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The role of Chinese herbal medicine in diminished ovarian reserve management

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Abstract

Diminished Ovarian Reserve (DOR) is characterized by a reduction in the number of available follicles in the ovaries, leading to hormonal imbalances, decreased ovarian reserve, and reduced fertility. Clinically, it presents with elevated follicle-stimulating hormone (FSH) levels, decreased anti-Müllerian hormone (AMH) levels, and a lower antral follicle count (AFC). In recent years, Traditional Chinese Medicine (TCM) has gained recognition for its multi-target, holistic regulation in treating DOR, offering broad therapeutic effects with minimal side effects. This review aims to summarize the mechanisms and clinical efficacy of Chinese herbal medicine (CHM) formulas and active compounds in the treatment of DOR, providing theoretical support for their clinical application and future research. A systematic literature search was conducted from June 2019 to June 2024, and 12 clinical studies along with 38 basic research papers were selected. The findings suggest that CHM formulas primarily act by counteracting oxidative stress, regulating immune defense, modulating sex hormone secretion via the hypothalamic-pituitary-ovarian axis, and inhibiting excessive apoptosis of ovarian granulosa cells. This review highlights the therapeutic potential of TCM for improving ovarian function, regulating endocrine balance, and alleviating DOR symptoms, offering valuable insights for clinical practice and research.

Keywords Diminished ovarian reserve, Chinese herbal medicine formulas, Active compounds of Chinese herbal medicine, Mechanism, Clinical efficacy

Introduction

The concept of DOR was first introduced in 1987 [1]. DOR refers to a reduction in the number of oocytes within the ovaries and/or a decline in their quality [2]. This condition is often accompanied by a decrease in AMH levels, a reduction in the antral follicle count, and an increase in FSH levels [3]. The etiology of DOR remains unclear. However, it is potentially associated with various factors, including genetic predisposition, autoimmune disorders, surgical interventions, and iatrogenic causes such as chemotherapy and radiotherapy [4, 5]. Additionally, other factors like infections, weight loss, smoking, drug abuse, and environmental pollution may also contribute to its development [6]. The decline in ovarian reserve not only leads to reduced fertility and a decrease in the quality of oocytes and embryos, but also makes women more susceptible to menstrual irregularities and menopause-related symptoms due to hormonal fluctuations. Moreover, it increases the risk of developing conditions such as osteoporosis and cardiovascular diseases, ultimately affecting the overall quality of life [7]. Without early intervention, DOR may progress to

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primary ovarian insufficiency, and in more severe cases, lead to premature ovarian failure (POF) [8]. In recent years, the incidence of DOR has been steadily increasing. Among infertile women under the age of 35, the prevalence of DOR is as high as 6.3%. Additionally, clinical pregnancy rates, live birth rates, and singleton live birth rates are significantly lower in patients with DOR [9]. DOR leads to a decline in embryo quality, negatively affecting the ability to achieve healthy pregnancy outcomes, and is one of the primary causes of female infertility. Moreover, it has a profound impact on women's physical and mental health, as well as on family harmony [10].

To date, there is no complete cure for DOR. Current treatment methods primarily include hormone replacement therapy, ovulation induction, assisted reproductive technologies (ART), stem cell therapy, and in vitro activation of follicles [11]. Currently, hormone replacement therapy is the predominant clinical treatment for DOR. Although this approach can effectively alleviate clinical symptoms, long-term medication use may increase the potential risk of complications such as endometrial cancer, breast cancer, and ovarian cancer. As a result, it fails to achieve the desired long-term outcomes [12]. Therefore, there is an urgent need to find a relatively safe and effective treatment for DOR. Numerous studies have shown that combining Chinese herbal medicine with conventional treatments provides significant advantages in regulating sex hormone levels, alleviating clinical symptoms, restoring ovarian reserve function, and improving pregnancy rates [13–15]. However, its complex composition, inconsistent efficacy, and geographical limitations in herb cultivation have restricted its widespread acceptance, mainly to countries like China [14]. This review primarily explores the potential mechanisms and clinical applications of Chinese Herbal Medicine in the treatment of DOR (Fig. 1). It analyzes their roles in improving ovarian function, regulating endocrine balance, and alleviating related symptoms. Additionally, this review also explores the prospects of integrating TCM with modern medicine to enhance the comprehensive treatment of DOR. By providing theoretical support for its clinical application in prevention and treatment, it aims to offer new insights and directions for future research on herbal therapies for DOR.

Etiology and pathological mechanisms of DOR

DOR results from various factors leading to ovarian dysfunction, primarily including follicle depletion, ovarian tissue damage, and hormonal imbalances [16]. As

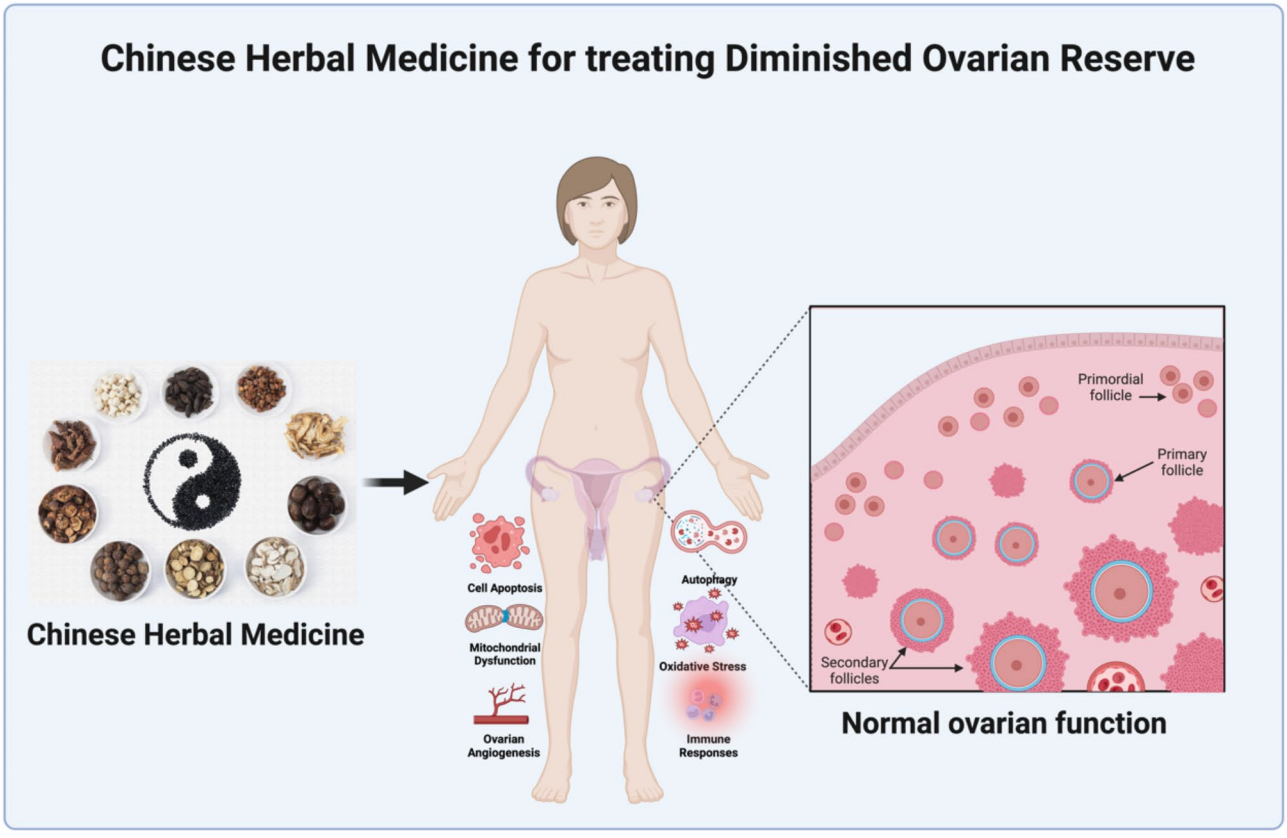

Fig. 1 Chinese herbal medicine for treating diminished ovarian reserve

women age, the number of follicles in the ovaries gradually decreases, and the quality of remaining follicles declines, ultimately causing ovarian dysfunction. Premature ovarian failure may be triggered by genetic factors or other pathological conditions. Autoimmune diseases and infections can also damage ovarian tissue, impairing its function. Hormonal abnormalities, such as decreased estrogen levels and elevated FSH levels, further exacerbate ovarian decline. In addition, environmental toxins and lifestyle factors—such as extreme diets and psychological stress—may negatively impact ovarian health [6]. Medical interventions, including ovarian surgeries, radiation therapy, and chemotherapy, can directly damage ovarian tissue. The pathological mechanisms of DOR that have been identified include processes such as apoptosis, autophagy, oxidative stress, mitochondrial dysfunction, ovarian angiogenesis, inflammation, immune responses, and microRNA regulation (Fig. 2). Understanding these mechanisms is essential for advancing the treatment and management of DOR [17, 18].

Clinical application of CHM formulas in DOR

In TCM, there is no direct equivalent to the term "Diminished Ovarian Reserve". However, based on its pathogenesis and clinical manifestations, DOR can be categorized under gynecological conditions such as "delayed menstruation" (Yue Jing Hou Qi), "scanty menstruation" (Yue Jing Guo Shao), "amenorrhea" (Bi Jing), "blood exhaustion" (Xue Ku), and "infertility" (Bu Yun). TCM treatment for DOR focuses on alleviating symptoms and improving sex hormone levels through various mechanisms. Herbal medicine is administered in different forms, including decoctions, pills, powders, and medicinal pastes [19–21]. CHM formulas are the main approach in diagnosis-based treatment and disease prevention, offering multi-target effects, holistic regulation, a wide range of actions, and minimal side effects [22]. The treatment of DOR in TCM primarily involves tonifying deficiencies, while also nourishing Yin, clearing heat, promoting blood circulation, and resolving stasis. Commonly used herbal compounds in DOR treatment include Dang Gui (*Angelica sinensis*), Bai Shao (*Paeonia lactiflora*), Shu Di Huang (*Rehmannia glutinosa*), Tu Si Zi (*Cuscuta chinensis*), Dang Shen

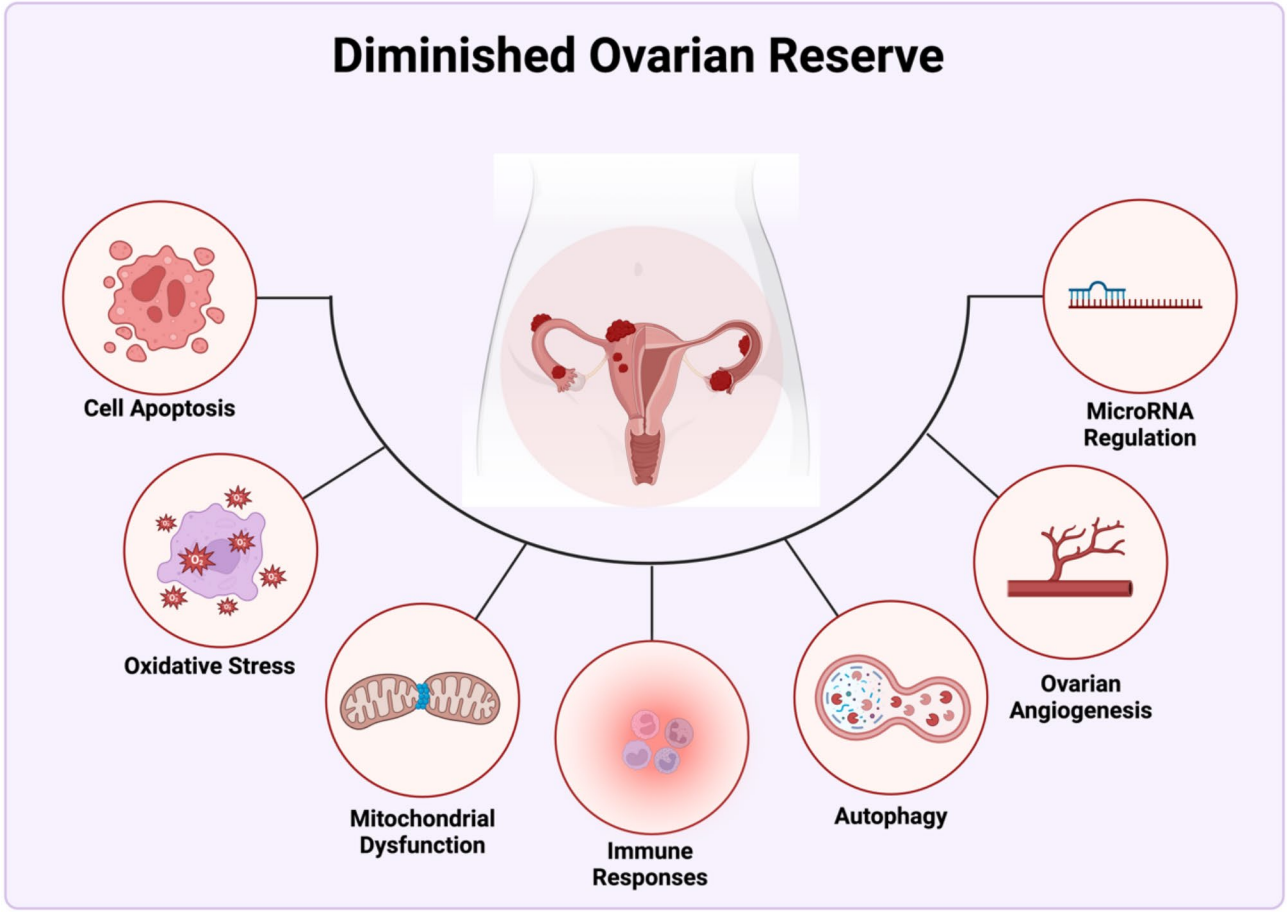

Fig. 2 The pathological mechanisms of diminished ovarian reserve include various processes such as cell apoptosis, autophagy, oxidative stress, mitochondrial dysfunction, ovarian angiogenesis, immune responses, and microRNA regulation

(*Codonopsis pilosula*), and Shan Yao (*Dioscorea opposita*). These herbs work to tonify the spleen and stomach, aiming to restore ovarian reserve function [14]. 。 Recent studies have shown that these formulas, either alone or combined with assisted reproductive technologies (ART), can increase the AFC, improve hormonal profiles (e.g., AMH, FSH), and enhance pregnancy outcomes. Additionally, TCM formulas are known for their minimal side effects and ability to address both the root cause and symptoms of DOR, making them a popular complementary therapy.

We systematically searched the databases PubMed, Web of Science, CNKI, Google Scholar, and Wanfang for clinical studies on CHM in the treatment of DOR from June 2019 to June 2024. The search terms included " Diminished Ovarian Reserve", "Chinese Herbal Medicine Formulas", "Active Compounds of Chinese Herbal Medicine" and "Clinical Efficacy". A total of 21 clinical research papers related to CHM treatment of DOR were retrieved. After evaluation, 12 articles that met all inclusion criteria were included in the study. The inclusion criteria were as follows: (1) the articles must be original clinical research studies, (2) they must report on the clinical efficacy of CHM in treating DOR, and (3) they must discuss pattern differentiation of DOR patients according to TCM principles. Table 1 outlines the composition of the herbal formulas and their clinical effects in treating DOR. In the clinical trials included, the control group received conventional Western medical treatments, while the intervention group was treated either with CHM in addition to conventional therapy or with CHM alone.

The most significant improvement in clinical efficacy was observed with the Bushen Tianjing formula (Kidney-Tonifying and Essence-Replenishing Formula). Compared to treatment with Western medications like estradiol valerate tablets or estradiol cyproterone acetate tablets, the *Bushen Tianjing* formula increased efficacy by 32.50% after three menstrual cycles of treatment [23]. However, this clinical trial had a small sample size, with only 20 cases in the observation group and 10 cases in the control group. As a result, the broader clinical applicability of these findings requires further exploration through larger-scale studies. The second most effective treatment was the *Yijing Huchao Decoction* (Menstruation-Benefiting and Ovary-Protecting Decoction). Studies found that in patients with DOR-related infertility, those who took *Yijing Huchao Decoction* along with letrozole starting on the fifth day of their menstrual cycle had a 22.73% higher pregnancy rate compared to those who took letrozole alone [24]. Xu et al. found that the combined use of *Tiaojing Kangshuai* Decoction (Menstruation-Regulating and Anti-Aging Decoction) with estradiol valerate tablets resulted in a total clinical efficacy rate that was 22.5% higher than using the decoction or estradiol valerate tablets alone. Additionally, the efficacy of using *Tiaojing Kangshuai* Decoction alone was 5% higher than that of estradiol valerate tablets alone, highlighting the formula's potential as a more effective treatment option [25]. Tian et al. conducted a study involving 120 patients to evaluate the efficacy of *Zishen Yijing Huoxue* Decoction (Kidney-Nourishing, Menstruation-Benefiting, and Blood-Activating Decoction) in treating DOR characterized by kidney deficiency and blood stasis [26]. The study results showed that the clinical efficacy rate of combining *Zishen Yijing Huoxue* Decoction with estradiol valerate cyproterone acetate tablets was 16.66% higher than using the tablets alone. Vaginal ultrasound examinations revealed that the treatment group had increased AFC, end-diastolic flow velocity, and peak systolic velocity in the ovarian arteries, indicating improved ovarian function. Additionally, it has been confirmed that T-lymphocyte dysregulation plays a key role in the development of DOR, as indicated by reduced levels of $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ ratios and increased $CD8^+$ levels. Tian's study showed that after treatment with *Zishen Yijing Huoxue* Decoction, the observation group had higher $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ ratios and lower $CD8^+$ levels compared to the control group, indicating improved immune function. The prospective randomized observational study by Xu's team found that *Zi Gui Nv Zhen* capsules can improve ovarian function and oocyte quality by regulating the neuroendocrine system [27]. This capsules also enhance uterine lining characteristics, leading to an increased clinical pregnancy rate. The pregnancy rate in patients taking *Zi Gui Nv Zhen* capsules was 12% higher than in the control group, demonstrating its potential efficacy in improving fertility outcomes. Chen et al.'s research demonstrated that the combination of *Bushen Huoxue* Formula (Kidney-Tonifying and Blood-Activating Formula) with dehydroepiandrosterone (DHEA) resulted in a 10.94% higher clinical efficacy in treating infertility caused by DOR compared to the use of DHEA alone [28]. Additionally, the treatment group showed higher peak systolic velocity (PSV) in the ovarian stromal arteries, as well as increased vascularization flow index (VFI) and flow index (FI), indicating improved ovarian blood flow and function. The clinical efficacy of *Jiawei Tiaogan* Decoction (Modified Liver-Regulating Decoction) combined with estradiol tablets or estradiol dydrogesterone tablets for treating DOR of the liver stagnation and kidney deficiency type was 6.7% higher than that of using estradiol tablets or estradiol dydrogesterone tablets alone [29]. This suggests that the combination therapy provides enhanced benefits in managing this specific pattern of DOR. The clinical efficacy of *Qizi Yishen Lichong* Decoction (Seven-Seed Kidney-Tonifying and Menstruation-Regulating Decoction) in treating DOR of the Kidney Qi deficiency type was only 3.4% higher compared to

Table 1 Clinical research on the treatment of DOR with CHM formulas

Pattern of syndrome	TCM formulas	Ingredients	Effects	Object (T/ C)	Overall efficacy rate	Period of treatment	Combined	Indicators of improvement	Ref
Kidney Deficiency and Boold Stasis syndrome	Zishen Yijing Huoxue Decoction	*Glycyrrhizae Radix et Rhizoma*, *Cyperus rotundus L*, *Ziziphi Spinosae Semen*, *Bupleuri Radix*, *Poria*, *Chuanxiong Rhizoma*, *Angelicae Sinensis Radix*, *Spatholobi Caulis*, *Corni Fructus*, *Lycii Fructus*, *Rehmanniae Radix*, *Epimedium brevicornu Maxim.*, *Eucommia ulmoides*, *Codonopsis Radix*, *Cuscuta chinensis*	Tonify the kidneys, invigorate blood circulation.	60/60	88.33%/71.67%	6 months	Estradiol valerate cyproterone tablets	FSH, RI↓ AFC, E_2,AMH, EDV, PSV, $CD3^+$, $CD4^+$, $CD4^+$/ $CD8^+$ ↑	[26]
Kidney Qi deficiency with Qi stagnation syndrome	Yijing Huchao Decoction	*Cuscuta chinensis*, *Rubi Fructus*, *Curculigo Gaertn*, *Rhizoma Epimedii*, *Cistanches Herba*, *Cyperus rotundus L*, *Curcuma longa L*, *Angelica sinensis*, *Paeoniae Radix Alba*, *Ligusticum chuanxiong hort*, *Eupatorium japonicum Thunb*, *Fluoritum*, *Rehmannia glutinosa*, *Citri Reticulatae Pericarpium*, *Bupleuri Radix*, *Glycyrrhiza*, *Salvia miltiorrhiza Bunge*, *Poria*	Tonify the kidneys, soothe the liver, nourish the blood, and regulate menstruation	44/4	68.18%/45.45%	3 months	Letrozole	FSH, LH↓AFC, E_2, AMH↑	[24]
Cold congealing and blood stasis syndrome	Wenjing Decoction	*Evodia rutaecarpa*, *Ophiopogon japonicus*, *Angelicae Sinensis Radix*, *Asini Corii Colla*, *Ligusticum chuanxiong hort*, *Paeoniae Radix Rubra*, *Codonopsis pilosula*, *Pinellia ternata*, *Glycyrrhiza uralensis*, *CassiaTwig*, *Ziziphus jujuba Mill*, *Zingiber officinale Roscoe*, *Glucidtemns*	Nourish the blood, warm the channels, and dispel cold to remove blood stasis.	169/169/169	71.0%/81.7%/92.3%	3 months	NA	FSH, LH, FSH/ LH↓, AFC, E_2, AMH, OV↑	[31].
Kidney Qi deficiency syndrome	Qizi Yishen Lichong Decoction	*Evodia rutaecarpa*, *Ophiopogon japonicus*, *Angelicae Sinensis Radix*, *Asini Corii Colla*, *Ligusticum chuanxiong hort*, *Paeoniae Radix Rubra*, *Codonopsis pilosula*, *Pinellia ternata*, *Glycyrrhiza uralensis*, *CassiaTwig*, *Ziziphus jujuba Mill*, *Zingiber officinale Roscoe*, *Glucidtemns*	Benefit the kidneys and replenish essence, regulate the Chong (penetrating) vessel and nourish the blood.	30/30	86.7%/83.3%	3 months	Femerton	FSH↓, AMH↑	[30]
Kidney Yin deficiency syndrome	Kuntai Capsules	*Scutellaria baicalensis Georgi*, *Coptis chinensis*, *Rehmanniae Radix*, *Poria*, *Cynanchum otophyllum Schneid*, *Asini Corii Colla*	Tonify the kidneys and boost qi, nourish yin, and invigorate blood circulation.	47/47	NA	3 months	Femerton	FSH, E_2, LH↓, AFC↑	[32]

Table 1 (continued)

Pattern of syndrome	TCM formulas	Ingredients	Effects	Object (T/ C)	Overall efficacy rate	Period of treatment	Combined	Indicators of improvement	Ref
Liver Qi stagnation with Kidney deficiency syndrome	Jiawei Tiaogan Decoction	*Cynanchum otophyllum Schneid*, *Angelicae Sinensis Radix*, *Cyperus rotundus L*, *Curcumae Radix*, *Bupleuri Radix*, *Aurantii Immaturus Fructus*, *Citri Reticulatae Pericarpium*, *Trichosanthis Fructus*, *Cuscuta chinensis*, *Ligustrum lucidum Ait.*, *Cornus officinalis*, *Dioscoreae Rhizoma*, *Rehmanniae Radix*, *Taxilli Herba*, *Achyranthes bidentata*, *Vaccariae Semen*, *Tetrapanax papyriferus*, *Glycyrrhiza*	Diffuse liver qi to relieve depression and regulate blood to balance menstruation.	30/30	96.7%/90.0%	3 months	Estradiol tablets/didrogesterone tablets	FSH, E_2↓, AMH↑	[29]
Liver and Kidney Yin deficiency syndrome	Bushen Tianjing Formula	*Testudinis Carapax et Plastrum*, *Rehmanniae Radix*, *Cuscuta chinensis*, *Fructus Ligustri Lucidi*	Tonify the kidneys and replenish essence.	20/10	87.5%/55.0%	3 months	Estradiol valerate tablets/estradiol cyproterone tablets	FSH, LH↓	[23]
Kidney deficiency with Blood stasis syndrome	Bushen Huoxue Decoction	*Rehmanniae Radix*, *Angelicae Sinensis Radix*, *Cynanchum otophyllum Schneid*, *Dioscoreae Rhizoma*, *Corni Fructus*, *Lycii Fructus*, *Eucommia ulmoides*, *Cuscuta chinensis*, *Polygoni Multiflori Radix*, *Cistanches Herba*, *Astragali Radix*	Tonify the kidneys, replenish essence, invigorate blood	39/34	NA	3 months	Ubidecarenone Soft Capsules	FSH, E_2, LH↓, AMH↑	[33]
Spleen and Kidney deficiency syndrome	Bushen Jianpi Formula	*Astragali Radix*, *Cuscuta chinensis*, *Dioscoreae Rhizoma*, *Atractylodis Macrocephalae Rhizoma*, *Achyranthes bidentata*, *Codonopsis Radix*, *Rehmanniae Radix*, *Eucommia ulmoides*, *Angelicae Sinensis Radix*, *Ligusticum chuanxiong hort.*, *Poria*, *Taxilli Herba*, *Dipsaci Radix*, *Cornus officinalis*, *Glycyrrhizae Radix et Rhizoma*	Tonify the kidneys and strengthen the spleen.	50/50	NA	3 months	Vitamin E softgel	FSH, AFC, AMH↑	[34]
Liver and Kidney Yin deficiency syndrome	Zi Gui Nv Zhen capsules	*Fructus ligustri Lucidi*, *Cordyceps*, *Radix rehmanniae preparata*, *Radix panacis quinquefolii*, *Radix angelicae sinensis*, *Radix astragali*, *Fructus corni*	Tonify the liver and benefit the kidneys, nourish yin and replenish blood.	75/34	NA	3 months	NA	FSH, LH↓, AFC, E_2, AMH↑	[27]
Kidney Deficiency with Blood Stasis syndrome	Tiaojing Kangshuai Decoction	*Rehmanniae Radix*, *Dioscoreae Rhizoma*, *Multiflori Radix*, *Eclipta Prostrata*, *Cornus officinalis*, *Fructus Ligustri Lucidi*, *Paeoniae Radix Rubra*, *Placenta Hominis*, *Persicae Semen*, *Carthami Flos*, *Glycyrrhizae Radix et Rhizoma*	Invigorate the blood and resolve blood stasis, tonify the kidneys and replenish essence.	40/40/40	92.50%/70.00%/75.00%	3 months	Estradiol valerate tablets + progesterone capsules	FSH, LH↓, E_2↑	[25].
Kidney Deficiency with Blood Stasis syndrome	Bushen Huoxue formula	*Cuscuta chinensis*, *Dipsaci Radix*, *Taxilli Herba*, *Rehmanniae Radix*, *Pseudostellariae Radix*, *Poria*, *Cinnamomi Ramulus*, *Radix Rubra*, *Persicae Semen*, *Moutan Cortex*, *Cornus officinalis*, *Uncaria rhynchophylla*, *Asini Corii Colla*	Benefit Qi and nourish the blood, nourish Yin and tonify the kidneys.	64/64	96.88%/85.94%	8 weeks	Dehydroepiandrosterone	FSH, LH, E_2↓, PSV, VFI, FI↑	[28]

patients who took estradiol tablets or estradiol dydrogesterone tablets alone [30]. Wang et al. analyzed the clinical efficacy differences of *Wenjing* Decoction in paste, granule, and decoction forms for treating DOR of the cold-induced blood stasis type [31]. A total of 507 patients were randomly assigned to three groups: paste, granule, and decoction. The results showed that the paste group had the best clinical efficacy, with a total effectiveness rate of 92.3%, followed by the granule group at 81.7%, and the decoction group at 71.0%. The superior efficacy of the paste form can be attributed to its preparation process, which involves repeated boiling and concentration, retaining the essence of the medicinal ingredients. The paste's slow-release properties and pleasant taste, free from the bitterness often associated with decoctions, also make it more advantageous in treatment. Furthermore, both the paste and granule forms offer the convenience of not requiring decoction, better taste, and higher utilization rates compared to traditional decoctions.

In the clinical studies of *Kuntai Capsules* [32], *Bushen Huoxue Decoction* [33], and *Bushen Jianpi Formula* [34], no overall clinical efficacy rates were summarized. However, the results from these studies demonstrated that the combination of Chinese herbal formulas with conventional medications showed superior outcomes in key hormonal indicators such as FSH, E2, and LH, compared to the use of conventional medications alone. This suggests that these herbal formulas enhance the effectiveness of standard treatments in regulating hormone levels for DOR patients.

Mechanisms of action of CHM formulas and active compounds of CHMs in DOR

We systematically searched the databases PubMed, Web of Science, CNKI, and Wanfang for foundational research literature on the treatment of DOR with CHM from June 2019 to June 2024. The search terms used included "Diminished Ovarian Reserve," "Chinese Herbal Medicine Formulas," "Active Compounds of CHMs," and "Effects and Mechanisms." The specific inclusion criteria were: (1) The articles had to be original animal or cellular studies, and (2) They must include animal ethics approval documentation. Ultimately, 38 articles met these criteria and were included in the review.

The effects and mechanisms of CHM formulas on DOR

The research on the mechanisms of TCM formulas in treating DOR mainly includes the inhibition of excessive apoptosis of ovarian granulosa cells, regulation of the hypothalamic-pituitary-ovarian axis (HPOA), antagonism of oxidative stress, and regulation of immune defense (Fig. 3; Table 2). The TCM formulas involved include ancient classical prescriptions, kidney-tonifying clinical experience prescriptions, and commercially available proprietary Chinese medicines.

Cell apoptosis in CHM formulas treatment

Ovarian follicle development progresses from primordial follicles to primary follicles, secondary follicles, and finally to mature follicles, with approximately 99% of follicles undergoing atresia at various stages of development [35]. In developing follicles, apoptosis ultimately leads to follicular atresia, with the apoptosis of granulosa cells being a significant direct cause of this process. Increased granulosa cell apoptosis is a primary reason for diminished ovarian function, resulting in accelerated follicular atresia and increased oocyte apoptosis [36, 37]. Yishen Tiaojing Formula can effectively inhibit the apoptosis of ovarian granulosa cells and improve ovarian function in rats, which may be related to the down-regulation of pro-apoptotic factors caspase-3 and Bax expression and up-regulation of anti-apoptotic factor Bcl-2 expression [38]. *Yangjing Zhongyu* Decoction can alleviate reproductive endocrine disorders and ovarian pathologies by regulating steroidogenesis, energy metabolism, and apoptosis. After treating a rat model of DOR with *Yangjing Zhongyu* Decoction, serum levels of FSH, E2, and AMH were restored, and ATP content increased. Furthermore, the expression of Bax in ovarian tissue was suppressed, while the expressions of SIRT1, PGC1α, NRF1, COX IV, FSH receptors (FSHR), CYP19A1, PI3K, Bcl-2, and p-Akt/Akt were enhanced [39]. *Yishen Shugan* Decoction exerts its effects by upregulating Bcl-2 and downregulating Bax and Caspase-3 proteins, thereby inhibiting granulosa cell apoptosis. Xiao et al. found that *Yishen Shugan* Decoction could restore the estrous cycle in DOR model rats, increase gonadal index, reduce follicular atresia, and modulate serum hormone levels. These actions collectively improve the pathological state of DOR in rats and enhance ovarian reserve function [40]. The accelerated apoptosis of ovarian follicular cells leads to diminished ovarian function. Modified *Yijing* Decoction can increase the expression of Bcl-2 protein in ovarian tissue while reducing the expression of Bax protein, thereby inhibiting follicular cell apoptosis and improving ovarian function [41]. The mechanism of *Yulin Formula* in treating DOR involves regulating the PI3K/AKT signaling pathway and key proteins such as cytochrome C, Caspase-3, Caspase-9, and BAX. This regulation helps to inhibit the apoptosis of ovarian granulosa cells in DOR rats, thereby slowing the progression of DOR [42].

Regulation of the HPOA by CHM formulas

The HPOA is central to the female reproductive endocrine system, regulating the menstrual cycle and reproductive function through a series of complex hormonal feedback mechanisms [43]. The hypothalamus secretes

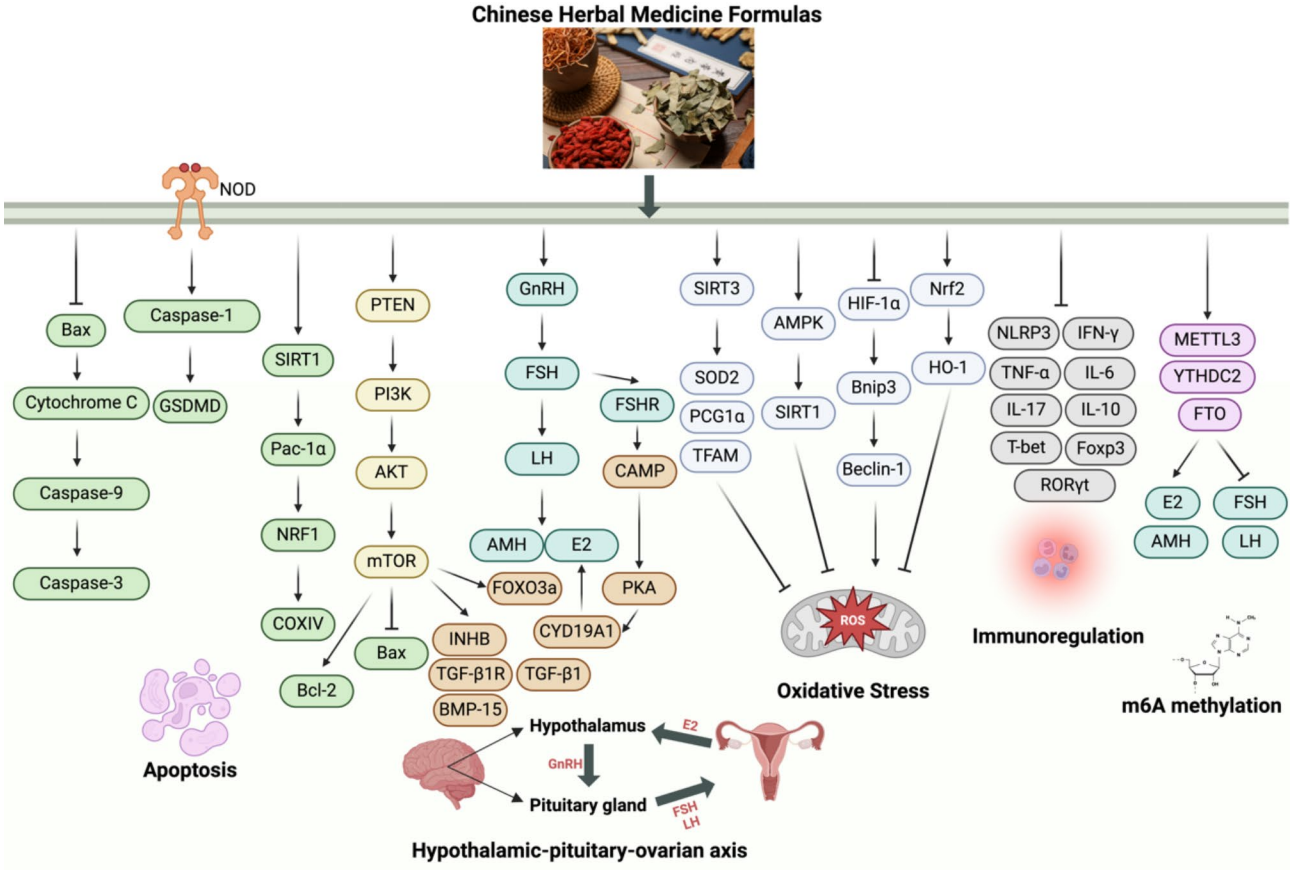

Fig. 3 Mechanism diagram of Chinese herbal medicine formulas in the treatment of DOR

gonadotropin-releasing hormone (GnRH), which stimulates the anterior pituitary to release FSH and LH. These hormones then act on the ovaries to promote follicular maturation and ovulation, as well as regulate the secretion of estrogen and progesterone. Diminished ovarian function may be associated with dysregulation of the HPOA [44]. High doses of *Bushen Cuyun* Recipe may treat DOR by regulating sex hormone levels in the HPOA and protecting ovarian granulosa cells from apoptosis. Network pharmacology analysis indicates that the NOD-like receptor signaling pathway is the most significant mechanism through which *Bushen Cuyun* Recipe impacts female infertility. Experimental results show that after treatment with *Bushen Cuyun* Recipe, serum levels of FSH in DOR rats significantly decreased, while levels of GnRH and E2 markedly increased. Additionally, levels of GSDMD, caspase-1, and IL-18 were significantly reversed [45]. *Zihuai* Recipe can improve ovarian reserve function in CTX-induced DOR rats. The mechanism by which *Zihuai* Recipe exerts its effects on DOR may involve regulating the levels of sex hormones (AMH, GnRH, E2, LH, and FSH) in the HPOA, increasing the number of antral follicles, and inhibiting granulosa cell apoptosis mediated by the PI3K/AKT pathway [46]. *Yishen Shugan Decoction* may regulate proteins associated with the PI3K/AKT/mTOR signaling pathway, leading to the upregulation of Bcl-2 and downregulation of Bax expression. This modulation of the hypothalamic-pituitary-gonadal axis in DOR rats helps to inhibit the apoptosis of ovarian granulosa cells and improve ovarian pathological changes [47].

Inflammatory responses modulated by TCM formulas

Recent studies have found that chronic sterile inflammation associated with conditions such as Crohn's disease [48], polymyositis [49], and obesity [50] can lead to decreased levels of AMH in women, a reduction in the number of primordial and antral follicles, and an increase in atretic follicles. These changes can deplete ovarian reserve and result in reduced fertility.

Bushen Huoxue Recipe helps to reconstruct immune balance by reducing autoimmune responses and immune modulation, thereby preventing the destruction of remaining oocytes and treating CTX-induced DOR. In mice with CTX-induced DOR, administration of *Bushen Huoxue* Recipe significantly decreased levels of IFN-γ, TNF-α, IL-6, IL-17, and IL-10, as well as the mRNA expression of T-bet, RORγt, and Foxp3, indicating its

Table 2 The regulatory effects of CHM formulas on DOR

CHM formulas	Main components	Model	Efficacy	Target	Ref.
Bushen Cuyun Recipe	*Polygon atumsibiricum Red., Discorea opposita L., Poria cocos (Schw.) Wolf, Lycium barbarum L., Morus alba L., Rubus chingii Hu, Cinnamomum cassia (L.) J.Presl, Foeniculum vulgare Mill., Syzygium aromaticum (L) Merr. & L.M.Perry, Citrus × aurantium L*	8-week-old Female SD rats	HPOA axis, granulosa cells in ovary against pyroptosis	NLRP3, ASC, caspase-1, GSDMD, IL-18	[45]
Bushen Huoxue Recipe	*Rehmannia glutinosa Libosch., Astragalus menbranaceus Bunge., Dioscorea opposita Thunb., Cornus officinalis Sieb.et Zucc., Cuscuta chinensis Lam., Angelica sinensis Diels, Ligusticum chuanxiong Hort., Paeonia lactiflora Pall, Paeonia suffruticosa Andr., Poria cocos Wolf*	8-week-old Female C57BL/6J mice	Augmented autoimmunity	IFN-γ, TNF-α, IL-17 A, IL-6, IL-10T-bet, RORγ, Foxp3	[51]
Gengnianchun Formula	*Rehmannia glutinosa (Gaertn.) DC, Epimedium acuminatum Franch, Paeonia lactiflora Pall, Lycium barbarum L., Carapax et plastrum Testudinis, Anemarrhena asphodeloides Bunge, Cuscuta australis R.Br, Morinda officinalis F.C.How, Cistanche deserticola Y.C.Ma, Phellodendron chinense Schneid, Coptis chinensis Franch., Poria cocos (Schw.) Wolf, Bupleurum abchasicum Manden., Angelica sinensis (Oliv.) Diels, Conioselinum chinense (L.) Britton, Picea mariana Britton, Sterns & Poggenb.*	6-8-week-old Female C57BL/6J mice	PI3K/AKT pathway	PTGS2, PTGS1, PGR, SCN5A, PRKCA, ADRB2, AR, HTR2A, NR3C2, ESR1	[59]
He's Yangchao Recipe	*Paeonia lactiflora pall, Cuscuta chinensis lam, Cistanche salsa (C.A.Mey.) beck, Angelica sinensis (Oliv.) diels, Rubus chingii Hu, Pueraria lobata (Willd.) Ohwi, Asparagus cochinchinensis (Lour.) Merr., Platycladus orientalis (Linn.) Franco*	8-month-old Female C57BL/6J mice	Oxidative stress	ROS, JNK, p53, BAX	[72]
He's Yangchao Recipe	*Asparagus cochinchinensis (Lour.) Merr., Pueraria lobata (Willd.) Ohwi, Angelica sinensis (Oliv.) Diels, Platycladus orientalis (Linn.), Cuscuta chinensis Lam., Cistanche deserticola Y. C., Rubus coreanus Miq., Paeonia lactiflora Pall.*	8-9-month-old Female ICR mice	Mitochondrial function, oxidative stress	ROS, SIRT3, SOD2, PCG1α, TFAM	[71]
ErZhiTianGui Decoction	*Cuscuta chinensis, Ligustrum lucidum, Herba Ecliptae, Lycium chinense Mill, Angelica Sinensis, Radix Rehmanniae Preparata, Ligusticum wallichii, Paeonia lactiflora Pall, Rhizoma cyperi, Radix Glycyrrhizae Preparata*	36-week-old C57BL/6 female mice	Mitochondrial homeostasis, lipid peroxidation, ferroptosis, ovarian aging	PINK, Parkin, GPX4, ACSL4	[73]
Yangjing Zhongyu Decoction	*Rehmannia glutinosa (Gaertn.) DC., Cornus officinalis Siebold & Zucc., Angelica sinensis (Oliv.) Diels, Paeonia lactiflora Pall.*	6-8-week-old Female SD rats	Steroidogenesis, energy metabolism, cell apoptosis	SIRT1, PGC1α, NRF1, COX IV, FSHR, CYP19A1, PI3K, p-Akt, Akt, Bcl-2, Bax	[39]
Yangjing Zhongyu Decoction	*Rehmannia glutinosa (Gaertn.) DC., Cornus officinalis Siebold & Zucc., Angelica sinensis (Oliv.) Diels, Paeonia lactiflora Pall.*	7-8-week-old Female SD rats	RNA-m^{6}A modification	METTL3, FTO, YTHDC2	[83]
Dingkun Pills	*Panax ginseng C. A. Mey., Cervus Nippon Temminck, Crocus sativus L., Panax notoginsen (Burk.) F.H.Chen, Paeonia lactiflora Pall, Rehmannia glutinosa Libosch, Angelica sinensi (Oliv.) Diels, Atractylodes macrocephala Koidz., Lycium barbarum L., Scutellaria baicalensis Georgi, Cyperus rotundus L., Leonurus japonicus Houtt., Ligusticum chuanxiong Hort., Asini Corii Colla, Corydalis yanhusuo W.T.Wang, Spatholobus suberectus Dunn*, Carthamus tinctorius L., *Leonurus japonicus Houtt.*, Poria cocos (Schw.) Wolf, Bupleurum chinense DC., Lindera aggregate (Sims) Kosterm., Eucommia ulmoides Oliv., Zingiber officinale Rosc., Amomum villosum Lour., Cyathula officinalis Kuan, Cinnamomum cassia Presl	8-week-old female Balb/c mice	Inhibition of follicular apoptosis	Bax, Cyt C, Caspase-3, Bcl-2, PI3K, AKT, mTOR	[62]
Buchong Tiaojing Formula	*Semen Cuscutae, Fructus Ligustri Lucidi, Radix Codonopsis, Radix Angelicae Sinensis, Radix Curcumae*	8-week-old Female SD rats	Inhibit ovarian NLRP3 inflammasome, alleviate the degree of ovarian iron death	NLRP3, ASC, Caspase-1, ACSL4, TFR1, GPX4	[55]
Modified *Guishen* Pills	*Semen Cuscutae, Epimedium, Fructus Ligustri Lucidi, Radix Rehmanniae Preparata, Radix Bupleuri, Radix Angelicae Sinensis, Radix Paeoniae Alba, Radix Salviae Miltiorrhizae*	8-week-old Female ICR mice	PI3K/AKT/mTOR pathway	PI3K, AKT, mTOR	[60]
Qilin Pills	*Semen Cuscutae, Mulberry, Fructus Lycii, Fructus Rubi, Herba Cynomorii, Herba Ecliptae, Herba Epimedii, Radix Codonopsis, Rhizoma Dioscoreae, Radix Astragali, Radix Polygoni Multiflori, Radix Paeoniae Alba, Pericarpium Citri Reticulatae Viride, Radix Curcumae, Radix Salviae Miltiorrhizae*	10-week-old C57BL/6 female mice	Reversing hypoxia and autophagy in ovaries	HIF-1α, Bnip3, Beclin-1	[75]

Table 2 (continued)

CHM formulas	Main components	Model	Efficacy	Target	Ref.
Wenzhong Bushen Formula	Astragalus membranaceus var. Mongholicus (Bunge) P.K.Hsiao, Codonopsis pilosula (Franch.) Nannf., Dioscorea opposita Thunb., Angelica sinensis (Oliv.) Diels, Foeniculum vulgare Mill., Ligusticum striatum DC., Paeonia lactiflora Pall., Atractylodes macrocephala Koidz., Poria cocos (Schw.) Wolf., Evodia ruticarpa var. officinalis (Dode) C.C.Huang, Aconitum carmichaelii Debeaux, Euryale ferox Salisb., Piper nigrum L., Zingiber officinale Roscoe, Amomum villosum Lour., Glycyrrhiza uralensis Fisch.	6-week-old ICR female mice	PI3K/AKT pathway	PI3K, AKT, FOXO3a	[61]
Modified *Congrong Tusizi* Decoction	*Semen Cuscutae*, *Cistanche*, *Rhizoma Polygonati*, *Epimedii*, *Fructus Rubi*, *Fructus Corni*, *Radix Rehmanniae Preparata*, *Radix Angelicae Sinensis*, *Lycopi*, *Radix Linderae*, *Rhizoma Dioscoreae*, *Fructus Lycii*	3-month-old Female SD rats	Improve mitochondrial dysfunction	AMPK, SIRT1, PGC-1α	[74]
Zihuai recipe	Placenta hominis, Dioscorea japonica Thunb., Cuscuta chinensis Lam., Lycium barbarum L., Astragalus menbranaceus Bunge., Angelica sinensis (Oliv.) Diels., Epimedium brevicornu Maxim., Scutellaria baicalensis Georgi., Taxillus chinensis (DC.) Danser, Dipsacus inermis Wall., Rehmannia glutinosa (Gaertn.) DC., Cyperus rotundus L., Glycyrrhiza glabra L.	8-week-old Female SD rats	HPOA, PI3K/AKT pathway, apoptosis	caspase-3, BAX, Bcl-2, PI3K, AKT	[46]
Zuogui Pills	Rehmanniae Radix Praeparata, Corni Fructus, Dioscoreae Rhizoma, Cuscutae Semen, Lycii Fructus, Achyranthis Bidentatae Radix, Testudinis Carapacis et Plastri Colla, Cervi Cornus Colla	8-week-old Female SD rats	Oxidative stress	Nrf2, HO-1, NQO1, Oct4, MVH, Cyclin D1, Cyclin E1, P21	[76]
Yishen shugan Decoction	*Fructus Ligustri Lucidi*, *Radix Rehmanniae Preparata*, *Ecliptae*, *Radix Glehniae*, *Herba Dendrobii*, *Radix Dipsaci*, *Herba Taxilli*, *Semen Cuscutae*, *Radix Paeoniae Alba*, *Rosa chinensis Jacq. var. Chinensis*, *Bupleuri Radix*, *Prunus mume*, *Salvia miltiorrhiza Bunge*, *Persicae Semen*, *Dianthus superbus L*, *Puerariae Lobatae Radix*, *Glycyrrhiza*	12-week-old Female SD rats	HPOA, PI3K/AKT pathway, apoptosis	PI3K, AKT, mTOR, Bcl-2, Bax	[47]
Yishen shugan Decoction	Fructus Ligustri Lucidi, Rehmannia glutinosa, Ecliptae Herba, Glehnia littoralis, Dendrobii Caulis, Dipsaci Radix, Loranthaceae, Cuscuta chinensis, Cynanchum otophyllum Schneid, Rosa chinensis Jacq. var. Chinensis, Bupleuri Radix, Prunus mume, Salvia miltiorrhiza Bunge, Persicae Semen, Dianthus superbus L, Pueraria lobata (Willd.) Ohwi, *Glycyrrhiza*	12-week-old Female SD rats	Apoptosis	Bcl-2, Bax, Caspase-3	[40]
Yishen Tiaojing Formula	*Rehmannia glutinosa*, *Angelicae Sinensis Radix*, *Testudinis Carapax et Plastrum.*, *Dioscoreae Rhizoma*, *Cornus officinalis Sieb et Zucc*, *Cistanche salsa*, *Cyperus rotundus L*, *Codonopsis pilosula*, *Salvia miltiorrhiza Bunge*, *Astragalus membranaceus L*, *Ycii Fructus*, Epimedium, *Cuscuta chinensis*, *Fructus Alebiae*	8-week-old Female SD rats	PI3K/AKT pathway	PTEN, PI3K, AKT	[63]
Yishen Tiaojing Formula	*Rehmannia glutinosa*, *Angelicae Sinensis Radix*, *Basiprionota bisignata*, *Dioscoreae Rhizoma*, *Cornus officinalis Sieb et Zucc*, *Cistanche salsa*, *Cyperus rotundus L*, *Codonopsis pilosula*, *Salvia miltiorrhiza Bunge*, *Astragalus membranaceus L*, *Lycii Fructus*, *Epimedium*, *Cuscuta chinensis*, *Fructus Alebiae*	8-week-old Female SD rats	Apoptosis	caspase-3, Bcl-2, Bax	[38]
Modified *Yijing* Decoction	*Rehmannia glutinosa*, *Atractylodes macrocephala Koidz*, *Dioscoreae Rhizoma*, *Angelica sinensis*, *Cynanchum otophyllum Schneid*, *Ziziphus jujuba*, *Paeonia suffruticosa Andr*, *Glehnia littoralis*, *Bupleuri Radix*, *Eucommia ulmoides*, *Ginseng Radix et Rhizoma*, *Morinda*, *Phyllolobium chinense*, *Cuscuta chinensis*, *Aucklandiae Radix*	8-week-old Female SD rats	PI3K/AKT pathway	PI3K, AKT, mTOR	[64]
Modified *Yijing* Decoction	*Radix Rehmanniae Preparata*, *Radix Codonopsis*, *Semen Cuscutae*, *Radix Salviae Miltiorrhizae*, *Radix Paeoniae Alba*, *Radix Angelicae Sinensis*, *Radix Bupleuri*	12-week-old Female SD rats	Transforming growth factor	AMH, INHB, BMP-15, TGF-β1, TGF-β1R	[65]
Modified *Yijing* Decoction	*Radix Rehmanniae Preparata*, *Semen Cuscutae*, *Radix Angelicae Sinensis*, *Radix Paeoniae Alba*, *Radix Salviae Miltiorrhizae*, *Radix Codonopsis*, *Radix Bupleuri*	12-week-old Female SD rats	Apoptosis	Bcl-2, Bax	[41]
Yulin Formula	*Cuscuta chinensis Lam.*, *Lycium barbarum L.*, *Angelica sinensis (Oliv.) diels*, *Rehmannia glutinosa Libosch.*, *Ligusticum chuanxiong Hort.*, *Morinda officinalis How*, *Cistanche salsa (C.A.Mey.) beck*, *Epimedium brevicornum Maxim.*, *Cnidium monnieri (L.) Cuss.*, *Rubus chingii Hu*	8-week-old Female SD rats	PI3K/AKT pathway	PI3K, PIP2, PIP3, AKT, p-AKT	[66]
Yulin Formula	*Cuscuta chinensis Lam.*, *Lycium barbarum L.*, *Angelica sinensis (Oliv.) diels*, *Rehmannia glutinosa Libosch.*, *Ligusticum chuanxiong Hort.*, *Morinda officinalis How*, *Cistanche salsa (C.A.Mey.) beck*, *Epimedium brevicornum Maxim.*, *Cnidium monnieri (L.) Cuss.*, *Rubus chingii Hu*	8-week-old Female SD rats	Apoptosis	Caspase-3, Caspase-9, BAX, cytochrome C, PI3K, P-AKT	[42]

immune regulatory effects that alleviate ovarian reserve damage [51]. These cytokines not only play a role in immune regulation but are also crucial in follicular atresia. Research shows that IFN-γ can trigger the activation of pro-atresia cytokines, while IL-6 and TNF-α can accelerate this process [52, 53]. Additionally, TNF-α can negatively impact oocyte quality, and IFN-γ has been suggested as a predictive marker for POF [54]. *Buchong Tiaojing* Formula can improve ovarian inflammatory damage and oxidative stress in DOR rats, enhancing ovarian reserve by inhibiting the NLRP3 inflammasome. This may be achieved through the alleviation of ovarian ferroptosis. Wang and colleagues focused on the inflammatory damage and ferroptosis in the ovaries of DOR rats, exploring the pathological relationship between the two [55]. Additionally, studies have shown that the activity of the NLRP3 inflammasome varies with the extent of ferroptosis when ferroptosis inhibitors are used to mitigate this process [56].

Impact of PI3K/AKT pathway in TCM formulas

The PI3K/AKT/mTOR signaling pathway is a crucial intracellular signaling pathway involved in the growth, development, atresia of oocytes, and the proliferation and differentiation of granulosa cells [57]. Rapid apoptosis of follicles can lead to premature ovarian aging. Research indicates that abnormal expression of various signaling molecules within the PI3K pathway can result in defects in the growth and development of primordial follicles, leading to pathological conditions in the ovaries [58]. Granulosa cell apoptosis is closely related to mitochondrial dysfunction, and the PI3K/AKT signaling pathway is a classical pathway associated with mitochondrial apoptosis.

Gao et al. validated the therapeutic effects of the Modified *Gengnianchun* Formula (MGNC) on a stress-induced DOR animal model. Subsequently, through network pharmacology, they identified five flavonoid compounds as the most common active components of MGNC and pinpointed multiple potential therapeutic targets, discovering that the PI3K-Akt pathway is the most promising pathway mediating the effects of MGNC [59]. High doses of *Modified Guishen* Pills can improve ovarian reserve function and delay ovarian aging by regulating the PI3K/AKT/mTOR signaling pathway. Research findings indicate that the ovarian tissue levels of PI3K and AKT proteins were elevated in the high and medium dose groups of *Modified Guishen* Pills, as well as in the estradiol group. Notably, the effects of the high-dose group were comparable to those of the estradiol group [60]. FOXO3a promotes autophagy by upregulating autophagy related genes [5]. *Wenzhong Bushen* Formula (WZBSF) may restore the estrous cycle in DOR mice and correct serum hormone imbalances by inhibiting the activation of the PI3K/AKT/FOXO3a signaling pathway, thereby improving ovarian function. Additionally, WZBSF can protect granulosa cells, restore follicle numbers at various stages, and reduce the extent of follicular atresia [61]. *Dingkun* Pills (DKP) exerts its effects by reducing the phosphorylation of several key proteins in the PI3K/AKT/mTOR signaling pathway, which helps decrease primordial follicle activation and inhibit follicular apoptosis. As a result, DKP has potential as an antidote to counteract the reproductive toxicity of Tripterygium wilfordii polyglycosides (TWP) in women of reproductive age [62]. *Yishen Tiaojing* Formula improves the estrous cycle in DOR rats by influencing the PTEN/PI3K/AKT pathway. This leads to an increase in the gonadal index, improvement in ovarian morphology, and inhibition or slowing of follicular atresia at various growth stages [63]. Modified *Yijing* Decoction can alleviate pathological damage in DOR rats and enhance ovarian reserve function by activating the PI3K/Akt/mTOR signaling pathway [64]. Additionally, research has shown that Modified *Yijing* Decoction can improve ovarian reserve function in cyclophosphamide-induced DOR rats by upregulating the expression of TGF-β superfamily members, including AMH, INHB, TGF-β1, TGF-β1R, and BMP-15 [65]. *Yulin* Formula may improve mitochondrial function in ovarian granulosa cells of DOR rats and inhibit granulosa cell apoptosis by regulating the mitochondria-dependent PI3K/Akt signaling pathway. This suggests that *Yulin* Formula could play a protective role in maintaining ovarian reserve by enhancing mitochondrial health and preventing cell death in DOR-related conditions [66].

Oxidative stress and CHM formulas intervention

Numerous studies have demonstrated that oxidative stress is a key factor contributing to ovarian dysfunction, poor oocyte quality, and ovulatory disorders in modern women [67]. Excessive reactive oxygen species (ROS) can lead to an imbalance in redox reactions, disrupting the dynamic equilibrium between oxidative and antioxidant systems. This oxidative stress promotes various ovarian pathologies, including granulosa cell apoptosis, mitochondrial dysfunction, inflammation, and telomere shortening [68–70]. Therefore, enhancing ovarian antioxidant capacity is a crucial approach to delaying the decline of ovarian reserve function. By regulating antioxidant defense mechanisms, it is possible to mitigate the damage caused by ROS to ovarian cells, thereby slowing ovarian aging and improving reproductive health.

He's Yangchao Recipe (HSYCR) may promote the in vitro maturation of mouse oocytes by regulating the SIRT3-dependent SOD2 pathway through deacetylation, primarily by improving mitochondrial function and reducing oxidative stress. The study found that HSYCR eliminated age-related ROS accumulation, thereby

inhibiting DNA damage and autophagy. Additionally, mitochondrial function was improved post- HSYCR treatment, indicated by increased mitochondrial membrane potential and decreased $Ca2^{+}$ levels. During the in vitro maturation of oocytes from aging mice, HSYCR upregulated SIRT3 expression, a key protein regulating mitochondrial function. Concurrently, the expression levels of SOD2, PGC1α, and TFAM were increased, while the acetylation level of SOD2 decreased, further demonstrating its antioxidant function [71]. Moreover, Zhao et al. discovered that HSYCR improves oxidative stress in the ovaries of aging mice undergoing continuous superovulation and promotes ovarian reserve, oocyte quality, and embryo hatching through the ROS/JNK/p53 pathway [72]. *ErZhiTianGui* Decoction maintains PINK1/parkin-mediated mitochondrial homeostasis, reduces lipid peroxidation caused by ROS accumulation, inhibits ferroptosis, and delays ovarian aging [73].

Modified *Congrong Tusizi* Decoction can activate the AMPK/SIRT1 signaling pathway to correct mitochondrial morphological damage and dysfunction in ovarian tissue, improve hormonal imbalance, promote follicular growth and development, and delay reproductive aging. After administration of the decoction, the rats partially restored their estrous cycles, increased the number of follicles at various stages, improved serum hormone levels, and restored ovarian function. Additionally, the treated rats showed less mitochondrial structural damage, reduced ROS accumulation, increased ATP synthesis, and restored MMP levels, indicating that it effectively corrects mitochondrial morphological damage and dysfunction [74]. Zhu et al. found that in the ovarian tissues of DOR mice, the expression of HIF-1α, Bnip3, and Beclin-1 proteins was significantly elevated, suggesting that autophagy was activated under excessive hypoxic conditions. After treatment with *Qilin* Pills, the expression of HIF-1α, Bnip3, and Beclin-1 proteins significantly decreased, indicating that it may reverse the hypoxic and autophagic state in the ovaries of mice by regulating this pathway, thereby improving fertility in DOR mice [75]. *Zuogui* Pills may restore normal ovarian function by regulating the Nrf2/HO-1 pathway, reducing oxidative stress in ovarian stem cells (OSCs) of aging rats, promoting the proliferation of OSCs, and restoring their stemness, thereby providing protective effects against CTX-induced ovarian aging [76].

Epigenetic modifications induced by CHM formulas

The dynamic and reversible m6A modification of RNA requires the collaboration of methyltransferases such as METTL3 [77], demethylases like FTO [78], and recognition proteins from the YTH family [79] to regulate mRNA functionality. Studies show that METTL3 can alter spindle morphology and the extrusion of the first polar body by modulating mRNA translation efficiency, thereby regulating oocyte maturation [80]. Mutations in METTL3 can obstruct oocyte maturation and disrupt steroid hormone synthesis [81]. A downregulation of FTO expression leads to an abnormal increase in m6A levels, impairing ovarian function and ultimately resulting in premature ovarian failure [82].

Li et al. found that in DOR rat models, the expressions of METTL3, FTO, and YTHDC2 in ovarian tissue were reduced, while serum levels of FSH and LH increased, and E2 and AMH levels decreased. Pathological observations of ovarian tissue indicated that the damage to ovarian function in DOR rats might be associated with abnormal m6A levels in ovarian RNA. After treatment, *Yangjing Zhongyu* Decoction was able to upregulate the levels of METTL3, FTO, and YTHDC2, while improving hormone levels and repairing damage to the ovarian cortex. In summary, *Yangjing Zhongyu* Decoction may improve ovarian reserve function in DOR model rats by regulating ovarian RNA m6A modifications [83].

The effects and mechanisms of active compounds in CHMs on DOR

In modern medical research, the impact of active compounds in TCM on DOR has garnered increasing attention. A decline in ovarian reserve not only affects female fertility but is also closely linked to various health issues [84]. Studies have shown that several active compounds found in TCM, such as flavonoids [85], polyphenols [86], and saponins [87], can modulate ovarian function through multiple mechanisms, improving the ovarian microenvironment, promoting follicular development, and enhancing oocyte quality. These active components may offer new therapeutic approaches for improving ovarian reserve by regulating endocrine functions, providing antioxidant effects, and inhibiting apoptosis (Fig. 4; Table 3). Therefore, a deeper exploration of the mechanisms of active compounds in CHMs is crucial for identifying effective intervention strategies.

Inhibition of oxidative stress

Oxidative stress (OS) plays a role in various stages of folliculogenesis, including the formation of primordial follicles, follicle development, maturation, and atresia. It may be a significant factor contributing to ovarian dysfunction, poor oocyte quality, and ovulatory disorders in modern women, as well as a crucial cause of DOR [88].

Curcumin, as an antioxidant, can alleviate ovarian failure during aging and improve embryo development. Researchers administered 100 mg/kg of curcumin daily via intraperitoneal injection to mice, and after 33 weeks, results showed an increase in the expression of ovulation-related genes GDF-9 and BMP-15, as well as anti-aging genes SIRT-1 and SIRT-3. Thus, curcumin may

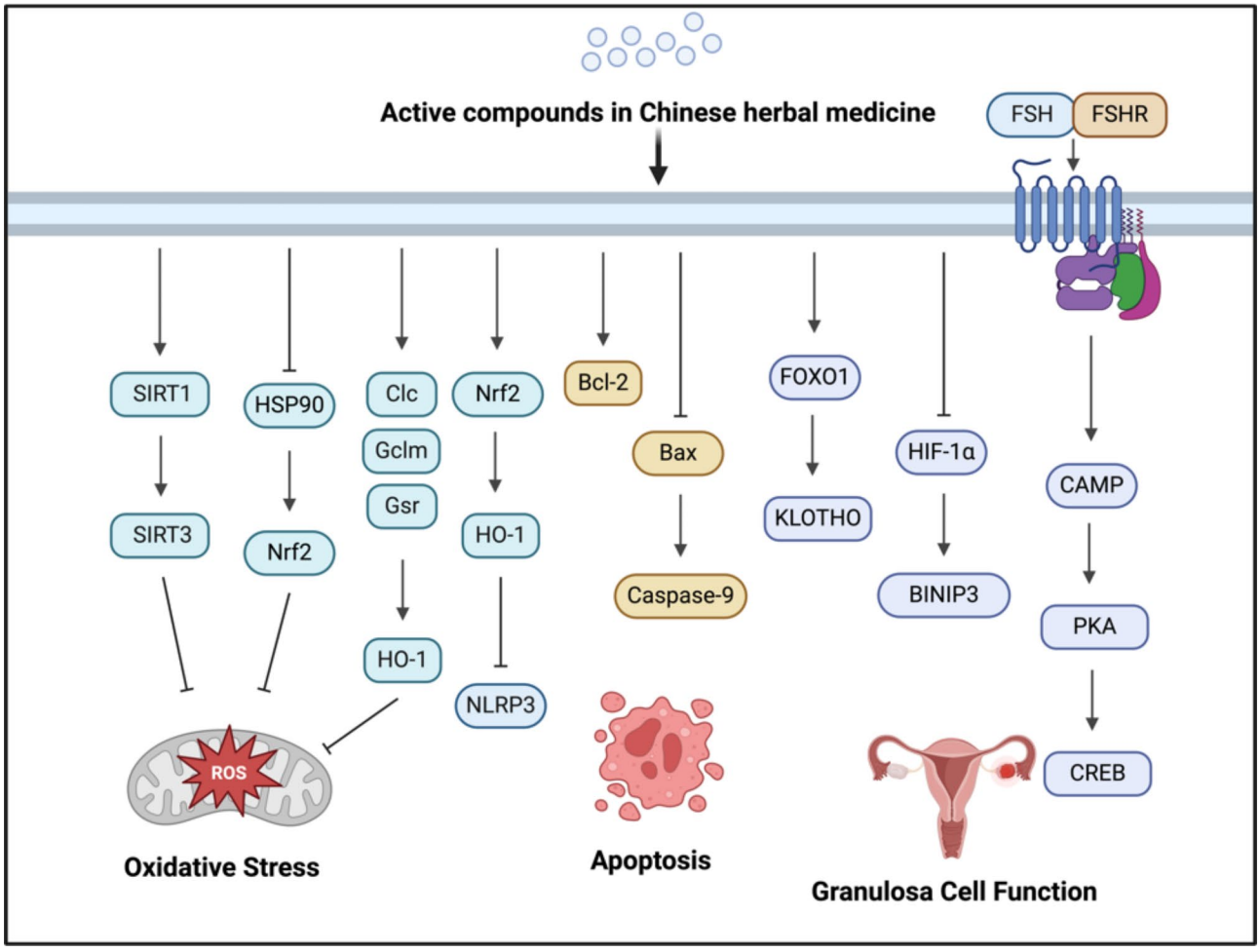

Fig. 4 The mechanism of active compounds in CHMs and its bioactive ingredients in treating DOR. These include processes like inhibition of oxidative stress, restoration of granulosa cell function and suppressing apoptosis

reduce ovarian functional decline and enhance embryo development by inhibiting oxidative stress and apoptosis [86]. Excessive ROS can lead to oocyte aging and impair female fertility. Research has indicated that Kaempferol, as an antioxidant, can reduce ROS production to alleviate neuroinflammation and inhibit acetaminophen-induced liver injury [89]. In a study by Hua et al., Kaempferol exerted antioxidant effects against age-related diminished ovarian reserve (AR-DOR) by inhibiting HSP90 expression and upregulating NRF2 expression, thereby reducing ROS production [85]. Isoquercitrin, an important natural flavonoid, has the ability to scavenge reactive oxygen species and exhibit antioxidant effects. It regulates glutathione peroxidase activity, inhibits apoptosis, suppresses the expression of oxidative stress-related genes such as Clc, Gclm, and Gsr, and enhances the expression of heme oxygenase-1, thereby protecting human ovarian granulosa cells from oxidative stress damage [90]. Soy isoflavones, primarily found in leguminous plants, are important secondary metabolites synthesized through the phenylpropanoid pathway, known for their strong biological activity. Research indicates that soy isoflavones have positive effects on human health, exhibiting antioxidant, anti-inflammatory, anti-tumor, and immune-enhancing activities, and they can influence the proliferation and apoptosis of endometrial and granulosa cells. C. P. Teixeira et al. found that soy isoflavones reduced follicle atresia, apoptosis, and oxidative stress in rat ovaries while increasing the total antioxidant capacity of ovarian tissues. Additionally, the anti-apoptotic effects of these compounds may be partly attributed to their antioxidant properties [91]. Osthole, a coumarin-type phytoestrogen and a major active component of Cnidium monnieri, has been shown in modern pharmacological studies to effectively improve endocrine metabolism in DOR rats, reduce ovarian inflammation and oxidative stress damage, and restore ovarian reserve function by regulating the Nrf2/HO-1/NLRP3 signaling pathway [92].

Table 3 The regulatory effects of active compounds in CHMs on DOR

Components	Classification	Model	Dose	Treatment period	Target	Plants source	Mechanisms	Ref
Curcumin	Polyphenols	21-day-old female NMRI mice	100 mg/Kg	Daily, 12 Weeks/ 33 Weeks	GDF-9, BMP-15, SIRT-1, SIRT-3	*Curcuma longa L.*	Oxidative stress	[86]
Hyperoside	Flavonoid	6-week-old C57BL/6 female mice, KGN cells	40 mg/Kg, 10 μM/L	Daily, 5 weeks	HIF-1α, bnip3,LC3B-II, Beclin1, P62	*Hypericum perforatum L.*	Autophagy	[108]
Kaempferol	Flavonoid	27-week-old C57BL/6 female mice	100 mg/kg	Daily, 4 weeks	HSP90, NRF2, HSF1, p-HSF1, Src, p-SRC	*Forsythia suspensa*	Oxidative stress	[85]
Paeoniflorin	Diterpenoid glycosides	6-week-old female Kunming mice, KGN cells	150 mg/kg, 10 μM/L	Daily, 4 weeks	FSHR, cAMP, PKA, CREB	*Paeonia lactiflora Pall.*	Restore ovarian granulosa cell function	[116]
Pueratin	Saponins	4-week-old Female SD rats	300 mg/kg	Daily, 45 days	Caspase-3, Bcl-2, Bax	*Puerariae Lobatae Radix*	Inhibit apoptosis	[87]
Rehmannioside D	Iridoid	8-week-old Female SD rats	76 mg/kg	Daily, 2 weeks	FOXO1, KLOTHO, Bax, Bcl-2	*Rehmannia glutinosa*	Inhibit apoptosis	[99]
Resveratrol	Polyphenol	70-day-old female Wistar Albino rats	20 mg/kg	Daily, 45 days	NA	*Veratrum album*	Inhibit apoptosis	[103]
Isoquercitrin	Flavonols	KGN cells	10 μM/L	24 h	HO-1, Nrf2, p-eIF2α, eIF2α, P-ERK, Gclc, Gclm, Gsr, Keap1, Fxol1, Srxn1, Txnrd1, Rhob, Pon2, Hepud1, Selenok, Dnajb1,Ddit3, Sesn2, Dhcr24	*Cercis canadensis*	Oxidative stress	[90]
Soy isoflavones	Flavonoid	12-month-old female Wistar albino rats	150 mg/kg	Daily, 8 days	cleaved-caspase-3, bcl2	*Glycine max*	Inhibit apoptosis and oxidative stress	[91]
Urtica pilulifera L. seed extract	NA	6-8-week-old female Balb/c mice	200 mg/kg	Daily, 14 days	NA	*Urtica fissa*	Inhibit apoptosis and oxidative stress	[105].
Osthole	Coumarins	10-week-old Female SD rats	80 μg·mL	Daily, 21 days	AMH, E2、IL-4, IL-10, TNF-α, Nrf2, HO-1, NLRP3	*Cnidium monnieri*	Inflammatory response and oxidative stress	[92]
Total Flavones from Semen Cuscutae	Flavonoid	21-day-old Female SD rats	530.1 mg/kg	Daily, 4 weeks	FSHR, PKA, p-PKA	*Cuscuta chinensis*	Restore ovarian granulosa cell function	[114]

Inhibition of cell apoptosis

Research indicates that the decline in ovarian reserve function is primarily due to the excessive death of granulosa cells, leading to follicle atresia [93]. The death of granulosa cells can occur through both autophagy and apoptosis, with follicle atresia typically resulting from the combined effects of these two processes [37, 93]. Autophagy is a crucial mechanism of cellular metabolism in mammalian cells [94, 95]. Alongside apoptosis, it plays a significant role in the development and atresia of ovarian follicles, contributing to the regulation of ovarian function [37, 96].

Pueratin, a natural flavonoid compound, exhibits various biological pharmacological activities and plays a positive role in combating cardiovascular diseases, osteoporosis, and neurodegenerative disorders [97]. Research has found that pueratin reduces FSH and LH levels in a dose-dependent manner, stimulates E2 secretion, upregulates Bcl-2 protein expression, downregulates Bax protein expression, inhibits apoptosis, and protects ovarian reserve function [87]. Rehmannioside D is a cyclic ether triterpenoid compound isolated from the extract of *Rehmannia glutinosa* [98]. Daily administration of Rehmannioside D (76 mg/kg for 2 weeks) can improve the estrous cycle in DOR rats, increase ovarian index, enhance the number of primordial and mature follicles, reduce the number of atretic follicles, decrease apoptosis in ovarian granulosa cells, inhibit FSH and LH levels, and upregulate E2 expression. Additionally, Liang et al. further discovered that Rehmannioside D reduces granulosa cell apoptosis through the FOXO1/KLOTHO axis [99]. Resveratrol, the main active component of Polygonum cuspidatum [100], is a natural activator of SIRT1 and an antioxidant [101, 102]. Resveratrol improves the decline

of ovarian reserve function induced by VCD by inhibiting follicular cell apoptosis and increasing the numbers of primary, primordial, and growing follicles [103]. Urtica pilulifera has shown good efficacy in conditions such as hypertension, hyperglycemia, and inflammation [104]. Extracts from Urtica pilulifera seeds contain fatty acids like linoleic and alpha-linolenic acid. Additionally, due to their high content of phenolic compounds and tocopherols, these extracts exhibit antioxidant properties [105]. Research by Sharareh Hekmat et al. found that Urtica pilulifera seed extract can alleviate ovarian oxidative stress and apoptosis while also dose-dependently modulating levels of steroid hormones such as FSH, LH, and E2 [106]. Hyperoside is a flavonoid compound known for its neuroprotective, anticancer, anti-inflammatory, and antioxidant properties [107]. Hyperoside inhibits excessive hypoxia and reduces autophagic death of granulosa cells by regulating the HIF-1α/BNIP3 pathway, consequently decreasing the loss of primordial follicles and follicle atresia, thus improving ovarian reserve function and fertility in mice [108].

Restoration of granulosa cell function

Ovarian granulosa cells play a critical role in ovarian dysfunction. They are responsible for the synthesis and secretion of estrogen, supporting follicular development and regulating endocrine feedback mechanisms. When their function declines, the hormone synthesis and follicular support capabilities of these cells decrease, leading to reduced estrogen levels and impaired follicle maturation. This can result in irregular menstruation, infertility, and health issues such as osteoporosis [109, 110].

Total Flavones from Semen Cuscutae, the main component of Cuscuta seeds from the plant *Cuscuta chinensis Lam*., is known for improving endocrine function, enhancing sexual function, and exhibiting antioxidant and immunomodulatory effects [111]. The FSH-cAMP/PKA signaling pathway is a classic route for regulating ovarian function. FSH binds specifically to FSHR on granulosa cells, activating cAMP through G protein-coupled receptors on the cell membrane, which increases intracellular cAMP concentration, disrupting the cAMP balance [112]. cAMP plays a crucial role in regulating oocyte maturation and follicular development during ovarian development [113]. Research by Dun et al. suggests that Total Flavones from Semen Cuscutae may enhance ovarian reserve function by modulating FSH and activating the cAMP/PKA signaling pathway, thereby increasing local cAMP levels and promoting follicular development [114]. Paeoniflorin, a major bioactive compound extracted from the peony plant (Paeonia), has been found to promote ovarian development in mice by activating mitophagy and preventing oxidative stress [115]. In the study by Wu et al., Paeoniflorin restored the E2 synthesis function of ovarian granulosa cells by activating the FSHR/cAMP/PKA/CREB signaling pathway, thus improving DOR [116].

Conclusion and prospects

DOR is characterized by a decrease in the quantity and/or quality of oocytes, with an incidence rate of approximately 10% in the infertile population [14], and as high as 31% among patients undergoing assisted reproductive technologies [117]. DOR is closely associated with adverse pregnancy outcomes, including poor ovarian response, low embryo quality, and increased miscarriage rates [2]. The etiology of DOR remains unclear, and conventional Western medicine often employs hormone therapy, which can yield rapid results; however, symptoms frequently persist after discontinuation, and patients may still lack mature follicles. Additionally, hormone therapies may increase the risk of conditions such as endometrial cancer, breast cancer, and thrombosis. In recent years, the advantages of TCM in treating DOR have become increasingly apparent. TCM posits that kidney function plays a crucial role in female ovarian reserve, emphasizing kidney treatment to regulate hormone levels and improve ovarian function [14]. Moreover, TCM recognizes the influence of menstrual cycle patterns and the physiological rhythms of yin, yang, qi, and blood, allowing for tailored treatment courses based on the physiological characteristics of patients during different phases of their menstrual cycles [63]. Research has identified several mechanisms by which TCM formulas and their active components may address DOR, including counteracting oxidative stress, modulating immune defenses, regulating the secretion of sex hormones from the HPOA, and inhibiting excessive apoptosis of ovarian granulosa cells.

Currently, there are several challenges associated with the use of TCM in treating DOR. Despite the broad potential applications of TCM formulas in both clinical practice and research, the complexity of their active ingredients poses a significant obstacle. First, the synergistic effects of various active components in TCM formulas are largely unexplored, making it difficult to systematically explain their efficacy and safety. Moreover, the multi-component and multi-target nature of these formulas complicates studies on drug metabolism, pharmacodynamics, and toxicology, particularly in terms of dose optimization and standardization. Additionally, individual variability in clinical applications and the diversity of formula components lead to challenges in ensuring quality control, bioavailability, and dose consistency, which can affect the stability of therapeutic effects. Furthermore, there is currently no comprehensive standardization and evaluation system for TCM formulas in the international academic community, as uniform

quality control standards are lacking, which further limits their promotion and application globally. Future research must delve deeper into the molecular mechanisms of TCM formulas and establish scientifically sound quality control standards. Refining extraction and purification techniques, developing reliable pharmacokinetic and pharmacodynamic models, and formulating comprehensive standardization protocols will be crucial to advancing the field.

Additionally, clinical studies on TCM for DOR face limitations such as small sample sizes, lack of rigorous trial designs, and short follow-up durations. Many studies do not address critical outcomes such as pregnancy rates and pregnancy outcomes, instead focusing on surrogate markers like hormone levels and antral follicle counts. More scientific data is needed to provide robust evidence supporting safer and more effective treatment options, thus offering a stronger evidence-based framework for TCM in treating DOR. Research on the active components of TCM in treating DOR has primarily focused on animal and cell experiments, with a lack of clinical trials. Although there have been some findings regarding the mechanisms of TCM formulas and their active ingredients, these studies have not sufficiently integrated emerging technologies and methods such as epigenetics, proteomics, and gut microbiota analysis. Consequently, the specific regulatory mechanisms of the relevant signaling pathways require further exploration and validation.

Building upon the inheritance and optimization of classic Chinese herbal formulas, it is essential to conduct in-depth studies on their mechanisms of action by integrating modern scientific theories. This approach will improve the formulation of TCM and enhance clinical efficacy. In addition to animal experiments, in vitro studies are also vital for exploring the mechanisms underlying TCM formulas. By utilizing cell culture models to simulate the human environment, researchers can investigate the effects of TCM formulas and their active components on signaling pathways and cellular activities. Employing cutting-edge technologies such as epigenetics and omics will further elucidate the molecular mechanisms of TCM formulas in the treatment of DOR. Utilizing network pharmacology and bioinformatics methods to reveal the multi-target and multi-component action patterns of TCM formulas will provide a more comprehensive understanding of their therapeutic mechanisms for DOR. Moreover, alongside mechanism studies, attention should also be given to large-scale, multi-center randomized controlled trials with long-term follow-up, incorporating comprehensive clinical endpoints, such as pregnancy rates, live birth rates, and long-term ovarian function. These studies should present data with confidence intervals and effect sizes to improve result interpretation. This will maximize the role of TCM formulas in women's reproductive health and contribute to the modernization of traditional Chinese medicine.

Author contributions
Xiaoyu Zhang wrote the manuscript and drew the pictures. Na Zhang collected and organize literature. Zhibin Dong, Hao Sun, and Zhihao Diao proofread the manuscript. Yujie Li, Dongqing Du and Yuning Ma are fully responsible for the study designing, research fields, drafting, and finalizing the paper.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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