Molecular mechanisms of astragaloside-IV in cancer therapy (Review)

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Abstract. Radix Astragali (RA) is widely used in traditional Chinese medicine (TCM), and astragaloside IV (AS-IV) is the most critical component of RA. Previous studies have demonstrated that AS-IV exerts effects on the myocardium, nervous system and endocrine system, among others. In the present review article, data from studies conducted over the past 20 years were collated, which have evaluated the effects of AS-IV on tumors. The mechanisms of action of AS-IV on malignant cells both *in vivo* and *in vitro* were summarized and it was demonstrated that AS-IV plays a vital role, particularly in inhibiting tumor growth and metastasis, promoting the apoptosis of tumor cells, enhancing immune function and preventing drug resistance. Moreover, AS-IV controls several epithelial-mesenchymal transformation (EMT)-related and autophagy-related pathways, such as the phosphoinositide-3-kinase (PI3K)/protein kinase B (AKT), Wnt/β-catenin, mitogen-activated protein kinase (MAPK)/extracellular regulated protein kinase (ERK) and transforming growth factor-β (TGF-β)/SMAD signaling pathways, which are commonly affected in the majority of tumors. The present review provides new perspectives on the functions of AS-IV and its role as an adjuvant treatment in cancer chemotherapy.

Contents

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1. Introduction

Cancer is the second leading cause of mortality worldwide and results in an increasing number of deaths annually. The World Health Organization postulates a 60% increase in cancer cases over the next 20 years globally (1). The medical treatment of the majority of cancers almost always involves several traditional approaches, such as surgery, chemotherapy and radiotherapy. Surgical resection is a suitable approach for tumor management in the early stages of primary tumors. However, surgery is still limited by post-operative recurrence and metastasis (2,3). Of late, chemoradiotherapy, molecular targeted therapy and immune checkpoint inhibitors have been considered the treatment approach for advanced stages of cancers; however, severe adverse events limit their use (4,5). Therefore, alternative therapeutic methods are required to address these existing shortcomings. Accordingly, traditional Chinese medicines (TCMs), such as ginseng, Radix Astragali (RA), *Scutellaria barbata*, *Curcumae* and turmeric, are used to enhance the efficacy and reduce the side-effects of chemoradiotherapy. TCMs are effective in suppressing tumor progression, relieving surgery-associated discomfort, improving immune function and preventing complications caused by the use of other treatment modalities (6).

RA is a dietary complement widely used in TCM and is known to modulate the immune system and attenuate the adverse effects of cytotoxic agents (7). Saponins are the primary constituents that are responsible for the suppression of tumor growth, which exert their effects via intrinsic and extrinsic apoptotic pathways, modulating intracellular signaling pathways, and inhibiting metastasis and angiogenesis. Astragaloside IV (AS-IV; chemical structure presented in Fig. 1) and astragaloside II are the 2 main components of RA (8).

AS-IV, chemically known as 3-O-β-D-xylopyranosyl-6-O-β-D-glucopyranosyl-cycloastragenol ($C_{14}H_{68}O_{14}$), is a lanolin-alcohol type of tetracyclic triterpenoid saponin. It is included in the Chinese and European Pharmacopoeia as a quality-control indicator of RA. It has long been used since ancient times in China without any evident hepatotoxic and nephrotoxic effects. Moreover, no side-effects have been reported in rats following 14 weeks of the continuous oral administration of AS-IV (10 mg/kg/day) (9,10). However, there is currently no data available regarding the safety of AS-IV in

humans, at least to the best of our knowledge. The methods used to extract AS-IV include ultrafiltration, high-speed centrifugation, ultrasonic extraction and alcohol precipitation. The present review article aimed to obtain and collate data from studies conducted over the past 20 years on the effects of AS-IV on tumors. In addition, the mechanisms of action of AS-IV on malignant cells both *in vivo* and *in vitro* are summarized in order to provide insight into the effects of AS-IV on cancer in humans.

2. Literature search

Search strategy. Studies in English and Chinese, as well as trials published before June 1, 2020, were searched on online databases. The databases in the English language that were used were PubMed, MEDLINE, Embase, ScienceDirect, Web of Science, BIOSIS Previews and the Cochrane Library and Cochrane Central Register of Controlled Trials (CENTRAL). The Chinese databases used for the searches included the China National Knowledge Infrastructure (CNKI) database and Wanfang Med Online.

In the present review, 'astragaloside IV', 'Cancer' and 'mechanism' were used as the key search concepts. Additionally, their synonyms were also included. Moreover, manual searches were also carried out using the aforementioned terms. The search methodology is described as follows as an example: i) astragaloside IV; ii) astraloside; iii) ASIV; iv) i OR ii OR iii; v) cancer[MeSH]; vi) tumor[MeSH]; vii) v OR vi; viii) pathway[MeSH]; ix) mechanism[MeSH]; x) viii OR ix; and xi) iv AND vii AND ix.

Inclusion criteria. The inclusion criteria were as follows: Studies exploring the molecular mechanisms of AS-IV in cancer; studies with comparable experimental and control groups, and those that successfully established animal models of cancer; studies in which animal experiments were approved by an ethics committee; and studies that investigated related pathways involving upstream and downstream molecular mechanisms and published experimental findings, which could be retrieved.

Exclusion criteria. The exclusion criteria were as follows: Studies that included only AS-IV or astragalus polysaccharide (APS) as the experimental group; studies that had an obvious risk of bias, including selection bias, performance bias, detection bias, reporting bias and attrition bias; case studies, cross-over studies and studies without a separate control group; studies combining AS-IV with other TCM interventions, in which data specific to the effect of AS-IV interventions on cancer could not be extracted separately.

3. Effects of AS-IV in cancer models

AS-IV has been widely used in the management of cardiovascular, digestive, endocrine, and nerve-related diseases (11-13). Furthermore, it exerts significant anticancer effects when used alone or as an adjuvant to other treatment modalities, as it sensitizes the host to other drugs (Table I).

To the best of our knowledge, there are no systematic reviews available that discuss the role of AS-IV in cancer; therefore, in the present review article, the efficacy and mechanisms of action of AS-IV in cancer therapy are presented and discussed.

Induction of apoptosis. Apoptosis, also known as programmed cell death, includes the initiation stage, effect stage and degradation stage. Apoptosis is characterized by surface blebbing, chromatin condensation, fragmentation of chromosomal DNA and the appearance of apoptotic bodies.

As shown in Table I and Fig. 2, AS-IV leads to apoptosis mainly by the mitochondrial-dependent intrinsic pathway and the death receptor-dependent extrinsic pathway. The intrinsic pathway leads to the release of cytochrome *c* (Cyt C) from the mitochondria, which activates caspase-9, -3 and -7 (14). However, Bcl-2 can inhibit the release of Cyt C and avoid the intrinsic apoptosis induced by Bax (15). Research has indicated that AS-IV can enhance the Bax/Bcl-2 ratio to induce intrinsic apoptosis in a number of types of cancer, including colorectal cancer (CRC), breast cancer, lung cancer, vulvar squamous cell cancer (VSCC) and hepatocellular carcinoma (HCC) (16-21).

In terms of extrinsic apoptosis, certain receptors, e.g., the Fas ligands and tumor necrosis factor (TNF)-α, can set off the caspase-8-dependent extrinsic apoptotic pathways and become activated following the caspase cascade, which finally triggers apoptosis (22). It has been reported that combined treatment with AS-IV and cisplatin (10 μM) markedly promotes the cleavage of caspase-8 and -3, and poly(ADP-ribose) polymerase (PARP) in MG-63 and 143B cells via the Fas/FasL signaling pathway, which considerably sensitizes the osteosarcoma cells to the effects of cisplatin (23). In CRC, AS-IV alone can increase the release of Cyt C into the cytoplasm and upregulate the Bax/Bcl-2 ratio, as well as activate PARP and the caspase cascade (16).

The IAP protein family may be the most important apoptotic regulator involved in both intrinsic and extrinsic apoptosis pathways, including the x-linked mammalian inhibitor of apoptosis (XIAP), survivin and cellular inhibitor of apoptosis protein 1 (cIAP1) (22,24).

HCC is associated with a high morbidity and mortality rate globally, and presents with increased levels of anti-apoptotic proteins, including myeloid cell leukemia 1 (MCL1), cellular FLICE-like inhibitory protein (c-FLIP) and XIAP. c-FLIP can suppress death receptor-mediated apoptosis, which inhibits caspase-8 (25-28). Additionally, studies have demonstrated that MCL1 can block apoptosis induced by various apoptotic stimuli, including chemoradiotherapy (29-31). Its high protein expression levels in cancer cells are associated with drug resistance (32). AS-IV has been shown to significantly decrease XIAP, MCL1, c-FLIP and survivin expression in HCC and C6 glioma cells (33,34).

Inhibition of proliferation. High levels of reactive oxygen species (ROS) are considered to be a driver of a number of diseases, such as cancer and neurodegeneration. ROS are capable of increasing the carcinogenic potential of cancer cells and activating hypoxia-inducing factor (HIF) in hypoxic tumor cells to maintain cell viability (32,35). On the other hand, cells are capable of eliminating surplus ROS via mechanisms involving superoxide dismutase (SOD) and glutathione

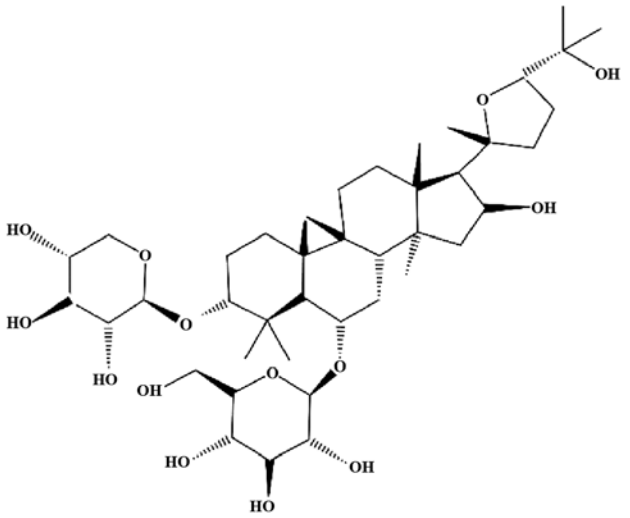

Figure 1. Chemical structure of astragaloside IV.

peroxidase (GSH-Px) (36). Yang proved that AS-IV interrupted the proliferation of Spc-A-1 cells and suggested that the mechanism was related to the activity of the antioxidant enzymes, SOD and GSH-Px, which modulate ROS levels in cancer (37).

In the B7/cluster of differentiation (CD)28 superfamily, the overexpression of B7-H3 is observed in various types of cancer. It can downregulate the T-cell-mediated immune responses, leading to immune escape (38-40). AS-IV can reduce B7-H3 by upregulating miR-29c, which inhibits cell growth and reduces the protein level of the cell-cycle regulators, cyclin D1 and CDK4, in CRC cells. Thus, the anticancer effects of AS-IV may be mediated via the B7-H3/nuclear factor (NF)-κB/cyclin D1 axis (41). It also increases the cytotoxicity of cisplatin in non-small cell lung cancer (NSCLC) by suppressing the expression of B7-H3 (42). Moreover, another study reported that AS-IV inhibited the proliferation of HCC HepG2 cells and promoted apoptosis by regulating oxidative stress and the NF-κB signaling pathway (43).

Inhibition of metastasis. Matrix metalloproteinases (MMPs) are a group of proteolytic enzymes containing active Zn^{2+}. Its functions include, but are not limited to, degrading the extracellular matrix (ECM). The interaction between MMPs and cell-surface ECM receptors affects the function of integrins and contributes to cell invasion (44). MMP-2 and MMP-9, in particular, have been considered to play a vital role in tumor progression (45).

The extracellular signal-regulated kinase pathway (ERK), an important upstream switch, has been known to regulate the secretion of MMPs in cells (46). Mitogen-activated extracellular signal-regulated kinase (MAPK) is a serine/threonine (Ser/Thr) kinase involved in cell proliferation, differentiation, growth and apoptosis. In general, the MAPK/ERK pathway, i.e., Ras-Raf-MEK-ERK pathway, is deregulated in various types of cancers (47). Recently, inhibitors against the MAPK/ERK pathway have been designed to combat glioma and have been shown to be effective in the U251, as well as the SGC7901 cell lines with the downregulation of the expression of MMP-2 and MMP-9 (48-52). Li *et al* and Cao reported that AS-IV inhibited the progression of glioma and gastric cancer by interfering with the MAPK/ERK signaling pathway (53,54). Moreover, ascites in H22-tumor-bearing mice have been shown to be decreased by AS-IV by inhibiting the angiogenesis- and metastasis-associated genes, as well as the expression of aquaporins (AQPs) (55).

Tissue inhibitors of metalloproteinases (TIMPs) comprise TIMP-1, TIMP-2, TIMP-3 and TIMP-4, all of which can form complexes with several MMPs via covalent bonds, thereby inhibiting MMPs (56,57). The NM23 gene is a widely studied metastasis suppressor gene. The protein encoded by NM23 has the function of inhibiting tumor metastasis (58). AS-IV can downregulate the mRNA and protein expression of MMP-2, -7 and -9, can mediate multidrug resistance/P-glycoproteins (MDR1/P-gp) and multidrug resistance-associated protein 1(MRP-1), and upregulate TIMP-1 and NM23 to inhibit the proliferation of BGC823 (gastric cancer) cells and reverse drug resistance (59).

Epithelial-mesenchymal transformation (EMT) is the conversion of a polarized epithelial cell, which interacts with the basement membrane by means of its basal surface, to a mesenchymal cell. As regards the metastatic process, EMT can be detected based on specific molecular changes, such as diminished E-cadherin and cytokeratin levels, and elevated levels of N-cadherin and vimentin (60). As the transforming growth factor β1 (TGF-β1) is a known factor in triggering the initiation and execution of EMT, the downregulation of TGF-β1signaling can prevent EMT in tumor cells. As shown in Fig. 3, AS-IV can affect EMT via several pathways.

The Wnt/β-catenin signaling pathway regulates EMT. Using U251 cells, Han *et al* found that AS-IV treatment inhibited TGF-β1-guided EMT by interrupting the Wnt/β-catenin pathway (61). β-catenin can also modulate glycogen synthase kinase 3β (GSK3β). AKT is an upstream molecule that activates GSK3β phosphorylation, eventually leading to the accumulation of β-catenin in the cell nucleus (62). AS-IV has also been shown to attenuate EMT in HCC and NSCLC via the modulation of the Akt/GSK-3β/β-catenin pathway (18,63).

Phosphoinositide-3-kinase/protein kinase B/nuclear factor κB (PI3K/Akt/NF-κB) is another common pathway suppressing TGF-β1-induced EMT. It has been reported that AS-IV can inhibit TGF-β1-induced EMT by interfering with the PI3K/Akt/NF-κB signaling pathway in SiHa and MGC-803 cells (21,64). Moreover, it inhibits the phosphorylation of MAPK and mTOR to varying degrees, which is related to the proliferation of cancer cells.

Apart from the signaling pathways discussed, AS-IV may also interrupt the migration and invasion of A549 cells. This process is associated with the suppression of PKC-α-ERK1/2-NF-κB and can be detected based on specific proteins, e.g., E-cadherin, integrin β1 and MMPs (65). PKC-α expression can be affected by ROS, which can induce the downstream signaling of ERK1/2 and activate NF-κB to initiate the metastasis of carcinoma cells (66).

In parallel, several miRNAs take part in the inhibition of EMT signaling (67). For example, miR-134 from the miRNA gene family has been proven to inhibit EMT (68,69). CREB1 is an important transcription enhancer. A previous study reported that miR-134 activated by AS-IV markedly inhibiting EMT signaling and increasing the chemosensitivity of SW-480 cells to oxaliplatin by inhibiting CREB1 expression (70).

Table I. Effects of AS-IV on anti-cancer properties depending on dose and various signaling pathways.

Cancer type	Observation	Cell type	Effects	Mechanism of action	(Refs.)
Colorectal cancer	*In vitro* (10, 20, 40 μg/ml); *in vivo* BAlB/c mice (20 mg/kg)	HT29, SW480	Inhibit proliferation, induce cell cycle G1 arrest, induce apoptosis	p21↑, Bax/Bcl-2↑, cleavage of PARP↑, caspase-3/9 ↑	(16)
Breast cancer	*In vitro* (10, 20, 40 μg/ml); *in vivo* BAlB/c nude mice (20 mg/kg)	MDA-MB-231	Inhibit proliferation	pERK1/2↓, pJNK↓, MMP-2/-9↓, Vav3↓, Rac1/MAPK pathway↓	(75)
Lung cancer	*In vitro* (≥20 μg/ml)	A549	Inhibit viability, invasion and migration	MMP-2↓, MMP-9↓, Integrin β1↓, E-cadherin↑, TGF-β1↓, TNF-α↓, IL-6↓, PKC-α-ERK1/2-NF-κB↓	(65)
Lung cancer	*In vitro* (40 μM-100 μM)l *in vivo* (40 mg/kg) male C57BL/6 J mice	A549, H1299	Inhibit invasion, migration, angiogenesis	AMPKα↓, blocking the M2 polarization of macrophages through AMPK signaling pathway	(99)
Cervical cancer	*In vitro* (5, 10, 25 μM); *in vivo* BAlB/c nude mice (25 mg/kg/day)	HeLa, SiHa	Inhibit tumor growth, inhibit invasion, induce autophagy	LC3I/II↑, DCP1A↑, TMSB4X↑, MGST3↓, AKR1C2↓, ERL1N1↓, Atg7↑, Atg12↑	(105)
Gastric cancer	*In vitro* (≥10 μmol/l)	BGC-823	Inhibit cancer-associated fibroblasts, regulate tumor microenvironment, inhibit proliferation-, migration- and invasion-promoting capacities of GCAFs	miR-214↑, miR-301a↓ SOX2↑, NANOG↑, M-CSF↓, TIMP2↑	(108)
Non-small cell lung cancer	*In vitro* (12, 24 ng/ml)	HCC827, A549, NCI-H1299	Inhibit migration and proliferation, induce apoptosis	Bax↑, Bcl-2↓, caspase-3↑, Akt/GSK3β/b-catenin↓	(18)
Gastric cancer	*In vitro* (10 ng/ml, 20 ng/ml)	BGC-823, MKN-74	Inhibit cell viability, invasion and migration	Inhibit TGF-β1-induced EMT through inhibition of PI3K/Akt/NF-κB pathway	(113)
Lung cancer	*In vitro* (10, 20, 50 ng/ml)	A549	Inhibit cell growth	VEGF↑, NF-κBp65↑, MMP-2↓	(66)
Liver cancer	*In vitro* (0.1 mM)	5-FU-resistant Bel-7402/FU human hepatic cancer cells	Reverse drug resistance of Bel-7402/FU cells	JNK/c-Jun/AP-1↓, p-JNK↓, p-c-Jun↓	(82)
Liver cancer	*In vitro* (0.08 mg/ml)	5-FU-resistant Bel-7402/FU human hepatic cancer cells	Reverse drug resistance of Bel-7402/FU cells to 5-FU, enhance intracellular accumulation of 5-FU	P-gp↓, MDR1↓	(83)
Liver cancer	*In vitro* (100 μg/ml)	Huh7, MHCC97-H	Suppress migration and invasion	Suppress EMT by regulation of the Akt/GSK-3β/β-catenin pathway, E-cadherin↑, N-cadherin↓, Vimentin↓, α-SMA↓, Slug↓	(63)
Liver cancer	*In vitro* (10, 20, 40, 80, 160 μg/ml)	SMMC-7721, Huh-7	Inhibit migration and cell viability, induce apoptosis	LncRNA-ATB↓, IL-11/STAT3 pathway↓	(74)
Vulvar squamous cell carcinoma	*In vitro* (100, 200, 400, 600 and 800 μg/ml)	SW962	Inhibit cell proliferation, induce apoptosis and autophagy, induce cell-cycle arresting in G0/G1 phase	P53↑, P21↑, Cyclin D1↓, Bax↑, cleaved caspase-3↑, Bcl-2↓, Bcl-xl↓, Beclin-1↑, LC3-B↑, P62↓, reverse dysregulation of TGF-β/Smad signaling by TGF-βRII↑ and Smad4↑	(19)

Table I. Continued.

Cancer type	Observation	Cell type	Effects	Mechanism of action	(Refs.)
Osteosarcoma	*In vitro* (20 mg/kg) *In vivo* (40 μM) BALB/c nude mice	MG-63, 143B	Inhibit cell survival, increase chemosensitivity, enhance cisplatin-induced apoptosis	Cleaved caspase-8↑, cleaved caspase-3↑, cleaved PARP↑, GAPDH↑, regulate Fas/FasL signaling	(23)
Glioma	*In vitro* (100 μg/ml); *in vivo* (20 mg/kg) athymic BAlB/c mice	U251	Inhibit proliferation *in vitro* and attenuate tumor growth *in vivo*, suppress migration and invasion	PCNA↓, ki67↓, MMP-2↓, MMP-9↓, VEGF↓, inactivation of MAPK/ERK signaling pathway	(53)
Liver cancer	*In vitro* (150 μg/ml)	HepG2, T47D, MB-AMD-231, PC-3, 293T	Attenuate the clonogenic survival and anchorage-independent growth of cancer cells, inhibit the colony formation	Vav3.1↓, alter level of proteins like BiP/GRP78, HSP70-2, HSPA1A, HSPA8	(76)
Liver cancer	*In vitro* (200, 400 μM)	SK-Hep1, Hep3B	Induced cytotoxicity, inhibit proliferation, suppress invasion, trigger G1 arrest	Caspase-3/-8/-9↑, XIAP↓, MCL1↓, CFLIP↓, Survivin↓	(33)
Cervical cancer	*In vitro* (50, 200, 800 μg/ml); *in vivo* BABLc/nude mice (120 mg/kg)	SiHa	Inhibit invasion and migration *in vitro* and *in vivo*, inhibit EMT	p-p38↓, p-MAPK↓, p-PI3K↓, p-AKT↓, p-mTOR↓, TGF-β1↓, N-cadherin↓, Vimentin↓, E-cadherin↑	(64)
Colorectal cancer	*In vitro* (≥50 ng/ml)	SW620, HCT	Reduce cell proliferation, arrest cell cycle in G0/G1 phase	B7-H3↓, miR-29c↑, cyclin D1↓, CDK4↓	(41)
Lung cancer	*In vitro* (80, 160 μg/ml); *in vivo* C57Bl/6 mice with 3LL-luc-EGFP, 3LL-luc-IDO (40 mg/kg)	Lewis lung carcinoma cell	Inhibit tumor progression and prolong survival time	Enhance immune response by inhibiting the Treg frequency and induce the activity of CTLs, blocked IDO induction *in vitro* and *in vivo*.	(98)
Glioma	*In vitro* (20, 40, 80 μg/ml)	U251	Inhibit migration and invasion, promote apoptosis, inhibit proliferation	Interfered with the TGF-β1-induced Wnt/β-catenin signaling pathway to inhibit EMT	(61)
Liver cancer	*In vitro* (≥20 μg/ml)	SMMC-7721, Huh7	Increase apoptosis	miR-150–5p↑, β-catenin↓, Bax↓, Bcl-2↑	(20)
Colorectal cancer	*In vitro* (5, 10, 20 μg/ml)	SW-480	Inhibit migration and invasion, increase chemosensitivity	CREB1↓, miR-134↑, EMT↓	(70)
Macrophages and Lewis lung carcinoma	*In vitro* (100 μg/ ml)	RAW264.7	Enhance immune function, induce G2/M phase arrest	NO↑, IL-4↓, IL-6↑, CD40↑, CD86↑, IL-1β↑, TNF-α↑, iNOS↑, cyclin D1↑, CDK4↑, CDK6↑, p50↑, p-p65↑, p50/β-actin↑, p-p65/p65↑, p-p38↑, pERK↑, pJNK↑, p38↓, ERK↓, JNK↓, NF-κB/MAPK signaling pathway↑	(102)
Breast cancer	*In vivo* (12 g/kg) 7, 12-dimethylbenzanthracene-induced SD rats	7, 12-dimethylbenzanthracene-induced liver cancer	Inhibit tumor progression	IL-2↑, IFN-γ↑, $CD3^+$↑, $CD4^+$↑, $CD4^+$/ $CD8^+$↑ IL-1↓, IL-6↓, TNF-α↓, $CD8^+$↓	(101)

Table I. Continued.

Cancer type	Observation	Cell type	Effects	Mechanism of action	(Refs.)
Gastric cancer	*In vitro* (20, 40, 60, 80 μmol/l)	MGC-803	Induce apoptosis, trigger G1 arrest	AKT/NF-κB↓, BAX↑, BCL-2↓, BCL-2/BAX↓, caspase-3↑	(21)
Liver cancer	*In vitro* (40 μg/ml)	HepG2/GCS	Increase chemosensitivity, Reverse MDR	GCS↓, caspase-9↑	(87)
Glioma	*In vivo* (AS-IV 12 g/kg, Cis 2 ml/kg) BABLc mice	C6	Increase chemosensitivity	Bcl-2↓, survivin↓, caspase-3↑	(34)
Gastric cancer	*In vitro* (5 μg/ml)	BGC823	Inhibit tumor growth and metastasis	MMP-2↓, MMP-7↓, MMP-9↓, TIMP-1↑, nm23 mRNA↑, MDR1/P-gp↓, MRP-1↓, Bcl-2↓, Bax↑, Bcl-2/Bax↓	(59)
Gastric cancer	*In vitro* (0.625 g/l)	SGC7901	Inhibit tumor growth	COX-2↓, VEGF↓, PGE2↓	(79)
Gastric cancer	*In vitro* (100 μg/ml)	SGC7901	Inhibit invasion	MMP-2↓, MMP-9↓, p-ERK↓	(54)
Liver cancer	In vivo (100 g/ml, 50 g/ml) C57 mice	BN-75	Inhibit tumor growth	$CD4^+$↑, CD4+/$CD8^+$↑, IFN-γ↑, IL-4↑	(100)
Lung cancer	*In vitro* (10-40 μmol)	SPC-A-1	Inhibit proliferation	SOD↑, GSH-Px↑, Bcl2↓, Bax↑, Bcl2/Bax↓	(37)
Liver cancer	*In vitro* (2.5, 5, 10 μM/ml)	HepG2	Promote apoptosis, inhibit proliferation	ROS/NF-κB pathway↓, Ki67↓, Bcl-2↓, NF-κB↓, IKK-α↓, IKK-β↓, ROS↑, Caspase-3↑, Bax↑	(43)
Liver cancer	*In vivo* (0.3, 1, 3 mg/kg) BALB/C mice	H22	Inhibit ascites, angiogenesis, metastasis	VEGF↓, MMP-2↓, MMP-9↓, AQP-1↓, CD31↓	(55)
Liver cancer	*In vitro* (40 μM) *In vivo* (50 mg/kg AS-IV)	HepG2 cell Balb/c mice with H22 tumors	Increase chemosensitivity, decrease cisplatin-induced kidney damage	Reverse MRP2 overexpression after Cis treatment	(114)
Non-small cell lung cancer	*In vitro* (10, 20, 40 ng/ml)	A549, HCC827, NCI-H1299	Increase chemosensitivity, induce apoptosis	B7-H3↓	(42)
Non-small cell lung cancer	*In vitro* (≥12 ng/ml)	NCI-H1299, HCC827, A549	Suppress cell viability, increase chemosensitivity	SIRT6 ↓	(85)
Breast cancer	*In vitro* (10 to 90 μM) *In vivo* Balb/c nude mice (50 mg/kg)	MCF-7, MDA-MB-231	Increase chemosensitivity with high safety, induce G2/M cell cycle arrest	Cleaved PARP↑, Bcl-2↓, Bax↑, p-ERK/p-JNK↓, p-p38↑, activate eNOS/NO/3NT signaling by inhibiting CAV-1	(17)
Colorectal cancer	*In vitro* (10, 15 ng/ml)	HCT116, SW480	Suppress tumor cell growth, Elevate chemosensitivity	NOTCH3↓	(86)
Precancerous lesions of gastric carcinoma	*In vivo* (50, 100 mg/kg male Sprague-Dawley rats	MNNG-induced PLGC	Reverse MNNG-induced PLGC, ameliorate dysplasia of gastric mucosa	LDHA↓, p53↑, TIGAR↑, MCT1↓, MCT4↓, HIF-1α↓, CD147↓, and miRNA-34a↑, reverse PLGC via regulating p53/miRNA-34a/LDHA pathway	(107)

Table I. Continued.

Cancer type	Observation	Cell type	Effects	Mechanism of action	(Refs.)
Doxorubicin treatment	*In vivo* (40 mg/kg) C57Bl/6 mice; *in vitro* (20 μM)	Neonatal cardiomyocytes of Sprague Dawley (SD) rats	Alleviate body weight loss, myocardial injury, apoptosis of cardiomyocytes, cardiac fibrosis and cardiac dysfunction in DOX-treated mice and *in vitro*	NOX2↓, NOX4↓, relieve oxidative stress	(111)

↑, an increase in target protein; ↓, a decrease in target protein; PARP, poly ADP-ribose polymerase; ERK, extracellular regulated protein kinases; TGF-β1, transforming growth factor-β1; MMP, mitochondrial membrane potential; AQP1, aquaporin 1; VEGF, vascular endothelial growth factor; AMPK, AMP-activated protein kinase; EMT, epithelial-mesenchymal transition; PI3K, phosphoinositide-3-kinase; JNK, c-Jun N-terminal kinase; NF-κB, nuclear factor-κB; PCNA, proliferating cell nuclear antigen; COX-2, cyclooxygenase-2; HIF-1α, hypoxia-inducible factor-1; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3 Rac1, Rac family small GTPase 1; MAPK, mitogen-activated protein kinase; TNF-α, tumor necrosis factor α; PKC-α, protein kinase C system -α; LC3I, the protein expressions of light chain 3I; LC3II, the protein expressions of light chain 3II; Atg7, autophagy related 7; AKT, protein kinase B; GSK3β, glycogen synthase kinase 3β; P-gp, P-glycoprotein; MDR1, multidrug resistance protein 1; α-SMA, alpha-smooth muscle actin; LncRNA-ATB, long non-coding RNA activated by transforming growth factor-β; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; HSP, heat shock protein; GRP78, glucose regulated protein 78; Bip, binding immunoglobulin protein; XIAP, X-linked inhibitor of apoptosis protein; MCL1, myeloid-cell-leukemia 1; cFLIP, cellular FLICE-like inhibitory protein; mTOR, mammalian target of rapamycin; B7-H3, GPI-linked CD59 and costimulatory molecule CD276; CTL, cytotoxic T lymphocytes; IDO-1, indolemaine-2,3-dioxygenase-1; CREB, cAMP-response element binding protein; GNF, gastric normal fibroblast; GCAF, gastric cancer-associated fibroblast; IFN-γ, interferon-gamma; MNNG, N-methyl-N'-nitro-N-nitrosoguanidine; TIGAR, TP53-induced glycolysis and apoptosis regulator; PLGC, precancerous lesions of gastric carcinoma; NOX, NADPH oxidase; iNOS, inducible nitric oxide synthase; CAV-1, caveolin-1; STAT3, signal transducers and activators of transcription 3; GCS, glucosylceramide synthase; TIMP-1, tissue inhibitor of metalloproteinases 1; MRP1, multidrug resistance-associated protein 1; PGE2, prostaglandin E2; ROS, reactive oxygen species; SOD, superoxide dismutase; GSH-PX, glutathione peroxidase; IKKα, IκB kinase α; IKKβ, IκB kinase β; 3NT, 3-nitrotirosina; LDHA, Lactate dehydrogenase; MCT1, monocarboxylate transporter 1; NOX4, NADPH oxidase, isoform-4; DOX, Doxorubicin.

Similar to miR-134, miR-150-5p markedly downregulates β-catenin in liver carcinoma, functioning as an inhibitor to attenuate the proliferation of cancer cells. It has been well-established that AS-IV can regulate the miR150-5p/β-catenin axis to induce the apoptosis of HCC cells (20).

Long non-coding RNAs (lncRNAs) are long nucleotide chains without protein-coding capability (71,72). LncRNAs have been identified to participate in several biological processes and are known to play a crucial role in the emergence and progression of cancers. For example, lncRNA-ATB promotes EMT by connecting to the miR-200 family, maintaining the viability of malignant cells via IL-11/STAT3 signaling, which can be prevented by AS-IV (73,74).

Vav3, a member of the Vav protein family, functions as an exchange factor for Rho family GTPases, such as Rac1. It consists of 8 domains, and the complexity of the structure contributes to its various functions. Vav3 modulates different members in the Rho family to participate in the MAPK, PI3K/Akt and NF-κB signaling pathways. Previous studies have demonstrated that MMPs and Rho GTPases play a pivotal role in the migration of the majority of malignant cells. AS-IV has been shown to have antitumor and anti-metastasis functions both *in vivo* and *in vitro*. These functions are accomplished by the downregulation of Vav3 in liver and breast cancer by blocking the Rac1/MAPK signaling pathway, as well as by decreasing MMP-2, MMP-9, and the proteins related to cellular responses during stress and cell signaling (75,76).

Inhibition of angiogenesis. Neovascularization relies on the secretion of vascular endothelial growth factor (VEGF) by tumor cells and the proliferation of endothelial cells (77). VEGF serves as a signal for cyclooxygenase-2 (COX-2)/prostaglandin E2 (PGE2). PGE2 is involved in the major process of COX-2 acting on malignant cells (78). AS-IV inhibits the growth of SGC7901 cells with the downregulation of COX-2, which leads to the suppression of its downstream product, PGE2 expression, and the downregulation of VEGF, thereby decreasing tumor growth (79). Apart from SGC7901, a reduction in VEGF expression has also been reported in studies using A549 and U251 cells.

MDR and increase in chemosensitivity. MDR is the leading cause of the failure of chemotherapy and cancer renascence. The key to reversing tumor drug resistance is to prevent MDR pathways to reduce drug efflux, which can enhance the chemosensitivity of tumor cells (80). It has been found that MDR can be attributed to several factors, including P-gps, lung resistance-related proteins (LRPs), breast cancer resistance protein (BCRP) and multidrug resistance-associated protein 2 (MRP2), all of which can pump drugs out from tumor cells and reduce the anticancer efficacy of drugs (81). Several studies have reported that AS-IV can reverse MDR and increase the chemosensitivity or radiosensitivity of tumors (17,82-87) (Fig. 4)

Caveolin-1 (CAV-1) is a constituent protein playing a role in signal transduction and other cellular activities. It has been confirmed that the expression of CAV-1 is positively associated with cancer metastasis and has, therefore, been identified as a potential target to reverse MDR (88). Zheng *et al* reported that AS-IV reduced CAV-1 expression and reversed the Taxol-induced increase in CAV-1 expression; furthermore,

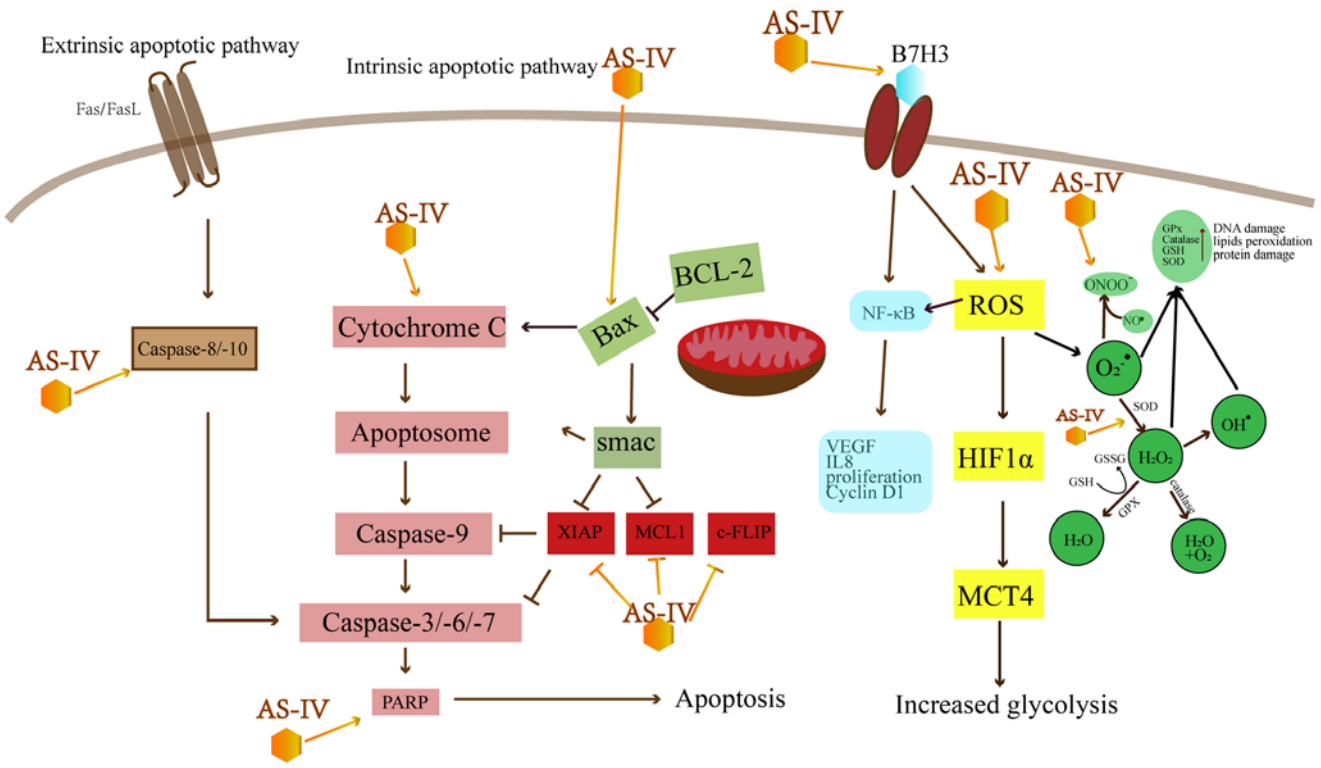

Figure 2. Effect of AS-IV on apoptosis-related pathways. AS-IV, astragaloside IV; XIAP, x-linked mammalian inhibitor of apoptosis; MCL1, myeloid cell leukemia 1; c-FLIP, cellular FLICE-like inhibitory protein; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor; MCT, monocarboxylic acid transporter; HIF, hypoxia-inducing factor; GPx, glutathione peroxidase; GSH, glutathione; SOD, superoxide dismutase.

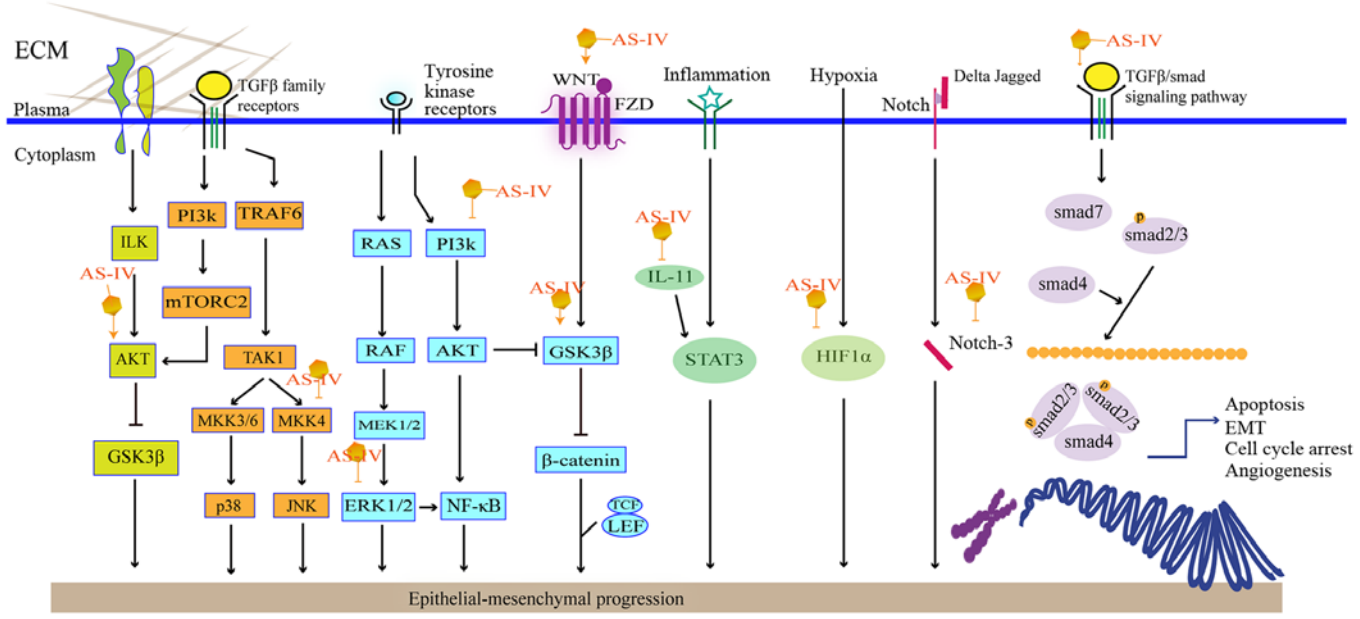

Figure 3. Effect of AS-IV on EMT-related pathways. AS-IV, astragaloside IV; GSK3β, glycogen synthase kinase 3β; mTOR, mammalian target of rapamycin; HIF, hypoxia-inducing factor.

AS-IV administration resulted in initiating the endothelial nitric oxide synthase (eNOS)/nitric oxide (NO)/peroxynitrite ($ONOO^-$) pathway and inhibiting CAV-1, which can induce severe oxidative stress and apoptosis (17).

Moreover, the MAPK pathway, which comprises the ERK, JNK and p38 pathways, controls several biological and cellular processes in cancer. Therefore, its activation is vital to MDR (89). Co-treatment with AS-IV and Taxol lowers ERK and JNK in malignant cells, which are associated with chemosensitizing effects (17).

Studies have found that inhibiting the JNK signaling pathway suppresses the expression of c-Jun and drug-resistant genes, e.g., MDR1 and P-gp, and increases drug-induced the apoptosis of tumor cells. Wang *et al* demonstrated that AS-IV

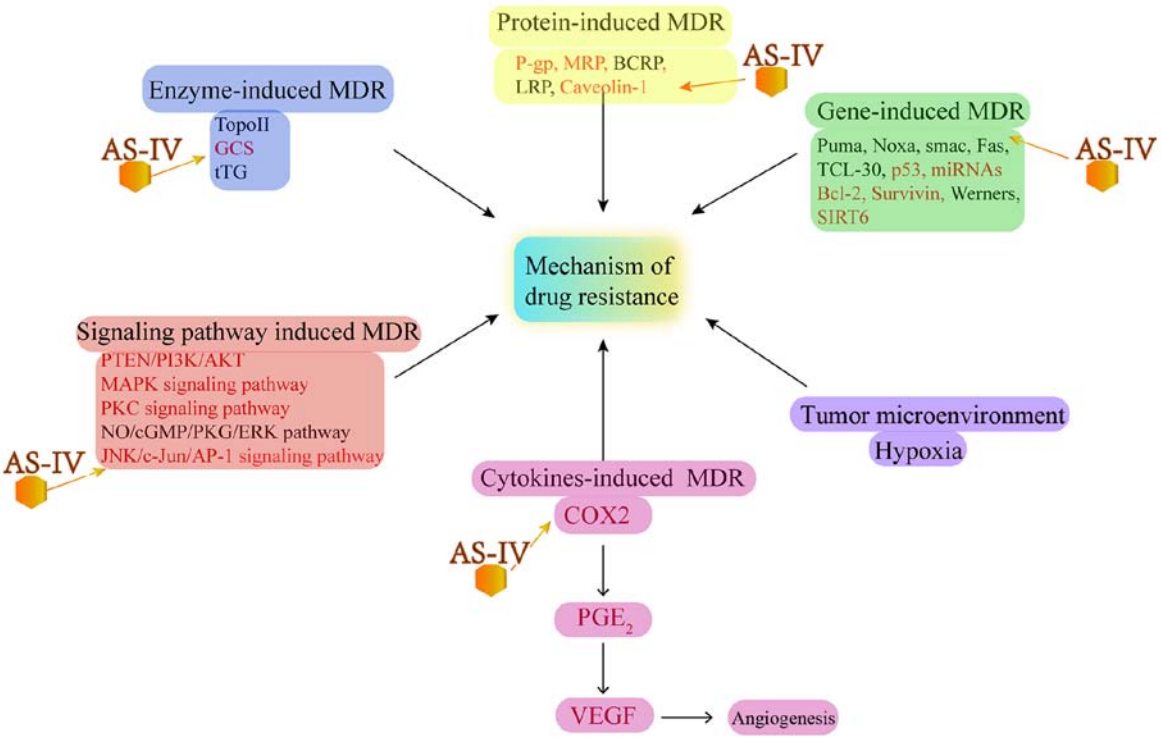

Figure 4. Effect of AS-IV on MDR-related molecular mechanisms. MDR, multidrug resistance; GCS, glucosylceramide synthase; P-gp, P-glycoprotein; LRP, lung resistance-related proteins; BCRP, breast cancer resistance protein; MRP, multidrug resistance-associated protein; COX2, cyclooxygenase 2; PGE2, prostaglandin E2; VEGF, vascular endothelial growth factor; SIRT6, sirtuin 6.

may reverse MDR by inhibiting the JNK/c-Jun/AP-1 pathway in Bel-7402/FU cells (82,83).

Silent information regulator 6 (SIRT6), an NAD^+-dependent deacetylase, plays a key regulatory role in genomic stability, metabolism, chromatin regulation, telomere integrity, gene transcription and glucose and lipid metabolism. Further exploration of these molecular mechanisms has indicated that the multiple roles of SIRT6 in tumorigenesis are realized by regulating the ERK, SMAD and Raf pathways (84).

SIRT6 also triggers lethal autophagy in human cancer cells (90). Recent studies have reported that the upregulation of SIRT6 enhances the sensitivity of NSCLC cells to other drugs and treatment modalities (91-93). Accordingly, the study by Dai *et al* illustrated that AS-IV acted on SIRT6 to heighten the tumor responses to gefitinib in the NCI-H1299, HCC827 and A549 lung cancer cell lines (85).

Studies have indicated that NOTCH3 is highly expressed in tumor cells. It also has been shown that the depletion of NOTCH3 by sorafenib and adriamycin can increase the expression of p53, promote GSK3β phosphorylation and downregulate p21, thereby enhancing the efficacy of chemotherapy (94,95). In addition, NOTCH3 may be used as a biomarker for RC. In a previous *in vitro* study, AS-IV was reported to enhance the chemosensitivity of CRC towards cisplatin by suppressing NOTCH3 (86).

The glucosylceramide synthase (GCS)-mediated abolishment of ceramide-induced apoptosis is one of the underlying mechanisms of acquired drug resistance in some resistant cells (96). AS-IV can reverse drug resistance to doxorubicin in HepG2/GCS cells, suggesting that MDR can be prevented using AS-IV as it reduces the expression of GCS (87).

Improvement of immunity. Owing to their high cytotoxicity and proliferation ability, cytotoxic T lymphocytes (CTLs) are useful in the monitoring and elimination of cancer cells. During tumor progression, the tumor microenvironment (TME) results in the suppression of immune function, which results in a loss of the functions of CTL, leading to immune escape.

Tumor-associated macrophages (TAMs) constitute the most important inflammatory cell group in the TME. Recent studies have revealed that TAM may polarize to the M2-type in terms of phenotypic characteristics. Macrophage colony-stimulating factor-1 (CSF-1), interleukin (IL)-4, IL-10, TGF-β and IL-13 benefit M2 subgroup differentiation. Moreover, M2 and Tregs can reduce the levels of CTLs. Type 2 (M2) macrophages do not exert antitumor effects, but rather participate in the occurrence, development, invasion and metastasis of tumors; therefore, the phenotype M2 is a novel potential target for tumor therapy (97).

There are multiple mechanisms by virtue of which tumor cells escape recognition by CTLs. Indoleamine-2,3-dioxygenase (IDO) is a tryptophan-degrading enzyme that participates in the immune-escape program. In C57BL/6 mice bearing Lewis lung carcinoma cells, AS-IV was shown to exert antineoplastic and immunity-boosting effects to inhibit Tregs and augment CTL activity by suppressing IDO expression (98). AS-IV has also been shown to partially block M2 differentiation via the AMPK signaling pathway, thereby inhibiting invasion, migration and angiogenesis (99).

In 7,12-dimethylbenzanthracene-induced liver and breast cancer in tumor-bearing mice, the effect of co-treatment of cisplatin and AS-IV against breast cancer *in vivo* was more

prominent than that of cisplatin alone. The mechanism of action may be related to the effective upregulation of the levels of immune factors IL-2, IFN-γ, $CD3^+$, $CD4^+$, $CD4^+/CD8^+$, and the downregulation of IL-1, IL-6, TNF-α and $CD8^+$ in liver and breast cancer (100,101).

Moreover, *in vivo* experiments have demonstrated that AS-IV promotes host immunity by regulating the levels of cytokines, NO and cycle-related mRNA and/or protein expression, particularly IL-1β, IL-6 and TNF-α, under the influence of the NF-κB/MAPK pathway. As an inhibitor of proliferation, AS-IV also modulates the levels of cyclin D1, CDK4 and CDK6 in the host, promotes the secretion of CDs, such as CD40 and CD86, and arrests cells in the G2/M stage (102).

Promotion of autophagy. Autophagy is a process in which proteins or organelles are engulfed into vesicles and fused with lysosomes to form an autophagosome. Subsequently, the enclosed contents are degraded, thus achieving the metabolic needs of cells and the renewal of some organelles (103). Autophagy has a dual-directional effect on the progression and survival of malignant tumors. This progression could be measured based on the distribution of LC3-I and LC3-II, which are biomarkers indicating autophagy vesicle accumulation (104).

AS-IV elevates the level of autophagy-associated proteins, such as LC3I/II, Atg7 and Atg12 in cervical cancer cells. It also mediates differentially expressed proteins, including MGST3, AKR1C2, and ERL1N1, which are related to cancer proliferation and cytoskeleton composition. Two autophagy-related proteins, namely, DCP1A and TMSB4X, have been found to be increased in HeLa and SiHa cells following the administration of AS-IV (105).

The TGF-β/SMAD signaling pathway plays a crucial role in a number of types of cancer and the dysfunction of this pathway is an important pathogenic mechanism in cancers. SMAD and downstream TGF-β intracellular signaling transfer the ligand-receptor interaction signal from the cytoplasm to the nucleus. In a previous study, in VSCC cells, AS-IV was shown to improve the dysfunctions of the TGF-β/SMAD pathway, determined based on the elevated TGF-βRII and Smad4 levels; it was also found that AS-IV induced autophagy in SW962 cells, and markedly increased Beclin-1 and LC3-II levels, and decreased p62 protein levels (19).

Prevention of cancer. Aerobic glycolysis and oxidative phosphorylation are common energy sources in tumor cells. Owing to the rapid growth and high energy demand of tumor cells, there is a tendency for an increased glucose uptake and lactate production. Monocarboxylic acid transporters (MCT)1 and MCT4 can transport large amounts of lactic acid produced by tumor cells to the extracellular environment and play a key role in maintaining the acidic environment required for the glycolysis in tumor cells (106). CD147 is indispensable to the activity of MCT1 and MCT4 in gastric cancer. The study by Zhang *et al* suggested that AS-IV reduced the precancerous lesions of gastric carcinoma (PLGC), inhibited glycolysis by regulating the p53/miRNA-34a/LDHA and p53/TIGAR pathways, and restored the levels of MCT1/4, CD147 and HIF-1α (107).

AS-IV inhibits the activity of gastric cancer-associated fibroblasts (GCAFs) with an increased miR-214 and decreased miR-301a expression. AS-IV also inhibits GCAFs from increasing key factors, such as SRY-box2 (SOX2) and NANOG, in inducing pluripotency in somatic cells, decreasing M-CSF expression and increasing TIMP2 expression (108). All these studies demonstrate that AS-IV hinders the development of gastric cancer. This topic is worthy of further exploration in a clinical setting.

Remission of side-effects from chemotherapy. NADPH oxidase (NOX) is a plasma membrane-related enzyme protein family consisting of 7 members of DUOX1-2 and NOX1-5 families. Among the NOXs, NOX2 and NOX4 are expressed in the heart and are responsible for increasing intracellular ROS levels. Oxidative stress has been identified as a main cause of doxorubicin (DOX)-induced cardiomyopathy (109,110). DOX administration has been shown to increase the levels of NOX2 and NOX4 in animal hearts, thereby increasing ROS-induced cardiomyopathy. By contrast, AS-IV noticeably reduces the cardiomyopathy induced by DOX, decreases the oxidative stress caused by NOX2 and NOX4, attenuates the complications of doxorubicin, and, thus, appears suitable as an adjuvant to chemotherapy (111).

4. Conclusions and future perspectives

TCMs are commonly used in clinical treatment in several Asian countries. They significantly contribute towards enhancing the effects of other therapies and reducing toxicity. The *in vitro* and *in vivo* effects of AS-IV in inhibiting tumor proliferation and invasion and in promoting tumor cell apoptosis have been well-documented. Current findings highlight the role of AS-IV in suppressing EMT, as EMT plays a role in the majority of processes related to AS-IV in cancer. Furthermore, AS-IV has also been proven to exert significant preventive effects against MDR and in the regulation of immunity in antitumor therapy. In addition, the low-cost and ready availability of AS-IV further accentuates its potential in tumor therapy.

Despite these advantages, the use of AS-IV is still limited by several means: i) Its mechanisms of action have not been adequately elucidated. A previous study demonstrated that AS-IV enhanced the efflux activity of P-gp and BCRP through the Nrf2-ARE signaling pathway, exerting the opposite effect on P-gp protein in liver cancer and gastric cancer cells, which may lead to herb-drug interactions following treatment with AS-IV (112); ii) there are no clinical studies (to the best of our knowledge) available that explore the role and safety of AS-IV in human cancers. The human body is complex compared to model organisms (*in vivo* or *in vitro*) used in a laboratory setting; iii) finally, the dose of AS-IV used in studies varies greatly; therefore, the safety window and effective dose of AS-IV need to be accurately established. Thus, further studies are warranted to determine the effects of AS-IV and large cohort clinical studies are required to further validate its efficacy in a clinical setting.

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Availability of data and materials

Not applicable.

Authors' contributions

All authors (TC, PY and YJ) were involved in the conception and design of the study. TC was invovled in the drafting of the manuscript and in the processing of the figures. PY and YJ were involved in the critical revision of the manuscript for important intellectual content. YJ was responsible for obtaining funding. TC and PY provided administrative, technical, or material support. PY and YJ supervised and edited the study. All authors have read and approved the final 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.

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