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The Mechanisms and Research Progress of Chinese Medicine Monomers in Reversing Chemotherapy Resistance in Ovarian Cancer

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Abstract: The development of chemotherapy resistance is a critical factor leading to treatment failure and high mortality in ovarian cancer. Among current research directions, Chinese medicine monomers (CMMs) have shown great potential in reversing chemotherapy resistance due to their multi-targeting properties and low toxicity. This review summarizes the research progress of various Chinese medicine monomers in reversing chemotherapy resistance in ovarian cancer, including polyphenols (such as quercetin, curcumin, epigallocatechin-3-gallate, resveratrol, kaempferol, myricetin, and ellagic acid), alkaloids (such as berberine, piperine, sanguinarine, and capsaicin), terpenoids (such as toosendanin and triptolide), and phenylpropanoids (such as myristicin and apiole). These monomers primarily exert their effects by regulating key signaling pathways (including PI3K/AKT/mTOR, p53, and NF-κB) and by interfering with critical processes such as drug efflux, DNA damage repair, apoptosis, and autophagy, thereby enhancing the sensitivity of ovarian cancer cells to chemotherapeutic agents like cisplatin. Furthermore, this review discusses the advantages of combination strategies involving Chinese medicine monomers, as well as the current challenges.

Keywords: Chinese medicine monomers; Ovarian cancer; Chemotherapy resistance; Reversal mechanisms; Combination therapy

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1. Introduction

Ovarian cancer (OC) ranks as the 18th most common cancer worldwide, but it's the 8th leading cause of cancer death among women. In 2022 alone, an estimated 324,000 new cases and 206,000 deaths were recorded [1]. The standard approach, primary cytoreductive surgery followed by paclitaxel and carboplatin, works initially, yet up to 70% of women with stage III-IV high-grade disease will relapse within three years [2]. Why? The answer is platinum resistance. While most patients with high-grade serous ovarian cancer (HGSOC) initially respond well, only about 20% have primary platinum-resistant disease. But for the majority who are initially sensitive, secondary resistance eventually develops after repeated recurrences. The result is a five-year survival rate that stubbornly hovers between 30% and 40% globally [3,4]. The sad reality is that platinum resistance catches up with nearly every OC patient over time, making it one of the strongest prognostic factors for overall survival. Clearly, we need new agents that can re-sensitize tumors to platinum-based drugs and reverse established resistance.

The roots of chemoresistance in ovarian cancer are complex and tangled. They involve multidrug resistance mechanisms, enhanced DNA damage repair, shifts in cell metabolism and oxidative stress, altered cell cycle control, the presence of cancer stem cells, immune evasion, and dysregulation of apoptosis, autophagy, and multiple signaling pathways [5]. Traditional Chinese Medicine (TCM) has long offered certain advantages in cancer care—fewer side effects, tailored formulas, and potential immune benefits [6]. But recent work shows something more direct: TCM can actually boost the sensitivity of OC cells to chemotherapy, block the cell cycle, stop proliferation, trigger apoptosis, cut off angiogenesis, reduce side effects, and improve patients' quality of life after surgery [7]. A growing body of evidence suggests TCM can be used alone in treating ovarian cancer or as an effective adjuvant therapy [8]. For example, specific Chinese medicine monomers (CMMs) have been proven to be able to modulate pathways like STAT3, PI3K/AKT, and Wnt/β-catenin, thereby inducing apoptosis and influencing the growth and survival of ovarian cancer cells [7]. Other monomers, such as bufalin, can make chemotherapy work better by curbing tumor cell proliferation and nudging resistant cells toward apoptosis [9].

These studies provide an important theoretical foundation for the application of Chinese medicine monomers in overcoming chemotherapy resistance in ovarian cancer. However, current research on this topic is relatively fragmented and lacks systematic synthesis and analysis. This review summarizes the mechanisms and research progress of major classes of Chinese medicine monomers in reversing drug resistance in ovarian cancer, aiming to provide theoretical support for their application and future development directions in ovarian cancer treatment [10,11].

2. The effects and mechanisms of Chinese medicine monomers on chemotherapy resistance in ovarian cancer

2.1. Polyphenols

2.1.1. Quercetin

Quercetin, a flavonoid known for its potent antioxidant and anti-inflammatory properties, has gained attention for its multifaceted mechanisms of action against various cancers, highlighting its potential as an adjunctive therapy in cancer treatments [12,13]. Quercetin significantly increases the chemosensitivity of ovarian cancer cell lines, particularly OVCAR-2 and A2780P, to cisplatin and paclitaxel, suggesting its potential as an adjuvant to improve chemotherapy efficacy [14]. Quercetin overcomes cisplatin resistance primarily by inhibiting key proteins like MMP1, whose upregulation in resistant cells is driven by the activated MAPK signaling pathway [15]. Quercetin-loaded solid lipid nanoparticles enhance chemosensitization and apoptosis in ovarian cancer by downregulating the expression of multiple cisplatin resistance genes, including ABCG2, MT-2A, GST-pi, and XIAP [16].

2.1.2. Curcumin

Curcumin is a natural hydrophobic polyphenol compound isolated from the rhizome of Curcuma longa (Turmeric) [17]. It combats cisplatin resistance in ovarian cancer through multifaceted molecular mechanisms. Curcumin reverses cisplatin resistance in SKOV-3 ovarian cancer cells by suppressing the expression of key antioxidant enzymes and the transcription factor Nrf2, while also inhibiting the PI3K/Akt/mTOR signaling pathway, thereby confirming the role of redox-dependent regulation in the reversal of cancer cells resistance to cisplatin [18]. In resistant ovarian cancer cells, curcumin and its analog demethoxycurcumin downregulate glutathione S-transferase P1 (GSTP-1) and miR-133b, key players in glutathione-mediated cisplatin detoxification [19]. Curcumin induces demethylation of the MEG3 promoter, restoring MEG3 expression [20]. This upregulation of MEG3 reduces the extracellular vesicle-mediated transfer of oncogenic miR-214, which otherwise contributes to chemoresistance [20]. By integrating these redox-dependent, epigenetic, and signaling pathway modulations, curcumin effectively sensitizes resistant ovarian cancer cells to cisplatin.

2.1.3. Epigallocatechin-3-gallate

Epigallocatechin-3-gallate (EGCG), a polyphenol present in green tea, offers a wide range of beneficial properties, including antioxidant, anti-inflammatory, hypoglycemic, antiviral, neuroprotective, cardioprotective, and anticancer effects [21–27]. It exhibits chemopreventive and therapeutic effects against ovarian cancer through multi-target mechanisms, including its dual roles as an antioxidant and pro-oxidant, epigenetic modulation via DNMT/HDAC inhibition, and suppression of key oncogenic pathways [28]. EGCG has been shown to effectively inhibit proliferation, mobility, and induce apoptosis in cisplatin-resistant ovarian cancer cells (OC/DDP) by downregulating the expression of S100A4 and NF-κB while upregulating p53 expression, an effect confirmed both in vitro and in vivo [29]. In addition, EGCG enhances cisplatin sensitivity by regulating the copper and cisplatin influx transporter CTR1; it inhibits the rapid degradation of CTR1 induced by cisplatin, increases the accumulation of cisplatin and DNA-Pt adducts, and subsequently enhances the sensitivity of ovarian cancer cells to the chemotherapeutic agent, while also exhibiting a protective effect against cisplatin-induced nephrotoxicity [30]. Another study found that EGCG delivers hydrogen peroxide to induce death of ovarian cancer cells, including those resistant to cisplatin, and amplifies cisplatin toxicity by three- to six-fold in various ovarian cancer cell lines by accentuating oxidative stress [31].

2.1.4. Resveratrol

Resveratrol is a natural polyphenol found in grapes, mulberries, peanuts, rhubarb, and several other plants, and it has antibacterial, anti-inflammatory, antioxidant, and anticancer activities [32,33]. This compound has a demonstrated effect against lysophosphatidic acid (LPA), a biolipid mediator that augments proliferation and metastasis of various cancer cells, including ovarian cancer invasion and metastasis [34]. By inhibiting the Hedgehog (Hh) pathway and restoring autophagy, resveratrol counteracts LPA-induced malignancy, supporting its inclusion in the therapy of ovarian cancer for limiting metastasis and chemoresistance [35]. Furthermore, resveratrol synergistically enhances the chemotherapeutic effect of cisplatin through a mechanism closely related to the significant inhibition of the PI3K/AKT/mTOR signaling pathway [36]. Specifically, it can prevent cisplatin-induced epithelial-to-mesenchymal transition (EMT) in ovarian cancer cells and increase cell death, demonstrating its potential as an effective adjuvant to chemotherapy [37]. Beyond these therapeutic mechanisms, a long-term study demonstrated that during 26 weeks of intermittent cisplatin treatment in initially sensitive ovarian cancer A2780 cells, the continuous presence of resveratrol-maintained cisplatin chemosensitivity, whereas clinically relevant cisplatin chemoresistance developed in its absence [38]. This suggests that resveratrol may also play a crucial role in preventing the onset of cisplatin resistance in ovarian cancer.

2.1.5. Kaempferol

Kaempferol, a dietary flavonoid widely found in fruits and vegetables, is known for its anti-inflammatory, antioxidant, and anticancer properties, and has been shown to elicit antitumor effects by controlling tumor cell cycle progression, proliferation, apoptosis, migration, and invasion, as well as by inhibiting angiogenesis [39,40]. Mechanistically, kaempferol enhances the effect of cisplatin in ovarian cancer cells through promoting apoptosis caused by down-regulation of cMyc and inhibition of ABCC6 gene transcription [41]. Kaempferol also increases the sensitivity of A2780 ovarian cancer cells to cisplatin by activating cytotoxic endoplasmic reticulum (ER)-mediated autophagy, evidenced by increased protein levels of GRP78, PERK, ATF6, IRE-1, LC3II, beclin 1, and caspase 4 via elevating intracellular Ca^{2+} levels, while also decreasing the protein levels of p-Akt [42]. Furthermore, kaempferol enhances the sensitivity of cancer cells to other traditional chemotherapy drugs, such as 5-fluorouracil, making it a promising therapeutic compound for combination with current anticancer agents [40].

2.1.6. Myricetin

Myricetin (MYR) is a flavonoid compound widely found in many natural plants, including bayberry, vegetables, fruits, nuts, and tea [43,44]. Myricetin has demonstrated multiple biological activities, among them antidiabetic, anticancer, immunomodulatory, cardiovascular, analgesic, antihypertensive, as well as preclinical activities on Alzheimer's, Parkinson's, and Huntington's diseases [44,45]. Myricetin is a potent natural inhibitor of CD147, a protein overexpressed in ovarian cancer that promotes malignant progression and is associated with poor prognosis. Myricetin exhibits a strong affinity for CD147 and down-regulates its protein level by facilitating proteasome-dependent degradation [46]. Myricetin also selectively induces apoptosis in cisplatin-resistant ovarian cancer cells (OVCAR-3 and A2780/CP70) through a p53-dependent apoptotic pathway involving both Bcl-2 family-mediated intrinsic and DR5-mediated extrinsic apoptosis, without toxicity to normal ovarian cells, thereby effectively overcoming platinum-based chemoresistance [47].

2.1.7. Ellagic acid

Ellagic acid (EA) Ellagic acid (EA) is a polyphenolic compound from the ellagitannins (ETs) family, found in various berries (such as strawberries, raspberries, blackberries, cranberries, goji berries), pomegranates, grapes, and walnuts. It has been shown to possess anti-angiogenic activity, as well as anticancer effects against various tumors and the suppression of metastasis [48].In the ovarian cancer A2780 cell line, ellagic acid (EA) inhibits cancer proliferation and migration by downregulating the expression of MMP2 and MMP9 both in vivo and in vitro [49]. Furthermore, in SKOV-3 ovarian cancer cells, EA suppresses growth, migration, and invasion through the inhibition of mTORC1 and Akt, alongside the activation of AMPK-mediated cytotoxic autophagy [50]. Regarding the mechanism of reversing ovarian cancer resistance, ellagic acid (EA) sensitizes cancer stem-like cells (CSLCs) to cisplatin treatment by enhancing the accumulation of DNA damage while simultaneously impairing their DNA repair capacity [51]. Additionally, EA pretreatment significantly reduces the frequency of cisplatin-induced mutations and improves intracellular drug retention, thereby suppressing the development of acquired resistance [51]. Another study demonstrated that ovarian cancer A2780 cells continuously treated with ellagic acid did not develop cisplatin resistance during intermittent cisplatin exposure, whereas resistance emerged in its absence, providing evidence that ellagic acid may protect against the development of cisplatin resistance in ovarian cancer [38].

2.2. Alkaloids

2.2.1. Berberine

Berberine, an isoquinoline quaternary alkaloid isolated from many kinds of medicinal plants such as *Coptis chinensis*, *Hydrastis canadensis*, *Berberis aristata*, *Coptis japonica*, *Phellondendron amurense* and *Phellondendron chinense Schneid*, is a nonprescription medicine traditionally used to treat diarrhea and gastroenteritis caused by bacterial and intestinal parasitic infections [52,53]. Accumulating evidence indicates that berberine can exert anticancer effects through multifaceted biological mechanisms across a broad spectrum of malignancies, including lung cancer, colorectal cancer, breast cancer, and ovarian cancer [54–57]. Berberine inhibits ovarian cancer cell growth by interfering with the expression and function of folate cycle enzymes (DHFR and TS) and upregulating the key polyamine catabolic enzyme SSAT, thereby restoring the sensitivity of drug-resistant cells to cisplatin [58]. Another study showed that berberine modulated the sensitivity of cisplatin in ovarian cancer A2780/DDP cells by inhibiting miR-93 expression, which in turn increased PTEN protein levels and regulated the PTEN/AKT pathway, a key signaling axis mediating miR-93-induced chemoresistance to cisplatin [59].

2.2.2. Piperine

Piperine is an alkaloid, a bioactive compound derived from barley (*Hordeum vulgare L., Poaceae*) and black pepper [60]. It is gaining attention due to its ability to directly inhibit tumor growth and enhance the bioavailability of chemotherapeutic drugs [61]. A study demonstrated that piperine effectively increases the sensitivity of drug-resistant ovarian cancer cells to chemotherapeutic agents like paclitaxel and topotecan by concurrently targeting multiple key resistance mechanisms: upregulating protein tyrosine phosphatase receptor type K (PTPRK) expression to reduce overall protein tyrosine phosphorylation, downregulating the drug efflux pumps P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), decreasing the production of extracellular matrix proteins (COL3A1, TGFBI) involved in cell adhesion-mediated drug resistance, and inhibiting cancer cell proliferation and migration [62].

2.2.3. Sanguinarine

Sanguinarine, a benzophenanthridine alkaloid isolated from Sanguinaria canadensis, has been shown by both in vivo and in vitro experiments to exert antioxidant, anti-inflammatory, proapoptotic, and antiproliferative effects on various tumor cells [12,54,63]. However, its low chemical stability and poor oral bioavailability remain key issues in its use as a medicinal molecule [64]. Sanguinarine effectively enhances the sensitivity of cisplatin-resistant ovarian cancer A2780 cells to cisplatin and synergistically promotes apoptosis by depleting intracellular glutathione (GSH) in a dose-dependent manner, offering a potential adjuvant strategy to overcome chemoresistance in ovarian cancer [65]. Another study, using an integrated bioinformatics approach, identified aberrant activation of the EGFR/ErbB2 signaling pathway as a key driver of cisplatin resistance in ovarian cancer and discovered that the natural product sanguinarine effectively targets this resistance network, significantly suppressing the growth of both sensitive and resistant ovarian cancer cells in vitro and inhibiting xenograft tumors in vivo [5].

2.2.4. Capsaicin

Capsaicin, a bioactive alkaloid derived from chili peppers, produces antioxidative, antitumor, antiulcer and analgesic effects and has demonstrated potential as a treatment for cardiovascular, gastrointestinal, oncological and dermatological conditions [66]. In ovarian cancer, capsaicin exhibits growth-suppressive activity and sensitizes cancer cells to the pro-apoptotic effects of chemotherapy [67]. Mechanistically, capsaicin modulates key regulators of chemoresistance, including the inhibition of P-glycoprotein (P-gp), the nuclear factor-kappa B (NF-κB) pathway, and the signal transducer and activator of transcription 3 (STAT3) pathway, thereby contributing to the reversal of multidrug resistance (MDR) [68]. In human ovarian cancer cell lines, including the cisplatin-resistant A2780(cisR) model, combinations of capsaicin with a novel platinum agent demonstrated synergistic activity, indicating its potential to enhance the efficacy of existing chemotherapeutics [69].

2.3. Terpenoid

2.3.1. Toosendanin

Toosendanin (TSN) is a tetracyclic triterpenoid derived from Melia toosendan and M. azedarach [70]. Modern studies have shown that TSN has strong anti-tumor, anti-botulinum, anti-viral and anti-parasitic potential [71]. Concerning the reversal of drug resistance, TSN can reduce DDP resistance in OC through regulating the miR-195/ERK/β-catenin pathway, highlighting the potential of TSN as an effective agent for overcoming clinical DDP resistance in OC both in vitro and in vivo [72].

2.3.2. Triptolide

Triptolide (TPL) is a biologically active diterpenoid triepoxide extracted from the traditional Chinese medicine *Tripterygium wilfordii*. It has presented potent pharmacological activity and anti-cancer, anti-tumor, anti-obesity and anti-diabetes effects [73,74]. TPL antagonizes cisplatin resistance in human ovarian cancer cell line A2780/CP70 via hsa-mir-6751 [75]. Triptolide triggers lethal autophagy in cisplatin-resistant SKOV3/DDP ovarian cancer cells through the ROS-mediated inhibition of the JAK2/STAT3 signaling pathway [76]. TPL negatively regulated the NF-κB pathway through mitochondria-derived ROS accumulation, promoting the apoptosis of the SKOV3PT cells, increasing the sensitivity of cells to chemotherapy-dependent apoptosis and reversing drug resistance in ovarian cancer[77].

2.4. Phenylpropanoids

2.4.1. Myristicin

Myristicin is an active natural compound from the alkylbenzene family, mainly found in nutmeg (*Myristica fragrans*), also present in parsley (*Petroselinum crispum*), black pepper (*Piper nigrum*), carrots (Umbelliferae family) and plants of the Apiaceae family [78]. Previous research showed that myristicin possesses anti-inflammatory, antimicrobial, anti-proliferative and anticancer properties, including hepatic carcinoma, gastric cancer and breast cancer [79–82]. Myristicin itself lacks direct cytotoxicity against multidrug-resistant ovarian cancer cells, but it significantly enhances the cytotoxic effects of chemotherapeutic agents like cisplatin and docetaxel by binding to and blocking the efflux function of P-glycoprotein (P-gp), thereby reversing multidrug resistance in ovarian cancer [78].

2.4.2. Apiole

Apiole is a phenylpropanoid found in parsley (Apiaceae), but also in the fruits of *Petroselinum crisp*, the seeds of *Enterolobium contortisiliquum*, and caraway (*Carum carvi L*) [83]. Apiole exhibits various pharmacological activities, including antioxidant, antibacterial, and anti-inflammatory effects, and has been identified as a potent calcium channel inhibitor [83,84]. In the context of ovarian cancer, Apiole reverses multidrug resistance in ovarian cancer cells by binding to the active site of P-glycoprotein (P-gp) (involving residues such as Phe728 and Tyr303), as confirmed by molecular docking, thereby inhibiting the efflux of chemotherapeutic drugs like doxorubicin and vincristine and synergistically enhancing their antiproliferative effects [85]. This suggests that apiole acts as an effective P-gp inhibitor and is a promising adjuvant agent to overcome multidrug resistance in ovarian cancer.

Table 1. Chinese medicine monomers reversing chemotherapy resistance in ovarian cancer

Monomer Class	Monomer Name	Mechanism of Action
Polyphenols	Quercetin	Inhibits MMP1; downregulates ABCG2, MT-2A, GST-pi, XIAP
	Curcumin	Inhibits PI3K/Akt/mTOR and Nrf2; modulates MEG3/miR-214 axis; downregulates GSTP-1 and miR-133b.
	Epigallocatechin-3-gallate (EGCG)	Regulates S100A4/NF-κB/p53 axis; upregulates CTR1; enhances oxidative stress
	Resveratrol	Inhibits Hedgehog/PI3K/AKT pathways; blocks EMT; prevents resistance development
	Kaempferol	Downregulates cMyc/ABCC6; activates ER stress-mediated autophagy
	Myricetin	Induces p53-dependent apoptosis; inhibits CD147
	Ellagic acid	Enhances DNA damage and impairs repair; improves drug retention
Alkaloids	Berberine	Interferes with folate enzymes (DHFR, TS); upregulates SSAT; regulates miR-93/PTEN/AKT axis.
	Piperine	Upregulates PTPRK; downregulates P-gp/BCRP; reduces ECM proteins (COL3A1, TGFBI).
	Sanguinarine	Depletes glutathione (GSH); targets EGFR/ErbB2 network.
	Capsaicin	Inhibits P-gp, NF-κB, and STAT3 pathways.
Terpenoids	Toosendanin	Regulates miR-195/ERK/β-catenin pathway.
	Triptolide	Modulates hsa-mir-6751/HK2, ROS/JAK2/STAT3, and ROS/NF-κB pathways
Phenylpropanoids	Myristicin	Blocks P-gp efflux function.
	Apiole	Binds to P-gp active site, inhibiting drug efflux.

Note: EGCG, epigallocatechin-3-gallate; EMT, epithelial-mesenchymal transition; ER, endoplasmic reticulum; P-gp, P-glycoprotein; BCRP, breast cancer resistance protein; ECM, extracellular matrix; GSH, glutathione; ROS, reactive oxygen species. Numbers in square brackets are reference citations.

3. Benefits of the combination of TCM monomers

Several studies have investigated the efficacy of mixtures combining two or three different Chinese medicine monomers. The combination of curcumin and resveratrol reverses chemoresistance in cisplatin-resistant epithelial ovarian cancer cells by synergistically inhibiting the PI3K/AKT/mTOR pathway [36]. When the novel monofunctional platinum agent LH6 was combined with curcumin and quercetin, it resulted in significantly enhanced cytotoxic effects against human ovarian cancer cells, confirming a synergistic interaction [86]. In a co-culture model of ovarian cancer and mesenchymal stem cells, the combination of fisetin and quercetin reversed microenvironment-induced chemoresistance by restoring ERK1/2 phosphorylation, thereby re-sensitizing cells to platinum drugs [87]. The combination of epigallocatechin gallate (EGCG) and sulforaphane (SFN) significantly enhances the efficacy of cisplatin against both sensitive and resistant ovarian cancer cells by potentiating G2/M phase arrest and upregulating p21 expression, offering a novel approach to overcoming chemotherapy resistance [88]. Another study found the sequenced combination of curcumin and EGCG added 4 hours after administering cisplatin produced the strongest synergistic inhibitive effect in both sensitive and resistant ovarian cancer cells by increasing cellular platinum accumulation and platinum-DNA binding levels [89]. The combination of curcumin and triptolide could synergistically inhibit ovarian cancer cell growth and induce apoptosis, which is accompanied by HSP27 and HSP70, indicating that HSP27 and HSP70 play an important role in this synergic effect [90].

Overall, polyphenols, alkaloids, terpenoids, and phenylpropanoids, as natural compounds derived from traditional Chinese medicine, exhibit potent preventive and therapeutic effects against ovarian cancer through pleiotropic pathways and mechanisms, including the reversal of chemotherapy resistance.

4. Challenges, limitations, and prospects

Although these traditional Chinese medicine monomers have obvious anti-cancer potential, they generally have poor bioavailability, which limits their clinical application. For example, phenols and terpenoids have poor solubility and low permeability. Alkaloids have efflux activity and are metabolized quickly. Phenylpropanoids are toxic [91–97]. These characteristics will cause the drug to fail to reach an effective therapeutic concentration in tumor tissues.

In response to these limitations, drug delivery systems based on nanotechnology have been developed. It includes nanoparticles, liposomes, micelles, dendritic polymers, nanocapsules and nanostructured lipid carriers. After encapsulating drugs with them, the pharmacokinetic characteristics of traditional Chinese medicine monomers can be improved, and the controlled release of drugs and tumor-specific accumulation can be achieved [98-100]. For example, in a study, lipid-chitosan hybrid nanoparticles were used to co-deliver curcumin and cisplatin, which significantly enhanced the cytotoxicity to ovarian cancer cells by increasing chemical sensitization and achieving controlled drug release [101]. Another study showed that quercetin-loaded solid lipid nanoparticles effectively reversed the resistance of ovarian cancer cells to cisplatin by down-regulating key drug resistance genes (such as ABCG2, MT-2A, GST-pi and XIAP), while inhibiting cell migration and promoting cell apoptosis, thereby improving the chemotherapy effect [16].

Another solution is to develop and synthesize derivatives or analogues by chemical modification. For example, the combination of hydrophilic groups or the design of prodrugs is another effective strategy to improve the solubility and metabolic stability of traditional Chinese medicine monomers, thereby enhancing their bioavailability [102,103]. For example, the curcumin derivative NL01 not only showed significantly stronger anti-tumor efficacy than its parent compound but also induced ferroptosis in ovarian cancer cells by down-regulating the HCAR1 / MCT1 signaling pathway, thereby overcoming therapeutic limitations [104].

In terms of research design, there are still several key limitations in the current literature. One of the most significant is the lack of clinical data. At present, most studies are still limited to animal models and in vitro cell experiments, and there is a lack of well-designed clinical trials and real-world studies to verify the specific efficacy and mechanism of traditional Chinese medicine monomers in the patient population. In addition, the existing research mainly focuses on a single monomer. There are obvious research gaps in exploring the synergistic effect of combined traditional Chinese medicine monomers on reversing chemotherapy resistance or enhancing chemotherapy sensitivity of ovarian cancer. It is worth pondering whether the combination of different Chinese medicine monomers or their active ingredients to target the same pathway can produce enhanced therapeutic effects, which is also a problem that needs further study.

5. Conclusion

The emergence of drug resistance remains a major challenge in the treatment of ovarian cancer. Traditional Chinese medicine monomers have shown the potential to reverse the drug resistance of ovarian cancer through a variety of ways and mechanisms, which is crucial for future treatment strategies. Traditional Chinese medicine monomers such as quercetin, curcumin, piperine, and triptolide have shown great potential to reverse ovarian cancer chemotherapy resistance through multiple key molecular pathways (including PI3K / AKT / mTOR, p53, and NF-κB). However, their clinical application is limited by challenges such as poor bioavailability and insufficient clinical trials. In order to solve these limitations, nanotechnology-based drug delivery systems, synthetic derivatives and combined treatment strategies have been developed to improve pharmacokinetic characteristics and therapeutic effects. Future research should focus on the study of joint strategies and conduct larger-scale, well-designed clinical trials. The goal is to verify the reversal effect of traditional Chinese medicine monomers on the drug resistance of ovarian cancer and to develop more effective drug regimens.

Disclosure statement

The authors declare no conflict of interest.

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