Original Article

Exploration of key pathogenic mechanisms and potential intervention targets of the traditional Chinese medicine Coptis chinensis in the treatment of cervical cancer based on network pharmacology and molecular docking techniques

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Background: Traditional Chinese medicine (TCM) has shown potential in the treatment of cancer. This study investigated the molecular targets and mechanisms of Coptis chinensis in the treatment of cervical cancer using network pharmacology and bioinformatics.

Methods: Effective Coptis chinensis components were screened from the Traditional Chinese Medicine Systems Pharmacology (TCMSP) platform based on the following criteria: drug-like properties (DLP) ≥0.18 and oral bioavailability (OB) ≥30%. Target genes were identified through DrugBank, while differentially expressed genes (DEGs) related to cervical cancer were sourced from the Gene Expression Omnibus (GEO) database (GSE7803) based on the following criteria: |log fold change| >2 and P<0.05. Common DEGs were identified through a Venn diagram analysis. The expression and prognostic relevance of the candidate genes were validated using The Cancer Genome Atlas (TCGA) database. Molecular docking was performed using Pubchem, Protein Data Bank (PDB), and CB-DOCK2. A gene set enrichment analysis (GSEA) was conducted to explore the potential mechanisms of DEGs. A retrospective analysis of cervical cancer patients (June 2021 to June 2022) was performed to examine the expression of key genes in the peripheral blood via enzyme-linked immunosorbent assay. A multivariate Cox regression was conducted to identify independent prognostic factors.

Results: In total, 10 effective Coptis chinensis compounds and 181 target genes were identified from the TCMSP database. The GEO analysis of GSE7803 identified 109 DEGs. The Venn diagram analysis identified the following seven shared DEGs: *AR*, *MAOB*, *CDKN2A*, *TOP2A*, *CXCL8*, matrix metalloproteinase 1 (*MMP1*), and *SPP1*. *MMP1* and *SPP1* were confirmed to be upregulated candidate genes in cervical cancer tissues, and to be associated with a worse prognosis [overall survival (OS), disease-specific survival (DSS), and progression-free interval (PFI), P<0.05]. Molecular docking showed that MMP1 had high binding affinity with quercetin (–9.2) while that of SPP1 was lower (–6.3). The GSEA indicated that MMP1 was involved in the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), Janus kinase/signal transducer and activator of transcription (JAK/STAT), transforming growth factor-β (TGF-β), mitogen-activated protein kinase (MAPK), and hypoxia-inducible factor 1 (HIF1) pathways, and apoptosis. The retrospective analysis demonstrated that *MMP1* expression was significantly decreased in the peripheral blood of patients receiving conventional chemotherapy and Coptis chinensis compared to those receiving chemotherapy alone. Multivariate Cox regression confirmed that high *MMP1* expression and a lack of Coptis chinensis treatment were independent risk factors for a poor prognosis (P<0.05).

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Conclusions: *MMP1* could be a predictive biomarker for cervical cancer. Coptis chinensis may exert therapeutic effects through *MMP1* regulation via multiple pathways. Our findings provide a theoretical foundation for the clinical application of *MMP1*.

Keywords: Traditional Chinese medicine (TCM); Coptis chinensis; cervical cancer; *MMP1*; network pharmacology

Submitted Dec 22, 2024. Accepted for publication Jan 15, 2025. Published online Jan 23, 2025.
doi: 10.21037/tcr-2024-2608
View this article at: https://dx.doi.org/10.21037/tcr-2024-2608

Introduction

According to the GLOBOCAN 2020 statistics, cervical cancer is now the fourth leading cause of cancer-related deaths among women (1). In 2020, there were 604,127 new cases of cervical cancer and 341,831 cervical cancer-related deaths worldwide (2). Persistent infection with high-risk human papillomavirus (HPV) is the primary risk factor for cervical cancer (3). In recent years, early screening for cervical cancer precursors, improvements in clinical diagnosis and treatment methods, increased HPV vaccination, and early screening have effectively reduced the incidence and mortality of cervical cancer (4). However, low- and middle-income countries still have low HPV vaccination coverage and inadequate cervical cancer screening, resulting in higher incidence and mortality rates compared to developed countries (5).

For non-metastatic cervical cancer patients, the main treatments remain surgery and radiation therapy, while for metastatic patients, the treatment is typically chemoradiotherapy. New, effective, low-cost, and low-toxicity therapeutic agents urgently need to be identified (6). Traditional Chinese medicine (TCM) has been widely used in the treatment of cancer, and has been shown to improve drug sensitivity, regulate immune function, enhance chemotherapy effects, and improve patient prognosis (7). The advantages of TCM lie in its multi-targeted and multi-pathway effects, which result in broad biological activity and lower toxicity, making it a viable alternative therapy for various cancers, including cervical cancer.

From the perspective of TCM theory, cervical cancer falls under categories like "abnormal bleeding" and "leukorrhea", and its etiological factors are often related to kidney deficiency, dampness-heat accumulation, and the disruption of the Chong and Ren meridians. Thus, TCM treatment for cervical cancer focuses on syndrome differentiation to restore the internal environment of the body, alleviate symptoms, control the disease, and prolong survival (8). Coptis chinensis, a TCM herb, is bitter and cold, affecting the heart, spleen, stomach, liver, gallbladder, and large intestine channels, and possesses heat-clearing, dampness-drying, and detoxifying properties. Based on its pharmacological properties, Coptis chinensis exerts multiple pharmacological actions, including antibacterial, antiviral,

Highlight box

Key findings

- This study identified matrix metalloproteinase 1 (*MMP1*) as a critical target gene associated with cervical cancer prognosis, and showed that Coptis chinensis may regulate MMP1 and thus may have therapeutic potential. Molecular docking confirmed strong binding affinity between quercetin (a component of Coptis chinensis) and *MMP1*, and a retrospective analysis showed that chemotherapy combined with Coptis chinensis significantly reduced *MMP1* expression, resulting in improved patient outcomes.

What is known, and what is new?

- Previous research indicates that traditional Chinese medicine, including Coptis chinensis, has potential anti-tumor effects. *MMP1* has been linked to tumor progression and a poor prognosis in various cancers.
- The present study identified *MMP1* as a significant predictive biomarker in cervical cancer, and highlighted the role of Coptis chinensis's in modulating *MMP1* through multiple pathways, reinforcing its potential as an adjuvant therapy to improve patient prognosis.

What is the implication, and what should change now?

- Our findings suggest that incorporating Coptis chinensis into conventional chemotherapy could improve treatment efficacy for cervical cancer by downregulating *MMP1* expression. Future clinical guidelines should consider the inclusion of Coptis chinensis or its active compounds as part of a comprehensive treatment strategy. Further research and clinical trials should be conducted to validate our findings and establish standardized treatment protocols.

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anti-inflammatory, anti-arrhythmic, antihypertensive, and anti-tumor effects (9). The choice to study Coptis chinensis for cervical cancer treatment is grounded in TCM theory and the pharmacological characteristics of the herb. Its heat-clearing and detoxifying effects align with the TCM causation of cervical cancer, while its anti-tumor properties offer significant advantages. Therefore, this study aimed to systematically explore the potential efficacy of Coptis chinensis on cervical cancer by using network pharmacology methods and preliminarily reveal its mechanism of action through bioinformatics means. Our research results not only provide a scientific basis for clarifying the role of Coptis chinensis in cervical cancer but also lay a theoretical foundation for the research and development and clinical application of new anti-cervical cancer drugs based on Coptis chinensis. We present this article in accordance with the REMARK reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-2024-2608/rc).

Methods

Screening of active components and target genes

The active components of Coptis chinensis were screened using the Traditional Chinese Medicine Systems Pharmacology (TCMSP) platform (http://tcmspw.com/) based on the following criteria: drug-like properties (DLP) ≥0.18 and oral bioavailability (OB) ≥30%. Predicted target genes for effective compounds were selected from the DrugBank (https://www.drugbank.ca/) database. The target information was also compared using the UniProt (https://www.uniprot.org/) database.

Screening of differentially expressed genes (DEGs)

DEGs from cervical cancer tumor and adjacent tissue samples were obtained from the Gene Expression Omnibus (GEO) dataset GSE7803 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE7803), and the Coptis chinensis target genes and DEGs in the GSE7803 dataset were intersected to identify the final candidate target genes.

Data analysis using The Cancer Genome Atlas (TCGA) database

The expression of the key genes in the cervical cancer tumor tissues and their correlation with patient prognosis were explored using TCGA (https://portal.gdc.cancer.gov/) database.

Molecular docking

The three-dimensional (3D) structures of the effective compounds were retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov/). The receptor proteins for the key targets genes were obtained from PDB (http://www.rcsb.org/pdb/home/home.do). The 3D structures of the active components and key target proteins were uploaded to the online analysis platform DockThor (https://dockthor.lncc.br/v2/) for molecular docking. Based on the DockThor calculations, a lower binding energy during ligand-receptor binding indicated a more stable and effective interaction. Finally, visualization was performed using the CB-DOCK2 (https://cadd.labshare.cn/cb-dock2/) database.

Gene set enrichment analysis (GSEA)

A functional analysis of the DEGs was conducted using Metascape (https://metascape.org/) online. A GSEA was conducted to determine whether the entire genomic set was significantly enriched or depleted in terms of the biological processes, which in turn helped to identify the common signaling pathways and regulatory network modules, and to understand the biological differences between the samples (10).

Study subjects and grouping

Cervical cancer patients admitted to Nanjing Lishui People's Hospital from June 2021 to June 2022 were selected as the study subjects. To be eligible for inclusion in this study, the patients had to meet the following inclusion criteria: (I) have been pathologically diagnosed with primary cervical cancer; (II) have not undergone any prior chemotherapy or radiotherapy before study enrollment; (III) provide informed consent or have a family member provide informed consent; (IV) have a Karnofsky Performance Status score >70; and (V) have complete medical records. Patients were excluded from the study if they met any of the following exclusion criteria: (I) had other malignant tumors; (II) had an estimated survival time of less than 3 months; (III) had severe heart, liver, or kidney dysfunction; (IV) had abnormalities in their complete blood count or electrocardiogram results; and/or (V) had an inability to comply with treatment and follow-up assessments.

A total of 60 patients were included in the study and randomly divided into the control and study groups. The control group received a chemotherapy regimen of docetaxel combined with carboplatin, while the study group

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Table 1 Total effective compounds of Coptis chinensis in the TCMSP database (OB ≥30% and DLP ≥0.18)

Palmatine
Magnograndiolide
(R)-Canadine
Quercetin
Worenine
Epiberberine
Berberine
Berlambine
Berberrubine
Coptisine

TCMSP, Traditional Chinese Medicine Systems Pharmacology; OB, oral bioavailability; DLP, drug-like properties.

was given berberine tablets on the basis of the control group (specification: 0.1 g, Hangzhou Sanofi Minsheng Health Pharmaceutical Co., Ltd., Hangzhou, China). Patients had to take berberine tablets twice a day, 5 tablets each time (11). Each treatment cycle lasted 21 days, and both groups underwent continuous treatment for three cycles. The general clinical data of the patients were collected, including age, body mass index (BMI), menstrual status, histological classification, clinical stage, lymph node metastasis, and maximum tumor diameter. The patients were followed up via telephone and outpatient interviews, with the follow-up period ending on patient death, resulting in a follow-up rate of 100%. The final cut-off date for follow-up was June 2024.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of the Nanjing Lishui People's Hospital (No. 2024KY1105-02), and informed consent was taken from all the patients or their family.

Detection of MMP1

Blood samples (3 mL) were collected from the elbow vein of patients in a fasting state both before and after treatment. After the addition of a coagulant, the samples were allowed to stand at room temperature for 2 hours, and then centrifuged at 2,500 rpm for 10 minutes to separate the serum. The serum levels of matrix metalloproteinase 1 (*MMP1*) were measured by enzyme-linked immunosorbent assay (ELISA) in strict accordance with the instructions provided in the reagent kit (CSB-E04672h, Wuhan CUSABIO Biotech Co., Ltd., Wuhan, China). The patients were classified into high- and low-expression groups based on the median value of the *MMP1* expression levels among all patients.

Statistical analysis

The statistical analysis and visualization were performed using R software (version 3.6.3). A GSEA was conducted to explore the potential cellular mechanisms of CCNA2. The Kaplan-Meier method was used to assess patient survival, and the log-rank test was employed for significance testing. Graphs were created using GraphPrism (version 8.0, GraphPad Software, La Jolla, CA, USA). For the continuous data that conform to a normal distribution, comparisons between two groups were performed using the independent samples *t*-test, and the results are expressed as the mean ± standard deviation ($\bar{x}$±s). For the categorical data, comparisons between groups were conducted using the χ^2 test, and the results are expressed as the frequency and rate [n (%)]. The factors potentially influencing the prognosis of cervical cancer patients were analyzed by univariate and multivariate Cox analyses. A P value <0.05 or a log-rank P value <0.05 was considered statistically significant.

Results

Screening the active components and target genes of Coptis chinensis

Using the TCMSP database, and a DLP ≥0.18 and OB ≥30% as the screening criteria, the study identified ten effective compounds in Coptis chinensis (see *Table 1*), and a total of 181 target genes were selected from the DrugBank database.

Screening of DEGs

The DEGs from the GSE7803 dataset in the GEO database were selected using the following criteria: |log fold change| >2 and P<0.05. This stringent threshold was chosen to ensure that the selected genes have robust and statistically significant differential expression, minimizing potential false positives. Volcano plots, principal component analysis (PCA) plots, heatmaps, and normalized box plots were

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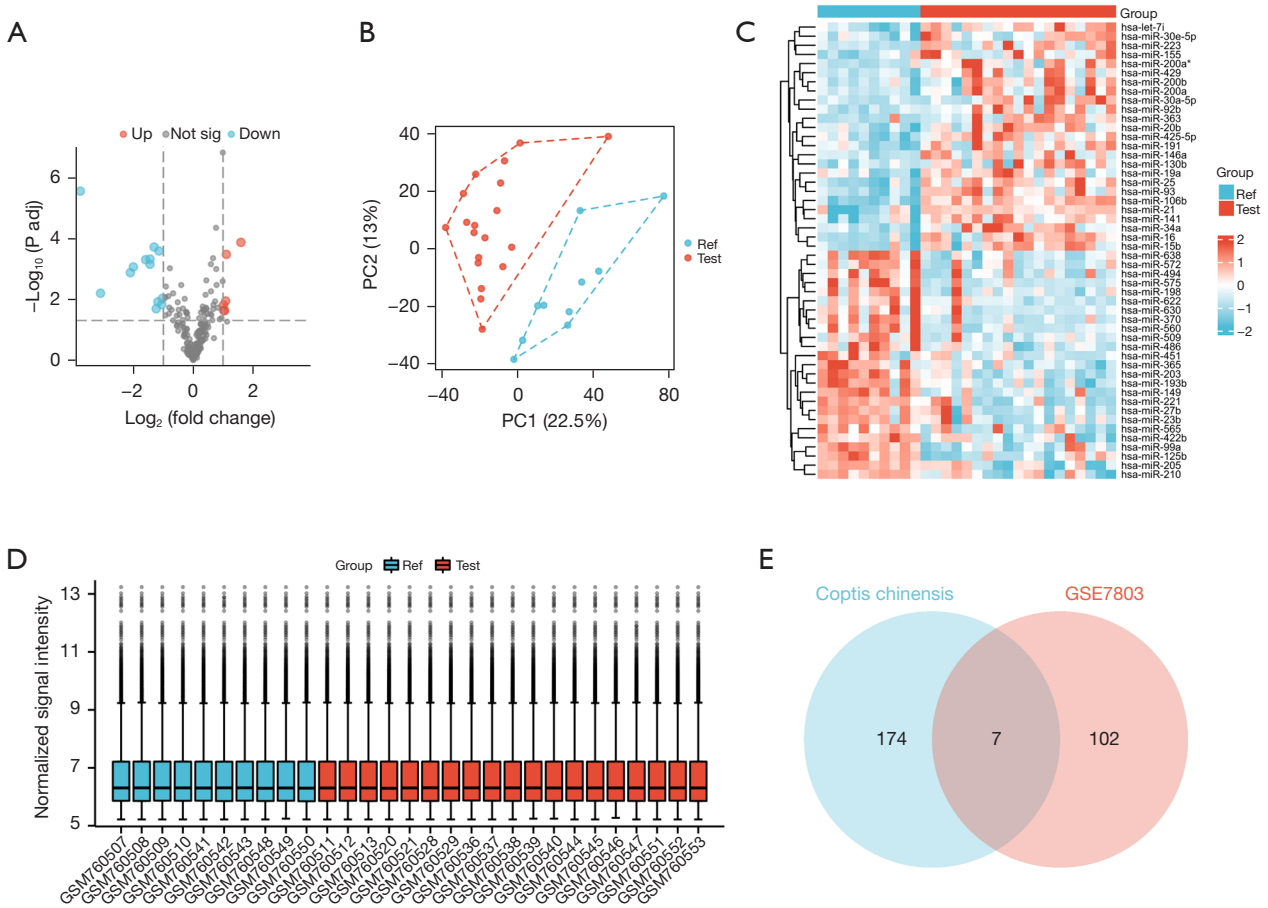

Figure 1 Screening of DEGs. (A-D) Volcano plot, PCA plot, heatmap, and normalized box plot of the GSE7803 dataset. (E) Venn diagram of target genes of effective compounds from Coptis chinensis and DEGs in the GSE7803 dataset. DEGs, differentially expressed genes; PCA, principal component analysis.

generated (*Figure 1A-1D*). The effective target genes of Coptis chinensis were intersected with the DEGs from this dataset, resulting in the identification of the following seven candidate target genes: *AR*, *MAOB*, *CDKN2A*, *TOP2A*, *CXCL8*, *MMP1*, and *SPP1* (*Figure 1E*).

Expression of DEGs in cervical cancer tissues from TCGA database and their predictive value

In TCGA database, the expression levels of the aforementioned seven genes were examined. Compared to normal tissues, in the non-paired cervical cancer tumor tissues, the expression of *AR* and *MAOB* was downregulated, while the expression of *CDKN2A*, *TOP2A*, *MMP1*, and *SPP1* was upregulated, and the differences were statistically significant (P<0.05). Only *CXCL8* showed no statistically significant difference in terms of expression between the cancerous and adjacent tissues (*Figure 2A*). The receiver operating characteristic (ROC) curve analysis in TCGA database indicated that except for *CXCL8*, the area under the curve (AUC) for the remaining six key genes was greater than 0.8, suggesting that these genes had good predictive discriminative value (*Figure 2B*).

Correlation between the expression of the key DEGs and the prognosis of cervical cancer patients

Kaplan-Meier survival curves were constructed in the TCGA database, and it was found that cervical cancer patients with low expression of *MMP1* or *SPP1* had better prognosis [overall survival (OS), disease-specific survival (DSS), and progression-free interval (PFI)] compared to

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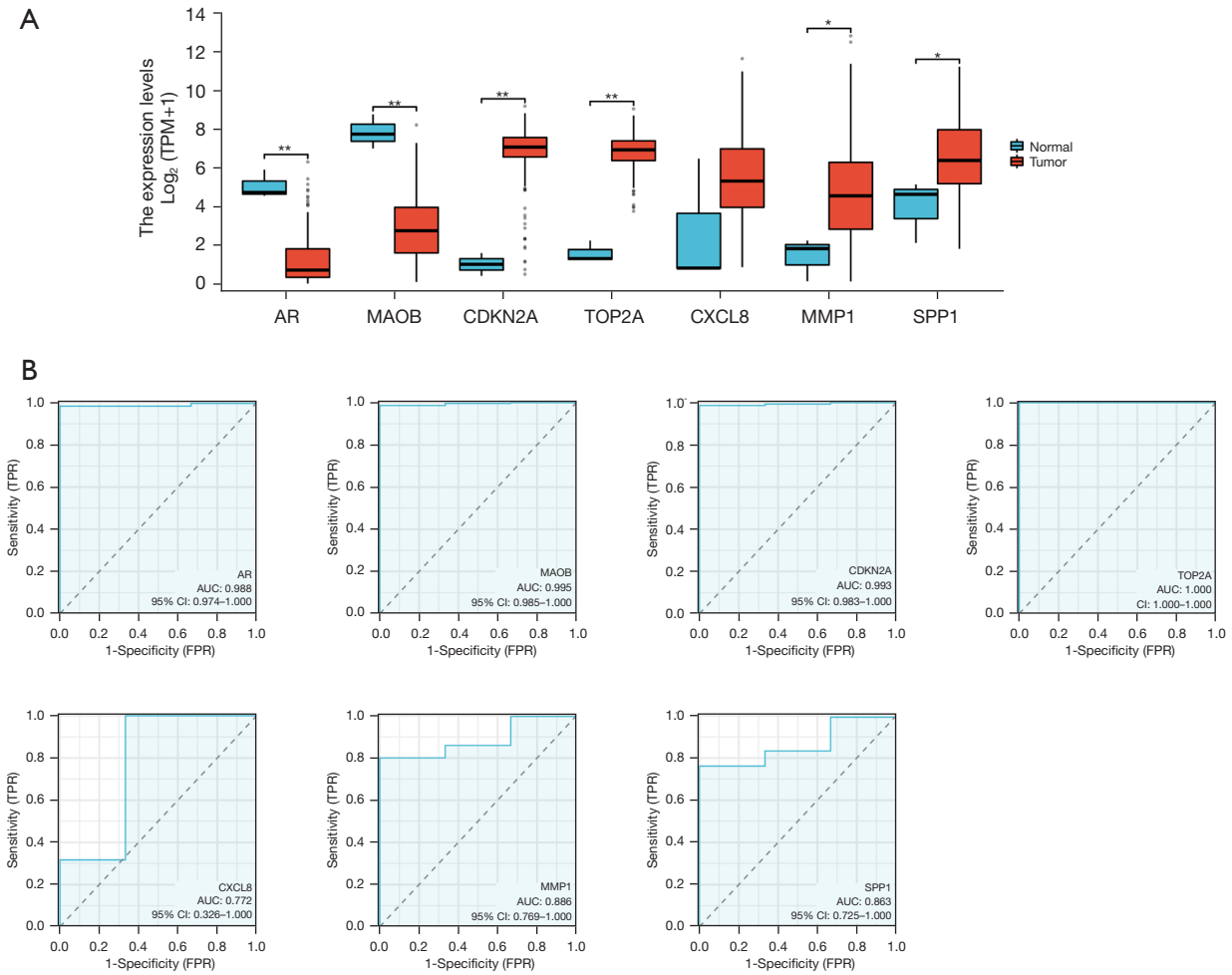

Figure 2 Expression of DEGs in cervical cancer tissues from TCGA database and their predictive value. (A) Expression of DEGs in non-paired cervical cancer tissues (306 cases of cancer tissue, 3 cases of adjacent tissue); (B) ROC curves of DEGs in TCGA database. *, P<0.05; **, P<0.01. TPM, transcripts per million; TPR, true positive rate; FPR, false positive rate; AUC, area under the curve; CI, confidence interval; DEGs, differentially expressed genes; TCGA, The Cancer Genome Atlas; ROC, receiver operating characteristic.

those with high expression, and all the differences were statistically significant (P<0.05) (*Figure 3A-3C*).

Molecular docking

During the DEG screening process, the expression of the candidate genes in the cervical cancer tumor tissues and their correlation with patient prognosis were examined. *MMP1* and *SPP1* were identified as candidate genes, and were both associated with quercetin, a compound found in Coptis chinensis. The 3D structure of quercetin was obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/), while the receptor protein structures of the two key targets were obtained from PDB (http://www.rcsb.org/pdb/home/home.do). The 3D structures of the active ingredient and the receptor proteins were uploaded to the online analysis platform DockThor (https://dockthor.lncc.br/v2/) for molecular docking. The results showed that *MMP1* had an affinity of –9.2 for quercetin, while *SPP1* had an affinity of –6.3. Further visualization was conducted using the CB-DOCK2 database (https://cadd.labshare.cn/cb-dock2/) (*Figure 4A,4B*). Based on the affinity strength, *MMP1* may be the key gene through which Coptis chinensis exerts its effects.

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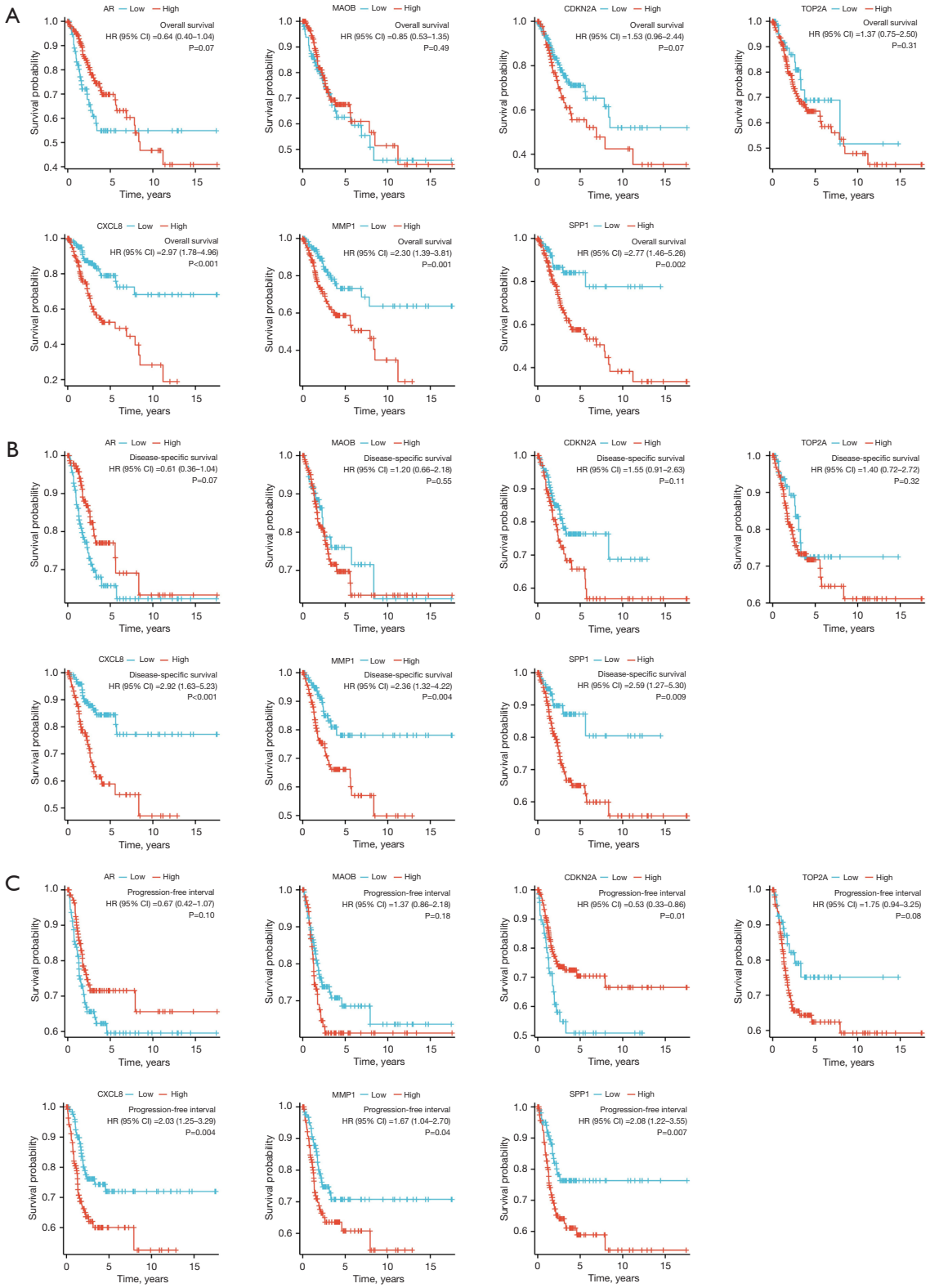

Figure 3 Correlation between the expression of the key DEGs and the prognosis of cervical cancer patients in TCGA database. (A-C) OS, DSS, and PFI curves, respectively. P<0.05, differences are statistically significant. HR, hazard ratio; DEGs, differentially expressed genes; TCGA, The Cancer Genome Atlas; OS, overall survival; DSS, disease-specific survival; PFI, progression-free interval.

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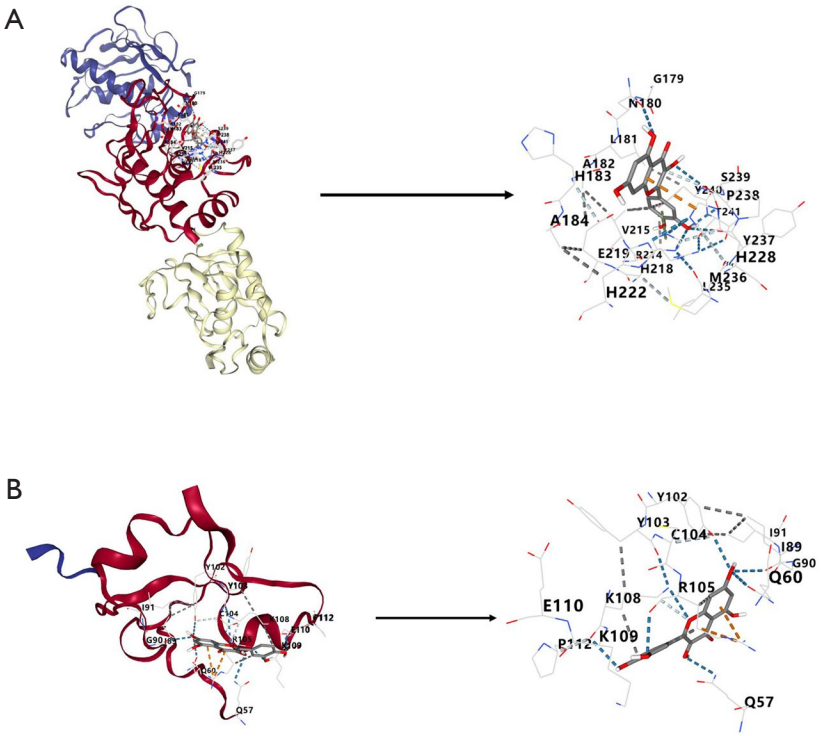

Figure 4 Molecular docking diagrams of the effective compound quercetin from TCM Coptis chinensis with the core targets *MMP1* (A) and (B) *SPP1*. TCM, traditional Chinese medicine.

Prediction of signaling pathways based on GSEA

A functional GSEA was conducted using the Metascape online platform. The results showed that *MMP1* appears to influence various biological processes in cervical cancer by participating in the regulation of the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), Janus kinase/signal transducer and activator of transcription (JAK/STAT), transforming growth factor-β (TGF-β), mitogen-activated protein kinase (MAPK), and hypoxia-inducible factor 1 (HIF1) pathways, and apoptosis (*Figure 5*).

Analysis of the clinical pathological characteristics of the control and study groups

There were no statistically significant differences in the clinical baseline characteristics between the two groups of patients (P>0.05, *Table 2*).

Expression of MMP1

There was no significant difference in *MMP1* expression between the study group and the control group before treatment (9.12±5.00 *vs.* 9.38±4.51 ng/mL, P=0.83). However, post-treatment, *MMP1* expression in the study group was significantly lower than that in the control group (5.05±2.74 *vs.* 9.00±4.70 ng/mL, P<0.001) (*Figure 6*).

Univariate and multivariate Cox regression analyses of prognosis in cervical cancer

Patients' age, BMI, menstrual status, histological classification, clinical stage, lymph node metastasis, maximum tumor diameter, and *MMP1* expression before and after treatment were used as independent variables, with follow-up time as the time variable and survival status as the dependent variable. The multivariate Cox regression analysis revealed that clinical stage III or IV, lymph node metastasis, high *MMP1* expression before treatment, high *MMP1* expression after treatment, and the absence of combined treatment with TCM Coptis chinensis were independent risk factors affecting the prognosis of cervical cancer patients, and the differences were statistically

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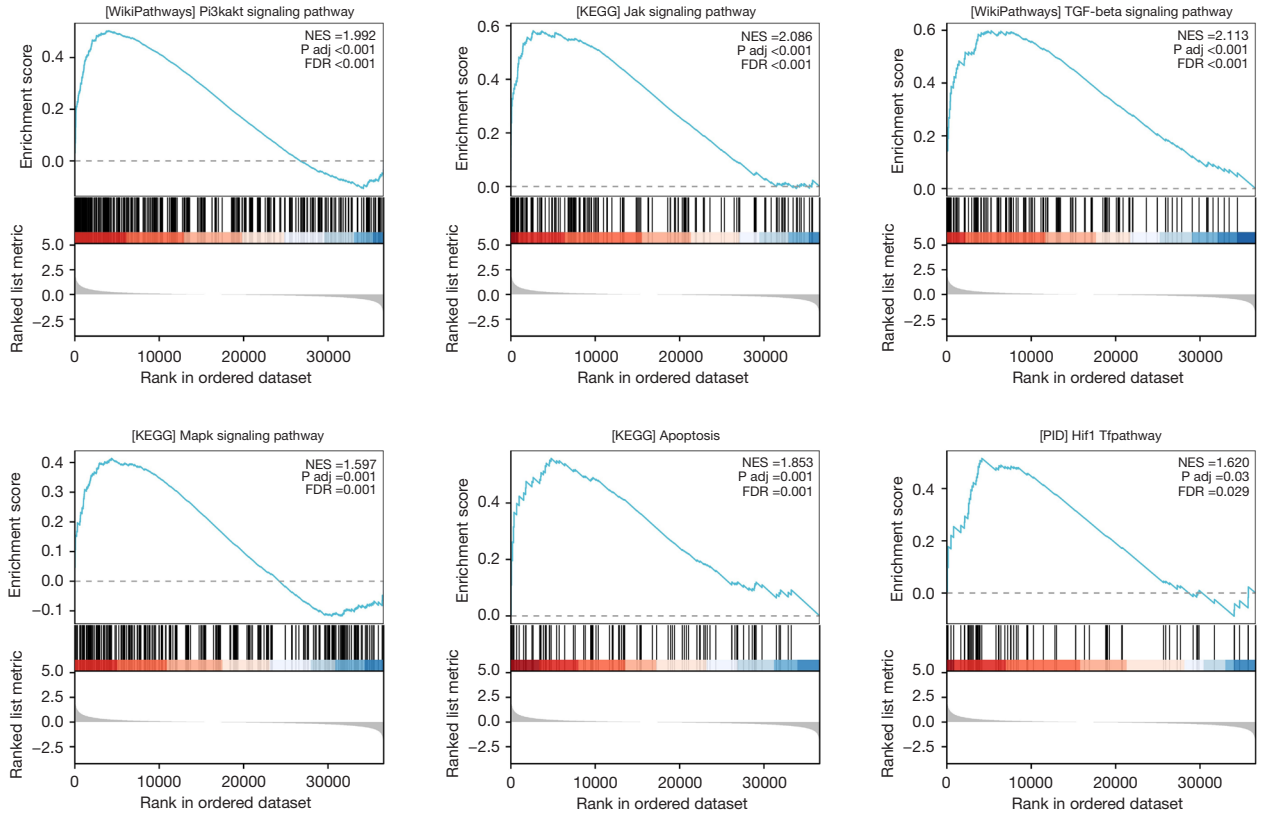

Figure 5 Statistically significant potential pathways in the GSEA. The gene set was sourced from Molecular Signatures Database (MSigDB, https://www.gsea-msigdb.org/gsea/msigdb). A total of 1,600 random-sample permutations were performed. NES, normalized enrichment score; FDR, false discovery rate; KEGG, Kyoto Encyclopedia of Genes and Genomes; GSEA, gene set enrichment analysis.

significant (P<0.05) (*Table 3*).

Discussion

TCM is a valuable treasure of medicine in China, with unique advantages in disease prevention and treatment. TCM aligns with the new generation of medical research paradigms that foster the development of network pharmacology (12,13). Network pharmacology is a multidisciplinary research method that integrates network science, systems biology, and pharmacology to reveal interactions between drugs and diseases (14-16). It can aid in understanding the multi-target and multi-component synergistic effects of drugs, providing new ideas and methods for the development and clinical application of drugs (17). Network pharmacology and TCM promote and complement each other, driving the development of drug research and clinical practice.

This study, which was based on network pharmacology and bioinformatics, identified core targets and mechanisms of Coptis chinensis in the treatment of cervical cancer. We verified the differential expression of the core target genes and their effects on the survival of cervical cancer patients from TCGA database, and further confirmed the direct interaction of the key gene *MMP1* with the effective compound through molecular docking.

MMP1 is a zinc-dependent protease belonging to the MMP family. Its main substrate is fibrillar collagen, which can degrade collagen fibers and gelatin in the extracellular matrix, altering the cellular microenvironment, and facilitating tumor invasion and metastasis. *MMP1* plays a critical role in the initial stages of tumorigenesis, promoting tumor formation (18,19). Zhao *et al.* (20) revealed that *MMP1* could be a novel immunotherapy biomarker for prognosis in cervical cancer patients. Li *et al.* (21) found that the protein-ligand complex between *MMP1* and a specific compound was the most stable target in exploring the pharmacological effects of a traditional Chinese herb

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Table 2 Baseline characteristics of cervical cancer patients in both groups

Clinical data	Control group (n=30)	Study group (n=30)	χ^2/t	P
Age (years)			0.1113	0.74
<45	6 (20.00)	5 (16.67)		
≥45	24 (80.00)	25 (83.33)		
BMI (kg/m^2)			0.2871	0.59
<24	18 (60.00)	20 (66.67)		
≥24	12 (40.00)	10 (33.33)		
Menstrual status			0.6932	0.41
Premenopausal	22 (73.33)	19 (63.33)		
Postmenopausal	8 (26.67)	11 (36.67)		
Histological classification			0.3175	0.57
Squamous cell carcinoma	20 (66.67)	22 (73.33)		
Adenocarcinoma	10 (33.33)	8 (26.67)		
Clinical stage			0.2778	0.60
Stage I/II	19 (63.33)	17 (56.67)		
Stage III/IV	11 (36.67)	13 (43.33)		
Lymph node metastasis			0.8000	0.37
No	24 (80.00)	21 (70.00)		
Yes	6 (20.00)	9 (30.00)		
Tumor diameter (cm)			0.3000	0.58
<4	21 (70.00)	19 (63.33)		
≥4	9 (30.00)	11 (36.67)		
MMP1 expression (ng/mL)				
Pre-treatment	9.12±5.00	9.38±4.51	–0.2106	0.83
Post-treatment	9.00±4.70	5.05±2.74	3.97	<0.001

Data are presented as n (%) or mean ± SD. BMI, body mass index; SD, standard deviation.

on cervical cancer, and observed a potential link between increased *MMP1* expression and interlukin-17 pathway activation. These studies support the research value of *MMP1* in cervical cancer.

The present study identified quercetin (a flavonoid compound found in many plants) as a compound binding to *MMP1*, and quercetin is known for its antioxidant, anti-inflammatory, anti-tumor, and antibacterial activities. Its molecular structure features a phenolic and a pyran ring that grant it unique chemical and biological properties. Previous studies have also highlighted the significance of quercetin in cervical cancer research (20-22); for example, quercetin can induce cell death in cervical cancer by reducing the O-GlcNAcylation of AMP-activated protein kinase, and exerts a synergistic inhibitory effect with cisplatin on cervical cancer cells (22). Quercetin may inhibit cancer cell proliferation, migration, and invasion, and promote apoptosis by downregulating the expression of *MMP2*, ezrin, *METTL3*, and P-Gp, thereby enhancing the anti-tumor effect of cisplatin (23). Additionally, quercetin can modify 5'CpG promoter methylation in human cervical cancer cells, and reactivate various tumor suppressor genes through epigenetic regulation (24).

The GSEA suggested that *MMP1* may influence different

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biological processes in cervical cancer through pathways, including the PI3K/AKT, JAK/STAT, TGF-β, MAPK, and HIF1 pathways, and apoptosis. The PI3K/AKT pathway plays a crucial role in cell survival, proliferation, migration, and invasion. Quercetin may inhibit cervical cancer cell proliferation and metastasis by suppressing the activation of the PI3K/AKT pathway, and reducing the expression of downstream growth-promoting and invasive factors (25). The JAK/STAT pathway participates in the signaling transduction of various cytokines, and regulates cell growth, differentiation, apoptosis, and the immune response, which are often abnormally activated in tumors, thus promoting tumor development and metastasis (26). The TGF-β pathway is significant for cell growth, differentiation, apoptosis, and immune regulation. In tumors, this pathway may have dual roles, inhibiting early tumor formation and promoting invasion and metastasis in late-stage tumors (27). The MAPK pathway is involved in transducing various extracellular signals, regulating cell growth, differentiation, apoptosis, and the stress response, and is frequently abnormally activated in tumors (28). The apoptosis pathway is the main route for programmed cell death, and it is crucial for maintaining homeostasis and inhibiting tumor development (29). The HIF1 pathway is one of the primary mechanisms by which cells adapt to hypoxic environments, and this pathway plays an essential role in tumor occurrence, development, and metastasis. HIF1 can regulate the expression of various genes associated with tumor invasion and metastasis (30). These studies provide insights into the potential mechanisms by which Coptis chinensis works in cervical cancer treatment. These pathways may interconnect and work together to form a complex regulatory network. For example, PI3K/AKT and the HIF1 pathway may jointly regulate the adaptation of tumor cells to the hypoxic microenvironment, enhancing tumor cell survival and invasiveness by promoting angiogenesis and metabolic reprogramming. In addition, the cross-action of TGF-β with the MAPK pathway may further promote

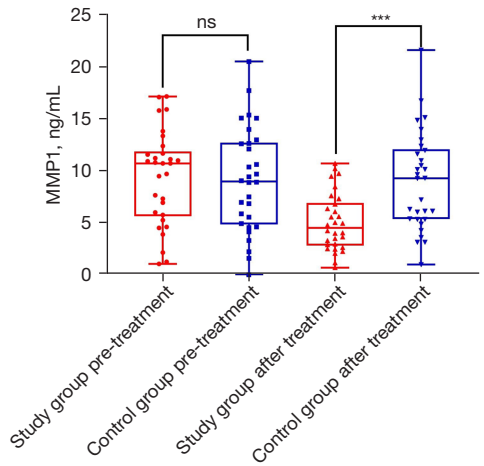

Figure 6 Comparison of *MMP1* expression levels between study and control groups. ***, P<0.001; ns, no significance.

Table 3 Univariate and multivariate Cox regression analyses of prognosis in cervical cancer patients

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age (≥45 years)	1.1600	0.2570–5.2370	0.85	–	–	–
BMI (≥24 kg/m^2)	0.7664	0.2360–2.4896	0.66	–	–	–
Menstrual status (postmenopausal)	2.9225	0.9809–8.7066	0.054	–	–	–
Histological classification (adenocarcinoma)	1.0714	0.3299–3.4799	0.91	–	–	–
Clinical stage (stage III/IV)	6.1369	1.6864–22.3321	0.006	15.5869	2.3514–103.3227	0.004
Lymph node metastasis (yes)	9.0899	2.7853–29.6651	<0.001	12.1178	1.5267–96.1812	0.02
Tumor diameter (≥4 cm)	1.8415	0.6187–5.4814	0.27	–	–	–
Pre-treatment *MMP1* expression (high)	14.2135	1.8454–109.4754	0.01	27.5654	1.8791–404.3689	0.02
Post-treatment *MMP1* expression (high)	14.5910	1.8950–112.3500	0.01	13.0921	1.0257–167.1045	0.048
Treatment regimen (docetaxel + carboplatin combined with Coptis chinensis)	0.2443	0.0671–0.8895	0.03	0.0118	0.0007–0.1899	0.001

BMI, body mass index; HR, hazard ratio; CI, confidence interval.

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tumor progression by enhancing inflammation and cell migration. This multi-channel synergy effect may be one of the key mechanisms of MMP1 regulation. Quercetin, the main active component of Coptis chinensis, may achieve its significant anti-tumor effect through multi-target and multi-pathway.

To further validate *MMP1* as a potential target for Coptis chinensis treatment in cervical cancer, this study conducted a retrospective analysis of *MMP1* expression in the peripheral blood of cervical cancer patients. The results indicated that the *MMP1* expression levels were significantly lower in patients receiving conventional chemotherapy combined with Coptis chinensis than those receiving conventional chemotherapy alone. Multivariate Cox regression analysis revealed that high *MMP1* expression and the absence of combined treatment with Coptis chinensis were independent risk factors affecting the prognosis of cervical cancer patients. This further suggests that *MMP1* may serve as an effective evaluation indicator for predicting the prognosis of cervical cancer patients. Additionally, the combination of Coptis chinensis with conventional chemotherapy could improve the prognosis of cervical cancer patients, possibly through mechanisms related to targeting *MMP1*.

Although this study confirms the critical role of *MMP1* in cervical cancer and explores its potential as a therapeutic target for Coptis chinensis, this study still has limitations. First, the retrospective analysis time of this study is short, which may not fully reflect the long-term effect of Coptis chinensis in cervical cancer treatment, and the peripheral blood samples are limited in representation, which may not fully reflect the molecular changes in the tumor microenvironment. Second, the specific molecular mechanism by which Coptis chinensis downregulates *MMP1* needs to be further investigated. Furthermore, our study is based on retrospective analysis and molecular docking techniques, which can only reveal correlations and cannot directly prove causation. Retrospective data can provide valuable observational evidence, but its results are susceptible to patient selection bias, incomplete data, and other potential confounding factors. Finally, although molecular docking experiments revealed that *MMP1* has a strong binding force to quercetin in Coptis chinensis, the molecular docking results only provide theoretical binding checkpoints and affinity, and there is a lack of sufficient *in vivo* and clinical experimental evidence to verify the actual biological role between these compounds and *MMP1*. Future studies will extend the study time, combine the analysis of peripheral blood and tissue samples, and systematically verify the specific molecular mechanism and clinical efficacy of Coptis chinensis down-regulating *MMP1* through *in vitro* cell experiments, *in vivo* animal models, and prospective multicenter clinical trials. At the same time, the molecular docking results will be further verified to provide a more solid scientific basis.

Conclusions

Using network pharmacology and bioinformatics analysis, this study explored the potential mechanisms through which Coptis chinensis inhibits cervical cancer via multiple targets and pathways. The preliminary validation of the interaction between Coptis chinensis and cervical cancer targets via molecular docking provides a theoretical basis for further *in vitro* experiments. In addition, the study also found that Coptis chinensis combined with conventional chemotherapy significantly reduced the expression of *MMP1* in the peripheral blood of patients with cervical cancer. High expression of *MMP1* is significantly associated with a poor prognosis in patients. These findings provide important support for the clinical application of Coptis chinensis as an adjuvant treatment for cervical cancer and offer new ideas for further research on its anti-tumor mechanism in the future. In the future, more extensive experimental validation and clinical trials are still needed to confirm its therapeutic effect and a more comprehensive mechanism.

Acknowledgments

None.

Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-2024-2608/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-2024-2608/dss

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-2024-2608/prf

Funding: None.

Conflicts of Interest: All authors have completed the ICMJE

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uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-2024-2608/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of the Nanjing Lishui People's Hospital (No. 2024KY1105-02), and informed consent was taken from all the patients or their family.

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References

1. Cao W, Qin K, Li F, et al. Comparative study of cancer profiles between 2020 and 2022 using global cancer statistics (GLOBOCAN). J Natl Cancer Cent 2024;4:128-34.
2. Singh D, Vignat J, Lorenzoni V, et al. Global estimates of incidence and mortality of cervical cancer in 2020: a baseline analysis of the WHO Global Cervical Cancer Elimination Initiative. Lancet Glob Health 2023;11:e197-206.
3. Momenimovahed Z, Mazidimoradi A, Amiri S, et al. Temporal trends of cervical cancer between 1990 and 2019, in Asian countries by geographical region and socio-demographic index, and comparison with global data. Oncologie 2023;25:119-48.
4. D'Augè TG, Donato VD, Giannini A. Strategic Approaches in Management of Early-Stage Cervical Cancer: A Comprehensive Editorial. Clin Exp Obstet Gynecol 2024;51:235.
5. Amatya Vaidya S, Roka Magar L, Magar SB. Knowledge of Cervical Cancer Screening and Prevention by Human Papillomavirus Deoxyribonucleic Acid and Human Papillomavirus Vaccination among Women Attending a Tertiary Care Centre. JNMA J Nepal Med Assoc 2023;61:658-61.
6. Abu-Rustum NR, Yashar CM, Arend R, et al. NCCN Guidelines® Insights: Cervical Cancer, Version 1.2024. J Natl Compr Canc Netw 2023;21:1224-33.
7. Wu D, Zhou R, Chen H, et al. The Role of Traditional Chinese Medicine in the Management of Cervical Cancer. Am J Chin Med 2024;52:1013-25.
8. Ma F, Wang Q, Zhang D, et al. Comparative efficacy and safety of Chinese medicine injections as an adjunctive therapy for cervical cancer in Chinese patients: a network meta-analysis. Pharm Biol 2024;62:170-82.
9. Lu Q, Tang Y, Luo S, et al. Coptisine, the Characteristic Constituent from Coptis chinensis, Exhibits Significant Therapeutic Potential in Treating Cancers, Metabolic and Inflammatory Diseases. Am J Chin Med 2023;51:2121-56.
10. Song Z, Yu J, Wang M, et al. CHDTEPDB: transcriptome expression profile database and interactive analysis platform for congenital heart disease. Congeni Heart Dis 2023;18:693-701.
11. Rondanelli M, Riva A, Petrangolini G, et al. Berberine Phospholipid Is an Effective Insulin Sensitizer and Improves Metabolic and Hormonal Disorders in Women with Polycystic Ovary Syndrome: A One-Group Pretest-Post-Test Explanatory Study. Nutrients 2021;13:3665.
12. Wang X, Wang ZY, Zheng JH, et al. TCM network pharmacology: A new trend towards combining computational, experimental and clinical approaches. Chin J Nat Med 2021;19:1-11.
13. Lv L, Zhao J, Wag X, et al. Fang-Xia-Dihuang decoction inhibits breast cancer progression induced by psychological stress via down-regulation of PI3K/AKT and JAK2/STAT3 pathways: An in vivo and a network pharmacology assessment. Biocell 2023;47:1977-94.
14. Nogales C, Mamdouh ZM, List M, et al. Network pharmacology: curing causal mechanisms instead of treating symptoms. Trends Pharmacol Sci 2022;43:136-50.
15. Xin Y, Sang Y, Ji X, et al. Explore the Constituents and Mechanism of Traditional Chinese Medicine Preparation Zhachong Shisan Pills Based on HPLC-QTOF-MS and Network Pharmacology. Curr Pharm Anal 2023;19:712-34.
16. Naqvi W, Singh A, Garg P, et al. Network biology: A promising approach for drug target identification against neurodevelopmental disorders. BIOCELL 2023;47:1675-87.
17. Han X, Wang C, Li R, et al. Network target theory and network pharmacology: Next generation drug research in medicine using AI models. Int J Clin Pharmacol Ther 2024;62:151-4.
18. Mao S, Xia A, Tao X, et al. A pan-cancer analysis of

the prognostic and immunological roles of matrix metalloprotease-1 (MMP1) in human tumors. Front Oncol 2022;12:1089550.
19. Zhang X, Deng Q, Wan X, et al. Pan-cancer analysis reveals the associations between MMP13 high expression and carcinogenesis and its value as a serum diagnostic marker. Aging (Albany NY) 2023;15:2115-35.
20. Zhao S, Yu M. Identification of MMP1 as a Potential Prognostic Biomarker and Correlating with Immune Infiltrates in Cervical Squamous Cell Carcinoma. DNA Cell Biol 2020;39:255-72.
21. Li X, Yu D, Wang Q, et al. Elucidating the molecular mechanisms of pterostilbene against cervical cancer through an integrated bioinformatics and network pharmacology approach. Chem Biol Interact 2024;396:111058.
22. Ali A, Kim MJ, Kim MY, et al. Quercetin induces cell death in cervical cancer by reducing O-GlcNAcylation of adenosine monophosphate-activated protein kinase. Anat Cell Biol 2018;51:274-83.
23. Xu W, Xie S, Chen X, et al. Effects of Quercetin on the Efficacy of Various Chemotherapeutic Drugs in Cervical Cancer Cells. Drug Des Devel Ther 2021;15:577-88.
24. Kedhari Sundaram M, Hussain A, Haque S, et al. Quercetin modifies 5'CpG promoter methylation and reactivates various tumor suppressor genes by modulating epigenetic marks in human cervical cancer cells. J Cell Biochem 2019;120:18357-69.
25. Ma C, Gu Y, Liu C, et al. Anti-cervical cancer effects of Compound Yangshe granule through the PI3K/AKT pathway based on network pharmacology. J Ethnopharmacol 2023;301:115820.
26. Zhang C, Gu L, Xiao J, et al. Knockdown of RBM15 inhibits tumor progression and the JAK-STAT signaling pathway in cervical cancer. BMC Cancer 2023;23:684.
27. Li L, Zhang R, Yang H, et al. GDF15 knockdown suppresses cervical cancer cell migration in vitro through the TGF-β/Smad2/3/Snail1 pathway. FEBS Open Bio 2020;10:2750-60.
28. Liu F, Chang L, Hu J. Activating transcription factor 6 regulated cell growth, migration and inhibiteds cell apoptosis and autophagy via MAPK pathway in cervical cancer. J Reprod Immunol 2020;139:103120.
29. Zhang K, Ji X, Song Z, et al. Butyrate inhibits the mitochondrial complex I to mediate mitochondria-dependent apoptosis of cervical cancer cells. BMC Complement Med Ther 2023;23:212.
30. Hao X, Zhao W, Zhang X, et al. Treatment of tumor-associated macrophages with PD-1 monoclonal antibodies affects vascular generation in cervical cancer via the PD-1/IRE1α/SHP2/HIF1α signaling pathway. Aging (Albany NY) 2024;16:12335-45.

(English Language Editor: L. Huleatt)

Cite this article as: Hou Y, Zhang L, Li H, Zhang R, Sun J, Jia H, Xu H. Exploration of key pathogenic mechanisms and potential intervention targets of the traditional Chinese medicine Coptis chinensis in the treatment of cervical cancer based on network pharmacology and molecular docking techniques. Transl Cancer Res 2025;14(1):626-639. doi: 10.21037/tcr-2024-2608

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