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Research Progress on Traditional Chinese Medicine Intervention in Cisplatin Resistance of Ovarian Cancer

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Abstract: ***Ovarian cancer (OC) is one of the most common malignant tumors in clinical practice. Platinum-based combination chemotherapy, primarily cisplatin, is the first-line standard treatment regimen. However, acquired resistance developed during treatment has become a bottleneck limiting clinical efficacy. In recent years, numerous studies have found that Traditional Chinese Medicine (TCM) plays a significant role in enhancing the sensitivity of ovarian cancer cells to cisplatin. This article reviews the research progress on the mechanisms by which TCM monomers and compounds reverse cisplatin resistance in ovarian cancer cells, focusing on eight aspects: increasing intracellular drug concentration, reversing apoptosis inhibition, inhibiting epithelial-mesenchymal transition (EMT), inducing ferroptosis, regulating metabolic reprogramming, modulating intracellular autophagy, increasing DNA damage and inhibiting DNA repair, and intervening in resistance-related signaling pathways. The aim is to provide references for discovering safe and effective cisplatin resistance reversal agents.***

Keywords: Ovarian cancer, Cisplatin, Drug resistance, Traditional Chinese Medicine (TCM), Research progress**.**

1. Introduction

Ovarian cancer (OC) ranks as the eighth most common malignancy globally and is a leading cause of cancer-related death among women. Among gynecological malignancies, it has the third highest mortality rate, following cervical and endometrial cancers [1]. Due to its deep pelvic location, lack of specific early symptoms, and absence of effective screening methods, the majority of patients are diagnosed at advanced stages. The 5-year survival rate for advanced patients is only 29%, posing a severe threat to women's health [2]. OC is a heterogeneous disease comprising two main histological subtypes: epithelial ovarian cancer (EOC), accounting for approximately 90% of cases, and non-epithelial ovarian cancer, accounting for about 10%. EOC includes high-grade serous ovarian carcinoma (HGSOC), low-grade serous ovarian carcinoma (LGSOC), endometrioid carcinoma, ovarian clear cell carcinoma (OCCC), and mucinous carcinoma. HGSOC is the most common subtype, representing about 70% of EOC cases [3]. Current treatment for advanced OC primarily involves cytoreductive surgery and platinum-based combination chemotherapy, with cisplatin or its analog carboplatin used as first-line therapy [4]. While most newly diagnosed OC patients are highly sensitive to initial chemotherapy, 50%-80% relapse within 18-28 months after initial treatment, gradually developing drug resistance which ultimately leads to death [5]. Therefore, reversing chemotherapy resistance in ovarian cancer to improve treatment efficacy and patient survival rates remains a major challenge and focus in oncology research.

Although the specific term "ovarian cancer" is not recorded in ancient Chinese medical texts due to historical limitations in anatomical knowledge, its symptoms and manifestations were likely categorized under terms like "Shijia", "Changtan", and "Zhengjia" based on etiology and clinical presentation [6]. In recent years, TCM has been widely applied in cancer clinical treatment due to its advantages of fewer adverse effects and proven efficacy. Chinese patent medicines, herbal formulas, and TCM injections play an irreplaceable role in comprehensive cancer therapy [7]. Resistance reversal agents developed by modern medicine are often limited in clinical application due to severe side effects like cardiovascular and renal toxicity. Research demonstrates that TCM shows significant efficacy in intervening in ovarian cancer resistance, characterized by high efficiency, low toxicity, and multi-target effects. Consequently, effectively utilizing TCM to reverse cisplatin resistance in ovarian cancer has become a crucial and urgent research priority. This review summarizes relevant literature retrieved from various databases on TCM reversal of cisplatin resistance in ovarian cancer.

2. Mechanisms of TCM in Reversing Cisplatin Resistance in Ovarian Cancer

2.1 Increasing Intracellular Drug Concentration

Cisplatin, an inorganic platinum complex, enters tumor cells and hydrolyzes to form aquated species that cross-link with DNA (primarily intrastrand links), inhibiting replication and damaging cell membrane structures, exerting broad-spectrum anti-cancer effects. Before cisplatin binds nuclear DNA, resistance can arise through reduced drug uptake, increased efflux, or enhanced cytoplasmic sequestration, decreasing effective intracellular cisplatin concentration and lowering cell sensitivity [8]. A key mechanism of multidrug resistance (MDR) involves tumor cells expressing proteins (e.g., ABC transporters) that bind chemotherapeutic drugs and actively efflux them out of the cell via exocytosis [9]. The ABC transporter superfamily, including P-glycoprotein (P-gp), multidrug resistance-associated protein (MRP), breast cancer resistance protein (BCRP), and lung resistance-related protein (LRP), plays a major role in this efflux, reducing intracellular drug accumulation and sensitivity [10]. TCM can increase intracellular drug transport and reduce efflux by modulating

these membrane transporters, thereby reversing cisplatin resistance.

2.1.1 TCM Monomers

Peng Jiaxin et al. [11] found that Acacetin (a flavonoid) increases intracellular cisplatin concentration and reverses chemotherapy resistance by inhibiting ABCA3 expression in ovarian cancer cells, suppressing proliferation and invasion, and promoting apoptosis. Chen Xinrui et al. [12] demonstrated that β-Elemene inhibits proliferation, promotes apoptosis, and reverses cisplatin resistance in SKOV3/DDP cells while strongly suppressing the expression of resistance proteins ABCB1, LRP, and P-gp. Yang Jiezhen [13] showed that Liposomal Curcumol reverses cisplatin resistance in human ovarian cancer cells by inhibiting P-gp expression, reducing resistance in the SKOV3/DDP cell line. Wang Lei [14] found that Naringin, within non-cytotoxic concentrations, inhibits SKOV3/DDP proliferation in a time- and dose-dependent manner. Combined with DDP, it enhances sensitivity and reverses resistance, likely by downregulating MDR1 mRNA and MRP2 mRNA expression, reducing P-gp and MRP2 protein expression, decreasing drug efflux, and increasing intracellular drug concentration. Jin Changhao et al. [15] reported that Piperine (PIP) downregulates mRNA and protein expression levels of ABC transporters P-gp, MRP1, and BCRP in cisplatin-resistant A2780/DDP and SKOV3/DDP cells, increasing intracellular cisplatin accumulation and reversing resistance.

2.1.2 TCM Compounds

Han Li et al. [16] found that serum containing Guizhi Fuling Wan (Cinnamon Twig and Poria Pill) inhibits the expression and function of P-gp and its encoding gene MDR1 in SKOV3/DDP cells, increasing intracellular drug concentration and reversing MDR.

2.2 Reversal of Apoptosis Obstruction

Reversing Apoptosis Inhibition Apoptosis is an active, complex physiological process regulated by multiple factors. While anti-tumor drugs induce apoptosis to exert their effects, they can also trigger changes in apoptotic regulators contributing to resistance [17]. Key pro-apoptotic genes include Bax, Fas, and wild-type p53, while anti-apoptotic genes include Bcl-2, mutant p53, ras, and Survivin [18]. Jing Jing et al. [19] noted cisplatin activates p53, inducing phosphorylation and apoptosis. p53 mutation decreases cisplatin sensitivity, suggesting p53 activation is crucial for enhancing sensitivity. Bcl-2 family proteins, located in mitochondria, regulate apoptosis; Bcl-2 overexpression inhibits apoptosis, prolongs cell survival, and is observed in cisplatin-resistant cells. Reducing Bcl-2 expression can increase cisplatin sensitivity [20]. Inducing Survivin overexpression in human ovarian cancer cells significantly increases cisplatin resistance and reduces sensitivity [21]. Cai Yuehong et al. [22] explored Ligustrazine's mechanism, finding high KDM2B expression in A2780/DDP cells. Ligustrazine or KDM2B knockdown inhibited proliferation, promoted apoptosis, upregulated Bax and caspase-3, and downregulated Bcl-2. Jing Jing et al. [23] found Gentiopicroside inhibited A2780/DDP proliferation, promoted deformation and apoptosis, and enhanced cisplatin sensitivity, likely by upregulating p53 expression/ phosphorylation and downregulating Bcl-2, XIAP, and Survivin. Shihong Ma et al. [24] demonstrated Oridonin enhanced cisplatin's cytotoxicity against resistant ovarian cancer cells by inducing apoptosis via the Bax/Bcl-2 pathway and inhibiting MMP-2/9 expression. Li et al. [25] showed β-Elemene induced apoptosis in cisplatin-sensitive (A2780) and resistant (A2780/CP, MCAS) ovarian cancer cells by reducing mitochondrial transmembrane potential, activating Caspase-3/8/9, downregulating Bcl-2, and upregulating Bax, indicating dependence on the mitochondrial apoptotic pathway.

2.3 Reversing Abnormal Intracellular Signaling Pathways

Ovarian cancer cells often exhibit dysregulation in multiple signaling pathways, including PI3K/Akt, MAPK, Wnt/β-catenin, NF-κB, and Notch.

2.3.1 PI3K/Akt Signaling Pathway

This pathway plays a key role in tumor proliferation, invasion, angiogenesis, and drug resistance, significantly impacting OC pathogenesis and treatment resistance [26]. Shu Meiling et al. [27] found Cinobufagin (CBG) induced apoptosis, reduced proliferation/migration/invasion in A2780/DDP cells, potentially by regulating PI3K/Akt signaling and inhibiting EMT. Liu Fei et al. [28] showed Triptolide (TP) combined with paclitaxel significantly increased inhibition and apoptosis in cisplatin-resistant COC1/DDP cells compared to single agents, with reduced p-Akt and p-GSK3β expression, suggesting synergy via PI3K/Akt/GSK3β pathway inhibition. Liang Ruojia et al. [29] found Hydroxysafflor Yellow A (HSYA) combined with DDP reduced tumor weight and increased necrosis. HSYA alone or combined downregulated Akt and p-Akt expression, suggesting HSYA enhances cisplatin sensitivity in A2780/DDP cells by inhibiting PI3K/Akt signaling.

2.3.2 Wnt/β-catenin Signaling Pathway

This pathway is crucial in tumorigenesis, development, and influences cell proliferation, differentiation, invasion, and apoptosis. Aberrant Wnt signaling is common in cancers, and its activation is linked to chemotherapy resistance [30].

Li Guanrong et al. [31] demonstrated that MTC21 (a C21 steroidal saponin from Marsdenia tenacissima) reversed cisplatin resistance in SKOV3/DDP cells by inhibiting Wnt/β-catenin pathway activation, suppressing cell viability, and inducing apoptosis. Duan et al. [32] found β-catenin accumulation in cisplatin-resistant ovarian cancer epithelial cells. Puerarin treatment significantly enhanced platinum sensitivity, possibly by inhibiting SIRT1 expression, reducing nuclear β-catenin accumulation, thereby inhibiting Wnt/β-catenin signaling.

2.3.3 NF-κB Signaling Pathway

There is a close link between NF-κB signaling and multidrug resistance (MDR). NF-κB complexes can bind to the MDR1 gene promoter, initiating its transcription and contributing to

MDR [33]. Yiqi Huoxue Jiedu Fang (Qi-invigorating, Blood-activating, Toxin-resolving Formula) [34] reversed platinum resistance in ovarian cancer by regulating miR-216a-5p/ATP7B to induce an anti-tumor phenotype in tumor-associated macrophages (TAMs) and inhibiting NF-κB-IL-6-STAT3 pathway activation. Wu Chaoyan et al. [35] found that Zincpolyphyllin (ZPT) from Polyalthia nemoralis increased cisplatin sensitivity in A2780/DDP cells, potentially by inhibiting elevated NF-κB transcriptional activity and p65 protein expression, and downregulating Bcl-2. Hong Zhu et al. [36] showed Naringin suppressed NF-κB and P-gp expression in SKOV3/CDDP cells in a dose-dependent manner, likely related to NF-κB pathway blockade.

2.3.4 MAPK Signaling Pathway

The MAPK pathway is vital for cell growth, development, differentiation, apoptosis, and is implicated in cisplatin resistance. Wang Xuzhen et al. [37] demonstrated Resveratrol (RES) reversed cisplatin resistance in SKOV3/DDP cells by upregulating miR-361-3p, inhibiting proliferation and inducing apoptosis, further associated with inhibition of MAPK/ERK pathway activation. Dihydroartemisinin (DHA) [38] reversed cisplatin resistance in A2780/DDP cells, potentially by regulating MAPK, inhibiting mTOR phosphorylation, and downregulating HIF-1α and P-gp expression (mechanism requires further study).

2.3.5 Notch Signaling Pathway

This highly conserved ligand-receptor pathway regulates cell survival, proliferation, differentiation, and apoptosis. Aberrant Notch activation plays a key role in ovarian cancer resistance [39]. Xiang Meng et al. [40] confirmed Curcumin inhibited proliferation of SKOV3 and 3AO ovarian cancer cells in vitro via the Notch1-Hes1 pathway. Combined with cisplatin, it exerted a synergistic effect, increasing cisplatin sensitivity. Gao Ying [41] found Theaflavin-3 (TF3) inhibited Notch1 cleavage and Akt phosphorylation in ovarian cancer cells. Combining TF3 with the Notch1 inhibitor DAPT further reduced NICD expression. Overexpression of NICD partially reversed TF3's effect, suggesting TF3 enhances cisplatin sensitivity by targeting Notch1/Akt.

2.4 Regulating Metabolic Reprogramming

Metabolic reprogramming is a hallmark of malignancy, allowing tumor cells to meet energy demands. Glucose, glutamine, and lipid metabolism are significantly altered pathways. Historically, research focused on glycolysis [42]. Shenqi Yiliu Fang (Ginseng-Astragalus Tumor-Suppressing Formula) [43] enhanced cisplatin sensitivity in A2780cisR cells, reduced lactate production, glucose consumption, and activity of glycolytic enzymes (GLUT, PK, PFK), inhibited PI3K/Akt/mTOR pathway activation, downregulated glycolytic proteins HK2 and PKM2, and promoted apoptosis. Its mechanism likely involves inhibiting PI3K/Akt/mTOR-mediated glycolysis.

2.5 Inducing Ferroptosis

Emerging evidence links chemotherapy resistance to ferroptosis, an iron-dependent, non-apoptotic cell death caused by lipid peroxidation. Key regulators include GPX4, antioxidants, ferroptosis inhibitors, and iron chelators. Inducing ferroptosis is a promising strategy to increase chemosensitivity [44]. Ma Bo [45] found Tripterygium glycosides (TG) inhibited cisplatin-resistant ovarian cancer cell proliferation in vitro and in vivo and enhanced cisplatin sensitivity. Mechanistically, TG likely targets the NRF2/GPX4 axis, downregulating antioxidant molecules HO-1, NQO1, GPX4, weakening antioxidant capacity, promoting lipid peroxidation, and inducing ferroptosis to reverse resistance. Li Xinxiao [46] found that Rhein derivative 4s increased cisplatin sensitivity in ovarian cancer cells by inducing ferroptosis. Weikang Guo et al. [47] showed that combining Angelica sinensis polysaccharide (ASP) with DDP promoted ferroptosis in SKOV3/DDP cells by inhibiting GPX4 expression, reversing cisplatin resistance.

2.6 Inhibiting Epithelial-Mesenchymal Transition (EMT)

EMT involves reduced epithelial cell adhesion and polarity, enhancing tumor invasion and metastasis. Evidence links EMT to both metastasis and drug resistance; inhibiting EMT may suppress both [48]. Chen Jingping et al. [49] studied Cinobufagin's active component Bufalin, finding it downregulated EMT-related proteins in resistant ovarian cancer cells, inhibited growth/migration/invasion in vivo, and enhanced DDP sensitivity. Shen Xiaoyan et al. [50] found HSYA inhibited ERK1/2 and p-ERK1/2 expression, interfering with MAPK/ERK signaling, further affecting E-cadherin, Vimentin, Snail, and Twist expression to inhibit EMT, ultimately reversing cisplatin resistance in A2780/DDP cells.

2.7 Increasing DNA Damage and Inhibiting DNA Repair

Cisplatin's primary target is genomic DNA (gDNA) and mitochondrial DNA (mtDNA), causing DNA damage, blocking replication/transcription/translation, activating transduction pathways, leading to necrosis or apoptosis. DNA repair mechanisms include homologous recombination (HR), non-homologous end joining (NHEJ), nucleotide excision repair (NER), and mismatch repair (MMR) [51]. NER, particularly involving ERCC1, is crucial for cisplatin-induced damage repair. ERCC1 overexpression is associated with cisplatin resistance in OC [2]. Reversion mutations in genes like BRCA1/2 can enable rapid DNA repair, conferring resistance. Loss of the mismatch repair gene hMLH1 plays a significant role in cisplatin resistance by impairing DNA repair fidelity, leading to genomic instability [52]. Xie et al. [53] showed Scutellarin combined with DDP increased Pt-DNA adduct levels, enhanced DNA damage, and synergistically promoted apoptosis in ovarian cancer cells. Jiao et al. [54] found Tanshinone IIA induced apoptosis and reduced cisplatin resistance in COC1/DDP cells, potentially by downregulating ERCC1, Survivin, and LRP mRNA expression.

2.8 Modulating Intracellular Autophagy

Autophagy is a highly conserved catabolic process degrading long-lived proteins or damaged organelles to maintain metabolic balance and cellular homeostasis [55]. Autophagy

plays a dual role in MDR tumors: it can act as a protective mechanism against chemotherapy but can also kill apoptosis-resistant MDR cells [56]. Triptolide (TP) induced autophagy in SKOV3/DDP cells, inhibited proliferation, suppressed tumor growth in vivo, and enhanced cisplatin sensitivity [57]. Zhu et al. [58] demonstrated Hyperoside inhibited viability and induced autophagic death in SKOV-3 and HO-8910 ovarian cancer cells via the PGRMC1/Akt pathway, sensitizing cells to DDP. Yun Zhou et al. [59] found Baohuoside I inhibited cisplatin resistance in vivo by suppressing autophagy via downregulating the HIF-1α/ATG5 axis. Ge Yu et al. [60] showed Salidroside overcame cisplatin resistance in A2780 cells by inhibiting autophagy mediated by the long non-coding RNA CRNDE. CRNDE knockdown suppressed autophagy, while CRNDE overexpression reversed Salidroside's effect.

3. Summary and Outlook

In summary, cisplatin resistance in ovarian cancer involves complex mechanisms encompassing multiple signaling pathways, proteins, and genes. TCM monomers, compounds, and injections can reverse resistance through diverse mechanisms: increasing intracellular drug concentration, reversing apoptosis inhibition, inhibiting EMT, inducing ferroptosis, regulating metabolic reprogramming, modulating autophagy, increasing DNA damage/inhibiting DNA repair, and targeting resistance-related signaling pathways. This highlights the significant advantages of TCM – multi-target and multi-pathway effects – demonstrating broad application prospects in the systemic treatment of ovarian cancer. However, as research deepens, it becomes evident that cisplatin resistance arises from a complex interplay of multiple mechanisms rather than one or two isolated pathways. Current research on TCM reversal mechanisms is still incomplete, with limited studies on gene regulation, immunomodulation, and the tumor microenvironment, warranting further exploration. Moreover, most current research is based on in vitro experiments; future efforts should prioritize in vivo animal studies and clinical research to provide more scientifically robust guidance for clinical practice.

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