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Review Article

Recent perspectives on chemosensitizing effects of Astragalus membranaceus-derived components: A mini review

Gihyun Lee[1], Kang-Hyun Leem[2], Wonnam Kim[2]*
[1]College of Korean Medicine, Dongshin University, Naju, Jeonnam, [2]Division of Pharmacology, College of Korean Medicine, Semyung University, Jecheon, Republic of Korea

For correspondence: **Email: wonnam_kim@semyung.ac.kr; **Tel:** +82-43-649-1697*

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Abstract

The dried root of Astragalus membranaceus (Fisch.) Bge (AM) is commonly used in herbal medicine in Korea, Japan and China. The traditional use of AM is to invigorate the Qi as a potential treatment for fatigue, loss of appetite, diarrhea, and anemia. Recent studies have expanded current understanding of AM as an antidiabetic, antioxidant, anti-inflammatory, antihyperlipidemic and anticancer agent. Active compounds derived from AM, including polysaccharides, saponins and flavonoids, appear to act as potent chemosensitizers when combined with conventional anticancer agents. Chemosensitizers represent a promising approach for enhancing anticancer efficacy and reversing multidrug resistance. This review highlights the chemosensitizing activity and related molecular mechanisms of components isolated from AM.

Keywords: *Astragalus membranaceus, Anticancer; Chemosensitizer, Multidrug resistance*

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INTRODUCTION

The dried root of *Astragalus membranaceus* (Fisch.) Bge or *Astragalus membranaceus* (Fisch.) Bge. var. *mongholicus* (Bge.) Hsiao (AM) (known as *Huangqi* in Chinese, *Ogi* in Japanese, and *Hwanggi* in Korean) is frequently used in traditional Korean, Japanese and Chinese herbal medicine. The first reference to AM is found in Shennong's Materia Medica, one of the oldest classics on herbal medicine [1]. Traditionally, the *Qi* tonifying function of AM is used to treat symptoms such as fatigue, loss of appetite, diarrhea, and anemia. Recent pharmacological studies describe the antidiabetic, antioxidant, anti-inflammatory, antihyperlipidemic, and anticancer effects of AM and its components; active components isolated from AM include saponins, polysaccharides, and flavonoids [1].

Chemotherapy can be a primary treatment option for tumors, and improving the therapeutic index is directly related to the survival rate of cancer patients [2]. There has been an increasing need for novel treatment strategies to improve clinical outcomes of chemotherapy [3]. One promising strategy is to use chemosensitizers, which are agents that improve the effectiveness of

conventional chemotherapy [3]. Although synthetic chemicals are used as anticancer treatments due to their efficacy and relatively low toxicity, natural products are also recognized as being anticancer candidates and could function as potent chemosensitizers combined with conventional chemotherapy agents [4]. This paper reviews the current understanding of the sensitization of cancer cells to chemotherapy by active components of AM.

Astragalus polysaccharides

Astragalus polysaccharide (APS) is one of the main active components extracted from AM. Studies report that APS reduces the toxic and adverse effects of chemotherapy; APS reduces doxorubicin-associated cardiotoxicity by regulating the PI3k/Akt and p38MAPK pathways [5]. APS also improves quality of life in non-small cell lung cancer (NSCLC) patients treated with vinorelbine and cisplatin [6]. Moreover, growing evidence indicates that APS sensitizes tumor cells to chemotherapeutics (Table 1). Adriamycin-resistant H22 hepatoma cell lines (ADMr H22) treated with a combination of APS and chemotherapy agents, such as cisplatin, 5-fluorouracil (5-FU), etoposide, cyclophosphamide, vincristine, and Adriamycin, show significantly reduced cell viability; APS increases intracellular levels of chemotherapeutic drugs by down-regulating *MDR1* mRNA expression, inhibiting the activity of efflux transporter P-glycoprotein (P-gp) and decreasing P-gp expression [7]. Similarly, compared to cisplatin only, it has been found that cisplatin co-treated with APS significantly inhibits cell proliferation and promotes apoptosis in nasopharyngeal carcinoma cell lines *in vitro* and *in vivo;* in both cell lines and xenografts, cisplatin cotreated with APS significantly enhances the Bax to Bcl-2 ratio and increases caspase-3 and caspase-9 levels [8]. APS (800 µg/mL) treatment has also been shown to increase the toxicity of cisplatin on SKOV3 ovarian cancer cells and to induce apoptosis by activating the JNK signaling pathway and increasing the Bax to Bcl-2 ratio [9].

Interestingly, the JNK pathway modulates P-gp expression and increases the accumulation of daunorubicin and doxorubicin in multidrug-resistant (MDR) cells [10]. APS may act as a chemosensitizer and block P-gp mediated resistance to chemotherapeutic agents, by regulating the JNK pathway in cancer cells.

Astragaloside II

Astragaloside II (AII) (3β, 6α, 16β, 20*R*, 24*S*)-3-((2-*O*-Acetyl-β-D-xylopyranosyl)oxy)-20, 24-epoxy-16, 25-dihydroxy-9, 19-cyclolanostan-6-yl β-D-glucopyranoside) is a key saponin purified from AM [11]. A nontoxic dose of AII increases sensitivity to 5-FU in a 5-FU resistant BEL-7402 (FUr Bel7402) hepatoma cell line; AII reduces the expression of *MDR1* and P-gp, leading to the inhibition of P-gp transport activity, and suppresses MAPK signaling mediated by ERK, p38, and JNK phosphorylation [11].

Autophagy is an intracellular homeostatic recycling system that has a possible pro-survival or pro-death effect on cancer cells [12]. Increasing evidence suggests that autophagy contributes to cisplatin resistance in cancer cells [13] by down-regulating the PI3K/Akt/mTOR pathway [14]. Results show that AII (50 µM) inhibits autophagy by interfering with autophagosome-lysosome fusion and the lysosomal function in human cancer cells; thus, AII blocks cisplatin-activated autophagy and enhances the chemosensitivity of cancer cells to apoptosis [14].

Astragaloside IV

Astragaloside IV (AIV) (3-*O*-ß-D-xylopyranosyl-6-*O*-ß-D-glucopyranosyl-cycloastragenol) is an active saponin found in AM [15]. AIV (0.08 mg/mL) increases the cytotoxicity of 5-FU in FUr Bel7402 cells by down-regulating *MDR1* gene expression, decreasing P-gp levels on the cell surface and increasing the accumulation of 5-FU, as measured by HPLC [15]. B7-H3 (CD276), a member of the B7 and CD28 superfamily, is associated with several cancer types and appears to regulate carcinogenesis, tumor progression, metastasis and chemoresistance; AIV has been found to reduce cell proliferation by inhibiting B7-H3 expression in colorectal cancer cell lines [16]. Furthermore, a combination of AIV (5 ng/mL) and cisplatin (2.5 µM) has been shown to increase apoptosis significantly in NSCLC cells compared to cisplatin only, by suppressing B7-H3 expression [17]. AIV appears to elevate microRNA (miRNA) miR-29c expression, a miRNA that binds to the 3'-UTR region of B7-H3, decreasing B7-H3 expression [16, 18].

Cisplatin co-treated with AIV significantly inhibits the viability of HCT116 and SW480 human colorectal cancer cell lines by suppressing NOTCH3 expression compared to cisplatin only [19]. NOTCH3 transcript levels are up-regulated in colorectal cancer and induce tumor growth [20].

AIV has also been found to inhibit the cell viability of NCI-H1299, HCC827, and A549 NSCLC cell lines, depending on dose; AIV (3 and

6 ng/mL) increases the chemosensitivity of gefitinib in NSCLC cell lines by SIRT6 stimulation [21]. A further study demonstrated that SIRT6 overexpression in A549 cells enhances the radiosensitization effect, inhibiting proliferation and promoting apoptosis [22]. In contrast, SIRT6 knockdown increases the sensitivity of A549 cells to paclitaxel [23]. Taken together, these findings indicate that further study is required to determine the role of SIRT6 in relation to the effect of AIV.

AIV treatment has been found to suppress proliferation and epithelial-mesenchymal transition (EMT) related proteins, such as vimentin, N-cadherin, and Snail, in SW-480 colorectal cancer cells; AIV increases the sensitivity to oxaliplatin (OXA) by promoting miR-134 via inhibiting CREB1-mediated proliferation, the EMT process, and drug resistance [24]. EMT is a complex cellular process that plays a central role in cancer progression and metastasis [25]. EMT develops invasiveness and chemotherapy resistance in tumor cells [26]. Anticancer agents can induce EMT, leading to metastatic behavior and poor clinical outcomes [27]. Colorectal cancer cells chronically exposed to OXA develop EMT-associated cell migration and invasion ability [28].

Cisplatin (2.5-80 μM) and AIV (40 μM) co-treatment significantly enhances growth inhibition and cell death in MG-63 and 143B osteosarcoma cell lines *in vitro*, and the chemosensitive actions of AIV have been confirmed by 143B xenografts *in vivo* [29]. Apoptosis by cisplatin involves caspase-dependent Fas/FasL signaling, which significantly increases with AIV co-treatment [29]. The chemosensitizing action of AII and AIV are summarized in Table 1.

Formononetin and calycosin

Formononetin (FM) and calycosin (CC) are isoflavones isolated from AM [30]. One study was undertaken *in vitro* to screen 16 flavonoids and 5 isoflavonoids and search for MDR modifiers, based on P-gp and multidrug resistance protein (MRP) overexpressed cells [31]. The results indicate that FM is an effective MDR modifier, and it increases the chemosensitivity of MDA-MB-231 breast cancer cells to epirubicin [31].

Table 1: Chemosensitizing role of *Astragalus membranaceus*-derived polysaccharides and saponins

Compound	Tumor type	Chemotherapy agents	Chemosensitizing action	Reference
Astragalus polysaccharides	H22 hepatoma cell line resistant to Adriamycin	Cisplatin, 5-fluorouracil, etoposide, cyclophosphamide, vincristine, and Adriamycin	*MDR1* expression, P-glycoprotein expression and activity	[7]
	Nasopharyngeal carcinoma cell line	Cisplatin	Bax to Bcl-2 ratio, caspase-3, and caspase-9	[8]
	Ovarian cancer cell line	Cisplatin	JNK signaling and Bax to Bcl-2 ratio	[9]
Astragaloside II	Hepatoma cell line resistant to 5-fluorouracil	5-fluorouracil	MAPK signaling, *MDR1* expression, P-glycoprotein expression and activity	[11]
	Gastric and hepatoma cell lines	Cisplatin	PI3K/Akt/mTOR signaling, autophagy, and lysosomal function	[14]
Astragaloside IV	Hepatoma cell line resistant to 5-fluorouracil	5-Fluorouracil	*MDR1* and P-glycoprotein expression	[15]
	Lung cancer cell line	Cisplatin	Apoptosis and B7-H3 expression	[17]
	Colorectal cancer cell line	Cisplatin	NOTCH3	[19]
	Lung cancer cell line	Gefitinib	SIRT6	[21]
	Colorectal cancer cell line	Oxaliplatin	miR-134/CREB1 signaling	[24]
	Osteosarcoma cell line	Cisplatin	Fas signaling	[29]

Table 2: Chemosensitizing role of *Astragalus membranaceus*-derived flavonoids

Compound	Tumor type	Chemotherapeutic agents	Chemosensitizing action	Reference
Formononetin	Breast cancer cell line	Epirubicin	Multidrug resistance protein	[31]
	Cervical cancer cell line	Epirubicin	Reactive oxygen species and multidrug resistance protein	[32]
	Glioblastoma cell line	Doxorubicin	Histone deacetylase 5 and epithelial-mesenchymal transition	[33]
	Breast cancer cell line	Sunitinib	Fibroblast growth factor 2 signaling and signal transducer and activator of transcription 3	[34]
Calycosin	Gastric cancer cell line	Cisplatin	Akt signaling	[35]

In another study, FM (25 µM) was also found to potentiate the cytotoxicity of epirubicin in HeLa cervical cancer cells; FM and epirubicin synergistically increase reactive oxygen species production, inducing MRP inhibition and cell death [32]. A combination of FM with doxorubicin was found to decrease cell viability significantly compared to doxorubicin alone in glioma cells [33]. Interestingly, the results also show that FM blunts the doxorubicin-promoted expression of EMT markers by association with histone deacetylase 5 (HDAC5); there is growing evidence that HDAC5 contributes to tumor proliferation and metastasis [33]. Sunitinib, a vascular endothelial growth factor receptor-2 inhibitor, cotreated with FM significantly inhibits tumor growth *in vivo* and endothelial cell invasion *in vitro* compared with FM or sunitinib alone [34]. Moreover, FM blocks fibroblast growth factor-2 (FGF2) from binding to its receptor FGF2R, inhibiting the FGFR2-dependent signaling that mediates tumor angiogenesis and growth through signal transducer and activator of transcription 3 (STAT3) [34].

CC (10 µg/mL) was found to enhance the inhibition effect of cisplatin (20 µg/mL) against gastric cancer cells by regulating Akt signaling; this result suggests that CC would act as a chemosensitivity enhancer for cisplatin, 5-FU, and Adriamycin [35]. The chemosensitizing action of FM and CC are listed in Table 2.

CONCLUDING REMARKS

The efficacy of antineoplastic agents is limited due to toxicity and drug resistance. Thus, the use of chemosensitizers to increase responsiveness to chemotherapy is an appealing strategy. Previous research has shown that active components derived from AM act as potent chemosensitizers. AM-derived compounds reduce P-gp and MRP expression, which are involved in drug resistance. In combination with chemotherapy, AM-derived components enhance apoptosis and inhibit autophagy-mediated cell survival. Sensitivity to chemotherapeutic agents has been achieved by inhibiting B7-H3 and NOTCH3, and activating SIRT6. However, the majority of research has used *in vitro* models to validate the pharmacological actions. Additional *in vivo* research is needed to expand the understanding of the chemosensitizing role of AM-derived compounds.

DECLARATIONS

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Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Gihyun Lee and Wonnam Kim conceived and designed the study, Gihyun Lee and Kang-Hyun Leem collected and analyzed the data. While Wonnam Kim wrote the manuscript. All authors read and approved the manuscript for publication.

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