Review

DOI: 10.5582/ddt.2024.01004

A systematic review of the mechanistic actions of microRNAs within integrated traditional Chinese medicine and western medical treatment for endometriosis

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SUMMARY Endometriosis (EM), also known as Zhengjia in traditional Chinese medicine, is a common disease that significantly impacts women's health. An integrated treatment approach combining traditional Chinese medicine (TCM) and western medicine has demonstrated significant clinical efficacy in the management of this condition. Specifically, it has been effective in addressing blood circulation and other diseases. MicroRNAs (miRNAs), which are molecules important in gene regulation, have been implicated in various physiologic and pathologic processes. In this review, we systematically summarized the potential mechanisms underlying the integrated EM treatment, with a focus on the role of microRNAs (miRNAs). Current research suggests that integrated TCM and western medicine treatment may exert their therapeutic effects on EM by influencing the expression of miRNAs. Through miRNA modulation, such a treatment approach may inhibit the growth of ectopic lesions and alleviate clinical symptoms. This review will shed light on the specific miRNAs that have been implicated in the integrated treatment of EM, as well as their potential mechanisms of action. By consolidating the existing evidence, we aim to provide clinicians and researchers with a clearer understanding of the therapeutic benefits of the integrated approach and potentially identify new avenues for improving clinical treatment outcomes. Ultimately, this review will contribute to the growing body of knowledge in this field, providing a basis for further research and the development of more targeted and efficient treatment strategies for EM.

Keywords endometriosis, microRNA, traditional Chinese medicine, herb

1. Introduction

Endometriosis (EM) is a chronic benign disease with malignant biological features (*1*). It is characterized by the presence of endometrioid tissue outside the uterine cavity, leading to chronic painful symptoms and various comorbidities, including infertility (*2*). The prevalence of EM ranges from 5% to 21% among women enduring pelvic pain and 5% to 50% among infertile women, affecting approximately 10% of reproductive-aged women (*3*). The impact of EM on patients is substantial and encompasses both physical and psychological aspects (*4,5*). The economic burden of EM is also noteworthy, with patients facing high medical expenses, work loss, and healthcare costs (*6,7*). Therefore, there is an urgent need to explore more efficient and cost-effective treatment options to alleviate the suffering and overall burden experienced by patients. Gynecology in relation to traditional Chinese medicine (TCM) has a 3,000-year history (*8*). EM is recorded as Zhengjia in TCM books, and first mentioned in Huangdi Neijing (*9*). TCM is widely used as Chinese medicinal compounds, patented Chinese patent medicines and acupuncture (*10*); and is a popular treatment for EM in China due to its significant therapeutic function and few side effects. Both Asian and international scholars are now experimenting with the combined use of TCM and western medicine for improved treatment of EM.

MicroRNAs (miRNAs) have emerged as critical regulators of gene expression (*11*). These small noncoding RNA molecules work by binding to the 3'untranslated region of target messenger RNA (mRNA),

thus modulating its stability (*12*). The regulation of miRNAs has been recognized in recent years as a therapeutic strategy in numerous diseases, with several drugs targeting specific miRNAs for therapeutic purposes (*13,14*). The role of miRNAs in the treatment of EM with TCM is currently an active area of research, and understanding the involvement of miRNAs in the mechanisms subserving TCM treatment for EM could provide valuable insights into their therapeutic effects and facilitate the identification of miRNA targets for possible intervention.

By summarizing the findings from previous clinical and experimental studies, we can gain a better understanding of the role of miRNAs in treatment approaches, and provide valuable insights into the superiority and effectiveness of this integrated treatment strategy. This review will shed light on the specific miRNAs that have been implicated in the integrated treatment of EM, as well as their potential mechanisms of action. We aim to provide clinicians and researchers with a clearer understanding of the therapeutic benefits of such an integrated approach and potentially identify novel avenues for improving clinical-treatment outcomes.

2. Research status of endometriosis

EM is a complex and heterogeneous disease that presents with various phenotypes, including ovarian endometriosis (OMA), superficial peritoneal lesions (SUP), and deep infiltrating endometriosis (DIE) (Figure 1) (*1*). It is worth noting that DIE lesions are typically multifocal rather than isolated (*15*).

The theory of retrograde menstruation is the most widely accepted pathophysiologic hypothesis for EM. However, other mechanisms, such as inflammation, immune dysregulation, hormones, genetics, epigenetics, and environmental factors may also contribute to the development of EM (*16*). However, how these mechanisms interact to give rise to different phenotypes of EM remains unclear. Further research is therefore required to elucidate the intricate interplay between these mechanisms and their roles in determining the phenotype of EM.

As EM is a disease with a significant global patient population and a long-standing history, it has become a major area of interest to both clinical and scientific researchers. The management of EM typically involves pharmacologic, surgical, or combination treatments (*17*); and numerous clinical studies have entailed the efficacy and outcomes of different treatment modalities on EM (*18-22*).

In this context, this article will primarily focus on the pharmacologic and nonsurgical methods for the treatment of EM; and we will review the advantages and disadvantages associated with these various approaches based on the existing literature. By synthesizing the available evidence, we expect to provide a comprehensive overview of the current treatment options for EM, facilitating informed decision-making for clinicians and patients alike.

3. Western medical treatment in endometriosis

There are currently several common clinical medical therapies available for the management of EM; these therapies can be classified into non-hormonal and hormonal treatments. Non-hormonal treatments for EM often involve the application of nonsteroidal anti-inflammatory drugs (NSAIDs), certain antidepressants and anticonvulsant medications that can be used as first-line treatments to alleviate the symptoms of

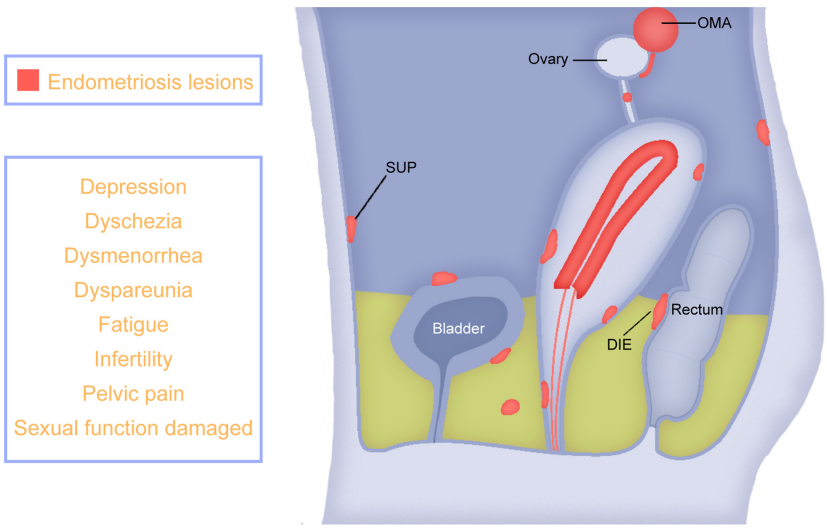

Figure 1. Clinical and disease characteristics of endometriosis. The endometrium can be ectopic to multiple sites. Three different phenotypes of endometriosis are common: superficial peritoneal endometriosis (SUP), ovarian endometriomas (OMA), and deeply infiltrating endometriosis (DIE). Endometrial tissue can also invade the myometrium leading to adenomyosis. Patients often experience physical and psychological discomforts.

dysmenorrhea (*23,24*). These medications can also assist in alleviating pain symptoms, but may not directly target the underlying mechanisms of EM.

Hormonal treatments, however, are commonly used in the management of EM. Combined oral contraceptives (COCs), which contain both estrogen and progestin, are often prescribed for the treatment of EM-related dysmenorrhea (*25*), and the continuous use of COCs has been shown to be superior in managing the dysmenorrheic symptoms of EM (*2*). Progestin use (another type of hormonal treatment) can be used in a cyclic or continuous manner to manage EM-associated pain; and continuous administration of progestogens (including medroxyprogesterone acetate) can help suppress the growth of endometrial lesions and alleviate pain symptoms (*26*). However, it is worth noting that the routine medical use required with these hormonal treatments can be tedious, leading to poor patient compliance (*2*).

In conclusion, non-hormonal treatments such as NSAIDs and certain medications may provide relief for the symptoms of EM, primarily by targeting pain management. Hormonal treatments, such as COCs, progestins, and gestrinone, offer additional options for managing dysmenorrhea and EM-associated pain. However, it is essential to consider individual patient preferences and factors such as patient compliance when selecting the appropriate treatment approach for EM.

Gonadotropin-releasing hormone analogues (GnRHa) comprise a popular treatment option, primarily due to their ease of use and high patient compliance (*27*). Emerging evidence from randomized controlled trials (RCTs) and meta-analyses suggests that GnRHa are effective in relieving symptoms of EM-associated pain (*9,28,29*). To mitigate the menopause-like symptoms of GnRHa treatment and to prevent bone loss, the addition of hormone replacement therapy (HRT) can be considered (*30*). While there is limited evidence on the optimal dosage, duration, and need for add-back HRT, the results of clinical trials combining GnRHa with HRT have shown promise (*31-33*). Individualized treatment plans, taking into account patient preferences and desired fertility outcomes, are crucial in the management of EM.

4. Traditional Chinese medicine in endometriosis

TCM has a long history of use in treating various gynecologic diseases, and new research on TCM for the treatment of EM is reported annually (Figure 2) (*34*). One study showed that combining dienogest, a conventional western medical treatment for EM, with TCM resulted in better outcomes in patients who did not respond well to standard western medical treatments (*9*). Moreover, RCTs and meta-analyses have revealed that TCM management of female infertility can lead to improved pregnancy rates compared to western medical drug therapy (*35*). These findings suggest that integrating TCM into the treatment of EM and female infertility may offer potential benefits and improved outcomes. However, it is important to note that additional research, including well-designed clinical trials, is needed to confirm the effectiveness and safety of combining TCM and western medicine in these treatments. Nonetheless, the increasing interest and research in this area indicate the potential value of an integrated approach. So we analyze the potential mechanisms of traditional Chinese medicine treatment through the following classic formulas for treating EM.

4.1. Guizhi Fuling pills (GZFLP)

GZFLP is a classical prescription in TCM that is commonly used for the treatment of EM. Its primary efficacy lies in invigorating the blood circulation and eliminating abnormal blood circulation (*33,36*). GZFLP is typically composed of five traditional Chinese herbs: *Cassia twig*, *Poria cocos*, *peach kernel*, *red peony root*, and *cortex moutan* (Paeonia suffruticosa *Andr.*) (*8*). When used together, GZFLP and western medicine have been found to significantly reduce the levels of leptin, vascular endothelial growth factor (VEGF), and interleukin-8 (IL-8) in the serum of EM patients. Moreover, this combination treatment has shown considerable effects in inhibiting the growth of ectopic lesions and relieving dysmenorrheic symptoms (*8*). It is intriguing that the activity and proportions of natural killer cells (NK cells) and $CD4^+$ T lymphocytes were significantly enhanced in the GZFLP-treatment group in a rat model of EM. This suggests that GZFLP may exert immune-modulating effects that lead to the regression of EM implants (*37*).

In addition to GZFLP, derivative drugs based on this

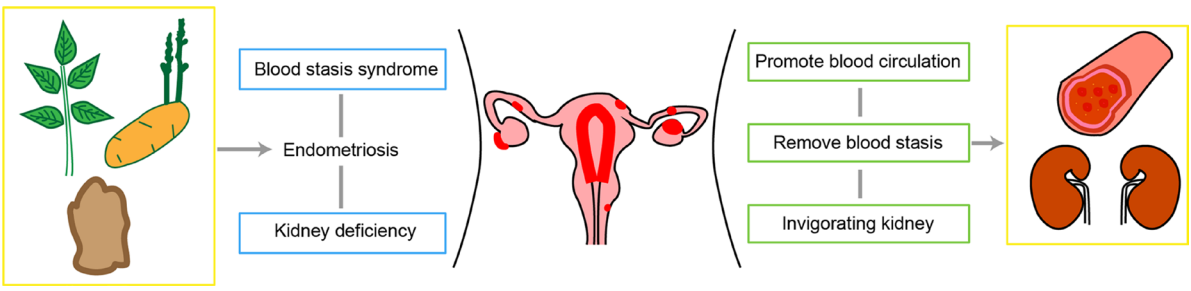

Figure 2. Endometriosis in Chinese traditional medicine treatment and theory. There is a correspondence between the clinical symptoms of endometriosis and the theories of Chinese medicine, which can be treated with Chinese herbs.

formulation have shown efficacy in treating EM (*33,37*). These findings suggest that TCM formulations may exert their therapeutic effects on EM through various mechanisms, including immune modulation and anti-inflammatory actions. However, further research is necessary to elucidate the exact mechanisms of action and to evaluate the safety and efficacy of these TCM formulations in human subjects.

4.2. Bushen Huoxue prescription (BSHXP)

BSHXP is commonly used in TCM to treat abnormal blood circulation in women, including EM. BSHXP is composed of *Rehmanniae Radix*, *Salviae miltiorrhizae Radix et Rhizoma*, *Puerariae lobatae Radix*, and *Ginseng Radix et Rhizoma*; and has been suggested to be effective and safe for EM patients (*38*). Combining BSHXP with laparoscopic surgery has shown promising results in improving clinical outcomes, as this combination treatment can significantly enhanced the clinical curative effect (*38*). However, more research is needed to further investigate the effectiveness and safety of this particular approach.

Additionally, Shaofu Zhuyu decoction, a TCM prescription known for activating the blood circulation, has demonstrated positive clinical effects when combined with western medicine in treating EM. This combination therapy has been found to improve endometrial receptivity scores, optimize oxidative stress levels, and reduce the recurrence rate for EM (*39*). While these TCM prescriptions show overall promise in treating EM, further high-quality analyses are necessary to provide more conclusive evidence regarding their effectiveness and safety.

4.3. Kuntai Capsule (KTC)

KTC is formulated with six herbs, *Rehmanniae Radix Praeparata*, *Coptidis Rhizoma*, *Paeoniae Radix Alba*, *Scutellariae Radix*, *Asini corii Colla*, and *Poria*. Authors have suggested that KTC inhibits the growth of ectopic lesions by regulating the level of tumor necrosis factor-α (TNF-α) and its downstream signaling molecules such as caspases and cytochrome c (*40*). These results provide some insights into the mechanisms by which KTC exerts its therapeutic effects on EM. KTC has also shown effectiveness in managing the peri-menopausal symptoms induced by postoperative GnRHa administration (*41*). This indicates the potential clinical value of KTC as a postoperative medication and in combined treatments with TCM and western medicine. However, it is important to note that clinical trials are necessary to further validate the efficacy and safety of KTC as a treatment for EM and peri-menopausal symptoms.

4.4. Fuke Qianjin capsule (FKQJC)

FKQJC is composed of eight TCMs: *Moghaniae Radix*, *Mahoniae Caulis*, *Andrographis Herba*, *Zanthoxylum dissitum Hemsl*, *Spatholobi Caulis*, *Angelicae sinensis Radix*, *Codonopsis Radix*, and *Rosae laevigata Radix.* FKQJC, when used in combination with dydrogestrel, inhibited the levels of VEGF, reduced inflammation, and diminished the incidence of adverse reactions in the treatment of EM (*42*). This suggests that FKQJC, along with dydrogestrel, may have potential benefits in managing EM symptoms. Additionally, it was observed that combining goserelin (a medication used to suppress hormone production) with FKQJC was both safe and effective in treating postoperative EM patients (*43*). This combination treatment also revealed improvements in hemodynamics and estrogen concentrations. Furthermore, when FKQJC was used in conjunction with gossypol acetate tablets, it improved ovarian function and attenuated the levels of carbohydrate antigen 125 (CA125, a biomarker for EM), retinol binding protein 4 (RBP4), and high mobility group box 1 (HMGB1) protein (*44*). These findings suggest that the combination of FKQJC and gossypol acetate exert potent therapeutic effects on ovarian function and biomarker levels in EM patients. However, more research, including clinical trials with larger sample sizes, is needed to further validate the safety, efficacy, and mechanisms of action of FKQJC in combination with these medications in the treatment of EM.

4.5. Sanjie Zhentong capsule (SJZTC)

SJZTC consists of the original powders of four natural plants products: *resina draconis*, *Panax notoginseng*, *Fritillariae thunbergii Bulbus*, and *Coicis semen*. In addition, a clinical study also revealed significant findings regarding acupuncture's effectiveness in reducing pain and serum CA125 levels in patients with EM, irrespective of the control intervention used (*39*). The use of SJZTC has shown promising results in effectively relieving dysmenorrheic symptoms (*41*), and both SJZTC itself and its two main components have demonstrated usefulness in reducing the development of the disease in a rat model (*41*). These findings indicate the potential benefits of SJZTC in managing EM symptoms and potentially slowing down the progression of the disease. However, further evaluation is needed of the efficacy and safety of SJZTC and its components in human subjects. Overall, these studies highlight the potential of acupuncture and SJZTC as alternative treatment options for EM, but additional study is needed to validate these findings and establish their clinical value.

4.6. Danefukang (DEFK)

The principal ingredients of DEFK are *Panax pseudoginseng* and *Salviae miltiorrhizae Radix et*

Rhizoma. DEFK has been shown to improve symptoms associated with EM, alleviate depression and anxiety, and reduce the levels of pro-inflammatory cytokines and CA125 (*42*). Investigators demonstrated that TCM treatment resulted in a significant drop in plasma levels of Prostaglandin F2α (PGF2α) and prostaglandin E2 (PGE2), while levels of 6-keto-PGF1 alpha, plasma beta-endorphin (beta-EP), and hydroxyproline (HYP) rose significantly. This suggests that TCM treatment not only provided symptom relief but also modulated the prostaglandin levels associated with EM (*43*). These findings demonstrate the potential effectiveness of DEFK and TCM in managing EM symptoms, and in modulating inflammatory and hormonal pathways. However, the findings necessitate elaboration to fully understand the underlying mechanisms of action and to validate them findings in larger clinical trials.

5. Roles of miRNAs in the integrated TCM and western medical treatment of EM

As research progresses, the roles of miRNAs in the treatment of EM are being explored. In one study, the authors investigated the effects of leuprolide acetate (a commonly used hormonal treatment) on the expression of miRNAs associated with EM (*45*). And their results showed that treatment with leuprolide acetate modulated the expression of seven miRNAs, and that expression correlated with the disease state. This suggests that miRNAs play a role in the pathogenesis of EM and could be potential targets for treatment. Another study focused on the use of aromatase inhibitors, specifically letrozole, in EM treatment (*44*). These authors ascertained that letrozole treatment significantly elevated the expression of a specific miRNA called miR-let-7f in Ishikawa cells and endometrial stromal cells (ESCs), and that it effectively arrested the migratory capability of endometrial cells. These studies highlight the role of miRNAs in the development and treatment of EM, and understanding their roles and deciphering their mechanisms of action should provide valuable insights for developing targeted therapies in the future.

Although miRNAs constitute a key factor in the treatment of many diseases, the role of miRNAs in the integrated treatment of TCM and western medicine remains arcane. By summarizing the roles and functions of miRNAs in TCM treatment, we can demonstrate the superiority of their integrated treatment in EM (Figure 3).

5.1. Role of miRNAs in GZFLP treatment

In a study that systematically summarized the active ingredients and pharmacologic mechanism of GZFLP, Kyoto Encyclopedia of Genes and Genomes (KEGG) results of the potential pathway of GZFLP included "miRNAs in cancer", which hinted at the critical importance miRNAs (*8*). A study on the molecular mechanisms and potential drug targets of Qu's formula (QUF) on EM indicated that "miRNAs in cancer" were also closely related to EM (*33*). Cais' Neiyi II prescription, of which GZFLP is the primary ingredient,

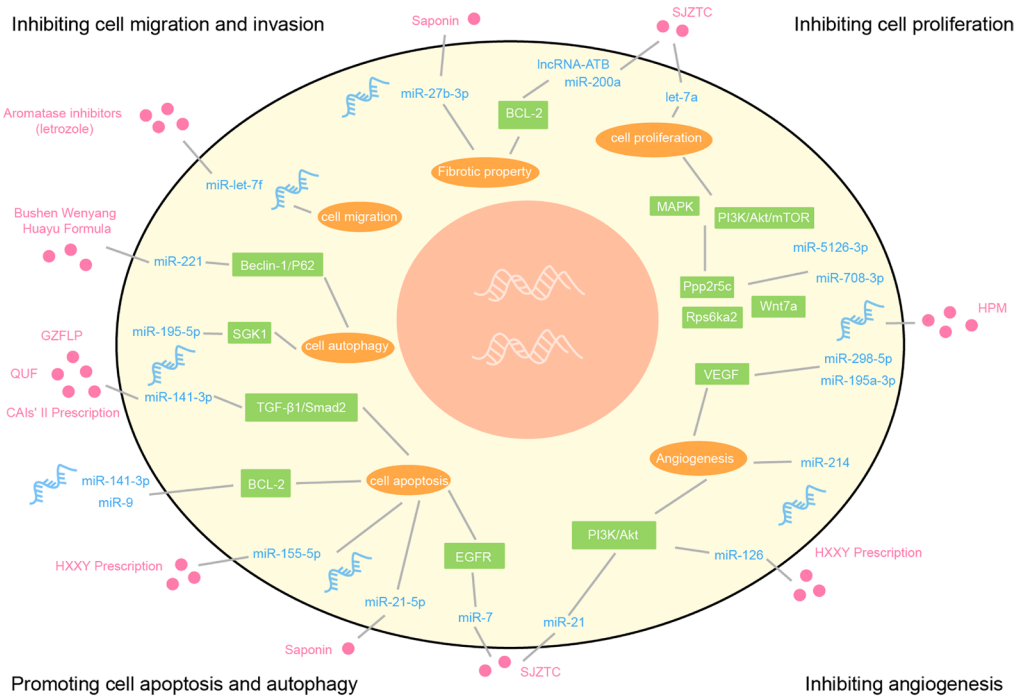

Figure 3. An overview of the role of miRNAs in the treatment of endometriosis by integrated Chinese and Western medicine. The combination of Western and Chinese traditional medicine regulates downstream genes and pathways by affecting the expression of miRNAs, through influencing cell proliferation, cell apoptosis and other functions to treat endometriosis.

was found to exert a therapeutic effect by elevating the expression levels of miR-141-3p in ESCs, inhibiting the activity of the downstream TGF-β1/Smad2 signaling pathway components, and promoting cellular apoptosis. GZFLP also affected the expression profile of miRNAs in a rat model of gynecologic diseases, suggesting that GZFLP was involved in a variety of biologic processes, including signal transduction and gene regulation. After treatment with high-dose of GZFLP, the expression of miR-187-3p and miR-330-5p was upregulated in the uterine tissue of EM rat models. According to another study on uterine fibroid patients, the expression of miR-214 increased and the miR-214-PI3K-AKT pathway was suggested to be one of the mechanisms with which to treat uterine fibroids as a women's abnormal blood-circulation disease. Although EM is usually known as a benign disorder, EM is also recognized as a precursor lesion for several malignant tumors and EM-related cancers in clinical practice (*46*). GZFLP possesses an anti-endometrial cancer activity, possibly *via* the inhibition of the lncRNA H19-mediated miR-195-5 pathway, suppressing tumor cell viability and promoting autophagy in endometrial cancer cells.

5.2. Role of miRNAs in activating blood circulation

Huoxue Xiaoyi granule (HXXY) is a traditional Chinese medicine that promotes blood circulation and improves abnormal circulatory function. When used to treat EM patients, HXXY was found to induce the differential expression of serum miRNAs. Specifically, certain miRNAs, such as miR-9-5p, miR-155-5p, and miR-202-3p, were up-regulated, while miR-216a-5p and miR-518a-5p were down-regulated. Among these, miR-155-5p was found to be associated with apoptosis. Treatment with HXXY resulted in smaller epithelial cells and reduced glandular cells in ectopic lesions, indicating that HXXY may restrained the growth of EM lesions by modulating the expression of miRNAs. This highlights the potential of miRNAs as novel targets in the treatment of EM.

Another effect of TCM treatments that promotes blood circulation and improves abnormal circulation is the inhibition of angiogenesis. This is achieved *via* the modulation of miR-126, which is highly expressed in vascular endothelial cells and regulates angiogenesis by affecting various transcription factors (*47*). Additionally, the TCM formula of Bushen Wenyang Huayu, which also promotes blood circulation, has been shown to inhibit autophagy by regulating the activities of the autophagy genes *Beclin-1* and *P62*; and this mechanism may be associated with a reduction in the expression levels of miR-221. These findings highlight the potential role of miRNAs in the therapeutic effects of TCM treatments in EM. Further research is required to sufficiently understand the mechanisms of action and to validate these findings in the clinical setting.

5.3. Role of miRNAs in herb-partitioned moxibustion (HPM)

HPM is a popular TCM treatment in the Chinese clinical field, particularly when combined with medical treatment (*48*). HPM is a combination of herbs and moxibustion and reflects the multiple functions of acupoint stimulation, moxibustion, and herb formulas, showing remarkable therapeutic effects in clinical use (*49*). Several studies have revealed that HPM reduced menstrual pain and improved quality-of-life for up to three months after a single treatment, or treatment combined with surgery or other medications (*50*). According to an investigation on the effect of HPM on miRNA expression profiles in nude rats using an EM model, five upregulated miRNAs and nine downregulated miRNAs were differentially expressed in the HPM group, but not in the model group. The Gene Ontology (GO) and KEGG results of the target genes of differentially expressed miRNAs were related to a combination of proteins, hormone metabolism, and downstream signaling pathways invloving cytochrome P450 drug metabolism. These differentially expressed miRNAs (miR-195a-3p and miR-298-5p) were found to be related to the *VEGF* and MAPK signaling pathways. After being verified by quantitative real-time PCR (qRT-PCR), miR-708-3p and miR-5126-3p were revealed to regulate the target gene expression of VEGF, protein phosphatase 2 regulatory subunit B gamma (*PPP2R5C*), Wnt-family member (*Wnt7a*) and ribosomal protein S6 kinase A2 (*RPS6KA2*). These studies preliminarily depicted the therapeutic mechanisms underlying HPM action, and indicated the possible functions of differentially expressed miRNAs and corresponding target genes that may regulate the mitogen-activated protein kinase (MAPK) signaling pathway and phosphoinositide-3-kinase/AKT serine threonine kinase/ mechanistic target of rapamycin kinase (PI3K/Akt/mTOR) signaling pathways. As a traditional treatment method, the role of HPM in reducing celluar adhesion, proliferation and angiogenesis deserves deeper exploration so as to elucidate the mechanisms underlying miRNA action.

5.4. Role of miRNAs in saponin action

As a well-known TCM herb, saponin is widely implemented in prescriptions to treat EM. A study conducted by Park *et al*. investigated the effects of saponin extracts from red ginseng on endometrial stromal cells (ESCs) in EM (*51*), and observed that treatment with saponin extracts led to a significant decline in the expression of miR-21-5p in ectopic ESCs; and that inhibition of miR-21-5p resulted in an increased apoptotic potential of ESCs. This suggests that saponins may exert their therapeutic potential on EM by modulating the expression of specific miRNAs,

such as miR-21-5p. Furthermore, another component of red ginseng called Rg3 was found to effectively alter the fibrotic properties of ESCs taken from EM patients (*52*). We posit that this effect may be attributed to the modulation of miR-27b-3p. These findings indicate that miRNAs, such as miR-21-5p and miR-27b-3p, play roles in the therapeutic effects of saponins extracted from red ginseng in EM. However, further research is needed to fully understand the mechanisms of action and to validate these findings in clinical settings. Nonetheless, these studies provide valuable insights into the potential of saponins from red ginseng to modulate specific miRNAs in the treatment of EM.

5.5. Role of miRNAs in analgesic Chinese medicine

Since SJZTC is frequently used in the treatment of diseases such as EM and several cancers, its work mechanism of action is of interest to scholars. Adenomyosis is characterized by the presence of endometrial stroma and glands within the myometrium, also constituting a disease caused by ectopic endometrium (*53*). SJZTC shows substantial clinical effects on treating adenomyosis, and several studies have suggested that its therapeutic mechanism is related to differentially expressed miRNAs. While these investigators ascertained that SJZTC treatment modulated the levels of miR-22-3p, miR-101-3p, miR-143-3p and miR-103-3p in the serum of EM patients, their exact mechanism of action needs further examination. These studies indicate that the activities of SJZTC are related to miRNAs in the treatment of tumors and adenomyosis and have provided avenues for exploring the possible mechanisms of miRNA action in the integrated TCM and western medical treatment of EM.

6. Discussion and Prospect

EM is a complex gynecological condition that causes various challenges and complications for women of reproductive age, including ovarian cysts, dysmenorrhea, and infertility. While western medical treatments are commonly used, they often possess disadvantages such as notable side effects and elevated recurrence rates. TCM treatments present a valuable alternative, as they offer potential benefits with fewer adverse effects. Many Chinese herbal medicines have shown promise in the treatment of EM, and understanding their mechanisms of action-particularly with regard to miRNAs-is of utmost importance. We herein analyzed articles that encompass pharmacology, animal experiments, and clinical trials so as to provide a comprehensive understanding of the role of miRNAs in the integrated treatment of EM using TCM and western medicine.

As EM belongs to a syndrome of abnormal blood circulation in classic TCM records, activating blood circulation and removing stagnation constitute its main treatment concept. miRNAs have been proven to display a wide range of effects in combined treatment, including affecting several key physiologic components and mechanisms such as cellular autophagy, proliferation, and migration; angiogenesis; and the release of prostaglandins (*54*). EM is now gradually being recognized as a fibrosis-related disease, and infertility in women with EM may be due to anatomical abnormalities caused by adhesions and fibrosis (*55*). In therapeutic fibrosis-related aspects, miRNAs are important in the therapeutic effects of TCM (*56*), as several studies on liver fibrosis indicated that miRNAs are related to regulatory mechanisms such as cellular growth, proliferation, apoptosis, differentiation, and angiogenesis in TCM treatments (*57*). Core herbs in the treatment of liver fibrosis are also the primary components in EM treatments, including *Salviae Miltiorrhizae* and *Astragali Radix* (*56*). These core prescriptions may regulate miRNA signaling and target the expression of *STAT3*, *PTGS2*, and *EGFR* (*56*). Researchers on heart fibrosis have demonstrated that cross-talk among miRNAs is involved in the underlying mechanism of TCM treatment (*54*). These anti-fibrotic effects of TCM are based on countering metabolic dysregulation, maintaining autophagic balance, and targeting miRNAs (*54*).

The exact mechanism of miRNAs in TCM prescription for EM treatment remains to be explored. The understanding of miRNAs as biomarkers on the degree of disease remission is insufficient. The exact mechanism of miRNAs affecting which gene's expression and which downstream pathway deserves to be further explored. The related researches on the principle of leading to a favorable reproductive outcome for the patients are few and lack experiments. The exploration of mechanism is conducive to the better research and development of related drugs and the combination of clinical treatments, so as to make contributions to relieving the symptoms of patients and improving the prognosis of patients.

Funding: This work was supported by grants from projects under National Natural Science Foundation of China (grant no. 82374243 to L Wang and grant no.82304906 to LS Li).

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received January 18, 2024; Revised February 24, 2024; Accepted February 25, 2024.

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Released online in J-STAGE as advance publication February 28, 2024.