doi.org/10.36721/PJPS.2025.38.6.REG.12345.1

Effect of Baofukang suppository on the relative indexes of epithelial mesenchymal transformation of tumor cells and prognosis in patients with cervical cancer

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Abstract: Cervical cancer, a prevalent female malignancy, is treated with surgery, radiotherapy, chemotherapy, immunotherapy and targeted therapy. Yet, prognosis remains influenced by multiple factors. Epithelial-mesenchymal transformation (EMT) is an important link in the malignant progression of tumor cells and has an important impact on the progression and prognosis of cervical cancer. This study aimed to analyze effect of Baofukang suppository on the related indexes of EMT of tumor cells in cervical cancer patients. Eighty patients with cervical cancer received in The First Affiliated Hospital of Anhui Medical University from March 2020 to March 2022 were randomized into a control group (chemotherapy alone, n=40) and a study group (chemotherapy + Baofukang, n=40). Post-treatment, the study group showed significantly lower mRNA levels of EMT markers Vimentin and N-cadherin, and higher E-cadherin and β-catenin (p<0.05). Additionally, interleukin-6 (IL-6) decreased while interleukin-2 (IL-2) and interferon-γ (INF-γ) increased (p<0.05). Immune function improved, with higher $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ ratios, and lower $CD8^+$ (p<0.05). The adverse reactions between two groups were not unconspicuous (p>0.05). The adjuvant therapy of Baofukang Suppository can effectively regulate the relevant indexes of tumor cell EMT, delay or prevent the EMT of tumor cells.

Keywords: Baofukang suppository; Cervical cancer; Cytokine; Epithelial mesenchymal transformation; Immune function; Patient safety

Submitted on 16-11-2023 – Revised on 06-11-2024 – Accepted on 19-11-2024

INTRODUCTION

Cervical cancer as the most common malignant tumors, seriously threatens women's health worldwide. Squamous cell carcinoma of the cervix is more common, accounting for about 80% of cervical cancers, while adenocarcinoma is less common, accounting for about 20% (Johnson *et al*., 2019). Persistent infection of high-risk human papillomavirus (HPV) is a major risk factor for cervical cancer, but not all people infected with HPV will develop cervical cancer (Yuan *et al*., 2021). Currently, the incidence and mortality of cervical cancer have decreased significantly with the extensive development and improvement of screening for precancerous lesions of cervical cancer (Singh *et al*., 2023). Early diagnosis and early treatment have significantly improved the prognosis of cervical cancer, but the treatment effect for middle and advanced patients is still not satisfactory (Stumbar *et al*., 2019). The invasion and metastasis of cervical cancer is an important cause of postoperative recurrence and death (Huang *et al*., 2022). For the past few years, a number of researches have illustrated epithelial mesenchymal transformation (EMT) acts a very important part in tumor invasion and metastasis (Liao *et al*., 2022; Xu *et al*., 2021). As one of the key mechanisms of cervical cancer invasion and metastasis, the occurrence and development of EMT are complicated regulated by a variety of molecular markers, transcription factors, signaling pathways and non-coding RNA. Among them, Vimentin, N-cadherin, E-cadherin and β-catenin are common indicators of EMT cells and their expression can reflect the EMT process.

E-cadherin is an important component of epithelial intercellular adhesion. In normal tissues, decreased or absent expression of E-cadherin can lead to loss of intercellular connectivity, morphologic changes and consequently increased mobility. In epithelial tumors, E-cadherin can cause cancer cells to detach from primary lesion and metastasize to the peripheral lymph nodes, therefore, E-cadherin is a crucial factor to inhibit the malignant transformation of tumors and invasion and metastasis (Bure *et al*., 2019). β-catenin is a basic component of intercellular adhesion and it can bind to intracellular region of E-cadherin to form β-catenin/E-cadherin complex, which mediates intercellular adhesion. When E-cadherin and/or β-catenin are deficient, intercellular adhesion is lost and cells detach from their original tissues and undergo metastasis and invasion (Zhou *et al*., 2019). Studies have confirmed that N-cadherin can promote cell movement, so the over expression of N-cadherin can reduce the adhesion ability between cancer cells and promote cancer cell invasion and metastasis, so it can be used as a reliable indicator to

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reflect the progression of cervical cancer (Meng *et al*., 2021). Vimentin is associated with cell migration and increased expression of Vimentin can change the composition of cytoskeletal proteins, so it is closely related to cancer cells invasion and metastasis (Xiong *et al*., 2021). Therefore, regulating the expression of the above mentioned EMT-related factors is of great significance for regulating EMT and controlling the disease progression of cervical cancer.

Surgery, radiotherapy and chemotherapy are main means of treatment for cervical cancer at present, but they can cause a decline in immune function and lead to many complications. Therefore, the therapeutic effect of these treatment methods still needs to be improved (Cohen *et al*., 2019). With the extensive penetration of Chinese medicine theory in clinic and the deepening of research in recent years, the Chinese medicine protocol for adjuvant treatment of cervical cancer has been widely recognized. Baofukang suppository is composed of *Curcuma zedoary* oil and borneol. It has effect of activating blood circulation and removing blood stasis, clearing away heat and removing toxins, and removing decay and regenerating muscle (Bin *et al*., 2023). Previous studies have shown that Baofukang suppository can improve the local immune microenvironment and reduce the risk of cervical progression in high-risk HPV infection patients (He *et al*., 2022; Cai *et al*., 2020). However, whether Baofukang suppository can affect EMT in cervical cancer patients is still controversial.

Therefore, this study was aimed to explore the impact of Baofukang suppository on the related indexes of EMT in cervical cancer patients and to further discuss the possible mechanism of prevention and treatment of cervical cancer by Baofukang Suppository.

MATERIALS AND METHODS

Patients

Cervical cancer patients were included in this study. Inclusion criteria: age range 18~60 years old; Tumor Node Metastasis (TNM) staging IIa~IIIb; the expected survival time is more than 6 months; all have indications for chemotherapy. Exclusion criteria: Allergy to the study drug; pregnant or lactating women; psychopath; poor compliance, difficult to cooperate with the whole treatment cycle; heart, liver and kidney dysfunction. According to the above criteria, total number of 80 cases were enrolled and randomly assigned to two groups, with 40 patients in each group.

Treatment method

Both groups were treated with electrolyte balance maintenance, nutritional support and conventional basic treatment. On this basis, control group received chemotherapy and regimen was as follows: 50mg/m^2 of cisplatin was added into 1500mL of 0.9% sodium chloride injection and then injected intravenously and dissolve 140mg/m^2 paclitaxel into 500mL of 0.9% sodium chloride injection and inject intravenously. After 7 days of treatment, rest for 21 days, 4 weeks for 1 chemotherapy cycle and the treatment lasted for 3 chemotherapy cycles.

The study group added Baofukang suppository on the basis of the above chemotherapy: Along with the first cycle of chemotherapy, after cleaning the vulva with topical lotion before going to bed every night, use a disposable finger cover to place Baofukang suppository into the deep part of the vagina, 1 capsule/time, 1 time/night, 3 weeks for a course of treatment. The effects and indexes of both groups were observed after 1 course of treatment.

Outcome measures

The relevant indicators of EMT of tumor cells before and after treatment were determined by real-time quantitative PCR method, the process is described below: the tumor tissues of all patient is collected during biopsy, and the tissue sample should be fixed and embedded as soon as possible after isolation to prevent RNA degradation, total RNA was extracted according to TRIzol kit instructions and calculated the RNA concentration. Then cDNA was synthesized by reverse transcription. The mRNA relative expression of Vimentin, N-cadherin, E-cadherin, β-catenin were detected by SYBR PT-PCR kit and real-time quantitative PCR system. All tests were carried out for 3 times and average value was taken. The relative mRNA expression was expressed as $2^{-\Delta\Delta Ct}$.

Th1/Th2 cytokines and immune function indicators are monitored before and after treatment, methodology is as follows: 5mL of fasting peripheral elbow venous blood was collected from all patients and serum was separated after centrifugation for 10 min. Interleukin-6 (IL-6), interleukin-2 (IL-2) and interferon-γ (INF-γ) were determined by enzyme-related immunosorbent assay; $CD3^+$, $CD4^+$ and $CD8^+$ were detected by flow cytometer and then calculated $CD4^+/CD8^+$ value.

The adverse reactions containing gastrointestinal reaction, alopecia, leukopenia, vaginal redness and swelling were observed in the two groups during treatment.

Immunohistochemical (IHC) method

Streptomyces antibiotin protein-peroxidase (S-P) method was used for IHC. The concentration of E-cadherin, N-cadherin, β-catenin and Vimentin working liquid is diluted at 1:300 and the specific operations are as follows: first, the slices were dewaxed and hydrated and then incubated at room temperature of 0.3% methanol-hydrogen peroxide for 20 min to eliminate endogenous peroxidase activity. After 3 times of washing with distilled water, the slices were placed in a beaker filled with pH6.0 citrate buffer, then placed in a microwave

oven to repair at 98ºC for 20 min. When the repair is complete, remove the container and cool to room temperature and wash with 0.01M PBS. Then 10% goat serum was added and incubated in a wet box at 37ºC for 30 min. After excess serum was absorbed with filter paper, the diluted primary antibody was added and incubated in the refrigerator at 4ºC overnight. Wash with 0.01M PBS for 3 times, add goat anti-rat working solution, incubate in a wet box at 37ºC for 30 min.

After cleaning with PBS, add horseradish peroxidase labeled streptin working solution, incubate in a wet box at 37ºC for 30 min. After cleaning with 0.01M PBS, color development was performed by 3,3'-diaminobenzidine (DAB), controlled under microscope for 2-5min and color development was terminated by full rinse with tap water. Finally, the nucleus was re-stained with hematoxylin for 1-2 min, dehydrated with gradient alcohol and sealed with neutral resin. E-cadherin, N-cadherin and β-catenin were positive when brown particles appear on the cell membrane, while Vimentin was positive when brown particles appear in the cytoplasm.

Statistical analysis

SPSS 24.0 statistical software was applied to analyze study data. Continuous variables conforming to normal distribution were presented as the mean ± standard deviation (SD), the comparisons between groups were made using the independent samples t-test and intra-group comparisons were using paired sample t test. Categorical data were reported by frequency and percentage and were analyzed with chi-squared test. $P<0.05$ was considered significant.

RESULTS

Baseline characteristics

No obvious differences in age, TNM staging, pathological types were observed between two groups ($p>0.05$), displayed in table 1.

Analysis of EMT-related indexes in cancer tissue

After treatment for one month, mRNA expression of Vimentin and N-cadherin in study group were decreased, while mRNA expression of E-cadherin and β-catenin were increased compared with control group ($p<0.05$), as displayed in table 2.

IHC analysis of EMT-related indexes

After treatment, the positive expression of Vimentin and N-cadherin in cervical cancer tissue was decreased, while the positive expression of E-cadherin and β-catenin were increased in the two group. And the positive expressions of Vimentin and N-cadherin in the study group were lower than those in the control group, and the positive expressions of E-cadherin and β-catenin were higher than those in the control group. Seen from fig. 1-4.

Th1/Th2 cytokines

After treatment, IL-6 in study group was decreased and the IL-2 and INF-γ levels were increased compared with control group ($p<0.05$), seen from table 3.

Immune function indicators

After treatment, $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ were higher and $CD8^+$ lower in study group than those in control group ($p<0.05$), as displayed in table 4.

Adverse reactions

During treatment, the overall incidence of adverse reactions in study group was 22.50%, with no evident difference from 27.50% in control group ($P>0.05$), as shown in table 5.

DISCUSSION

Cervical cancer is a malignant tumor with high morbidity and mortality rates, and it mostly occurs in women of reproductive age (Pimple *et al.*, 2019). Clinical studies have shown that the occurrence of cervical cancer is closely related to a variety of cervical diseases, such as cervical erosion, cervical polyps, cervical gland cysts, cervical intraepithelial neoplasia, as well as poor dietary habits and unclean sexual behavior (Balasubramaniam *et al.*, 2019).

In recent years, incidence of cervical cancer shows a rising trend year by year and the incidence group is gradually getting younger, which is a heavy burden to the society and the family. EMT has received much attention in the invasive metastasis of tumors in recent years, and its mechanisms may be invasion, intravascular infiltration, extra vasation, adhesion and colonization. Numerous studies have confirmed that EMT is an key link in promoting cervical carcinogenesis (Ren *et al.*, 2021; Guo *et al.*, 2019).

Baofukang suppository as a Chinese medicinal preparation, its good anti-inflammatory, antibacterial and immunity-enhancing efficacy has received wide attention from clinicians. Currently, numerous studies on the treatment of cervical cancer with Baofukang suppository have been reported, while its regulation role for EMT process has not been reported.

It was found that Vimentin and N-cadherin expression in study group was lower and E-cadherin and β-catenin expression was higher than control group. Meanwhile, IHC analysis showed that positive expression of facilitate in cervical cancer tissues of study group decreased and E-cadherin and β-catenin increased after treatment, suggesting that Baofukang suppository can inhibit the E-cadherin and β-catenin and facilitate E-cadherin and β-catenin expression.

Table 1: Clinical characteristics of patients in two groups

Variable	Study group (*n*=40)	Control group (*n*=40)	t/X^2-values	p-values
Age (years)	55.47±5.63	56.09±5.74	0.488	0.627
TNM staging				
IIa	18 (45.00)	20 (50.00)	0.507	0.917
IIb	12 (30.00)	10 (25.00)		
IIIa	6 (15.00)	7 (17.50)		
IIIb	4 (10.00)	3 (7.50)		
Pathological type			0.328	0.849
Squamous carcinoma	30 (75.00)	28 (70.00)		
Adenocarcinoma	8 (20.00)	9 (22.50)		
Adenosquamous carcinoma	2 (5.00)	3 (7.50)		

Table 2: Comparison of EMT-related indexes in cancer tissue

Groups	Vimentin		N-cadherin		E-cadherin		β-catenin	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Study group (*n*=40)	4.57±1.13	1.52±0.29$^{\alpha}$	3.39±1.02	0.99±0.26$^{\alpha}$	0.25±0.05	0.57±0.10$^{\alpha}$	0.31±0.09	0.77±0.09$^{\alpha}$
Control group (*n*=40)	4.61±1.21	2.74±0.46$^{\alpha}$	3.27±0.98	2.03±0.28$^{\alpha}$	0.27±0.06	0.41±0.08$^{\alpha}$	0.34±0.07	0.56±0.11$^{\alpha}$
t-values	0.153	14.189	0.536	17.214	1.620	7.902	1.664	9.345
p-values	0.879	0.000	0.593	0.000	0.109	0.000	0.100	0.000

Note: $^{\alpha}p<0.05$ versus before treatment.

Table 3: Comparison of Th1/Th2 cytokines between two groups

Groups	IL-6 (pg/mL)		IL-2 (pg/mL)		INF-γ (pg/mL)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Study group (*n*=40)	43.44±7.58	29.75±6.38$^{\alpha}$	16.48±2.94	26.32±3.39$^{\alpha}$	14.26±3.56	22.46±3.35$^{\alpha}$
Control group (*n*=40)	42.98±8.46	36.55±6.74$^{\alpha}$	16.36±3.86	20.52±3.58$^{\alpha}$	14.83±3.27	17.47±3.24$^{\alpha}$
t-values	0.256	4.634	0.156	7.440	0.746	6.772
p-values	0.798	0.000	0.876	0.000	0.458	0.000

Note: $^{\alpha}p<0.05$ versus before treatment.

Table 4: Comparison of immune function indicators in two groups

Groups	$CD3^+$ (%)		$CD4^+$ (%)		$CD8^+$ (%)		$CD4^+/CD8^+$	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Study group (*n*=40)	64.34±8.32	70.67±6.36$^{\alpha}$	36.33±4.31	42.36±5.36$^{\alpha}$	38.54±4.52	32.41±4.12$^{\alpha}$	0.94±0.23	1.31±0.28$^{\alpha}$
Control group (*n*=40)	63.89±7.21	66.96±6.04$^{\alpha}$	35.98±4.68	38.84±5.22$^{\alpha}$	38.72±5.34	36.25±4.26$^{\alpha}$	0.93±0.24	1.07±0.25$^{\alpha}$
t-values	0.258	2.675	0.348	2.976	0.163	4.098	0.190	4.044
p-values	0.797	0.009	0.729	0.004	0.871	0.000	0.850	0.000

Note: $^{\alpha}p<0.05$ versus before treatment.

Table 5: Comparison of the incidence of total adverse reactions between the two groups

Groups	Gastrointestinal reaction	Alopecia	Leukopenia	Vaginal redness and swelling	Total adverse reactions incidence
Study Group (*n*=40)	3 (7.50)	4 (10.00)	1 (2.50)	1 (2.50)	9 (22.50)
Control Group (*n*=40)	4 (10.00)	6 (15.00)	1 (2.50)	0 (0.00)	11 (27.50)
χ^2-values					1.558
p-values					0.212

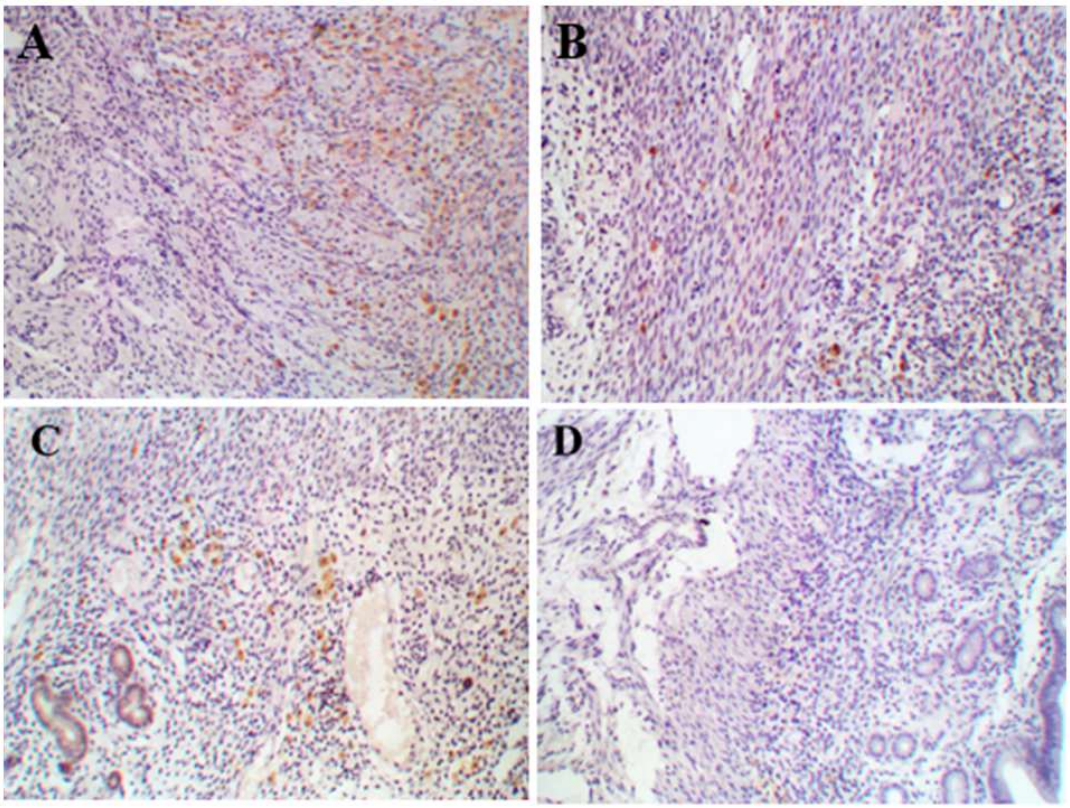

Fig. 1: IHC analysis of Vimentin in cervical cancer tissue in control group: A. Before treatment; B. After treatment. Study group: C. Before treatment; D. After treatment.

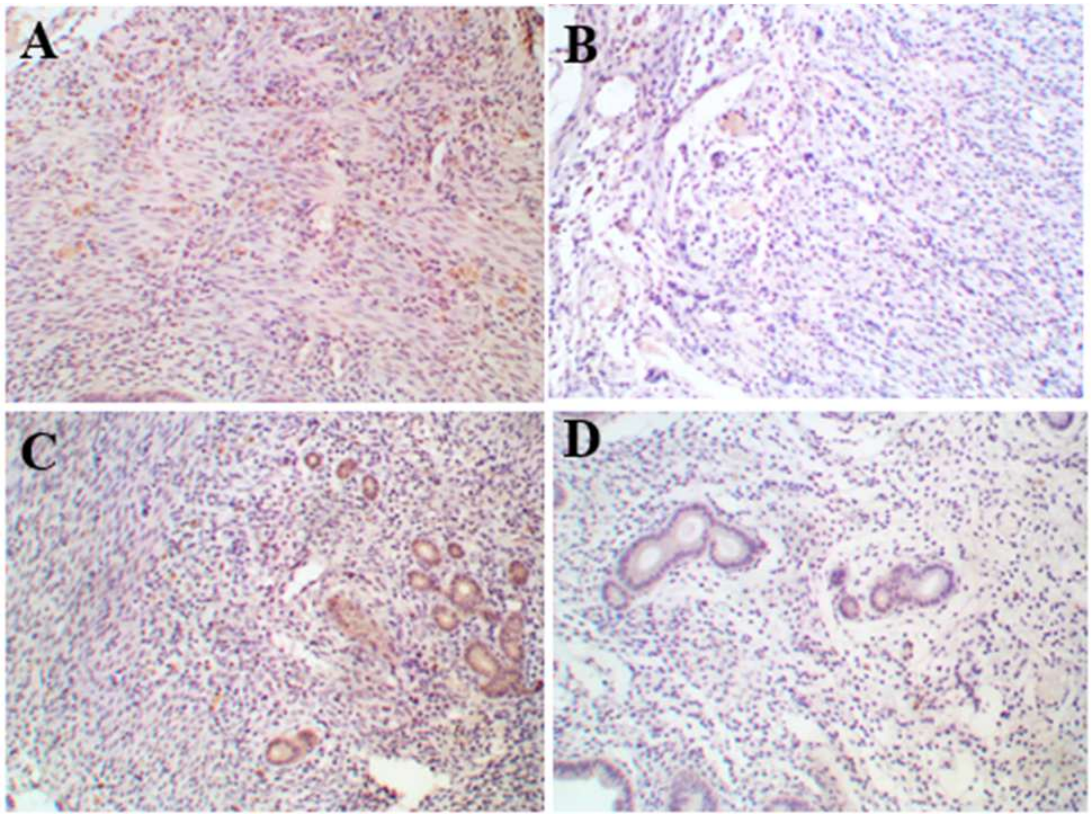

Fig. 2: IHC analysis of N-cadherin in cervical cancer tissue in control group: A. Before treatment; B. After treatment. Study group: C. Before treatment; D. After treatment.

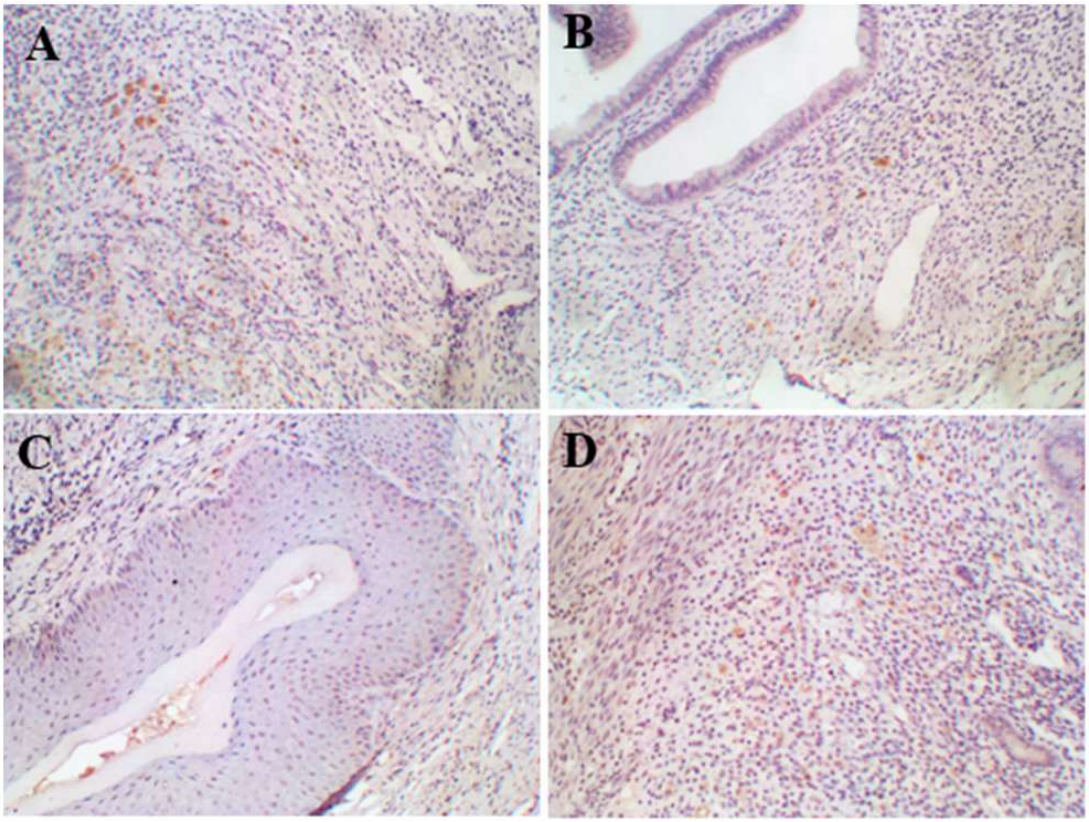

Fig. 3: IHC analysis of E-cadherin in cervical cancer tissue in control group: A. Before treatment; B. After treatment. Study group: C. Before treatment; D. After treatment.

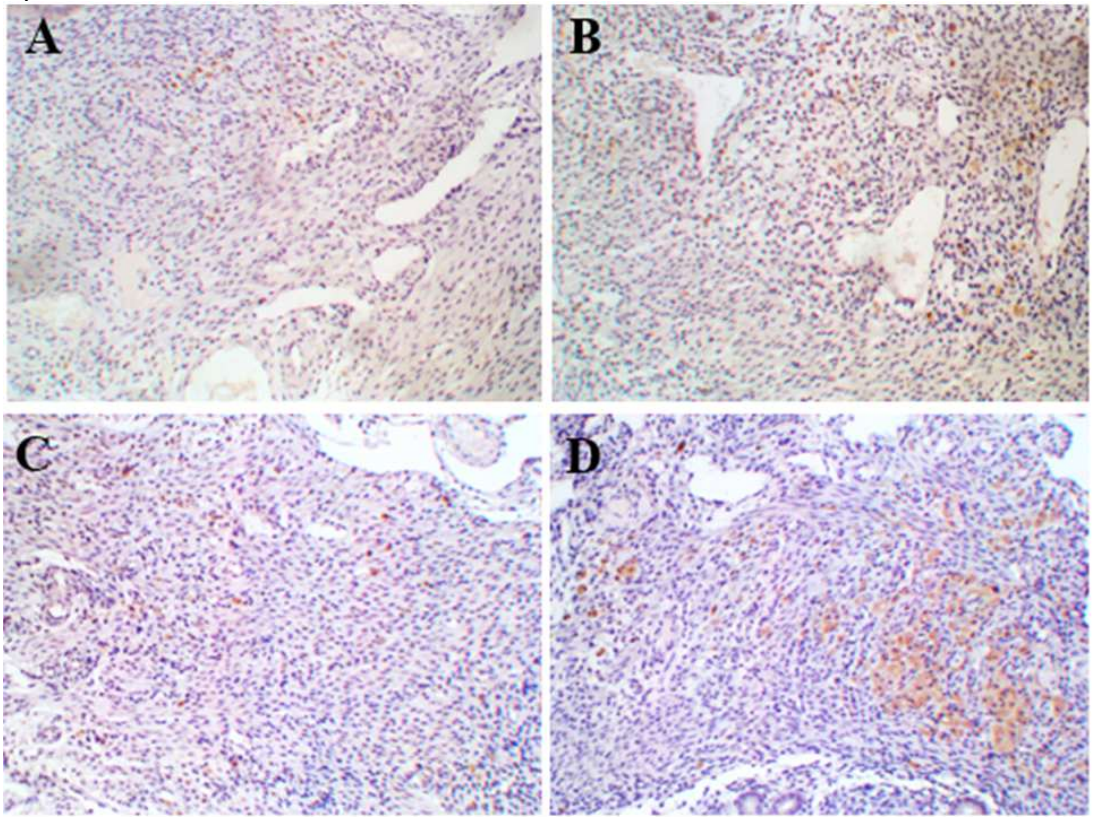

Fig. 4: IHC analysis of β-catenin in cervical cancer tissue in control group: A. Before treatment; B. After treatment. Study group: C. Before treatment; D. After treatment.

We speculate that this may be attributed to the fact that one of the main ingredients of Baofukang suppository is curcuma oil, which contains β-elemene, curcuminoids and curcumol and other effective ingredients, can inhibit the proliferation and division of the human papillomavirus, thus blocking the stimulation of the human papillomavirus on the epithelial cells, slowing down the progression of the disease and indirectly regulate the EMT-related indicators (Zou *et al.*, 2021; Feng *et al.*, 2021). In Chen's research confirmed that β-elemene can suppress cancer migration by regulating EMT (Chen *et al.*, 2020). In Deng's study illustrated that β-elemene may inhibit cell proliferation and invasion and metastasis by inhibiting EMT signaling pathway in human colon cancer cell line HCT116 (Deng *et al.*, 2022). The above researches further provided a possible mechanism for the effect of Baofukang Suppository on factors related to EMT of cervical cancer.

Under normal conditions of the body, Th1/Th2 cytokines will keep a balance state to maintain the immune function of the body. In cervical cancer patients, Th1/Th2 cytokine balance is destroyed and immune function is abnormal. IL-6 belongs to Th2 cytokines, which can promote inflammatory response and mediate tumor cell metastasis and growth. IL-2 and IFN-γ are Th1 cytokines, which mainly mediate the cellular immune process (Lin *et al.*, 2020). The results showed that IL-6 level in study group was decreased, while the IL-2 and INF-γ levels were increased obviously after treatment. This results suggested that Baofukang Suppository can regulate the balance of Th1/Th2 cytokines and enhance immune function. The results showed that $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ in study group were higher than control group after treatment, further indicating that Baofukang suppository can enhance the body immune function. The anti-inflammatory and immune-enhancing effects of Baofukang suppository may be attributed to its active ingredient of curcuma oil, containing β-elemene, which can attenuate macrophage activation and proinflammatory factor production via crosstalk with Wnt/β-catenin signaling pathway (Fang *et al.*, 2018). The results further showed that overall incidence of adverse reactions in two groups was no obvious differences during treatment, revealing the safety of Baofukang suppository in the treatment of cervical cancer. However, there are still some limitations in this study. Firstly, this research is a prospective study with limited sample size and single source. Secondly, this study lacks the long-term prognostic effect of Baofukang suppository in the treatment of cervical cancer. Therefore, it is necessary to expand sample size and conduct more long-term follow-up to confirm the conclusion.

CONCLUSION

Baofukang suppository can delay or prevent the EMT process of cervical cancer by regulating EMT-related indexes of tumor cell. Furthermore, Baofukang suppository can regulate cytokines and enhance the immune function of patients and have a high safety for cervical cancer treatment.

Acknowledgement
Not applicable.

Authors' contributions
Lin Liu, Conceived and designed the experiments; Performed the experiments; Analyzed the data; wrote the manuscript
Li Ma, Conceived and designed the experiments; Analyzed the data; Contributed reagents/materials/ analysis tool
Yan Wang, Conceived and designed the experiments; Analyzed the data; Contributed reagents/materials/ analysis tool
Yan Chen, Conceived and designed the experiments; Analyzed the data; Contributed reagents/ materials/analysis tool
Ying Zhang, Conceived and designed the experiments; Analyzed the data; Contributed reagents/materials/ analysis tool.

Funding
There was no funding.

Data availability statement
The data are free access to available upon request.

Ethical approval
The ethic approval was reviewed and approved from the The First Affiliated Hospital of Anhui Medical University (approval no. PJ2020-03-02) and informed written consent from all of the patients.

Conflict of interest
All authors declare no conflict of interest.

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