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Research Progress on the Anti-Breast Cancer Effect and Mechanism of Oxymatrine

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Abstract: Oxymatrine (OMT), an alkaloid derived from Sophora flavescens, possesses a diverse array of pharmacological activities, encompassing anti-inflammatory, antiviral, antitumor, and immune regulatory properties. In recent times, significant strides have been made in investigating the efficacy of OMT against breast cancer. OMT exerts its anticancer influence through various mechanisms, including inhibition of tumor cell proliferation, suppression of tumor cell invasion and migration, induction of tumor cell apoptosis, and disruption of the cell cycle. This article systematically reviews the underlying mechanisms of OMT in breast cancer therapy by conducting a comprehensive search across multiple databases, such as CNKI, Wanfang, and PubMed, utilizing keywords like "OMT," "breast cancer," "pharmacology," and "pharmacokinetics," as well as incorporating both Chinese and English terms for "OMT," "triple-negative breast cancer," and "breast cancer." The objective is to delve into the potential applications of OMT in breast cancer treatment and furnish a valuable reference for future clinical investigations exploring the utilization of OMT in this field.

Keywords: OMT; Breast Cancer; Mechanism of Action; Research Progress.

1. Introduction

Breast cancer, as one of the most prevalent malignant tumors among women, poses a significant threat to patients' physical and mental wellbeing. Its high morbidity and mortality rates are alarming, not only severely impacting patients' quality of life but also potentially imposing a substantial burden on families and society [1-3]. Currently, the therapeutic modalities for breast cancer encompass surgery, chemotherapy, radiotherapy, endocrine therapy, and targeted therapy; however, numerous challenges persist. Surgical intervention may fail to eradicate cancer cells entirely, resulting in recurrence. Chemotherapy and radiotherapy are frequently accompanied by severe adverse effects that deteriorate patients' quality of life. Furthermore, some patients exhibit drug resistance, significantly diminishing treatment efficacy. Given these circumstances, the pursuit of novel and more efficacious treatments has emerged as a top priority [4-6].

OMT, a naturally occurring alkaloid, has garnered significant attention due to its promising anti-tumor properties, particularly in combating breast cancer. Its distinctive chemical makeup and pharmacological attributes offer fresh perspectives in addressing the intricate challenges of breast cancer therapy [7-14]. This paper comprehensively reviews the inhibitory impact of OMT on breast cancer and delves into the pivotal molecular mechanisms that have been unravelled in recent years. Through a meticulous synthesis and analysis of existing literature, we further elaborate on OMT's modulation of breast cancer cell behaviors, encompassing proliferation, apoptosis, invasion, and metastasis, as well as its immunomodulatory effects and suppression of tumor angiogenesis. Additionally, we underscore the potential efficacy and synergy of OMT when combined with other anti-tumor agents. It is anticipated that this review will serve as a valuable resource for future endeavors in exploring the therapeutic application of OMT in breast cancer treatment, thereby contributing to the advancement of more efficacious therapeutic strategies."

2. Biological Characteristics of OMT

OMT, chemical name is 1,2,3,4,6,7,12,12 a-octahydro-1, 10-dihydroxy-6-methoxy-9, 11-dimethyl-3-(methylamino)-6h-pyridinium [1,2-a] pyridinium [3,4-c] quinazoline-12-one, it is an alkaloid derived from the leguminous plant Sophora flavescens. Matrine (MT) is widely distributed in China, Japan and Korea, and has a long history of medicinal use. The molecular formula of OMT is $C_{15}H_{24}N_2O_2$ and its molecular weight is 264.36 g/mol. Its structure contains a tetrahydroquinazolone skeleton, which has a certain lipid solubility, which makes OMT have good absorption and distribution characteristics in organisms [15].

OMT is white or light-yellow crystalline powder at room temperature, bitter taste, soluble in water and ethanol. Its stability is good, stored at room temperature is not easy to decompose. In pharmacological studies, OMT has shown a variety of biological activities, including anti-inflammatory, antiviral, anti-tumor and immunomodulatory activities. Its anti-tumor activity is mainly achieved by affecting the proliferation, differentiation, apoptosis and invasion of tumor cells [16].

3. Mechanism of OMT Against Breast Cancer

3.1. Inhibition of Tumor Cell Proliferation

Cancer cells have the ability to proliferate indefinitely and destroy normal cells, which is one of the reasons why malignant tumors are difficult to cure. Therefore, the search for drugs that can inhibit the infinite proliferation of tumor cells is an important direction for breast cancer treatment research [17].

Xu Xiao et al. found that different concentrations of OMT

significantly inhibited the proliferation of breast cancer MCF-7 cells within the concentration range of 0-32mg/ml ($P<0.05$), and the inhibitory effect of OMT on breast cancer MCF-7 cells was dose-dependent and time-dependent [18]. The main mechanism of action is to inhibit cell proliferation by the expression of related miRNA in OMT MCF-7 cells. OMT can significantly increase the expression level of miRNA-140-5P in MCF-7 cells, and overexpression of miRNA-140-5P can simulate the inhibitory effect of OMT on breast cancer cells, including reducing cell proliferation and promoting cell apoptosis. The target genes of miRNA-140-5P include TGFβR1 and FGF9, which play a key role in cell proliferation and apoptosis. Studies have shown that OMT can inhibit the proliferation and promote apoptosis of MCF-7 cells by regulating micrornA-140-5p (miRNA-140-5P) and its target genes. It has been reported that the PI3K/Akt signaling pathway plays a complex and extremely important role in regulating cell growth, apoptosis, proliferation and division [19]. Some studies have shown that the expression rate of PI3K in tumor cells is higher than that in normal cells, which indicates that PI3K is involved in activating the function of tumor cells, and inhibiting its expression may be an important strategy to fight cancer [20]. OMT inhibits the proliferation and invasion of tumor cells by inhibiting the PI3K/Akt signaling pathway. This pathway plays an important role in cell growth, survival and metabolism. OMT inhibits the proliferation of tumor cells by reducing the phosphorylation levels of PI3K and Akt [21]. Cell proliferation and division throughout the cell cycle are regulated by a complex mechanism composed of cyclin and cyclin-dependent protein kinase (CDK) [22]. Studies have shown that OMT can reduce the expression of MMP9 in gastric cancer cells. OMT significantly inhibited the migration and invasion of MCF-7 cells and the down-regulation of MMP9 expression. MMP9 is also downstream of PI3K/Akt, so OMT oxidation can inhibit the proliferation of breast cancer cells through the PI3K/Akt/ MMP9 signaling pathway. In addition, as indicated by western blotting, OMT significantly decreased PI3K expression in a dose-independent manner [23].

3.2. Inhibition of Fine Tumor Cell Metastasis and Invasion

The death of about 90% of patients with malignant tumors is related to the metastasis and invasion of cancer cells, which is a process of interaction between tumor cells and host cells. Tumor metastasis and invasion are a continuous biological event regulated by multiple factors, and inhibition of tumor metastasis and invasion is the key to anti-tumor therapy [24]. Many molecules and signal transduction pathways are involved in the adhesion, migration and invasion of tumor cells, the former including laminin, matrix metalloproteinases and their tissue inhibitors (MMPs/TIMPs), integrins, etc., the latter including focused adhesion kinase (FAK) pathway. FAK is a tyrosine kinase that mediates focused adhesion, and its phosphorylation and dephosphorylation play an important role in the migration and adhesion of malignant tumors [25].

OMT can effectively inhibit the mRNA transcription levels of endogenous proteolytic enzymes MMP-2 and MMP-9, exert important biochemical effects on the adhesion activity of proteins on the surface of tumor cells and the metastasis, proliferation and transformation ability of tumor cells, and indirectly inhibit the metastasis and invasion ability of breast cancer cells [26]. In addition, OMT can inhibit the adhesion, invasion and metastasis of various tumor cells. One of the most common ways to block tumor mechanisms is to regulate the activation of NF-κB signaling pathway induced by tumor necrosis factor. Inhibiting the expression of gene fragments related to the invasion-related regulatory genes MMP-9 and MMP-2 in tumor cells, thus blocking the adhesion and infiltration of malignant tumor cells or the spread and metastasis of cancer cells, thereby inhibiting the metastasis and proliferation of cells [27].

3.3. Induction of Tumor Cell Apoptosis

Apoptosis is a multi-gene controlled process, which can maintain the stability of various tissues and organs in the whole life process, and when the apoptosis process is in progress, the cell proliferation can be excessive, causing the occurrence of various tumors [28-29]. Therefore, promoting apoptosis of cancer cells is also one of the important research directions of anti-breast cancer therapy.

Both Bcl-2 and Bax belong to the Bcl-2 family, and the formation of homologous dimer can induce apoptosis, while the formation of heterodimer can inhibit apoptosis and participate in the regulation of apoptosis[30]. OMT can significantly down-regulate the expression of Bax and Bcl-2 in anti-apoptotic gene B-cell lymphoma in breast cancer cells MCF-7 cells, and promote the cleavage of polyadenosine diphosphoribose polymerase (PARP), a protein factor characteristic of apoptosis, thereby inhibiting the growth of breast cancer cells [31]. A significant decrease in the Bcl-2/Bax ratio was also observed in breast cancer cells treated with OMT, while the activities of cysteine protease caspase-3 and caspase-9 were significantly increased in the dosed group, but not in the control group [32]. Xu Xiao et al. found that OMT can effectively promote the expression of miRNA-140-5P in MCF-7 cells, and the relative expression level of miRNA-140-5P increases significantly with the increase of OMT dose, which may help regulate miRNA-140-5p and its target genes[33] .

3.4. Block the Tumor Cell Cycle

The process of cell division plays a crucial role in cancer progression. Normal cells have a controlled cell cycle, and problems in cell cycle regulation may lead to unlimited cell growth, proliferation, and malignant transformation [34].

The energy metabolism of tumor cells is different from that of normal cells. The metabolism of tumor cells adopts the "Warburg" effect of glycolysis to produce lactic acid in both aerobic and anaerobic environments [35]. Studies have shown that miRNA-122 is the regulatory non-coding RNA of PKM and CS, PKM and CS are important metabolic enzymes in the Warburg effect, and the high expression of miRNA-122 can significantly inhibit the expression of metabolic enzymes, thus inhibiting the occurrence of Warburg effect [36]. After treating MCF-7 cells with 5, 10, and 20μmol /L OMT, Wu et al.found that the expression of miRNA-122 was significantly increased, the proportion of G0 /G1 phase was significantly increased, while the cell viability was significantly decreased, and the invasion and cloning ability were significantly inhibited. The expression of PKM, CS and HK proteins in cells was significantly reduced, and the Warburg effect was reduced, and OMT played an anti-tumor role[37].

OMT can inhibit the expression of cyclin D1 and CDK2, which play a key role in the G1/S phase transition of the cell cycle, thus inhibiting the proliferation of breast cancer cells. Wu et al. found that the cell cycle of breast cancer cells treated with OMT was mostly blocked in the S phase. Mt and OMT

regulate cell cycle mainly by blocking the regulation of several signaling pathways such as PI3K/Akt, NF-κB, Notch and EGFR, and are accompanied by the regulation of miRNA expression, thus affecting the expression of cell cycle-related proteins[38] .

3.5. Inhibition of Tumor Angiogenesis

Tumor proliferation and metastasis are closely related to neovascularization, so inhibition of tumor neovascularization is an important target for anti-tumor. vascular endothelial growth factor (VEGF) and Ang-1, Ang-2 are the major VEGF promoting factors. The imbalance between angiogenic factors and inhibitory factors promotes the formation of neoplasms. It plays an important role in angiogenesis [39].

Studies [40] have shown that OMT may inhibit tumor angiogenesis by affecting the expression of key factors such as vascular endothelial growth factor (VEGF) and blocking the binding of VEGF and its receptor VEGFR2. In addition, OMT may further regulate tumor angiogenesis by affecting other angiogenesis related signaling pathways, such as PDGF/PDGFR, FGF/FGFR, and TGF-β/TβR. Due to the important role of tumor angiogenesis in tumor growth and metastasis, the anti-angiogenic effect of OMT may provide a new strategy for tumor therapy. Especially when traditional anti-angiogenic drugs have side effects or stability problems, OMT, as a natural compound, may become a new source of anti-tumor angiogenic drugs [41].

3.6. Enhance the Sensitivity of Chemotherapy Drugs

Chemotherapy as one of the main means of breast cancer treatment, although in many cases has achieved remarkable efficacy, but the generation of drug resistance is still a key factor restricting its efficacy. Improving the sensitivity of chemotherapeutic drugs and reducing drug resistance is one of the important directions of current cancer treatment research. OMT also shows its unique advantages in this respect. Clinical studies have proved that OMT can play an anti-tumor role in synergy with a variety of drugs [42].

Zhang Beibei et al. showed that OMT could reverse Bevacizumab induced EMT by inhibiting the abnormal activation of Wnt/β-catenin signaling pathway caused by Bevacizumab, thereby reducing the invasion and metastasis of MCF-7 cells[43] . The combination of the two drugs not only retained the anti-tumor effect of OMT , but also retained the anti-tumor effect of OMT . At the same time, the side effects caused by bevacizumab were reduced. The combination of OMT and astragaloside (As) not only improves the invasion and function of tumor infiltrating lymphocytes (TILs), but also significantly improves the anti-tumor effect, reduces tumor weight, volume and tumor index, and induces a large number of tumor cell apoptosis [44]. Ni Xue found that OMT combined with UTD1 can inhibit the expression of AKT, Bcl-2 and caspase-9 precursor proteins, and up-regulate the expression of phosphorylated caspase-3, suggesting that OMT combined with UDT1 regulates the PI3K/AKT signaling pathway. Activation of caspase cascade ultimately promotes apoptosis of MCF-7 cell line [45].

4. Summary and Prospect

In summary, OMT has significant pharmacological activity in anti-breast cancer, and its mechanism of action involves inhibiting tumor cell proliferation, inhibiting tumor cell invasion and migration, inducing tumor cell apoptosis, blocking cell cycle, inhibiting tumor angiogenesis and enhancing the sensitivity of chemotherapy drugs, etc. However, the following problems still exist when applied in clinical treatment of breast cancer: (1) At present, there are relatively few clinical studies on OMT treatment of breast cancer, and most of the studies have small sample sizes. Therefore, the reliability and universality of the research results are limited. (2) Lack of long-term follow-up data. (3) Due to individual differences, a large number of clinical trials are needed to conduct in-depth research and discussion on the route of administration, dosage and course of treatment. Future studies should further explore the optimal dose of OMT for long-term use and the synergistic effect of individualized administration and combination with other drugs, so as to improve the immunomodulatory function of tumor patients, induce residual cancer cells to differentiate into normal cells, prevent tumor recurrence or metastasis, and provide safer and more effective treatment options for breast cancer patients.

Conflicts of Interest

The authors declare that they have no conflict of interest.

Acknowledgments

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