Proceedings of the 4th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/40/20241225

Antitumor effects and molecular mechanisms of matrine

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Abstract. Matrine possesses various pharmacological activities such as anti-fibrosis, antiviral, anti-inflammatory, and immunosuppressive effects, especially playing a crucial role in antitumor activities. Studies have shown that matrine exerts antitumor effects through multiple pathways, including inhibiting tumor cell proliferation and metastasis, inducing tumor cell apoptosis, and suppressing tumor angiogenesis. This paper reviews the recent research progress on the antitumor effects and molecular mechanisms of matrine, aiming to provide theoretical references for its further research and application.

Keywords: Matrine, Antitumor effects, Mechanisms, Research progress

1. Introduction

Matrine, as a representative of quinolizidine alkaloids, belongs to the tetracyclic quinolizidine compound class (Figure 1), widely present in leguminous plants such as Sophora flavescens [1], Sophora tonkinensis [2], and Sophora alopecuroides [3]. First isolated and identified in 1958, matrine has a molecular formula of $C_{15}H_{24}N_{20}$ and a molecular weight of 266. Modern pharmacological studies have shown that besides its anti-inflammatory, antiviral, hepatoprotective, cardiovascular protective, and analgesic effects [4-7], matrine also exhibits significant inhibitory effects on various tumor cells cultured in vitro, with minimal damage to normal cells and even enhancing the immune function of cancer patients by increasing white blood cell counts [8-9]. Compared to traditional chemotherapy, matrine has lower toxicity and a lower chance of inducing drug resistance, thus possessing broader clinical application prospects. This paper provides a review of the research progress on the antitumor effects and molecular mechanisms of matrine.

DOI: 10.54254/2753-8818/40/20241225

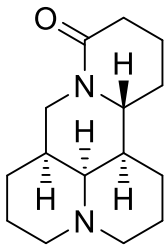

Figure 1. Chemical structure of Matrine

2. Antitumor Mechanisms of Matrine

2.1. Inhibition of Tumor Cell Proliferation

Tumors are products of excessive proliferation of cells from organ tissues under the long-term influence of external and internal harmful factors, and unrestricted proliferation is one of the important biological characteristics of tumor cells. Direct killing of tumor cells is the main action of many antitumor drugs. In vitro, matrine has a certain inhibitory effect on the proliferation of various tumor cells.

Fu Tingting et al. [10], by treating cervical cancer Hela cells with different concentrations of matrine, found that matrine significantly inhibited the proliferation of Hela cells in vitro. Moreover, after treatment with 1.0g/L matrine at different times, the phosphorylation levels of elF4E and 4E-BP1 proteins in Hela cells decreased, showing a time-dependent manner. This indicates that matrine may interfere with the expression of tumor cell proteins by reducing the phosphorylation levels of proteins associated with protein translation, thereby inhibiting tumor cell proliferation. ShaoHM [11] et al. selected three breast cancer cell lines and found that matrine significantly reduced the number of cells by using the MTT assay, confirming the effective inhibition of breast cancer proliferation by matrine. Additionally, Wang Yong et al. [12] demonstrated that different concentrations of matrine applied to liver cancer stem cells for 72 hours in vitro significantly inhibited their proliferation in a concentration-dependent manner. Cao et al. [13] experimentally verified that Src is a target of matrine in various tumor cells. Matrine can inhibit the kinase activity and tyrosine phosphorylation of Src, thereby downregulating the phosphorylation levels of downstream signaling pathways such as MAPK/ERK, JAK2/STAT3, and exerting inhibitory effects on tumor cells.

2.2. Induction of Tumor Cell Differentiation

Poor differentiation is also an important biological characteristic of tumor cells. Studies have shown that matrine can inhibit the proliferation of leukemia K-562 cells and induce differentiation accompanied by the loss of telomerase activity [14]. Additionally, matrine can induce partial differentiation of U937 cells, and its mechanism may be related to the upregulation of $p21^{Waf1/Cip1}$ expression [15]. Therefore, inducing tumor cell differentiation is a pathway to reverse tumor cells towards normal or near-normal cell differentiation, which has become a new strategy for tumor treatment.

2.3. Promotion of Tumor Cell Apoptosis

The dynamic balance between cell proliferation and apoptosis is an important mechanism for maintaining homeostasis in the body [16]. The occurrence of tumors is caused by the imbalance between the two, which is related to the weakening of pro-apoptotic gene expression or the enhancement of anti-apoptotic gene expression [17].

Dai et al. [18] found that matrine inhibits the proliferation of gastric cancer SGC-7901 cells, and the expression of FAS/FASL is positively correlated with the rate of cell apoptosis. Moreover, caspase-3 activity is also positively correlated with the rate of cell apoptosis. These findings indicate that matrine may promote apoptosis of gastric cancer cells by regulating the expression of FAS/FASL and caspase-3 activity. Luo Juan et al. [19], using flow cytometry to detect the apoptosis rate, and the colorimetric method to detect the relative activity of caspase-8, conducted single-factor analysis of variance using

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SPSS16.0 software. The results showed that matrine can induce apoptosis of SH-SY5Y cells by upregulating the activity of caspase-8, and its effect gradually increases with prolonged time. Liu Ye et al. [20], in their research on colon cancer, conducted experiments with matrine on SW-480 cells. The results showed that matrine at a concentration of 3 mg/mL can inhibit the proliferation of SW-480 cells. Protein detection showed that matrine can induce upregulation of p53 protein, increase the expression of downstream Bax, and induce apoptosis of cells. It has been experimentally verified that matrine has a downregulatory effect on miR-10b-5p in colon cancer, thereby upregulating the action protein PTEN of miR-10b-5p and inducing apoptosis of colon cancer cells [21]. The study by Zhang Xuelian et al. [22] demonstrates that matrine's regulatory effect on apoptosis can be achieved by reversing the high expression of circ_0013958 and low expression of miR-532-3p in ovarian cancer. Research has explored the pharmacological effects of matrine on ovarian cancer using CAOV-3 cells. The experimental results showed that matrine can significantly reduce the protein expression levels of Bcl-2 and Bcl-xl, and exert inhibitory effects on tumors through the p38 MAPK-mediated ERK/JNK signaling pathway [23]. The PI3K/Akt signaling pathway plays a certain role in mediating the apoptotic induction effect of matrine on acute lymphoblastic leukemia cells. Studies have reported an increase in the survival rate of mice in a mouse leukemia cell model, immunohistochemical results showed increased levels of caspase 3 and VEGF positive expression in bone marrow samples from matrine experimental group mice, and Western Blot results showed that matrine downregulated the protein levels of p-PI3K and p-Akt in bone marrow homogenates from experimental group mice [24]. Tang et al. [25] found that matrine can induce apoptosis of human thyroid cancer TCP-1 cells and BCPAP cells by downregulating the expression of miR-182-5p to upregulate cleaved caspase 3 and downregulate Bcl-2. This study proves that miR-182-5p is a potential target of matrine in the treatment of human thyroid cancer.

2.4. Inhibition of Tumor Cell Invasion and Metastasis

Tumor invasion and metastasis are among the main reasons for the high mortality rate of tumors, which are associated with certain genes and cytokines. Matrine can downregulate the expression of cytokines MMP-9 and MMP-2 in osteosarcoma cells and laryngeal squamous cell carcinoma cells [26-27].

Luo Yaoling [28] used Transwell assay to detect the effects of different concentrations of matrine on HepG2 cells and found that matrine inhibited the invasive ability of HepG2 tumor cells. Lin Shuyi et al. [29] established an in vitro model of tumor cell adhesion, migration, and invasion, and after staining with MTT, the number of adherent, migrating, and invading cells was indirectly reflected under a microscope at 400 times magnification using cell counting. They found that a certain concentration of matrine effectively inhibited the adhesion, migration, and invasion of Raji cells and K562 cells under low oxygen environment by inhibiting the expression of HIF-1α and thereby suppressing the expression of target genes such as VEGF. Zhang L J et al. [30] found that matrine could change the structure, subcellular distribution, expression, and phosphorylation of vasodilator-stimulated phosphoprotein (VASP) in gastric cancer cells, thereby inhibiting the adhesion and migration of cancer cells. Zhang et al. [31] found that matrine could increase the expression of downstream AHNAK by inhibiting the expression of miR-93-5p, thereby negatively regulating the proliferation and migration of gastric cancer cells. The team of Lin and Du [32] reported the pharmacological effects of matrine on colon cancer cells. Experimental results showed that matrine could synergistically inhibit the EMT process and the MAPK signaling pathway in cells, and suppress the formation of vasculogenic mimicry (VM) and cell invasion by downregulating Cldn9. Studies have shown that matrine has a time- and concentration-dependent inhibitory effect on the migration and invasion of SW480 cells. Matrine can increase the ratio of E-cadherin protein expression to N-cadherin protein expression, while the downregulation of TGF-β1, Smad 2/3, and p-Smad2/3 related protein expression levels suggests that matrine can inhibit cell EMT through the TGF-β1/Smad signaling pathway [33]. Similarly, research has shown that when matrine acts on gastric cancer cells, it can inhibit the EMT process of cancer cells and tumor invasion by regulating the TGF-β signaling pathway, exerting antitumor effects [34].

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2.5. Inhibition of Telomerase Activity

Telomerase is a ribonucleoprotein enzyme complex capable of adding telomeric repeat sequences (5-TTAGGG-3) to the ends of chromosomes. Telomerase reverse transcriptase (hTERT) is the catalytic subunit of telomerase and is a key enzyme that affects telomerase activity, playing an important role in maintaining chromosome stability and cellular viability [35]. Studies have found that after treating MCF-7 cells with different concentrations of matrine for 24h, 48h, and 72h, telomerase activity gradually decreases with increasing concentration and duration of matrine treatment, showing a positive correlation between dose-effect and time-effect [36-37]. Additionally, research suggests that matrine can significantly inhibit the cell cycle, and this mechanism may be related to the downregulation of telomerase reverse transcriptase expression [38].

2.6. Inhibition of Tumor Angiogenesis

Angiogenesis plays a crucial role in maintaining tumor growth. There are many factors involved in angiogenesis, with vascular endothelial growth factor (VEGF) being the most extensively studied. Matrine can inhibit tumor angiogenesis by downregulating the expression of VEGF. Luo et al. [39] demonstrated that matrine can reduce the transcription levels of VEGF and VEGFR1 mRNA and inhibit the activity of MMP-2 and MMP-9, thereby suppressing the proliferation of the breast cancer cell line MDA-MA-231.

2.7. Induction of Autophagy in Tumor Cells

Autophagy is closely associated with the occurrence and development of tumors. Autophagy in normal cells can maintain cellular integrity and stability, thereby inhibiting tumor initiation and metastasis. However, in tumor cells, autophagy functions to provide nutrients to cells and enable survival by evading apoptosis in a metabolic stress environment. Studies have shown that matrine can inhibit autophagy in tumor cells and trigger autophagic cell death. Matrine treatment of C6 glioma cells and HepG2 hepatocellular carcinoma cells results in the formation of numerous autophagic vacuoles within the cells, as observed by electron microscopy. Additionally, co-treatment with the autophagy inducer 3-MA significantly reduces matrine-induced autophagic vacuoles in HepG2 cells [40-41]. In human gastric cancer SGC7901 cells, matrine blocks autophagic degradation by altering the pH environment of lysosomes, leading to a decrease in the activity of lysosomal protein hydrolases and accumulation of autophagic vacuoles within the cells. Moreover, matrine increases the expression of the autophagy gene Beclin1 in a dose-dependent manner [42-43]. However, some studies have reported that matrine induces protective autophagy in SGC7901 cells, hindering the apoptosis process of gastric cancer cells [44]. Research by Jia Shaohua's team [45] has demonstrated an association between matrine-induced cellular autophagy and the PI3K/Akt signaling pathway. Experimental results show a dose-dependent upregulation of autophagy-related proteins LC3 and Beclin-1, along with a decrease in the phosphorylation expression of PI3K, Akt, and mTOR. Similarly, matrine can induce autophagy in breast cancer MCF-7 cells [46], cervical cancer Hela cells, and SiHa cells [47] by regulating the Akt/mTOR signaling pathway. In a study by Lv Yang et al. [48], matrine treatment led to a concentration-dependent decrease in the expression of the p65 protein in esophageal cancer Eca-109 cells, accompanied by an increase in the expression of LC3-II/LC3-I and upregulation of Beclin1 mRNA and protein expression. Detection of related pathway proteins showed an upregulation of the p-LKB1/LKB1 ratio and p-AMPK/AMPK ratio, and a downregulation of the p-mTOR/mTOR ratio, indicating the involvement of the LKB1/AMPK/mTOR signaling pathway in matrine-induced autophagy in Eca-109 cells.

2.8. Promotion of Host Anti-Tumor Immune Response

The functions of NK cells and T cells largely reflect the body's immune function, playing a crucial role in immune surveillance against tumors. Tumor cells inhibit the body's immune function by secreting immune suppressive factors, which is an important mechanism for tumor immune evasion. Huangfu Chaoshen et al. [49] conducted a study to observe the effects of matrine on tumor-infiltrating lymphocytes (TIL) in patients with liver cancer. They found that moderate concentrations of matrine

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could promote TIL proliferation and enhance in vitro antitumor activity. Matrine increased the number of $CD8^+$ immune cells and decreased the $CD4^+/CD8^+$ ratio, suggesting that matrine has a bidirectional regulatory effect on immune function. Application of moderate concentrations of matrine can stimulate the differentiation of $CD8^+$ cells, thereby enhancing the immune response against tumor cells.

2.9. Combination Therapy

Combining matrine with other anticancer drugs has shown excellent synergistic effects. Matrine combined with the histone deacetylase inhibitor, trichostatin A, significantly downregulates the expression of the anti-apoptotic protein Bcl-2 and upregulates the expression of the pro-apoptotic protein Bax in lung cancer A549 cells, thereby inducing apoptosis [50]. Hu et al. [51] found that in nude mice with gastric and pancreatic cancer SGC7901 cell xenografts, the combination of matrine and 5-fluorouracil exhibited significant synergistic effects. Although both drugs inhibited the proliferation of bone marrow cells in the mice, they did not damage quiescent bone marrow stem cells. Studies have reported that the combination of matrine with cisplatin can inhibit the growth of liver cancer by suppressing survivin protein and activating caspase cascade reaction, effectively exerting efficacy in mouse xenograft experiments [52]. Mo and Guo et al. [53] reported that combining matrine with cisplatin in a ratio of 2000:1 for the treatment of urothelial carcinoma of the bladder can induce cell cycle arrest, inhibit migration and invasion, and promote apoptosis in bladder cancer cells. Mechanistic studies confirmed that this synergistic effect is related to the regulation of the VEGF/PI3K/Akt signaling pathway. Additionally, the combination of matrine with Docetaxel effectively inhibits the proliferation, migration, and invasion of prostate cancer cells, induces apoptosis in DU145 and PC3 cells, alters the metabolism and survival environment of tumor cells, and ultimately exerts anticancer effects [54].

3. Conclusion

In summary, matrine exhibits a comprehensive and extensive anti-tumor effect, including inhibition of tumor cell proliferation, induction of tumor cell differentiation and apoptosis, inhibition of tumor cell invasion and metastasis, suppression of telomerase activity, and inhibition of tumor drug resistance, among other aspects. Additionally, it can enhance the body's immune function without significant toxicity or side effects. Matrine represents a promising anticancer drug with great potential for development, surpassing many conventional chemotherapeutic agents. Therefore, further exploration of matrine's inhibition of tumor growth and its regulatory effects on tumors, along with research focusing on enhancing its in vivo activity, combination therapy, and new formulations tailored to its characteristics, can fully harness the unique efficacy of traditional Chinese medicine in cancer treatment.

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