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***Astragalus membranaceus* : A review study of its anti-carcinoma activities**

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ABSTRACT

Astragalus L., is one of the largest genus of flowering plants in the Leguminosae family. The aim of this study was to review anti-carcinoma activities of this valuable herb. This review article was carried out by searching studies in PubMed, Medline, Web of Science, and Iran Medex databases. The initial search strategy identified about 128 references. In this study, 113 studies were accepted for further screening and met all our inclusion criteria (in English, full text, therapeutic effects of *Astragalus membranaceus* and dated mainly from all years of study). The search terms were “*Astragalus membranaceus*”, “anti-carcinoma activities”, pharmacological effects. The results were indicated that different parts and forms of this herb including its leaves, roots and stems has anti-cancer and anti-tumor activities i.e. lung, colorectal, breast, ovarian, liver, colorectal, stomach, colon, gastric, cervical, nasopharyngeal cancers. Based on the results of this study, it was indicated that *Astragalus membranaceus* has high anti-carcinoma activities.

Keyword: *Astragalus membranaceus*, anti-carcinoma activities, pharmacological effects, anti-cancer, anti-tumor

INTRODUCTION

Astragalus L. belongs to the Leguminosae family, is an annual or perennial herb, subshrub, or shrub, herb grown widely in the arid regions. It possesses anti-inflammatory, immunostimulant, antioxidative, anti-cancer, antidiabetic, cardioprotective, hepatoprotective, and antiviral activities [1]. *Astragalus membranaceus* is one of the important “Qi tonifying” or adaptogenic herbs from the Chinese materia medica. It has been prescribed for centuries for general debility, chronic illnesses, and to increase the overall vitality of the system. Currently, much of the pharmacological research is focused on its immune stimulating polysaccharides and other active ingredients from the plant, useful in treating immune deficiency conditions.

It is traditionally used for antiperspirants, diuretics, empyrosis, nephritis, diabetes mellitus, hypertension, cirrhosis, leukemia, and uterine cancer [2, 3], for its antimicrobial, antiperspirant, anti-inflammatory, diuretic and tonic effects [4], hepatoprotective, immunostimulant, and antiviral activities [5]. Of its properties, its anti-cancer and anti-tumor activities are overwhelming. Thus, the purpose of this study was to review anti-carcinoma activities of this valuable herb.

Chemical compound

Saponins, flavonoids, and polysaccharides are believed to be the principle active constituents of *Astragalus* [6]. It also includes components such as anthraquinones, alkaloids, amino acids, β -sitosterol, and metallic elements. The chemical compositions in *Astragalus* genus appeared highly uniform, which mainly include terpenoids, flavonoids, and polysaccharides. The interesting compounds, such as terpenoids and flavonoids are always in free or glycosidic forms. The fatty acid contents of some *Astragalus* L. (Fabaceae) species from Turkey were determined by GC and GC-MS techniques. The seed oils of *Astragalus* sp. (*A. echinops* Aucher ex. Boiss., *A. subrobustus* Boriss., *A. jodostachys*, Boiss. & Buhse., *A. falcatus* Lam., *A. fraxinifolius* DC.) contained linolenic (between 23–41%), linoleic (23–37%), and oleic acids (8–19%) as the major components. Fatty acid composition of the studied *Astragalus* taxa showed uniform fatty acid patterns. Palmitic and stearic acids were the major saturated fatty acids in the seed oils. The amounts of unsaturated fatty acids were higher than saturated fatty acids [7].

Astragalus contains the plant pigments: formononetin, astraisoflavan, astrapterocarpan, 2'-3'-dihydroxy-7,4'-dimethoxyisoflavone, andisoliquiritigenin.2 Other major constituents include D- β -asparagine, calycosin, cycloastragenol, astragalosides IVII, choline, betaine, kumatakenin, sucrose, glucuronic acid, β -sitosterol1, and soyasaponin. Astragalan, a polysaccharide fraction with a molecular weight between 20,000 and 25,000, has been extracted and researched in China for its ability to enhance the *in vitro* secretion of tumor necrosis factor[8].

Anti-tumor activity

In an animal study, the efficacy of extracts of *Astragalus membranaceus* (AM) was assessed at different tumor stages of an orthotopic nude mouse model of human ovarian cancer expressing red fluorescent protein and it was concluded that CDDP, AM, and its combination with CW-induced significant growth inhibition of Stage I tumors. Strong efficacy of the combination of AM and CW at high dose was observed. Combination treatments did not significantly inhibit Stage II and III tumors. Its expression was significantly reduced in Stage I tumors treated with AM, CW, and their combination, suggesting a possible role of these angiogenesis- and apoptosis-related genes in the observed efficacy of the agents tested [9].

In an *in vitro* study, anti-tumor effect and mechanism of dendritic cell (DC) tumor vaccine induced by *Astragalus* polysaccharin (APS) was investigated and it was suggested that the morphological observation and phenotypic identification of APS induced DCs were in accordance with the characteristics of mature DCs. CTL cells activated by sensitization of DCs could significantly kill tumor cells, and the killing effect increased along with increased effector-to-target ratio. APS could *in vitro* induce DCs to mature, promote its antigen-presenting capacity, effectively activate CTLs, and enhance anti-tumor function of the organism.[10]

The functions of APS on intestinal intraepithelial $\gamma\delta$ T cells, a major subset in IELs and an essential component of maintaining homeostasis and immune regulation in enteric mucosa was investigated. Results showed that APS could promote proliferation and function of intestinal intraepithelial $\gamma\delta$ T cells *in vitro*, the IFN- γ , FasL and GrB mRNA levels in $\gamma\delta$ T cells were all significantly increased. In conclusion, this study demonstrated that APS could improve proliferation and function of intestinal intraepithelial $\gamma\delta$ T cells, which might an important pathway for immunomodulation of APS in cancer therapy. [11]

In vitro and *in vivo* antitumor effects of *Astragalus* and synergistic antitumor efficacy in combination with pterostilbene were investigated. Melanoma cells were treated with pterostilbene (Pt), graduated doses of *Astragalus* injection (AI), or these in combination. AI significantly inhibits the growth of melanoma *in vitro* and *in vivo* by inducing apoptosis. These data suggest that combined treatment of *Astragalus* with pterostilbene enhances antitumor efficacy. [12]

The antitumor and immunomodulatory activity of *Astragalus membranaceus* polysaccharide (AMP) on liver cancer using murine H22 hepatocarcinoma model was investigated. The results showed that AMP (100 and 400 mg/kg) could effectively inhibit the solid tumor growth of H22 hepatocarcinoma transplanted in BALB/c mice. Besides, the body weight, spleen/thymus indexes and phagocytotic function of macrophage of H22 tumor bearing mice were also improved in two AMP treated groups. Furthermore, AMP treatment could promote the secretion of IL-2, IL-12 and TNF- α and decreased IL-10 level in serum. Taken together, these findings indicate that AMP has antitumor activity *in vivo* at least partly via improving immune responses of host organism, and seems to be safe and effective for the use of anti-tumor therapy.[13]

The adjunct anticancer effect of *Astragalus* polysaccharides in H22 tumor-bearing mice was investigated and it was shown that APS exerts a synergistic anti-tumor effect with ADM in H22 Tumor-bearing mice. This may be related to its ability to enhance the expression of IL-1 α , IL-2, IL-6, and TNF- α , decrease IL-10, and down-regulate MDR1 mRNA and P-GP expression levels.[14]

The effect of APS on the function of Treg cells in the tumor microenvironment of human hepatocellular carcinoma (HCC) was assessed and it was demonstrated that APS can inhibit the growth and proliferation of CD4+CD25+Treg cells in vitro in a dose- and time-dependent manner. APS can restore the cytokine balance in the tumor micro environment and suppress the expression of FOXP3 mRNA to inhibit the immune suppressive effects of Treg cells. The application of APS in the tumor microenvironment might act to enhance the anti-tumor effects of the immunotherapy-based methods, and consequently to increase the survival rate in HCC.[15]

In an in vitro study, for the first time three different natural compounds, isolated from hairy roots of *Astragalus membranaceus*, cultivated in airlift bioreactor were tested for their cytotoxic potential and apoptosis induction in a panel of human tumor cell lines. Root cultures, cultivated in bioreactor gave 18.5 g l(-1) dry wt roots with the highest astragaloside production in vitro up to now - 1.64% (astragaloside I), 1.12% (astragaloside II) and 1.08% (astragaloside III). In this manner the production in airlift bioreactor can be used as means of reliable supply of cycloartanesaponins to extend the research to human clinical studies [16].

The effect of *Astragalus membranaceus* efficacy enhancing and toxicity reducing on chemotherapy in patients of malignant tumor was evaluated and it was found that *Astragalus* injection supplemented with chemotherapy could inhibit the development of tumor, decrease the toxic-adverse effect of chemotherapy, elevate the immune function of organism and improve the quality of life in patients [17].

Anti-cancer activity

In a clinical trial study, peripheral blood mononuclear cells (PBMNC) of 37 lung cancer patients and 19 healthy subjects were prepared and used for examination of cytokine secretion and gene expression was assessed and it was shown that traditional Chinese medicine AG might reverse the Th2 predominant status in lung cancer patients, which is a probable alternative therapeutic regime in future [18].

The effect of the couplet medicines (*Astragalus membranaceus* and Jiaozhen) on intestinal barrier functions of postoperative colorectal cancer patients was evaluated and CM showed similar effect with that of WM in improving blood D-lactic acid levels and DAO levels, and urinary L/M ratio. But they showed better effect than that of the blank control group ($P < 0.05$). Besides, the couplet medicines (*Astragalus membranaceus* and Jiaozhen) had obvious protection for intestinal barrier dysfunction of postoperative colorectal cancer patients, showing similar efficacy to that of WM. It was even superior to glutamine in restoring bowel functions, reducing toxin absorption, and lowering levels of pro-inflammatory factors. [19]

Cytotoxicity of bee products and their effects on the expression of proapoptotic genes have been investigated. Propolis extract was shown to increase the expression of the Bcl-2 gene in all cell lines whereas the honey had a reverse action i.e. reduce that significantly ($P < 0.05$). Also, it was found that honey and Propolis decreased p53 gene expression in HepG2 and 5637 significantly but not in L929 cells. The sugar solution increased the expression of p53 in two cancer cell lines but no significant changes were observed in the expression of this gene in L929 as normal mouse cell. Bydown regulation of Bcl-2 expression it could be concluded that the cytotoxicity of honey was more than two fold against tested cancer cells compared with the sugar solution. No significant changes were observed in the expression of p53 in honey-treated cells. Propolis had no significant effect on Bcl-2 and p53 gene expressions ($P > 0.05$).[20]

In an animal study, the antitumor effect of AM was evaluated on the subcutaneous tumors of human colorectal cancer cell line HCT116 grafted into nude mice. The mice were treated with either water or 500 mg/kg AM once per day. The results showed that administration of AM eliminate chromosome organization, histone modification, and regulation of macromolecule metabolic process. A separate analysis focused on differentially expressed microRNAs revealing involvement of macromolecule metabolism, and intracellular transport, as well as several cancer signaling pathways. Besides, it was suggested that many chemopreventive agents of natural origin produce similar gene expression profiles to that of AM. Thus the therapeutic effect of this drug was confirmed for colorectal cancer. [21]

The effects of *Astragalus* polysaccharides (APS) combined with cisplatin on growth of Lewis lung cancer (LLC), serum content of collagen type IV (Col4) and hyaluronic acid (HA), and CD44 protein level in LLC-bearing mice was investigated. It was suggested that APS can inhibit the growth of LLC cells, reduce the Col4 and HA content in serum, down-regulate the expression of CD44 protein in LLC-bearing mice, and enhance the therapeutic effect when combined with cisplatin, indicating that it can decrease the toxicity of cisplatin against tumor.[22]

In an in vitro study, the effects of FAC on human breast cell proliferation, apoptosis, and metastasis, as well as their active mechanism was indicated. FAC has an important role in breast cancer growth and metastasis suppression in vitro and in vivo. Its active mechanism involves promoting programmed cancer cell death and regulates metastasis-related gene expression. [23]

In another study, the effect and mechanism of AMs to human stomach cancer was discussed and it was demonstrated that this plant have been proved to be effective in treating cancers from lots of clinical cases. However, its mechanism of the anti-tumor was not clear. All results show that AMs is effective in treating human stomach cancer and the mechanism might be regulated by TLR4 mediated signal transduction of DCs. the result show that AMs can great reduce the amount of cell lines by MTT assay (Fig-4) and induce apoptosis with Immunofluorescence (Fig-5). From animal in vitro in vivo studies it was concluded that AMs can delay tumor development from the diameter and weight of the tumor, prolong life-span and improve life-quality. It is able to play a great role in treating human stomach cancers through precipitating DCs maturation.[24]

In an in vivo study, the role of GRP in endoplasmic reticulum (ER) stress-mediated apoptosis during colon cancer occurrence was investigated and it was suggested that calpains, in particular calpain II, play a permissive role in the modulation of GRP78 and consequent regulation of ER stress-induced apoptosis. Combination of calpain inhibitors and AST could exhibit a more pronounced pro-apoptotic effect. These results showed a new therapeutic approach in colon cancer by targeting calpain and GRP.[25]

The potential synergistic anticarcinogenic effects of AST and a vinca alkaloid vinblastine was investigated. Significant growth inhibition and cell cycle arrest at G2/M phase were achieved by either drug treatment with apparent synergistic effects. VBL-induced apoptosis was confirmed but was shown not to be related to induction of the novel apoptotic protein NSAID-activated gene 1. Besides, downregulation of proangiogenic and proliferative factors was also envisaged, via improving efficacy through combined drug therapy. The results was demonstrated that AST combined with adjuvant chemotherapeutics like VBL could reduce cancer development through varied modes of action [26]

The efficacy of *Astragalus* combined with radiotherapy for NSCLC was evaluated.it was concluded that the combination of *Astragalus* and radiotherapy may be helpful through increasing the therapeutic effectiveness and reducing the toxicity of radiotherapy. Finally, futher studies are required to confirm the exact benefits. [27]

In an in vivo study, CASE's suppression of HCC modulated by TGF- β /Smad signaling was investigated and the results suggest that CASE remarkably suppresses HCC progression via mediating TGF- β /Smad signaling, especially through modulating Smad3 phosphorylation both at the C-terminal and linker region.[28]

In an animal study, the efficacy of *Astragalus* and Salvia Compound on diethylnitrosamine -induced hepatocarcinogenesis in rats was investigated and it was shown that CASE treatment significantly reduced the incidence and multiplicity of DEN-induced HCC development in a dose-dependent manner. CASE suppresses DEN-induced hepatocarcinogenesis by inhibiting fibrosis and PAI-1 mRNA transcription, suggesting its potential clinical application in preventing and treating human HCC.[29]

The effect of *Astragalus membranaceus* on proliferation, invasion and apoptosis of gastric cancer BGC-823 cells was investigated in an animal study. The results demonstrated that total *Astragalus* saponins could inhibit human gastric cancer cell growth both in vitro and in vivo. Besides, *Astragalus* saponins decreased the invasion ability and induced the apoptosis of gastric cancer BGC-823 cells. Total *Astragalus* saponins inhibited human gastric cancer cell growth, decreased the invasion ability and induced the apoptosis. This suggested that *Astragalus* is an alternative treatment and adjuvant chemotherapeutic agent in gastric cancer therapy.[30]

The effects of PAE on the apoptosis, proliferation, migration and invasion of the human hepatoma cell lines HepG2 and SMMC-7721 were investigated. The results of wound healing assay and Matrigel invasion assay showed that PAE displayed inhibitory activity on the migration and invasion of HCC cells. thus, it showed that PAE is a potential antineoplastic drug that is useful for the treatment of HCC.[31]

In an in vitro study, efficacy of combination of Ginseng and *Astragalus* was investigated on the proliferation, the cloning, apoptosis and migration of human gastric cancer MGC-803 cells. Compared with CGA or 5-FU alone, CGA +5-FU could better inhibit the cell growth of human gastric cancer MGC- 803 cells, suppress the formation of cell cloning, induce cell apoptosis, block the cell cycle at G0/G1 phase, and inhibit the cell migration.[32]

The efficacy of AST in controlling angiogenesis was investigated with elaboration of the underlying molecular mechanism in human colon cancer cell and tumor xenograft. These results suggest that AST exerts anti-carcinogenic activity in colon cancer cells via modulation of mTOR signaling and down regulation of COX-2 decreasing VEGF level in tumor cells ,subsequently suppress angiogenesis.[33]

The anti-proliferation activity of *Astragalus* on human hepatocellular carcinoma (HCC) cells and its mechanism was investigated. The results was suggested that *Astragalus* has significant anti-tumor effect in vivo in inducing apoptosis of H22 tumor cells through promoting protein expression of Bax, decreasing protein expression of Bcl-2 gene, and significantly improving the Bax/Bcl-2 ratio.[34]

In another study, the mechanism of such anti-proliferation properties have been investigated. AML induced apoptosis in a caspase-dependent manner in the chronic myeloid leukemia cell line, K562. Furthermore, it was observed that cytotoxicity and apoptosis of K562 cells induced by AML were completely abolished in presence of lactose or galactose.the results suggest that AML could act as a potential anti-cancer drug.[35]

The effects of *Astragalus* polysaccharide on proliferation of basal-like breast cancer cell line MDA-MB-468 cells and Akt phosphorylation in MDA-MB-468 cells was investigated and it was concluded that it can inhibit proliferation of basal-like breast cancer cell line MDA-MB-468, and down-regulate the expression of Akt phosphorylation. The antiproliferation mechanisms may be related to its effects of up-regulating the expressions of p53 and PTEN by regulating p53/MDM2 positive and negative feedback loops.[36]

In a clinical trial study, the efficacy of APS injection integrated with vinorelbine and cisplatin (VC) offered an improved QOL over VC for patients with advanced NSCLC was determined. It was shown that the treatment of APS integrated with VC had significantly improved QOL in patients with advanced NSCLC compared with VC alone.[37]

The anti-angiogenic property of AST in human gastric adenocarcinoma cells (AGS) and its underlying mechanism were investigated and it was indicated that the number of AGS cells invaded through the Matrigel membrane was significantly reduced upon AST treatment, with concomitant down-regulation of the pro-angiogenic protein vascular endothelial growth factor (VEGF) as well as the metastatic proteins metalloproteinase (MMP)-2 and MMP-9. These results also suggest that AST is an effective chemotherapeutic agent in treating advanced and metastatic gastric cancers.[38]

In a study, all of the compounds was tested for cytotoxic activities against a number of cancer cell lines. Among the compounds, only 8 exhibited activity versus human breast cancer at 45 μ M concentration.[39]

The effect of *Astragalus* in regulating the imbalance between naive helper T cells (Th1/Th2) cytokines expression in patients with cervical cancer was investigated and it was found that Th1/Th2 cell function imbalance existed in patients with cervical cancer, showing a Th2 predominant reaction mode; AI can regulate the imbalance, offset to Th1, thus to display its anti-tumor effect.[40]

The effects of *Astragalus* on human nasopharyngeal carcinoma (NPC) viability and apoptosis and to investigate the mechanism of *Astragalus* in a NPC cell line (CNE2) was evaluated. These findings suggest that the immunomodulatory and anticancer effects of DDP + *Astragalus* were better than those of DDP alone, and *Astragalus* could inhibit immunosuppression induced by DDP. The combination of CDDP + *Astragalus* could be developed as an effective chemotherapeutic regimen in the treatment of nasopharyngeal carcinoma.[41]

The proapoptotic effects of AST and its mechanism of action were investigated in cytokine-induced cells. It was suggested that AST induces the extrinsic apoptotic cascade and causes cell cycle arrest in cells by modulation. Most of the above processes are more remarkable in cytokine-induced cells.[42]

Effects of *Astragalus* injection, astragaloside IV and formononetin on proliferation and Akt phosphorylation of basal-like human breast carcinoma cell line was investigated. It suggested that *Astragalus* injection, astragaloside IV and formononetin can inhibit proliferation of breast cancer cell lines, and the antiproliferation effects vary according to their concentrations. Its the mechanisms of action may be related to their down-regulation effects. [43]

In a human study, The effect of *Astragalus mongholicus* injection on proliferation and apoptosis in hormone sensitive breast cancer cell lines (MCF-7) with physiological dose E2 was investigated. In some dose limit, *Astragalus mongholicus* injection may inhibit proliferation, induce apoptosis and interrupt caryocinesia at G0-G1 phase or S phase in hormone sensitive (MCF-7) breast cancer cell lines with physiological dose E2.[44]

In a clinical trial study, Jinfukang had no significant impact on the pharmacokinetics of docetaxel. Median time to progression or withdrawal from treatment was 7 weeks. Jinfukang did not change the pharmacokinetics of docetaxel nor appear to affect survival.[45]

In a clinical trial, combination of *Astragalus* with platinum-based chemotherapy (versus platinum-based chemotherapy alone) showed to improve survival, increase tumor response, improve performance status, or reduce chemotherapy toxicity. *Astragalus*-based Chinese herbal medicine may increase effectiveness of platinum-based chemotherapy when combined with chemotherapy. These results require confirmation with rigorously controlled trials.[46]

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