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Systematic Review and Meta-analysis of Monomers in Traditional Chinese Medicine for Overcoming Cisplatin Resistance in Ovarian Cancer

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ADMINISTRATIVE INFORMATION**Support** - No external funding declared.**Review Stage at time of this submission** - Completed but not published.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY2025100059**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 October 2025 and was last updated on 17 October 2025.**INTRODUCTION**

Review question / Objective To systematically evaluate the efficacy of Traditional Chinese Medicine (TCM) monomers in reversing cisplatin resistance in ovarian cancer cell models and summarize the reported molecular mechanisms involved.

Rationale Platinum resistance severely limits the efficacy of cisplatin-based chemotherapy in ovarian cancer. Although multiple TCM-derived monomers have shown reversal potential, their effects and mechanisms remain inconsistent across studies. This review aims to systematically synthesize available in vitro data and provide quantitative evidence for the ability of TCM monomers to overcome cisplatin resistance in ovarian cancer cells.

Condition being studied Ovarian cancer (OC) is a leading cause of death among gynecologic malignancies. Cisplatin remains a key

chemotherapeutic drug, but the development of cisplatin resistance severely limits treatment efficacy. This condition involves reduced drug accumulation, enhanced DNA repair, and evasion of apoptosis. The present review focuses on cisplatin-resistant OC models to evaluate the ability of TCM monomers to reverse platinum resistance.

METHODS

Search strategy A comprehensive literature search was conducted in Chinese databases, including the China National Knowledge Infrastructure (CNKI), the China Science and Technology Journal Database (VIP) and the Wanfang database, as well as in major international databases, including PubMed, Web of Science and Google Scholar. The main keywords and search terms in Chinese or in English were as follow:

(1)"ovarian cancer" OR "ovarian carcinoma" OR "ovarian neoplasm", AND

(2)"traditional Chinese medicine" OR "TCM" OR "herb" OR "monomer" OR "medicinal plant" OR "herbal drug" OR "plant extract" OR "plant ingredient", AND

(3)"platinum resistance" OR "cisplatin resistance" OR "chemoresistance" OR "chemotherapy resistance" OR "drug resistance" OR "reversal" OR "DDP" OR "cisplatin" OR "MDR" OR "multidrug resistance" OR "chemosensitivity".

Participant or population Cisplatin-resistant ovarian cancer cell lines (e.g., SKOV3/DDP, A2780/DDP, COC1/DDP, CAO3/DDP, etc.) or animal models established from these cell lines.

Intervention Treatment with non-cytotoxic concentrations of TCM-derived single monomers in combination with cisplatin.

Comparator Cisplatin treatment alone at equivalent concentrations and exposure times.

Study designs to be included Experimental studies including in vitro cell culture experiments and in vivo animal models investigating the effects of Traditional Chinese Medicine (TCM) monomers combined with cisplatin on ovarian cancer drug resistance. Review articles, clinical studies, and qualitative reports will be excluded.

Eligibility criteria Only original experimental studies published in English or Chinese up to September 2024 were included. Studies must report quantitative data on cisplatin sensitivity or IC50 values before and after TCM monomer intervention. Eligible monomer concentrations were required to be non-cytotoxic (cell viability $\geq$ 80%). Studies with incomplete data, unclear treatment design, or without a control group were excluded. Reviews, conference abstracts, and gray literature were also excluded.

Information sources A comprehensive literature search was conducted in both English and Chinese databases from their inception to September 2024. The English databases included PubMed, Web of Science, and Google Scholar. The Chinese databases comprised China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (VIP), and Wanfang Data. Reference lists of relevant reviews and eligible articles were also screened manually to identify additional studies. Only peer-reviewed journal articles written in English or Chinese were included. Conference abstracts, dissertations, preprints, and other forms of grey literature were excluded.

Main outcome(s) Change in cisplatin IC50 values before and after TCM monomer co-treatment.

Additional outcome(s) Expression changes in drug-resistance-related genes and proteins and involvement of signaling pathways.

Data management All retrieved records from the selected databases were imported into EndNote 21 for organization and management. Duplicate publications were automatically removed, and the remaining records were screened based on titles and abstracts within EndNote. Two reviewers independently evaluated the eligibility of studies, with discrepancies resolved through discussion or consultation with a third reviewer. Full texts of potentially eligible studies were reviewed in detail. Data extraction and coding were performed using standardized Microsoft Excel spreadsheets to record bibliographic information, compound characteristics, experimental design, and outcome data. When numerical data were only available in graphical format, WebPlotDigitizer (version 4.8) was used to obtain quantitative values. All extracted data were cross-checked for accuracy and securely stored in a password-protected institutional repository.

Quality assessment / Risk of bias analysis The Toxicological Data Reliability Assessment Tool (ToxRTool) was used to evaluate study quality for both in vitro and in vivo experiments.

Strategy of data synthesis A random-effects meta-analysis was performed using STATA v14. Effect sizes were expressed as standardized mean differences (SMDs) with 95% confidence intervals. Heterogeneity was assessed using I^2 and Q statistics. Subgroup and meta-regression analyses explored potential sources of heterogeneity (e.g., monomer category, dose range, assay type, cisplatin concentration). Publication bias was examined with funnel plots and Begg's test.

Subgroup analysis

Monomer category (phenolics, alkaloids, flavonoids, etc.);
Monomer dose range (≤ 10 μ M, 10–50 μ M, > 50 μ M);
Highest cisplatin concentration used;
Cell line type (SKOV3/DDP, A2780/DDP, COC1/DDP);
Assay method (MTT, CCK-8, MTS, real-time label-free).

Sensitivity analysis Sensitivity analyses were conducted to assess the robustness of the pooled estimates. Each study was sequentially removed

(“leave-one-out” approach) to evaluate its influence on the overall standardized mean difference (SMD). The analysis was repeated using both fixed-effects and random-effects models to compare consistency of results.

Language restriction English and Chinese.

Country(ies) involved Germany; China.

Keywords Ovarian cancer; cisplatin resistance; TCM monomers; meta-analysis.

Contributions of each author

Author 1 - Shuanger Lu - Shuanger Lu designed the study, performed the literature search, data extraction, and statistical analysis, and drafted the manuscript.

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Author 6 - Hugo Murua.Escobar - Hugo Murua Escobar provided conceptual and methodological guidance, critically reviewed the study design, offered senior supervision throughout the project, and contributed to manuscript revision. Hugo.Murua.Escobar provided conceptual and methodological guidance, critically reviewed the study design, and offered senior supervision throughout the project.

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