducing autophagy-mediated cell death in vivo and in vitro. *Phytother Res* 37: 3009-3024, 2023.
89. Wang S, Wang L, Xu J, Wang Y, Xiang L and He X: Synergistic combination of the total steroidal saponins from the berries of black nightshade and Adriamycin to overcome leukemia multidrug resistance. *J Agric Food Chem*: Feb 8, 2023 doi: 10.1021/acs.jafc.2c07740 (Epub ahead of print).
90. Lou W, Chen Y, Zhu KY, Deng H, Wu T and Wang J: Polyphyllin I overcomes EMT-Associated resistance to erlotinib in lung cancer cells via IL-6/STAT3 pathway inhibition. *Biol Pharm Bull* 40: 1306-1313, 2017.
91. Feng FF, Cheng P, Sun C, Wang H and Wang W: Inhibitory effects of polyphyllins I and VII on human cisplatin-resistant NSCLC via p53 upregulation and CIP2A/AKT/mTOR signaling axis inhibition. *Chin J Nat Med* 17: 768-777, 2019.
92. Bhuvanlakshmi G, Basappa, Rangappa KS, Dharmarajan A, Sethi G, Kumar AP and Warriar S: Breast cancer stem-like cells are inhibited by diosgenin, a steroidal saponin, by the attenuation of the wnt β -Catenin signaling via the wnt antagonist secreted frizzled related Protein-4. *Front Pharmacol* 8: 124, 2017.
93. Chen JR, Jia XH, Wang H, Yi YJ, Wang JY and Li YJ: Timosaponin A-III reverses multi-drug resistance in human chronic myelogenous leukemia K562/ADM cells via downregulation of MDR1 and MRP1 expression by inhibiting PI3K/Akt signaling pathway. *Int J Oncol* 48: 2063-2070, 2016.
94. Xie Y, Yan X and Sun L: The mechanism of Bufalin-induced apoptosis of K562/A02. *Med Sci Monit* 25: 2542-2552, 2019.
95. Wang G, Tang X, Zhao F, Qin X, Wang F, Yang D, Zhu H and Chen X: Total saponins from *Trillium tschonoskii* maxim promote neurological recovery in model rats with Post-stroke cognitive impairment. *Front Pharmacol* 14: 1255560, 2023.
96. Wang H, Zhai Z, Li N, Jin H, Chen J, Yuan S, Wang L, Zhang J, Li Y, Yun J, *et al*: Steroidal saponin of *Trillium tschonoskii*. Reverses multidrug resistance of hepatocellular carcinoma. *Phytomedicine* 20: 985-991, 2013.
97. Li Y, Sun Y, Tang T, Niu Y, Li X, Xie M, Jin H and Mei Q: Paris saponin VII reverses chemoresistance in breast MCF-7/ADR cells. *J Ethnopharmacol* 232: 47-54, 2019.
98. Tang GE, Niu YX, Li Y, Wu CY, Wang XY and Zhang J: Paris saponin VII enhanced the sensitivity of HepG2/ADR cells to ADR via modulation of PI3K/AKT/MAPK signaling pathway. *Kaohsiung J Med Sci* 36: 98-106, 2020.
99. Wang H, Fei Z and Jiang H: Polyphyllin VII increases sensitivity to gefitinib by modulating the elevation of P21 in acquired gefitinib resistant non-small cell lung cancer. *J Pharmacol Sci* 134: 190-196, 2017.
100. Chai D, Yuan J, Zhu X, Zeng Y, Yang R, Chen Y, Wang Y and Zhou Y: Total Saponins from paris forrestii reverse multidrug resistance of MCF-7/ADM cells by suppression of P-gp via ERK signaling pathway. *Biol Pharm Bull* 43: 1823-1830, 2020.
101. Yang L, Zhang C, Chen J, Zhang S, Pan G, Xin Y, Lin L and You Z: Shenmai injection suppresses multidrug resistance in MCF-7/ADR cells through the MAPK/NF- κ B signalling pathway. *Pharma Biol* 58: 276-285, 2020.
102. Yu J, Xin YF, Gu LQ, Gao HY, Xia LJ, You ZQ, Xie F, Ma ZF, Wang Z and Xuan YX: One-month toxicokinetic study of SHENMAI injection in rats. *J Ethnopharmacol* 154: 391-399, 2014.
103. Siddiqi MH, Siddiqi MZ, Ahn S, Kang S, Kim YJ, Sathishkumar N, Yang DU and Yang DC: Ginseng saponins and the treatment of osteoporosis: Mini literature review. *J Ginseng Res* 37: 261-268, 2013.
104. Lyu CG, Kang CZ, Kang LP, Yang J, Wang S, He YL, Deng AP, Wang HY, Huang LQ and Guo LP: Structural characterization and discrimination of *Ophiopogon japonicus* (Liliaceae) from different geographical origins based on metabolite profiling analysis. *J Pharm Biomed Anal* 185: 113212, 2020.
105. Mbaveng AT, Chi GF, Nguenang GS, Abdelfatah S, Tchanga Sop RV, Ngadjui BT, Kuete V and Efferth T: Cytotoxicity of a naturally occurring spirostanol saponin, progenin III, towards a broad range of cancer cell lines by induction of apoptosis, autophagy and necroptosis. *Chem Biol Interact* 326: 109141, 2020.
106. Saxena M, Stephens MA, Pathak H and Rangarajan A: Transcription factors that mediate epithelial-mesenchymal transition lead to multidrug resistance by upregulating ABC transporters. *Cell Death Dis* 2: e179, 2011.
107. Lee WK and Kolesnick RN: Sphingolipid abnormalities in cancer multidrug resistance: Chicken or egg? *Cell Signal* 38: 134-145, 2017.
108. Brachtendorf S, Wanger RA, Birod K, Thomas D, Trautmann S, Wegner MS, Fuhrmann DC, Brüne B, Geisslinger G and Grösch S: Chemosensitivity of human colon cancer cells is influenced by a p53-dependent enhancement of ceramide synthase 5 and induction of autophagy. *Biochim Biophys Acta Mol Cell Biol Lipid* 1863: 1214-1227, 2018.
109. Rivel T, Ramseyer C and Yesylevskyy S: The asymmetry of plasma membranes and their cholesterol content influence the uptake of cisplatin. *Sci Rep* 9: 5627, 2019.
110. Gelsomino G, Corsetto PA, Campia I, Montorfano G, Kopecka J, Castella B, Gazzano E, Ghigo D, Rizzo AM and Riganti C: Omega 3 fatty acids chemosensitize multidrug resistant colon cancer cells by down-regulating cholesterol synthesis and altering detergent resistant membranes composition. *Mol Cancer* 12: 137, 2013.
111. Bernardes N and Fialho AM: Perturbing the dynamics and organization of cell membrane components: A new paradigm for Cancer-Targeted therapies. *Int J Mol Sci* 19: 3871, 2018.
112. Zalba S and Ten Hagen TL: Cell membrane modulation as adjuvant in cancer therapy. *Cancer Treat Rev* 52: 48-57, 2017.
113. Golombek SK, May JN, Theek B, Appold L, Drude N, Kiessling F and Lammers T: Tumor targeting via EPR: Strategies to enhance patient responses. *Adv Drug Deliv Rev* 130: 17-38, 2018.
114. Yao J, Man S, Dong H, Yang L, Ma L and Gao W: Combinatorial treatment of Rhizoma Paridis saponins and sorafenib overcomes the intolerance of sorafenib. *J Steroid Biochem Mol Biol* 183: 159-166, 2018.
115. Liu H, Yang J, Li L, Shi W, Yuan X and Wu L: The natural occurring compounds targeting endoplasmic reticulum stress. *Evid Based Complement Alternat Med* 2016: 7831282, 2016.
116. Man S, Lv P, Cui J, Liu F, Peng L, Ma L, Liu C and Gao W: Paris saponin II-induced paraptosis-associated cell death increased the sensitivity of cisplatin. *Toxicol Appl Pharmacol* 406: 115206, 2020.

117. Zou P, Chen Z, He Q and Zhuo Y: Polyphyllin I induces ferroptosis in castration-resistant prostate cancer cells through the ERK/DNMT1/ACSL4 axis. *Prostate* 84: 64-73, 2024.
118. Bai S, Sun Y, Cheng Y, Ye W, Jiang C, Liu M, Ji Q, Zhang B, Mei Q, Liu D and Zhou S: MCP mediated active targeting calcium phosphate hybrid nanoparticles for the treatment of orthotopic drug-resistant colon cancer. *J Nanobiotechnology* 19: 367, 2021.
119. He DX, Li GH, Gu XT, Zhang L, Mao AQ, Wei J, Liu DQ, Shi GY and Ma X: A new agent developed by biotransformation of polyphyllin VII inhibits chemoresistance in breast cancer. *Oncotarget* 7: 31814-31824, 2016.
120. Upadhyay S, Jeena GS, Shikha and Shukla RK: Recent advances in steroidal saponins biosynthesis and in vitro production. *Planta* 248: 519-544, 2018.
121. Asgaritarghi G, Farsani SSM, Sadeghizadeh D, Najafi F and Sadeghizadeh M: Anti-Cancer role of dendrosomal nano solanine in chronic myelogenous leukemia cell line through attenuation of PI3K/AKT/mTOR signaling pathway and inhibition of hTERT expression. *Curr Mol Pharmacol* 16: 592-608, 2023.
122. Liu G, Feng S, Sui M, Chen B and Sun P: Extraction and identification of steroidal saponins from *Polygonatum cyrtoneura* Hua using natural deep eutectic solvent-synergistic quartz sand assisted extraction method. *J Sep Sci* 46: e2200823, 2023.
123. Maliwong J, Chimnoi N, Thamniyom W, Ruchirawat S and Kanchanapoom TJPL: Steroidal saponins from the rhizomes of *Tacca integrifolia*. *Phytochemistry Lett* 53: 66-72, 2023.



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