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Review

Mechanism Underlying Antitumor Effects of Sinomenine*

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ABSTRACT Sinomenine (SIN) is a bioactive alkaloid compound extracted from a Chinese medicinal plant *Sinomenium acutum*. It is a multitarget antitumor natural substance. Various mechanisms have been proposed for the antitumor effects of SIN, such as direct cytotoxicity, induction of apoptosis, sensitization attenuating radiotherapy and chemotherapy, reversal of drug resistance, resistance to distant metastasis, and anti-angiogenesis. SIN can be used as a tumor cell killer and an adjuvant to radiotherapy and chemotherapy. However, recent studies are mostly limited to the basic experimental stage; no systematic clinical studies have yet been reported. Therefore, this paper aimed to review the mechanism underlying the antitumor effects of SIN by consulting relevant domestic and foreign studies and to provide a relevant reference for further development, use, and exploration of SIN.

KEYWORDS antitumor, mechanism, pharmacology, sinomenine, Chinese medicine

The alkaloid sinomenine (7,8-didehydro-4-hydroxy-3,7-dimethoxy-17-methyl morphinane-6-one, $C_{19}H_{23}NO_4$) is extracted from the Chinese medical plant *Sinomenium acutum*. It has been used to treat neuralgia and rheumatic diseases in China for more than 2000 years. The pure alkaloid extract possesses anti-inflammatory, immunoregulatory, mild sedative and analgesic properties due to its chemical structure, which is similar to that of morphine.[1,2] Sinomenine (SIN) has been widely used in the last 30 years for treating rheumatoid arthritis and mesangial proliferative nephritis due to its excellent therapeutic effects and minimal side effects.[3,4] Some new pharmacological actions and mechanisms have been discovered with the in-depth study of SIN in recent years. Also, its antitumor effect, in particular, has received increasing attention from scholars at home and abroad. Many experimental studies have demonstrated a significant inhibitory effect of SIN on lung cancer, breast cancer, liver cancer, gastric cancer (GC), and other tumors.[5] Therefore, this paper aimed to review the mechanism underlying the antitumor effects of SIN by consulting relevant domestic and foreign studies and to provide a relevant reference for further development, use, and exploration of SIN.

Overview of SIN

Inhibition of Tumor Cell Proliferation and Induction of Tumor Cell Apoptosis

A large number of *ex vivo* studies showed that SIN inhibited tumor cell proliferation, induced tumor cell apoptosis, and exerted its antitumor effects via various pathways. Yang, et al[6] found that SIN (8 and 10 mmol/L) could block the G_1 phase *in vitro*, reduce the level of cyclooxygenase-2 (COX-2), and inhibit the proliferation of human colon cancer cell line SW1116. *In vivo* experiments also confirmed that SIN (25, 50, and 100 mg/kg) could inhibit tumor growth in a time- and dose-dependent manner. Its molecular mechanisms might be associated with the inhibition of COX-2 levels, increased expression of p21, and decreased expression of cyclin D1 and cyclin E. Lv, et al[7] found that the overexpression of COX-2 is associated with enhanced proliferation and angiogenesis of GC. Human gastric adenocarcinoma SGC-7901 cells were treated with different concentrations of SIN (0.125, 0.25, 0.5, and 1 mmol/L). The results showed that SIN inhibited the proliferation of SGC-7901 cells in a time- and dose-dependent manner. The expression of COX-2 was inhibited by SIN in a dose-dependent manner at both the mRNA and protein levels. These findings

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indicated that the protective effects of SIN were mediated through inhibiting the expression of COX-2, suggesting a novel therapy for inflammation-mediated gastric adenocarcinoma. Jiang, et al[8] reported that SIH potently inhibited the viability of glioblastoma U87 and SF767 cells *in vitro* and did not cause caspase-dependent cell death, as demonstrated by the absence of significant early apoptosis and caspase-3 cleavage. Instead, SIN activated an autophagy-mediated cell death pathway. SIN-mediated autophagy in the two cell lines was implicated in the generation of reactive oxygen species (ROS), suppression of protein kinase B (Akt)–mammalian target of rapamycin (mTOR) pathway, and activation of c-Jun N-terminal kinase (JNK) pathway. *In vivo* studies also found that SIN effectively suppressed glioblastoma growth without exhibiting any significant toxicity. Therefore, this study revealed a novel mechanism of action of SIN in cancer cells via the induction of autophagy through the generation of ROS and activation of autophagy–lysosome pathway, providing a new potential therapeutic agent for treating human glioblastoma.

Apoptosis is one of the ways of programmed cell death. Drug-induced apoptosis is an important approach for cancer treatment. Tumors are caused by uncontrolled growth and excessive proliferation of cells. From the perspective of apoptosis, tumor development is a result of the inhibition of apoptosis and failure of normal cell death clearance. At present, inhibition of anti-apoptotic activity has become a therapeutic hotspot for inducing apoptosis and selectively killing tumor cells.

SIN (0.25, 0.5, and 1 mmol/L) was found to inhibit cell viability, induce G_1/S cell cycle arrest, cause cell apoptosis, and induce checkpoint gene protein (ATM)/cell cycle checkpoint kinase 2 (Chk2)- and anthrax toxin receptor (ATR)/Chk1-mediated DNA-damage response in breast cancer cell lines MDA-MB-231 and MCF-7. Its molecular mechanism of action was related to the induction of ROS production and activation of mitogen-activated protein kinase apoptosis-related signaling pathways. At the same time, the overall experimental findings showed that SIN (75 and 150 mg/kg) exerted a significant antitumor effect on an MDA-MB-231 xenograft tumor nude mouse model, further verifying the results of *in vitro* studies.[9] Further, SIN (0.5, 1, and 2 mmol/L) inhibited the proliferation of human hepatocellular carcinoma cell lines Hep3B, SMMC7721, HepG2, MHCC97H, MHCC97L, HHCC, and BEL7402 cells *in vitro*. SIN promoted cell cycle arrest in the G_1 phase and sub-G_1 peak formation associated with the increased expression of p21 in Hep3B and SMMC7721 cells. Additionally, SIN induced caspase-dependent apoptosis, which involved the disruption of mitochondrial membrane potential, increased release of cytochrome C and Omi/HtrA2 from the mitochondria into the cytoplasm, downregulation of Bcl-2 and upregulation of Bax, activation of a caspase cascade (caspase-8, -10, -9, and -3), and decreased expression of surviving.[10] SIN (20, 40, 80, 120, 160, and 200 μg/mL) also exerted a similar effect on human lung cancer cell line NCI-H460 cells, inducing apoptosis through the mitochondrial pathway, including the collapse of mitochondrial membrane potential, release of cytochrome C, activation of caspase-9 and -3, and increase in Bax and decrease in Bcl-2 protein levels, thereby inhibiting tumor cell proliferation in a time- and dose-dependent manner.[11] Another study showed that the activation of the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt) and extracellular regulatory protein kinase signaling pathways antagonized SIN-induced lung cancer cell apoptosis.[12] Hence, SIN may serve as a promising chemo-preventive agent for lung carcinoma.

Autophagy is a highly conserved protein degradation pathway from yeasts to humans. It is essential to remove protein aggregates and misfolded proteins in healthy cells. Previous study showed that SIN reduced the viability by reducing the sphere-forming ability and enhancing the pro-apoptotic effect in renal cell carcinoma (RCC) cells in a dose-dependent manner. In addition, SIN significantly regulated the level of autophagy-related proteins with decreased expression of p62, and increased the expression of Beclin1 and LC3 Ⅱ/LC3 Ⅰ. Furthermore, PI3K/Akt/mammalian target of rapamycin (mTOR) pathway, the negatively regulated cell autophagy signaling pathway, was inhibited by SIN with decreased membrane translocation of Akt. This study demonstrated that SIN promoted apoptosis in RCC via enhancing autophagy through PI3K/Akt/mTOR signaling pathway.[13]

Sensitization Attenuating Radiotherapy and Chemotherapy

Chemotherapy is currently one of the main methods for cancer treatment. However, many antitumor drugs have some side effects and are

expensive. Therefore, searching for low-toxicity antitumor adjuvant drugs from low-priced Chinese herbal medicines has become a research hotspot. Modern experimental studies have demonstrated a synergistic effect of SIN with various antitumor drugs. Previous studies[14-16] showed that the combined effects of SIN and 5-fluorouracil (5-FU) on human colon cancer cell line LoVo, human esophageal cancer cell line Eca-109, and GC cell line MKN-28 *in vitro* and *in vivo* were greater than that if each was used alone. However, the combination did not improve the side effects of chemotherapy. The molecular mechanism might be related to the synergistic activation of mitochondrial apoptosis pathway, which is enhanced by the upregulation of the expression of Bax and downregulation of the expression of Bcl-2. In conclusion, SIN may serve as a promising chemotherapeutic agent in combination with 5-FU.

Radiation therapy is one of the most important treatments for unresectable and locally advanced esophageal squamous cell carcinoma (ESCC). SIN could inhibit the growth of ESCC cells and markedly increas their radiosensitivity by inducing G_2/M phase arrest. SIN combined with radiation therapy could also significantly increas ESCC cell apoptosis. The molecular mechanism by which SIN enhanced the radiosensitivity of ESCC cells may be related to the down-regulation of the expression of Bcl-2, cyclin B1, CDK1, Ku86, Ku70, and Rad51 and the up-regulation of the expression of Bax. SIN combined with radiation considerably could delay the growth of tumor xenografts *in vivo*. Therefore, SIN seems to be a prospective radiosensitizer for improving the effect of radiotherapy on ESCC.[17]

Reversal of Drug Resistance

Multidrug resistance (MDR) limits the efficacy of chemotherapy. The up-regulation of P-glycoprotein encoded by MDR1 gene results in a decrease in the concentration of drugs entering tumor cells, leading to MDR in tumor cells. A previous study showed that a multidrug-resistant human colon cancer cell line Caco-2 (MDR-Caco-2) was induced by gradually increasing the doxorubicin dose.[18] The study found over-expression of COX-2 and MDR-1 genes and activation of nuclear factor kappaB (NF-κB) pathway in MDR-Caco-2 cells. However, SIN (500 μmol/L) could inhibit the expression of NF-κB, decrease the protein expression of MDR-1, and down-regulate the expression of COX-2, which decreased the secretion of prostaglandin E_2 (PGE_2). Further, PGE_2 could enhance the drug resistance of Caco-2. Therefore, SIN could enhance the sensitivity of MDR-Caco-2 cells to doxorubicin and improve drug resistance via the aforementioned two pathways. Another study reported that SIN (100, 200, and 400 μg/mL) also induced tumor cell apoptosis by down-regulating the expression of P-glycoprotein and reversing the MDR status of human bladder cancer cell line 253J/DOX.[20]

Resistance to Distant Metastasis

Tumor invasion and metastasis lead to the death of cancer patients. Therefore, searching for new drugs against tumor invasion and metastasis is of great significance.

Osteosarcoma is the most common primary malignant tumor of the bone. The long-term survival of a patient with metastatic and recurrent disease continues to be unsatisfactory. Previous study[20] found that SIN (50, 100, and 400 μmol/L) inhibited proliferation by inducing S-phase arrest and suppressing the clone formation of osteosarcoma cell lines U2OS and HOS cells. The tested concentrations exhibited little cytotoxicity. Exposure to SIN resulted in suppression of invasion and migration in osteosarcoma cells and tube formation ability in the human umbilical vein endothelial cells (HUVECs) and U2OS cells. The molecular mechanism underlying its inhibitory effect on invasion was related to the inhibition of protein phosphorylation of CXC chemokine receptor 4 (CXCR4) and signaling and activator of transcription 3 (STAT3), besides the downregulation of the expression of matrix metalloproteinase-2 (MMP-2), MMP-9, receptor activator of NF-κB ligand (RANKL), and vascular endothelial growth factor (VEGF), thereby inhibiting RANKL-mediated osteoclastogenesis-induced bone destruction and VEGF-mediated neovascularization. At the same time, *in vivo* experiments also showed that SIN (150 mg/kg) inhibited the proliferation of osteosarcoma cells, osteoclastogenesis, and bone destruction.[20]

Song, et al[21] reported that SIN dose-dependently inhibited the invasion and migration of human breast cancer cell line MDA-MB-231. By using the co-immunoprecipitation technology, the study showed that SIN (0.25, 0.5, and 1 mmol/L) enhanced the

binding of NF-κB and its inhibitory protein IκB in a dose-dependent manner, suggesting that SIN had an effect on the inactivation of NF-κB. Western blot analysis and enzyme-linked immunosorbent assay results showed that the inhibitory effect of SIN was related to the phosphorylation of IκB kinase (IKK) and its negative regulatory protein CUE domain containing 2 (CUEDC2). The study also found that SIN blocked the expression of miR-324-5P and upregulated the expression of the target gene CUEDC2, thereby blocking the phosphorylation of IKK by changing the upstream pathway. Transfection with miR-324-5P inhibited the effect of SIN on the invasion and migration of MDA-MB-231 cells. Hence, SIN could inhibit the invasion and migration of breast cancer cell line MDA-MB-231 cells probably via the regulation of the IL4/miR-324-5p/CUEDC2 axis. Another study demonstrated a better inhibitory effect of SIN compared with cyclopamine on breast cancer metastasis to lungs *in vivo* and *in vitro*.[22]

Cancer stem cells are tumor cells with self-renewal and multi-differentiation potential. They are the origin of tumor occurrence and development, and may be the root of the initial tumor metastasis. SIN treatment inhibited breast cancer, human glioblastoma, and clear-cell RCC metastasis by inhibiting epithelial–mesenchymal transition and cancer stem cell properties without obvious hepatotoxicity and renal toxicity. Thus, SIN might serve as a new potential anti-metastasis agent for treating glioblastoma and breast cancer.[23-25]

Anti-angiogenesis

Angiogenesis is important for the development of tumors. Inhibiting the generation of tumor blood vessels has a deterrent effect on cancer progression, but the long-term use of anti-angiogenic drugs aggravates tumor blood vessel abnormalities, reduces oxygen supply, and produces hypoxia and acidic microenvironment, making the tumor cells more invasive and metastatic. It also blocks the delivery of drugs and oxygen and reduces the effect of chemotherapy. However, the rational use of anti-angiogenic drugs to repair abnormal tumor vasculature before vascular regression helps retain normal tumor blood vessels, which can effectively transport oxygen and drugs to tumor cells, thereby increasing the sensitivity of chemotherapy.[26-28] Angiogenesis is critical in the development of rheumatoid arthritis, and anti-angiogenic therapy has been proposed as a new therapeutic strategy for treating RA. In this study, SIN disrupted tube formation and suppressed chemotaxis in HUVECs and reduced neovascularization and microvascular outgrowth in rat aorta ring assay, suggesting that SIN may serve as a classic anti-angiogenic drug.[29]

In a previous study, SIN (100 mg/kg) was intraperitoneally injected into the mouse model of 4T1 transplanted BALB/c mouse breast cancer cell line for 14 days, which significantly inhibited tumor growth and reduced tumor migration.[30] The mechanism of action might be related to the induction of the normalization of blood vessels, enhancement of tumor perfusion, improvement in the efficacy of chemotherapy, and tumor immunity. In addition, the effect of SIN on tumor vasculature stems in part from its ability to restore the balance between pro-angiogenic (bFGF) and anti-angiogenic (PF4) factors. However, SIN (200 mg/kg) did not show similar inhibitory effects during the development of tumors, which might be due to excessive blood vessels, up-regulation of recombinant human granulocyte colony-stimulating factor, and down-regulation of the immunosuppressive microenvironment induced by the expression of recombinant human granulocyte-macrophage colony-stimulating factor protein. Therefore, SIN at specific concentrations exerts its antitumor effect by inhibiting angiogenesis and inducing the normalization of blood vessels, thereby enhancing chemosensitivity and tumor immunity. In addition, SIN could inhibit bone destruction stimulated by osteoclastogenesis and VEGF-related neovascularization *in vitro* and *in vivo*. Hence, it might serve as a new potential anti-angiogenic agent for treating osteosarcoma and breast cancer.[31]

Future Perspectives

Many antitumor drugs have limitations, including immune suppression, toxicity, and side effects. Therefore, finding some new antitumor drugs and methods, reducing the toxic side effects of chemotherapy, and improving the quality of life of patients are the targets of medical research. Chinese medicine is associated with thousands of years of Chinese culture and is highly popular due to its abundant resources and low prices. It has broad application prospects in treating cancer.[5]

Recent findings on the antitumor effect of SIN have been encouraging. SIN is an effective

antitumor agent, which works by inhibiting tumor cell proliferation, inducing tumor cell apoptosis, promoting normalization of tumor blood vessels, inhibiting tumor cell invasion and migration, and inducing MDR of tumor cells. Its mode of action has multitarget and multipath characteristics. At the same time, SIN can be combined with a variety of chemotherapeutic drugs to take effect. Further, SIN also has an obvious analgesic effect on postoperative pain.[32] With no addictive nature, SIN can also reduce morphine dependence and improve withdrawal symptoms.[33] Thus, SIN has a great potential for application in the clinical treatment of cancer (Figure 1).

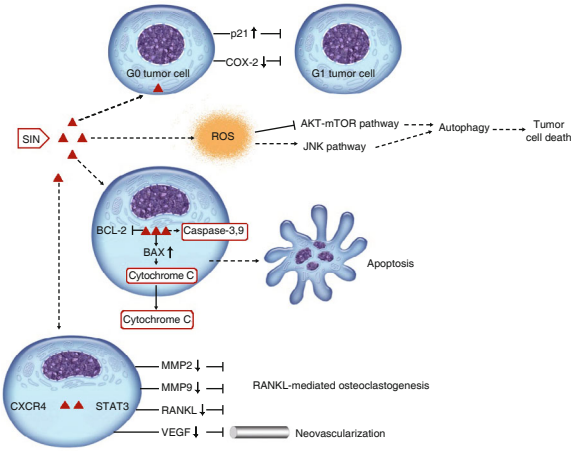

Figure 1. Mechanism Underlying Antitumor Effect of SIN

Notes: SIN: sinomenine; VEGF: vascular endothelial growth factor. SIN reduces the level of cyclooxygenase-2, which is associated with enhanced proliferation and angiogenesis. SIN also induces autophagy through the generation of reactive oxygen species, activation of autophagy–lysosome pathway, suppression of Akt-mTOR pathway, and activation of JNK pathway. It promotes cell cycle arrest in the G_1 phase and sub-G_1 peak formation associated with the increased expression of p21. It can induce apoptosis through the mitochondrial pathway by disrupting the mitochondrial membrane potential, releasing cytochrome c, activating caspase-9 and -3, and increasing the levels of Bax and decreasing the levels of Bcl-2. The mechanism underlying its inhibitory effect on invasion is related to the inhibition of protein phosphorylation of CXCR4 and STAT3, besides the downregulation of the expression of MMP-2, MMP-9, RANKL, and VEGF, thereby inhibiting RANKL-mediated osteoclastogenesis-induced bone destruction and VEGF-mediated neovascularization.

Although modern science and technology methods have been used to clarify the pharmacological basis of the antitumor effect of SIN, still some limitations exist. (i) The methods used in some experimental studies are relatively time-consuming, and the number of high-quality experimental studies is small, demanding further in-depth investigations. (ii) The mode of antitumor effects of SIN has multipath and multitarget characteristics; hence, the design of future studies should take into account the effects of various pathways. (iii) Recent studies are mostly limited to the basic experimental stage, and no systematic clinical studies have yet been reported. (iv) The impact of SIN on the tumor microenvironment remains unclear and requires further exploration.

Therefore, the pharmacology, pharmacokinetics, and pharmacodynamics of SIN need to be further studied to fully explore the potential mechanism underlying its antitumor effects and clinical application value.

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