

Anti-tumor Pharmacological Effects and Molecular Mechanisms of Ailanthone

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Abstract Ailanthone is a triterpenoid compound isolated from the traditional Chinese medicinal plant *Ailanthus altissima*, which exhibits broad-spectrum anti-tumor activity. This paper reviews its mechanisms of action against lung cancer, melanoma, prostate cancer, nasopharyngeal carcinoma, and tongue squamous cell carcinoma. Ailanthone blocks cell migration and invasion by inhibiting cell proliferation, inducing G₀/G₁ phase cell cycle arrest, upregulating Bax/Caspase-3, downregulating Bcl-2 to activate the mitochondrial apoptotic pathway, and reducing the expression of MMP-2/MMP-9 as well as the activation of the PI3K/AKT signaling pathway. It also inhibits DNA replication through the downregulation of RPA1. Current research mainly involves *in vitro* studies, while the detailed molecular mechanisms and *in vivo* evaluations require further investigation. This review offers a theoretical foundation for future research and the development of novel therapeutic agents.

Key words Ailanthone, Anti-tumor, Cell proliferation, Apoptosis

1 Introduction

Ailanthus altissima is primarily distributed in northeastern and central China, as well as in the Taiwan region of China. It has pharmacological properties including heat clearance, dampness elimination, regulation of liver blood to control leukorrhea, and the ability to arrest diarrhea and bleeding^[1]. Ailanthone, a major triterpenoid compound isolated from *A. altissima* and also known as quassin, is easily soluble in alcohol and ether solvents, with limited solubility in water. Contemporary pharmacological research has showed that ailanthone exhibits anti-tumor activity by mechanisms such as inhibition of cell proliferation, induction of apoptosis, and ferroptosis. This article presents a systematic review of recent advances in the anti-tumor effects and molecular mechanisms of ailanthone, aiming to provide a theoretical foundation for its further development and clinical application.

2 Anti-lung cancer effect and its molecular mechanism

Lung cancer is a malignant tumor originating from the bronchial mucosa or pulmonary glands. Clinically, it frequently manifests as a persistent cough^[2]. Through the CCK assay, Fan Minhui *et al.*^[3] found that the inhibitory effect of ailanthone on the proliferation of H460 cells was concentration-dependent (0.2, 0.4, 0.6, 0.8, and 1.0 μM). Results from the Cultrex cell migration and invasion assays revealed a significant reduction in the migra-

tion and invasion rates of H460 cells following treatment with ailanthone. Western blot analysis further indicated that ailanthone downregulated the expression levels of phosphorylated SRC (P-SRC), phosphorylated AKT (P-AKT), and Cyclin D1, suggesting that its anti-lung cancer effects are mediated through the inhibition of proliferation and migration, as well as the induction of cell cycle arrest.

Ni Zhongya^[4] investigated the inhibitory effects of ailanthone on the proliferation of H1299 and H1975 cells using the BrdU assay. The findings showed that ailanthone suppressed the proliferation of these cells in a concentration-dependent manner (0.625, 1.25, and 2.5 μM). Flow cytometric analysis revealed that, compared to the control group, the proportion of cells in the S phase of the cell cycle decreased as the concentration of ailanthone increased, indicating an inhibition of DNA replication in H1299 and H1975 cells. Western blotting and real-time quantitative polymerase chain reaction (qPCR) analyses were further conducted to assess the regulatory effects of ailanthone on key factors involved in the DNA replication signaling pathway. The results indicated that treatment with ailanthone (0.625, 1.25, and 2.5 μM) significantly reduced both protein and mRNA expression levels of replication protein A1 (RPA1) in H1299 and H1975 cells. These findings illustrate that ailanthone exerts anti-lung cancer effects by inhibiting DNA replication in these lung cancer cell lines.

Wu Cui^[5] detected the inhibitory effects of ailanthone on the proliferation of lung cancer cell lines A549 and H1299 using the MTT assay. The findings displayed that ailanthone suppressed the proliferation of A549 and H1299 cells in both a concentration-dependent manner (0, 0.25, 0.5, 1, 2, and 4 μM) and a time-dependent manner (24, 48, and 72 h). Cell scratch and Transwell assays were further employed to assess the impact of ailanthone on the migratory and invasive capacities of these human lung cancer cells. Results indicated that, relative to the control group, increasing concentrations of ailanthone significantly reduced the

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scratch healing rate and the number of transmembrane cells in both A549 and H1299 cell lines. Further analysis of cell cycle alterations via flow cytometry revealed a decrease in the proportion of cells in the S phase and an increase in the G_0/G_1 phase population in both cell lines. These findings show that ailanthonone exerts anti-lung cancer effects by inhibiting proliferation, migration, and invasion of A549 and H1299 lung cancer cells.

Di Jinna *et al.*^[6] examined the inhibitory effects of ailanthonone on the proliferation of lung cancer A549 cells using the CCK-8 assay. Their findings demonstrated that ailanthonone inhibited A549 cell proliferation in both a concentration-dependent manner (0, 2, 4, 6, 8, and 10 μM) and a time-dependent manner (24, 48, and 72 h). The apoptosis-inducing effect of ailanthonone on A549 cells was assessed via flow cytometry, revealing a significant increase in apoptosis rates correlating with higher concentrations of ailanthonone compared to the control group. Furthermore, Western blot analysis was employed to evaluate the expression levels of apoptosis-related proteins in A549 cells following treatment with ailanthonone (0, 2, 4, 6, 8, and 10 μM). The results indicated a significant downregulation of B-cell lymphoma 2 (Bcl-2) and a significant upregulation of Bcl-2-associated X protein (Bax). These findings indicate that ailanthonone exerts anti-lung cancer effects by inhibiting A549 cell proliferation and inducing apoptosis.

3 Anti-melanoma effect and its molecular mechanism

Melanoma, a highly malignant tumor originating from melanocytes in the skin, often manifests as irregular alterations in the morphology of pre-existing nevi. Through the CCK-8 assay, Zhou Zhengwei *et al.*^[7] found that ailanthonone inhibited the proliferation of A375 cells in a concentration-dependent manner (0.25, 0.5, 1, 2, and 4 $\mu\text{mol/L}$). The inhibitory effect of ailanthonone on the invasive capacity of A375 cells was assessed using a Transwell assay, revealing a significant reduction in invasion rates correlating with increasing concentrations of ailanthonone compared to the control group. Protein immunoblotting assays indicated that treatment with ailanthonone (0.25, 0.5, 1, 2, and 4 $\mu\text{mol/L}$) significantly downregulated the expression levels of matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9) in A375 cells. These findings suggest that ailanthonone exerts anti-melanoma effects by inhibiting both the proliferation and invasion of A375 cells.

Through the MTT assay, Chen Xiaoyu^[8] confirmed that ailanthonone inhibited the proliferation of A375 cells in a concentration-dependent manner (0, 4, 8, 12 μM). Apoptosis in A375 cells treated with ailanthonone was assessed via flow cytometry, revealing a significant increase in apoptotic cells corresponding to higher concentrations of ailanthonone compared to the control group. Western blot analysis was conducted to evaluate the expression of apoptosis-related proteins in human melanoma A375 cells following ailanthonone treatment. The findings showed that ailanthonone exposure led to higher protein levels of Bax and Caspase 3, while the

expression of Bcl-2, p-AKT, phosphorylated extracellular signal-regulated kinase (p-ERK), and phosphatidylinositol 3-kinase (PI3K) decreased significantly. These results state that ailanthonone exerts anti-melanoma effects by inhibiting proliferation and inducing apoptosis in human melanoma A375 cells.

Through the CCK-8 assay, Liu Wenjing *et al.*^[9] found that ailanthonone inhibited the proliferation of B16 and A375 cells in a concentration-dependent manner (0.25, 0.5, 1, 2, 4, 8 and 16 μM). Flow cytometry analysis revealed that, relative to the control group, increasing concentrations of ailanthonone resulted in a decrease in the proportion of cells in the S phase and an increase in the G_0/G_1 phase population in both B16 and A375 cells. Further investigation using Western blotting showed that ailanthonone treatment significantly upregulated the expression of the cyclin-dependent kinase inhibitor p21, while markedly downregulating the levels of Cyclin E and Cyclin B proteins in these cells. These findings suggest that ailanthonone exerts anti-melanoma effects by inhibiting the proliferation of mouse B16 and human melanoma A375 cells through the induction of cell cycle arrest.

4 Anti-prostate cancer effect and its molecular mechanism

Prostate cancer is a malignant tumor originating in the prostate gland of males. Early clinical symptoms are often inconspicuous, but as the disease advances, patients may experience increased urinary frequency, urgency, and other urinary abnormalities. Bao Xizhao *et al.*^[10] investigated the inhibitory effects of ailanthonone on the proliferation of prostate cancer 22RV1 cells using the MTT assay. Their findings demonstrated that ailanthonone inhibited 22RV1 cell proliferation in both a concentration-dependent manner (0.4, 0.8, and 1.0 $\mu\text{mol/L}$) and a time-dependent manner (24, 48, and 72 h). The apoptosis-inducing effect of ailanthonone on 22RV1 cells was assessed via flow cytometry, revealing a significant increase in apoptosis rates of 22RV1 cells correlating with higher concentrations of ailanthonone compared to the control group. Real-time quantitative PCR analysis was employed to evaluate the impact of ailanthonone on the mRNA expression levels of genes associated with the endogenous androgen receptor (AR) signaling pathway in 22RV1 cells. Treatment with ailanthonone (0.4, 0.8, and 1.0 $\mu\text{mol/L}$) resulted in a significant upregulation of NDRG1 mRNA expression, alongside a marked downregulation of PSA, FKBP5, and SLC45A3 mRNA levels. These results suggest that ailanthonone exerts its anti-tumor effects on prostate cancer 22RV1 cells by inhibiting proliferation and promoting apoptosis.

He Yundong^[11] tested the inhibitory effects of ailanthonone on the proliferation of prostate cancer 22RV1 cells using the sulforhodamine B (SRB) assay. The results showed that ailanthonone suppressed the proliferation of 22RV1 cells in a concentration-dependent manner (0.05, 0.1, 0.2, and 0.4 $\mu\text{mol/L}$). The inhibitory effect of ailanthonone on the migration of 22RV1 cells was assessed via Transwell assay, revealing a significant decrease in the

invasion rate of these cells compared to the control group, correlating with increasing concentrations of ailanthone. Western blot analysis was employed to evaluate the impact of ailanthone on AR protein expression in 22RV1 cells. Treatment with ailanthone (0.05, 0.1, 0.2, and 0.4 $\mu\text{mol/L}$) resulted in a marked down-regulation of AR protein levels. These findings illustrate that ailanthone exerts anti-prostate cancer effects by inhibiting both the proliferation and migration of prostate cancer 22RV1 cells.

5 Anti-nasopharyngeal carcinoma effect and its molecular mechanism

Nasopharyngeal carcinoma is a malignant tumor originating from the mucosa of the nasopharynx. Clinically, it is often characterized by symptoms such as aspirated bloody nasal discharge, unilateral nasal obstruction, tinnitus, and a painless cervical mass. Guo Juan^[12] evaluated the inhibitory effects of ailanthone on the proliferation of CNE-2 cells using the MTT assay. The findings demonstrated that ailanthone suppressed CNE-2 cell proliferation in both a concentration-dependent manner (0, 0.2, 0.4, 0.8, 1.6, and 3.2 μM) and a time-dependent manner (24, 48, and 72 h). Apoptosis induction by ailanthone in CNE-2 cells was assessed via flow cytometry, revealing a significant increase in apoptosis rates of CNE-2 cells correlating with higher ailanthone concentrations compared to the control group. Western blot analysis was employed to evaluate the expression of apoptosis-related proteins following treatment with ailanthone (0, 1.6, 3.2, and 6.4 μM). Results indicated a significant upregulation of Bax and Caspase 3, alongside a marked downregulation of Bcl-2. These findings indicate that ailanthone exerts anti-nasopharyngeal carcinoma effects by inhibiting proliferation and inducing apoptosis in human nasopharyngeal carcinoma CNE-2 cells.

6 Anti-tongue squamous cell carcinoma effect and its molecular mechanism

Tongue squamous cell carcinoma is the most prevalent malignant tumor of the oral cavity, originating from the squamous epithelium of the tongue mucosa. In clinic, it typically presents as persistent, non-healing ulcers on the tongue, cauliflower-like exophytic lesions, or erythro-leukoplakic patches, often accompanied by pain and masticatory dysfunction. Using the MTT assay, Wang Shuhan *et al.*^[13] showed that ailanthone inhibited the proliferation of Cal-27 and Tca8113 cells in a concentration-dependent manner. The apoptosis-inducing effect of ailanthone on these cells was assessed via Annexin V-FITC/PI double staining combined with flow cytometry, revealing a significant increase in apoptosis rates of Cal-27 and Tca8113 cells correlating with higher ailanthone concentrations. Further analysis by Western blotting indicated that treatment with ailanthone (0.25, 0.5, 1, 2, 4, 8, 16, and 32 μM) resulted in a marked upregulation of proteins Bax, cleaved Caspase-9, and cleaved Caspase-3, alongside a significant down-regulation of the protein Bcl-2 in both Cal-27 and Tca8113 cells.

These findings suggest that ailanthone exerts anti-tumor effects against tongue squamous cell carcinoma by inhibiting cell proliferation and inducing apoptosis in human tongue squamous cell carcinoma cell lines Cal-27 and Tca8113.

7 Prospects

Ailanthone is a triterpenoid compound extracted from *A. altissima* and is one of the primary active constituents of this plant. According to existing literature, this compound exhibits pharmacological activities including anti-tumor, anti-malarial, anti-allergic, and anti-ulcer effects. Nevertheless, current research mainly emphasizes the observation of drug efficacy, with insufficient systematic investigation into its molecular mechanisms of action and clinical application potential. Future studies should prioritize the integrative application of multidisciplinary approaches, such as molecular biology, structural biology, physiology, molecular pharmacology, and biopharmaceuticals, to advance fundamental research at the cellular, molecular, and animal model levels. Such efforts will provide a robust theoretical foundation for the comprehensive development of ailanthone.

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(From page 24)

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(From page 33)

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