



Review

Research progress on the mechanism of action of *Salvia miltiorrhiza* and its components in the treatment of endometrial carcinoma

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Abstract



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The incidence and mortality of endometrial carcinoma (EC) are increasing year by year. Although the curative effect of surgery and commonly used drugs is clear, it is accompanied by obvious side effects, and safe and effective means are urgently needed to promote the curative effect and decrease the toxicity of drugs. Traditional Chinese medicine has been passed down for thousands of years in China and has proved to be advantageous in the treatment of various cancers and the auxiliary enhancement and reduction of toxicity. This paper reviewed the role and internal mechanism of *Salvia miltiorrhiza* in preventing and treating endometrial carcinoma by referring to relevant literature and works, so as to more comprehensively understand and grasp the research status, effective components, curative effect and effective mechanism of *S. miltiorrhiza* in preventing and treating endometrial carcinoma, and provide ideas and basis for clinical use and basic research.

Keywords: Endometrial carcinoma, Mechanism, *Salvia miltiorrhiza*, Tanshinone, Traditional Chinese medicine, Tumor.

1. Introduction

Endometrial carcinoma (EC) is one of the most common malignant tumors in women, and its incidence and mortality rates are increasing year after year. According to statistics, about 1.42 million people worldwide suffer from EC every year, of which about 420,000 women die [1], and the incidence of EC has a trend of younger age. EC has become a severe threat to women's lives and health. It is necessary and urgent to study the effective prevention and treatment methods and effective mechanisms of EC. At present, the treatment of EC is mainly surgery combined with chemoradiotherapy, corticosteroids, and targeted drugs, and its efficacy is relatively clear, but it is often accompanied by significant side effects and drug resistance [2]. Traditional Chinese medicine can play a synergistic and detoxifying role in preventing and treating endometrial cancer and can regulate the proliferation, invasion, migration, as well as apoptosis of cancer cells through a variety of mechanisms to exert anti-tumor effects, which is of great significance for alleviating patients' pain and improving their quality of life. As a typical representative of traditional Chinese medicine for increasing blood circulation and removing blood stasis, *S. miltiorrhiza* is often

applied in cancer treatment in Chinese traditional medicine [3]. Based on this, the effects and mechanisms of *S. miltiorrhiza* and its components on EC were reviewed in this paper, so as to grasp the frontier trends and provide reference for its clinical application and scientific research ideas.

2. Progress in EC diagnosis and treatment

The 2021 International Federation of Obstetrics and Gynecology (FIGO) Guidelines for Gynecological Malignant Tumors, the 2022 National Comprehensive Cancer Network (NCCN) Guidelines (1st edition), and China's Guidelines for the Diagnosis and Treatment of Endometrial Cancer (2021 edition) [4, 5] all recommend the diagnosis of four molecular subgroups of EC. Namely, POLE hypermutant, microsatellite instability (MSI), high copy type, and low copy type. The diagnosis of molecular typing reduces the differences in the observation of different pathologists, improves the accuracy and reproducibility of EC diagnosis, and can assist physicians in selecting treatment options and predicting prognosis. For instance, the prognosis of POLE hypermutant is very good, patients with surgical stage I-II can not be treated adjuvant after

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surgery; the microsatellite unstable type is sensitive to immune checkpoint inhibitor therapy; the high-copy form has the worst prognosis and may be sensitive to chemotherapy [6].

Immunotherapy and targeted therapy are the focus of EC therapy. Immune checkpoint inhibitors are considered as potential treatment strategies for EC. For example, mismatch repair deficiency type (MMRd) has strong CD8⁺ immune infiltration, and the effective rate of PD-1 and PD-L1 inhibitors in the treatment of metastatic MMRd type EC can reach 43% [7]. Molecularly targeted drugs should be used for positive biomarkers and second-line and above treatments, such as patients with neurotrophic factor receptor tyrosine kinase gene fusion-positive can be treated with larotrectinib, and human epidermal growth factor receptor 2 positive patients can be treated with trastuzumab or bevacizumab to achieve better therapeutic effects.

Chemotherapy is still one of the main clinical treatment measures for EC, but the side effects and multi-drug resistance caused by chemotherapy affect the efficacy of chemotherapy, so it is the direction of clinical research to explore high-efficiency and low-toxicity therapeutic drugs. Traditional Chinese medicine and natural medicine have the characteristics of low toxicity and low drug resistance and can play anti-tumor effects by reducing tumor invasion ability, improving immune function, inducing tumor cell apoptosis, reversing tumor cell drug resistance, sensitizing chemotherapy and other ways, which are important auxiliary measures in tumor treatment in China. *S. miltiorrhiza* has the function of supporting healthy energy and regulating the qi and blood. In recent years, the anti-tumor effect of *S. miltiorrhiza* has received extensive attention, and in-depth research on the anti-tumor mechanism of *S. miltiorrhiza* has positive clinical significance for expanding the clinical application of traditional Chinese medicine and promoting the prognosis and quality of life of cancer patients [8].

3. Effective components of *S. miltiorrhiza* and their anti-tumor effects

The taste of *S. miltiorrhiza* is bitter, and slightly cold in nature. The action of drug is located in the heart and liver channels and has the function of accelerating blood circulation to remove blood stasis, cooling blood to reduce swelling, and clearing the heart to remove dysphoria. At present, more than 50 active components of *S. miltiorrhiza* have been found, and the chemical components of *S. miltiorrhiza* are majorly divided into two categories: fat-soluble diterpenoid quinones and water-soluble phenolic acids [9]. The fat-soluble components include tanshinone I, dihydrotanshinone I, tanshinone IIA, tanshinone IIB and cryptotanshinone. The water-soluble (phenolic acid) components include salvianic acid, salvianolic acid A, salvianolic acid B, alkannic acid, protocatechualdehyde and rosmarinic acid. A large number of pharmacological studies have revealed that these bioactive ingredients have anti-tumor, anti-inflammatory, anti-oxidative stress as well as anti-myocardial ischemia effects, and can play an important role in protecting brain tissue, activating immunity, improving microcirculation, dilating blood vessels, resisting atherosclerosis, resisting thrombosis and improving renal function [10].

Among the components of *S. miltiorrhiza*, the role of tanshinone and salvianolic acid in gynecological cancer

has been studied. Tanshinone is a red crystalline powder that is effective against a variety of gynecological cancers. Studies have shown [11] that tanshinone can induce apoptosis of ovarian cancer cells, promote autophagy, and further repress tumor growth by regulating PI3K/AKT/mTOR pathway. A large number of in vitro experiments have proved that tanshinone I can regulate the proliferation and apoptosis of cancer cells, such as Nizamutdinova *et al.* [12], which observed the effect of tanshinone I on inducing MCF-7 and MDA-MB-231 human breast cancer cells, and found that tanshinone I repressed MCF-7 and MDA-MB-231 cells proliferation in a dose- and time-dependent manner by MTT assay, and TUNEL assay and flow cytometry revealed that tanshinone I could also induce apoptosis in cancer cells, The death of apoptotic cells is mediated by the activation of caspases 3, the downregulated level of the anti-apoptotic protein Bcl-2 and the upregulated level of the pro-apoptotic protein Bax.

In addition to fat-soluble tanshinones, water-soluble components have also been shown to have anti-cancer effects, among which salvianate B belongs to a bioactive compound extracted from the root of *S. miltiorrhiza* with powerful antioxidant and anti-inflammatory properties. In vitro experiments, salvianolic acid B reduces the proliferation of human breast cancer cells in a concentration- and time-dependent manner. Studies have shown that in tumor-positive mice injected with Ehrlich solid cancer cell lines, the administration of salvianate B or cisplatin can reduce tumor tissue levels of tumor necrosis factor- α (TNF- α), matrix metalloproteinase-8 (MMP-8), and cyclin D1, and unlike cisplatin, salvianate B reduces COX-2 level in model mice, suggesting that it may play an anti-breast cancer role by promoting apoptosis and lessening oxidative stress, inflammation and angiogenesis [13].

Salvianolic acid A, another water-soluble component of *S. miltiorrhiza*, is a multi-target drug with various pharmacological activities and has a crucial role in anti-tumor therapy [14]. For example, Yin *et al.* [15] revealed that salvianolic acid A could repress esophageal cancer cell proliferation by inactivating the PI3K/Akt/mTOR pathway, inducing G1 phase arrest and cell apoptosis. S-3-1, a derivative of salvianolic acid A, can improve the gap junction of pancreatic cancer cells and lung epithelial cancer W1-38 cells, inhibit the expression of c-myc proto-oncogene in human lung adenocarcinoma A549 cells, and increase the content of intracellular P53 to play an anti-tumor role [16]. In addition, salvianolic acid A can inhibit thymidine and uridine transport of ascites cancer cells, enhance the cytotoxicity of 5-fluorouracil, mitomycin C and methotrexate on KB cells and liver cancer BEL-7402 cells, and enhance the anti-tumor effect of chemotherapy drugs [17]. In terms of gynecological tumors, Leng *et al.* [18] showed that salvianolic acid A combined with sophordine oxide could cooperatively regulate the cell cycle of cervical epithelial immortalized cells (H8), inhibit the expression of Bcl-2 protein, elevate the expression of Bax and Cleaved Caspase-3 protein, block H8 cells in the G2/M stage, and impede the proliferation of H8 cells. Promote their apoptosis.

4. Mechanism of *S. miltiorrhiza* components in EC treatment

4.1. Blocking EC cell cycle

The blocking effect of tanshinone IIA on the EC cell

cycle was obviously concentration-dependent. Studies have shown that low concentration of tanshinone IIA (<50 µg/mL) had no significant repressive effect on KLE cell proliferation, and high concentration of tanshinone IIA (100 µg/mL) significantly inhibits the proliferation of EC cells so that cancer cells are significantly prevented from G0-G1 phase and G2 phase cells are significantly reduced. This effect gradually increases with the increase of time and concentration, indicating that tanshinone IIA significantly inhibits proliferation and promotes apoptosis of KLE cells of EC in vitro [19]. In addition to tanshinone IIA, other components of *S. miltiorrhiza*, such as water-soluble tanshinone, can also significantly hinder KLE cells growth of EC and promote their apoptosis by affecting cell cycle distribution, thus playing an anti-tumor role. Yue *et al.* [20] observed the morphological changes of tumor cells under a light microscope and detected their OD values. They found that the apoptosis rate in the 24 h *S. miltiorrhiza* group was higher relative to the other control group, while the cell growth was stagnated in the G0-G1 phase, while the cells in the S phase and G2 phase were significantly reduced.

4.2. Regulating EC-related signaling molecules and pathways

Tanshinone and cryptotanshinone extracts from *Salvia miltiorrhiza* have significant therapeutic effects on endometrial lesions in rats with ovarian polycystic disease, and the therapeutic effect of traditional Chinese medicine monomeric cryptotanshinone is superior to metformin, and its mechanism is closely related to the regulation of signaling molecules such as steroid hormone synthesis, cell proliferation (AKT3, RAC1) and endometrial carcinogenesis (PTEN, Kras) [21]. Jin *et al.* [22] detected the effect of tanshinone IIA on the proliferation of endometrial cancer cells by crystal violet staining and compared the expressions of P53, Cleaved caspase-3, Bcl-2, CK2 α , DBC1, SIRT1 and p-DBC1 in endometrial cancer cells in the model group, tanshinone IIA and found that tanshinone IIA could significantly repress endometrial cancer cells proliferation and induce apoptosis. The mechanism may be related to the CK2/DBC1/SIRT1/P53 signaling pathway. In addition, salvianolic acid B in the components of *S. miltiorrhiza* can hinder MFE-280 cell proliferation and further induce autophagy of MFE-280 cells by repressing the PI3K/AKT signaling pathway, leading to cell senescence and death. This effect has been shown to be dose-dependent [23].

4.3. Regulating EC-related hormone levels and gene expression

Cryptotanshinone has insulin-sensitizing and androgenic-lowering effects. Bing *et al.* [24] confirmed that cryptotanshinone can improve insulin resistance and reduce the expression level of androgen genes secreted by ovarian granulosa cells, and its mechanism is linked to the reduction of testosterone and androstenedione levels, down-regulation of the mRNA expression levels of AKT2 and GSK3 β , and improvement of PI3K/AKT and MAPK signaling pathways. In addition, tanshinone IIA has also been shown to inhibit the expression of androgen receptor mRNA [25], and Tanshinone IIA may also induce the increase of Fas/Caspase-3 expression by blocking MAPK/P38 signal transduction, leading to apoptosis [26].

Fengjuan *et al.* [27] scraped the endometrial tissue of pa-

tients with polycystic ovary syndrome and extracted RNA, and used gene chip technology to screen the genes with differential expression before and after tanshinone treatment, and performed bioinformatics analysis of the differential genes, and screened a total of 7 effective differential genes, among which has-miR-149-5p, has-miR-664b-3, and has-miR-6763-3p were significantly down-regulated by has-miR-630, has-miR-1273g-3, has-miR-6746-5, and has-miR-6774-5p were up-regulated. Further analysis using gene prediction, GO analysis, Pathway analysis, cluster analysis, and other methods showed that there were differences in the expression of AKT3 and RAC1 in related cell proliferation and carcinogenesis signaling pathways. The expression of AKT3, RAC1 and other genes related to cell proliferation and carcinogenesis decreased. This study clarified the role of tanshinone in the prevention and treatment of polycystic ovary syndrome-related endometrial lesions and the specific types of endometrial proliferative carcinogenesis genes that it specifically improved, which laid a foundation for further research.

4.4. Regulating the expression of EC-related proteins

Tanshinone IIA can enhance the effect of cisplatin on Ishikawa cells of EC. Ting *et al.* [28] detected the cell proliferation activity, cell migration ability and Caspase-3 protein expression in the 4 groups of blank control group, tanshinone IIA group, cisplatin group and tanshinone IIA+cisplatin combined intervention group, and found that tanshinone IIA could enhance the chemotherapy effect of cisplatin. The mechanism may be related to inhibiting cell migration and regulating the expression of Caspase-3 apoptosis-related proteins.

5. Effect of *S. miltiorrhiza* combined with other antitumor drugs

5.1. Reversing chemotherapy resistance and chemotherapy sensitization

Hui *et al.* [29] showed that after 4 µg/mL salvianolic acid A was applied to human lung cancer-resistant cell line A549/MTX tumor cells, the IC₅₀ of the resistant cell line decreased from (105.72±4.62) µg/mL to (26.13±1.36) µg/mL, with a reversal ratio of 4.05 times. In their experiments, Zhang *et al.* [17] showed that salvianolic acid A and 5-fluorouracil alone inhibited tumor of transplanted sarcoma in mice by 41% and 17%, respectively, and combined inhibited tumor by 63%. Dong *et al.* [30] found that during the postoperative chemotherapy stage of endometrial cancer, the expression levels of CA125 and HE4 proteins in the peripheral blood of patients were significantly reduced, the postoperative quality of life was significantly improved, the prognosis of the disease was significantly improved, and the treatment effect was significantly better than that of the chemotherapy group alone.

The mechanisms of *S. miltiorrhiza* sensitization chemotherapy and reversal of tumor resistance include [31, 32]: (1) Inhibition of P-glycoprotein expression: Overexpression of P-glycoprotein on tumor cell membrane can promote the efflux of chemotherapy drugs, reduce the accumulation of drugs in cells, induce drug resistance in tumor cells, and reduce the effect of chemotherapy [33]. Dihydrotanshinone I and cryptotanshinone can inhibit P-glycoprotein by down-regulating P-glycoprotein mRNA and protein expression, enhance the cytotoxicity of chemotherapy drugs in tumor cells, reverse the chemotherapy

resistance of tumor cells, and improve the chemotherapy effect. (2) Regulating the expression of apoptosis-related genes: Overexpression of anti-apoptotic Bcl-2 family proteins is an important factor in the occurrence and progression of tumors. Tanshinone IIA and cryptotanshinone can reduce the expression of Bcl-2 and increase the expression of pro-apoptotic Bax protein, which can cooperate with the anti-tumor effects of chemotherapy drugs [34]. (3) Influencing the PI3K/Akt and JAK/STAT signaling pathways: PI3K/Akt and JAK/STAT signaling pathways regulate cell growth, differentiation and apoptosis, and salvianolic acid A can down-regulate PI3K/Akt signaling pathway and reverse drug resistance of tumor cells [35]; cryptotanshinone can inhibit the phosphorylation of JAK2 and STAT3Tyr706, inhibit the proliferation of tumor cells, and inhibit the activity of STAT3 to enhance the anti-tumor proliferation effect of chemotherapy drugs. (4) Inducing the production of reactive oxygen species (ROS): Long-term chemotherapy can reduce the ROS level in tumor cells and cause drug resistance in tumor cells; Cryptotanshinone, salvianolic acid B and Tanshensu can induce endoplasmic reticulum stress to produce ROS and enhance the anti-tumor activity of chemotherapy drugs. (5) Enhancing the role of tumor necrosis factor-associated apoptosis-inducing ligand (TRAIL): TRAIL can induce apoptosis and kill tumor cells, and cryptotanshinone can induce the expression of TRAIL receptor 2 and induce apoptosis of cancer cells [36].

5.2. Reducing the side effects of chemotherapy drugs and enhancing the body immunity

The study of Azizi *et al.* [37] showed that the pain index, fever time, length of hospital stay, recurrence rate within 3 years, quality of life (QLQ-C30) score, pregnancy status after 1 year, term productivity and treatment satisfaction scores were better than those of the surgery group after hysteroscopic resection of early endometrial cancer. Liu *et al.* [38] showed that the application of supplemented Chinese herbal decoction could improve pain symptoms, and quality of life, enhance cellular immunity and reduce adverse reaction rates in patients with endometrial cancer undergoing chemotherapy. The above results indicate that the combination of *S. miltiorrhiza* with postoperative chemoradiotherapy or combined with Western medicine can be used to enhance clinical efficacy and improve patients' related symptoms. In addition, according to different syndrome differentiation, *S. miltiorrhiza* can be combined with different formulations to enhance efficacy and reduce adverse reactions. For example, in patients with menopausal syndrome after endometrial cancer surgery, after treatment with Qingxin Zishen formula combined with Livmin, the apparent efficiency, effective rate, bone mineral density, and quality of life scores of patients treated with Livmin alone were higher than those of patients using Livmin alone, while the patients' renal yin deficiency symptom score, modified Kupperman score, and serum sex hormones were lower than those of patients using Livmin alone [39].

The mechanism of *S. miltiorrhiza* to alleviate the toxic side effects of chemotherapy drugs and increase the body's immunity may be as follows: (1) Cryptotanshinone can reduce the level of inflammatory factors such as interleukin 6 and interleukin 11 in the body, and reduce the body's inflammatory response [40]; increase the total triglyce-

ride content in the serum and decrease the total cholesterol content and lipase activity [41]; regulate the intestinal flora, so that the intestinal flora is close to the normal state; regulate related genes and growth factors, and inhibit apoptosis of gastrointestinal mucosal cells; increase serum nitric oxide and prostaglandin E2 levels to enhance gastrointestinal mucosal defenses [42]. (2) Chemotherapy induces oxidative stress in the body, resulting in inflammatory infiltration of neutrophils, increased secretion of proteases, and the production of a large number of oxygen free radicals, causing liver and kidney damage. *S. miltiorrhiza* can inhibit oxidative stress, scavenge oxygen free radicals, and alleviate liver and kidney damage [43, 44]. (3) *S. miltiorrhiza* can stimulate the proliferation and differentiation of T lymphatic cells and NK lymphocytes, and exert immunomodulatory effects; cryptotanshinone enhances macrophage phagocytosis and induces macrophage differentiation to M2, improving immune function [45, 46]. (4) *S. miltiorrhiza* has the effects of activating blood circulation and removing blood stasis, promoting qi and relieving pain, and alleviating pain symptoms; tanshinone IIA can inhibit the activation of spinal astrocytes, reduce the expression of inflammatory cytokines in the body, relieve mechanical hyperalgesia and thermal hyperalgesia, and thus relieve the pain response caused by chemotherapy drugs [47].

6. Summary and prospect

EC is one of the most common tumors of the female reproductive system, which seriously affects the life, health, and quality of life of patients. Traditional Chinese medicine has certain advantages in the prevention and treatment of EC, especially in the use of adjuvant surgery, radiotherapy, and chemotherapy drugs, which has significantly improved related symptoms, increased efficiency, and reduced toxicity. The Shennong Herbal Classic mentioned that *S. miltiorrhiza* has the function of "accumulating main cold and heat, getting rid of disease and addiction," and listed *S. miltiorrhiza* as the top product. A large number of modern studies have also found that *S. miltiorrhiza* plays an important role in regulating tumor microenvironment, inhibiting tumor cell proliferation and migration, and inducing apoptosis.

The role of *S. miltiorrhiza* in gynecological tumors has been gradually paid attention to, but the role and mechanism of *S. miltiorrhiza* on EC are relatively scarce, and the underlying mechanism remains to be clarified. Objectively, *S. miltiorrhiza* has different varieties and comes from different places, and subjectively, there are many human factors such as storage time and storage conditions, so the contents of various chemical components in different experiments are different, and there is a possibility of difference in the content of effective components. How to purify the active components of *S. miltiorrhiza* can improve the comparability of experimental conclusions. Moreover, experiments have found that *S. miltiorrhiza* and other blood-activating drugs have the potential effect of promoting tumor angiogenesis, so more experimental verification is needed for the clinical treatment of endometrial cancer [48].

In addition, literature has shown that *S. miltiorrhiza* plays a role in regulating the inflammatory microenvironment of the uterus [49], improving endometrial receptivity during the implantable window period [50], reversing drug

resistance, inhibiting angiogenesis and lymphangiogenesis [51], and antioxidant activity [52], which remains to be further explored and verified. There is a lot of research on *S. miltiorrhiza* anti-EC, but the effect and mechanism of preventing cancer are still insufficient. The early intervention and conditioning of traditional Chinese medicine can help prevent or delay the occurrence and development of the disease. Strengthening the role and mechanism of traditional Chinese medicine such as *S. miltiorrhiza* and its extracts in preventing EC should also be one of the important directions of future research. The effects of other medicinal plants have been reported in previous researches [53-59].

Informed consent

The authors report no conflict of interest.

Availability of data and material

We declared that we embedded all data in the manuscript.

Authors' contributions

ZC conducted the experiments and wrote the paper; QZ and LQ analyzed and organized the data; CW and ZL conceived, designed the study and revised the manuscript.

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