

Research progress of the Antitumor Mechanism of Schisandra Chinensis

Ziang Yan

School of Macau University of Science and Technology, Macau, China

2009853yc211001@student.must.edu.mo

Abstract. This paper provides an in-depth analysis of the antitumor mechanisms of the active components of Schisandra chinensis. The application of traditional Chinese medicine in tumor therapy has received attention, and the polysaccharide and lignan-like components in Schisandra chinensis, especially Schisandra chinensis alpha- and beta-substituted, show remarkable anticancer effects, inhibiting tumor cell proliferation, promoting apoptosis, enhancing chemotherapeutic drug sensitivity, and counteracting the invasion and metastasis of tumor cells. The anticancer effects of the active ingredients in Schisandra chinensis were not only limited to direct effects on tumor cells, but also included indirect mechanisms through the regulation of body immune response, antioxidant and free radical scavenging. This indicates the research potential of the active ingredients in Schisandra chinensis to achieve anticancer effects through direct action as well as modulation of the immune system, which provides a new direction for the study of new anticancer drugs. However, the current research on Schisandra chinensis mainly focuses on the cellular level and lacks in-depth molecular mechanisms and clinical studies. The anticancer active components of Schisandra chinensis are complex, and there may be interactions between different components, but the current studies are mostly focused on the analysis of single components, and there is insufficient research on the interactions between active components. This paper summarizes the progress of research on the anticancer mechanism of the active components of Schisandra chinensis, points out the shortcomings of the current research, and looks forward to the future research direction. This provides a theoretical basis for the application of Schisandra chinensis in the field of anticancer, and points out the direction for further scientific research and clinical application.

Keywords: Schisandra chinensis, tumor signal pathway, schisandra chinensis b, schisandra chinensis methylin.

1. Introduction

According to Chinese medicine, the main reason for the occurrence of tumors is the insufficiency of positive qi, and the insufficiency of positive qi is the root cause of the internal invasion of evil poisons. Therefore, it has long been an important therapeutic principle for Chinese medicine to treat tumors. From the point of view of Chinese medicine, its tonic effect of astringency, benefiting qi, generating fluid, tonifying the kidney and tranquilizing the heart can take care of the positive qi, play the role of supporting the positive and strengthening the body's immunity.

In recent years, the incidence of malignant tumors remains high, and the research on the application of Chinese herbs to a variety of malignant tumors has received widespread attention. In recent years, the

incidence rate of malignant tumors remains high, and the research on the application of Chinese herbal medicines to a variety of malignant tumors has received extensive attention. Studies have shown that traditional Chinese medicine with radiotherapy and chemotherapy comprehensive treatment of tumors to reduce the side effects of radiotherapy and chemotherapy at the same time, significantly enhance the therapeutic effect, and the presence of a variety of anti-tumor active ingredients in *Schisandra chinensis* has a great potential for application.

At present, the research on the antitumor effect of *Schisandra chinensis* and its mechanism has been more abundant, and the study reveals that the polysaccharide and lignans in *Schisandra chinensis*, such as *Schisandra chinensis* A and *Schisandra chinensis* B, have significant antitumor effects. These components can inhibit the proliferation of tumor cells, promote apoptosis, enhance the sensitivity of chemotherapeutic drugs, and fight against the invasion and metastasis of tumor cells, to achieve the effect of enhancing the efficacy of treatment and reducing toxic side effects. The above pharmacological effects have been demonstrated in cell models or mouse models.

The antitumor effect of *Schisandra chinensis* is not only limited to the direct action on tumor cells, but also includes indirect mechanisms through the regulation of body immune response, antioxidant and free radical scavenging. At present, improving body immunity is a major direction in the study of antitumor drugs, which shows that the active ingredients in *Fructus schisandrae chinensis* have great research value and potential for clinical application.

2. Main active components of *Schisandra chinensis*

2.1. Schisandra chinensis methylin (SchA)

2.1.1. Affects the cell cycle of tumor cells

Studies have shown that Sch A inhibits the expression of Cyclin E, a key regulatory protein in the G1 phase, in a dose- and time-dependent manner, and significantly increases the number of ovarian cancer (OC) cells A2780 in the G0/G1 phases, while the number of apoptotic and necrotic cells (sub-G1 phase) remains unchanged [1].

2.1.2. Induction of tumor cell apoptosis

In the study of Qiuli et al, the expression of β -catenin in TPC-1 cells, a thyroid cancer cell line treated with Sch A, was significantly reduced. Sch A down-regulated the expression of miR429, which significantly inactivated the Wnt/ β -catenin and MEK/ERK signaling pathways in TPC-1 cells, and thus significantly up-regulated the expression of apoptosis-associated proteins, such as caspase3, 9, which significantly upregulated the expression of apoptosis-related proteins caspase3, 9, and increased the rate of apoptosis. And when SchA cisplatin is used in combination, the pro-apoptotic effect is significantly greater than that of a single drug [2-4].

2.2. Inhibition of tumor cell invasion

Some studies have confirmed that the expression levels of EGFR and SRC in Sch A-treated pancreatic cancer cells decreased significantly, while the expression of adhesion plaque-associated proteins p-Y397FAK and p-Y181Paxillin was significantly reduced, suggesting that Sch A may inhibit PANC-1 cell invasion by targeting the EGFR-SRC pathway and reducing the activation of adhesion plaque-associated proteins FAK and Paxillin, and thus inhibit the invasion of pancreatic cancer cells by targeting the EGFR-SRC pathway. Sch A may inhibit the invasion and migration of pancreatic cancer PANC-1 cells by targeting the EGFR-SRC pathway and reducing the activation of adhesion plaque-associated proteins FAK and Paxillin [5-8].

2.3. *Schisandra chinensis* B (Sch B)

2.3.1. *Pro-apoptotic effect*

Studies have shown that Sch B can significantly inhibit the proliferation of colorectal cancer SW620 cells, prompting their apoptosis, and the mechanism may be related to the down-regulation of the activation of the PI3K/Akt signaling pathway by Sch B, which then initiates apoptosis [9,10].

2.3.2. *Antioxidant effects*

It was found that Sch B intervention in cisplatin-induced oxidative stress injury in HK-2 cells can activate the Nrf2/ARE pathway, causing Nrf2 nuclear translocation, inducing the expression of downstream II-phase detoxification enzymes and some antioxidant target genes, scavenging of oxygen free radicals, improving the antioxidant capacity of the cells, and alleviating the nephrotoxicity of cisplatin, but the Nrf2/ARE will inhibit the apoptosis of the tumor cells at the same time, so its combination needs to be confirmed in clinical trials. However, Nrf2/ARE inhibits tumor cell apoptosis at the same time, so its combination needs to be confirmed by clinical experiments.

2.4. *Schisandra chinensis* polysaccharide

Fructus schisandrae chinensis polysaccharide was shown to inhibit hepatocellular carcinoma transplantation tumors in mice at high and medium doses. The high dose of Fructus schisandrae chinensis polysaccharide can enhance the spleen index of tumor-bearing mice extremely significantly, indicating that it can improve the body's immunity from the level of organ and thus achieve an indirect anti-tumor effect [11,12].

3. Mechanism of action

3.1. *Regulation of immune system*

Fructus schisandrae chinensis polysaccharide can indirectly inhibit tumor development by activating immune cells, and its intratumor and peritumor inflammatory response is more obvious, in the results of the study of (Yu He) et al. Fructus schisandrae chinensis polysaccharide in high and medium doses has an inhibitory effect on the transplantation of H22 hepatocellular carcinoma tumors in mice. The high dose of Fructus schisandrae chinensis polysaccharide can enhance the spleen index as well as thymus index of the tumor-bearing mice extremely significantly, indicating that Fructus schisandrae chinensis polysaccharide can enhance the immune ability of the organism at the organ level, thus exerting an indirect anti-tumor effect [13,14].

3.2. *Promote tumor cell apoptosis and inhibit tumor cell proliferation*

In a study by Qiuli et al, TPC-1, a thyroid cancer cell line treated with Sch A, significantly reduced the expression of β -catenin protein. β -catenin is a protein that plays a key role in intercellular junctions and signaling, and its multiple roles in tumor development have received widespread attention. β -catenin is a key component of the Wnt/ β catenin signaling pathway, which plays a crucial role in cell proliferation, differentiation and migration. When Wnt signaling is activated, β -catenin accumulates in the nucleus and binds to T-cell factor/lymphoid enhancer factor family (TCF/LEF) transcription factors to activate the expression of downstream genes. Sch A inhibited Wnt/ β -catenin and the MEK/ERK signaling pathway, which is closely related to tumorigenesis, in TPC-1 cells by decreasing the expression of miR429. ERK signaling pathway, which in turn promoted the expression of apoptosis-associated proteins caspase 3 and 9 [3-5].

Ji et al. showed that Sch A reduced cell viability of pregnant choriocarcinoma cells JEG-3 and BeWo in a concentration-dependent manner compared to control cells. The number of apoptotic cells was significantly increased in treated JEG-3 and BeWo cells, and the nuclei showed apoptotic features such as irregular edges, nuclear consolidation and nuclear fragmentation. Meanwhile, the expression levels of P53 and Bax proteins were significantly increased. Bax is a protein downstream of the P53 signaling

pathway, which acts to promote apoptosis and therefore inhibits tumorigenesis and development. In contrast, caspase-3 protein showed a significant breakage. The induction of tumor cell apoptosis by Schisandra chinensis ethanol can be achieved through the caspases-related pathway. The apoptotic process is mainly divided into two basic pathways: the extrinsic pathway, which relies on the activation of cell-surface death receptors, such as Fas and tumor necrosis factor receptor family (TNFR), triggering a series of reactions to promote apoptosis; and the intrinsic pathway, also known as the mitochondrial pathway, which involves the regulation of bcl-2, Bax and other factors bcl-2 is an apoptosis inhibitory factor, and Bax is a pro-apoptosis factor. Its ratio determines whether a cell enters the apoptotic state [6-8]. Studies have shown that Sch B inhibits the proliferation and induces apoptosis of human hepatocellular carcinoma cell line sMMC-7721 through early caspase-3-dependent and caspase-9-independent pathways, accompanied by a decrease in the heat shock protein Hsp70. In addition, Sch B significantly increased the expression levels of caspase-3, 8, and 9 in hepatocellular carcinoma cells when used alone or in combination with cisplatin [9,10]. Gu Ying et al. showed that Sch B-promoted apoptosis was dependent on caspases, mainly through the mitochondrial pathway. Sch B also significantly enhanced the apoptosis-inducing effect of adriamycin in human hepatocellular carcinoma cell line SMMC7721, which was not related to the inhibition of P-glycoprotein (P-gp) or the generation of reactive oxygen species (ROS), but was achieved through the activation of caspase-9. 9 activation is realized [11].

Liu Xiaoni et al found that the compound Schisandrin B (a synthetic preparation containing Sch B, Aloe vera rhodopsin and Astragalus polysaccharides) was able to induce gastric cancer cell differentiation and apoptosis, and had a significant inhibitory effect on the proliferation of gastric cancer cell line sGC-7901. Compound Schisandrin B regulates the cell cycle by decreasing the expression of Cyclin D1 mRNA, blocking gastric cancer cells in the G0/G1 phase and preventing them from entering the S phase. In addition, compound Schisandrin B can also reduce the proliferative activity of gastric cancer cells by decreasing the expression of cell proliferation nuclear antigen (PCNA) protein. It has also been noted that Sch B improves the survival rate of transplanted ascites-type hepatocellular carcinoma mice by enhancing the phagocytosis function of abdominal macrophages and serum hemolysin content, and inhibits DNA synthesis in tumor cells, possibly by interfering with DNA metabolism [12,13].

Sch B interrupts the chain oxidation reaction of free radicals by easily losing electrons and converting them to substances that are harmless to the human body upon reaction with free radicals. Studies have shown that Sch B is one of the most potent antioxidant components of Schisandra chinensis lignans. It scavenges free radicals by activating the activities of endogenous glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT). Sch B significantly inhibited MDA production in hepatocytes due to free radical generating system induced by carbon tetrachloride and cysteine, showing a clear quantitative and quantitative effect relationship, which demonstrated its potent antioxidant ability. In addition, Sch B also significantly inhibited lipid peroxidation in rat brain, liver and kidney microsomes triggered by vitamin C-NADPH or Fe²⁺ and cysteine. Recent studies also found that Sch B increased intracellular glutathione levels, attenuated oxidative damage induced by solar radiation, and decreased elastase activity and matrix metalloproteinase-1 (MMP-1) expression in light-irradiated fibroblasts, suggesting that Sch B has a significant antioxidant function.

In addition, Sch A and Sch B have the potential to enhance the efficacy of mainstream drugs and reduce the toxic side effects when combined with other drugs, and Haibing et al. found that Sch A combined with gefitinib effectively inhibited the proliferation of Gefi-resistant non-small-cell lung cancer cells HCC827/GR in the G0/G1 phase and significantly increased the early and late apoptosis rates of the cells.

Schisandrin plays a key role in tumor therapy, and its ability to induce apoptosis is a crucial part of the treatment process. According to research literature, the combination of Sch B with cisplatin significantly enhances the expression of caspase-3, 8, and 9, which in turn activates these enzymes, ultimately leading to apoptosis in HepG2 tumor cells. In addition, it has also been shown that the combination of Sch B with 5-fluorouracil (5-FU) can effectively inhibit the proliferation of gastric

cancer cells and synergistically enhance cytotoxicity, leading to complete cell death. A study by Sun Deyi et al. found that even low concentrations of Sch B enhanced the internalization of adriamycin, and when the concentration reached 100 $\mu\text{mol/L}$, it was able to induce apoptosis in HepG2 cells in a dose-dependent manner [15].

Li Mei et al. found that when cisplatin induced oxidative stress injury in HK-2 cells, the intervention of Sch B was able to activate the Nrf2/ARE signaling pathway, promote the intranuclear translocation of Nrf2, induce the expression of downstream II-phase detoxification enzymes and antioxidant target genes enzymes, scavenge oxygen radicals, and improve the antioxidant capacity of the cells, thus attenuating the nephrotoxicity induced by cisplatin. Meanwhile, it was also found that Sch B at a concentration of 1.5-15 $\mu\text{mol/L}$ may act on the FAS-FADD-Caspase-8 signaling pathway to inhibit apoptosis induced by H₂O₂-induced hepatocyte death, showing its protective effect [16].

Adriamycin, as a widely used anthracycline anticancer drug, has significant therapeutic effects on a variety of cancers. However, it is more toxic to the heart, which is related to its induced production of free radicals in cardiac tissues. Sch B, with its potent antioxidant and free radical-scavenging abilities, may reduce the cardiotoxicity of adriamycin when used in combination with adriamycin, thus permitting adriamycin to exert its antitumor effects more effectively. Meng Xianjun et al. showed that Sch B-adriamycin liposomes were able to significantly reduce the acute toxicity of adriamycin and significantly improve its antitumor effect. Therefore, the combination of Sch B with other antitumor drugs may bring better therapeutic effects.

4. Reversal of multidrug resistance

According to reports, NF- κ B and Stat3 signaling pathways are key factors in regulating the expression of multidrug resistance genes.

In many kinds of cells, the abnormal activation of NF- κ B due to gene mutation and chronic inflammation can inhibit apoptosis, promote cell proliferation, accelerate tumor cell metastasis, increase the resistance of tumor cells to radiotherapy, and ultimately promote the occurrence and development of tumors. Therefore, NF- κ B activity inhibitors would be helpful for tumor prevention and treatment. However, the extensive and continuous blockade of NF- κ B activity, while exerting anti-tumor effects, will also affect the normal immune function, and even lead to immunodeficiency and apoptosis of healthy cells. The stat3 signaling pathway is also closely related to tumorigenesis, tumor development, and the emergence of drug resistance.

In the field of breast cancer therapy, studies have shown that inhibition of these signaling pathways can reduce the expression of P-gp, which recognizes and exocytoses a wide range of structurally different anticancer drugs, leading to a decrease in the accumulation of these drugs in tumor cells and affecting their therapeutic efficacy. Therefore, inhibiting the expression of P-gp protein can effectively reverse the generation of multidrug resistance in tumor cells [17,18].

Sch A has a significant blocking effect on the NF- κ B and STAT3 signaling pathways and inhibits the expression of P-gp. By competitively inhibiting the function of P-gp, it increased the accumulation of adriamycin (DOX) in drug-resistant MCF-7/DOX cells, which enhanced DOX-induced apoptosis and specifically reversed P-gp-mediated DOX resistance. In lung cancer treatment, Haibing et al. found that Sch A reversed multidrug resistance by inhibiting the IKK β /NF- κ B pathway, directly binding to IKK β , blocking Gefi-induced phosphorylation of IKK β and I κ B, and reducing intranuclear translocation of NF- κ B p65 through inhibition of the IKK β /NF- κ B pathway, as revealed by Sch A versus by surface plasmon resonance (SPR) experiments. Schisandra chinensis methylin made 5-FU-resistant cells more sensitive to 5-FU by up-regulating the expression of miR-195 in colon cancer cells HCT116 and SW480, while inhibiting the PI3K/AKT and NF- κ B signaling pathways. A study by Chen Peng et al. confirmed that Sch A in combination with gemcitabine enhanced the killing effect on cholangiocarcinoma TFK-1 cells, activated Caspase apoptosis signaling and targeted the EGFR/PI3K pathway, inhibited the activation of AKT and enhanced the pro-apoptotic effect of gemcitabine. Xue Yan et al. showed that Sch A enhanced gemcitabine-induced apoptosis in hepatocellular carcinoma Hepg2 cells by inhibiting the expression of β -catenin and TCF-4 proteins [19].

Schisandra chinensis B has also shown potential in tumor therapy. It has been shown that Sch B can significantly inhibit the efflux function of P-gp, thereby suppressing the phenomenon of multidrug resistance. The experiments of Xu Qiuling et al. found that the combination of Sch B and oxaliplatin (OXA) could reduce the expression of BCRP in human colon cancer cells and was proportional to the dose of Sch B, showing a sensitizing effect on OXA, reducing the toxicity of the chemotherapeutic drugs and enhancing its antitumor activity. The experimental results of Yan Meihua et al. showed that the combination of Sch B and paclitaxel (PTX) could increase the tumor growth inhibition rate by more than 10%, enhance the anti-tumor effect of PTX, and at the same time, reduce the side effects of the drug on mice with breast cancer.

5. Conclusion

This review summarizes the antitumor effects of the main active components in Schisandra chinensis and their related mechanisms. The main antitumor active components in Schisandra chinensis are schisandra chinensis acephaloside, schisandra chinensis ethoside, and schisandra chinensis polysaccharide. The active ingredients in Schisandra chinensis are Schisandra A, Schisandra B, and Schisandra polysaccharides, which work by inhibiting tumor cell growth, promoting apoptosis, and reversing multidrug resistance. The apoptosis-promoting effect is the most common pharmacological effect among the active ingredients of Schisandra chinensis, and its mechanism of action is to increase the ratio of Bax to Bcl-2 to achieve the effect of apoptosis-promoting. Thus, the effect of Schisandra chinensis active ingredients on Bax and Bcl-2 is an important research direction to study the anti-tumor mechanism of Schisandra chinensis.

At present, the anti-tumor mechanism of Schisandra chinensis and even traditional Chinese medicine are mainly focused on the anti- multidrug resistance and its apoptosis-promoting activity, which can be shown in the study of the anti-tumor of the natural products of traditional Chinese medicine, and the lower toxicity of the natural products of traditional Chinese medicine, which also makes the direction of its use in the direction of the combination of drugs with a great prospect for application, such as the text of the Schisandra chinensis mentioned in the text of the B, in the mainstream drug cisplatin combination with the inhibition of tumor growth effect of the very good. tumor growth. Although the effects of the active ingredients of Schisandra chinensis have been demonstrated in tumor cell models as well as mouse models, there is a lack of clinical studies. Therefore, the efficacy of Fructus schisandrae chinensis is still in the theoretical stage and needs to be further verified by clinical experiments.

References

- [1] Zhou Y & Wang Y 2019 Schisandrin A inhibits triple negative breast cancer cells by regulating Wnt/ER stress signaling pathway Biomedicine & Pharmacotherapy 115 108922
- [2] Brady H J M & Gil-Gómez G 1998 Molecules in focus Bax The pro-apoptotic Bcl-2 family member Bax The International Journal of Biochemistry & Cell Biology 30 6 647-650
- [3] Antonsson B et al 1997 Inhibition of Bax channel-forming activity by Bcl-2 Science 277 5324 370-372
- [4] Bonni A 1999 Cell survival promoted by the Ras-MAPK signaling pathway by transcription-dependent and -independent mechanisms Science 286 5443 1358-1362
- [5] Ding W X et al 2004 Bid-dependent generation of oxygen radicals promotes death receptor activation-induced apoptosis in murine hepatocytes Hepatology 40 2 403-413
- [6] Ding Q L et al 2019 Schizandrin A inhibits proliferation migration and invasion of thyroid cancer cell line TPC-1 by down regulation of microRNA-429 Biomedicine & Pharmacotherapy 497-508
- [7] Ji Z N & Liu G Q 2002 Reversal of multidrug resistance mediated by P-Glycoprotein Chinese Journal of Clinical Pharmacology and Therapeutics 7 3 269-272
- [8] Shen Y Y et al 2019 Inhibition of migration and invasion of pancreatic cancer PANC-1 cells by Schisandrin A and its mechanism Tumor 39 10 775-783

- [9] Liu X N Zhang C Y Li Y Z et al 2007 Inhibition of gastric cancer cell proliferation in vitro by compound Schisandra B and its components *World Chinese Journal of Digestology* 15 23 2526-2529
- [10] Kumar K J S Liao J W & Hsiao J H et al 2012 Hepatoprotective effect of lucidone against alcohol-induced oxidative stress in human hepatic HepG2 cells through the up-regulation of HO-1/Nrf-2 antioxidant genes *Toxicology in vitro* 26 5 700-708
- [11] Yu H Li J & Qi Y 2010 Inhibitory effect of Schisandra chinensis polysaccharides on tumor growth in liver cancer mice and its immunological mechanism *Chinese Medicine Information* 27 2 26-27
- [12] Xu Q L Jin X D Guo R et al 2011 Reversal of multidrug resistance in human colon cancer cells by Schisandrin B *China Food & Nutrition* 17 12 64-66
- [13] Yu S Y & Yu Z A 2006 Effect of Danshen Pian on the volume of infarction and the expression of apoptosis-related proteins bcl-2 and caspase-3 in rats with focal cerebral ischemia *Chinese Traditional Patent Medicine* 28 9 3
- [14] Yamamoto Y & Gaynor R B 2001 Role of the NF- κ B pathway in the pathogenesis of human disease states *Current Molecular Medicine* 1 3 287-296
- [15] Agarwal M L et al 1998 The p53 network *Journal of Biological Chemistry* 273 1 1-4
- [16] Lü D X et al 2009 Study on the expression of caspase-3 8 9 in apoptosis of H22 hepatocellular carcinoma xenografts induced by Schisandrin B combined with cisplatin *Journal of Gerontology* 29 4 416-418
- [17] Wang M Liu H Y Yan M et al 2010 Experimental study on the reversal of multidrug resistance in bladder tumors by Schisandrin B *Chinese Medical Frontier* 23 2
- [18] Wang P Zhang D Zhou Y Li Y Fang Y Wei H Ding Y & Sheng Y 2018 A well-defined biodegradable 123-triazolium-functionalized PEG-b-PCL block copolymer: facile synthesis and its compatibilization for PLA/PCL blends *Ionics* 24 3
- [19] Ji Z N & Liu G Q 2002 Reversal of multidrug resistance mediated by P-Glycoprotein *Chinese Journal of Clinical Pharmacology and Therapeutics* 7 3 269-272