

Research Advances on Modified Yulinzhu Decoction in Clinical Applications and Fundamental Studies of Gynecological Diseases

Mengmeng Zhang¹, Hongli Zhu^{2,*}, Jing Li¹, Yang Liu¹

¹Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China

²First Clinical Medical College, Shaanxi University of Chinese Medicine, Xianyang 712000, Shaanxi, China

*Correspondence Author

Abstract: *Yulinzhu Decoction, originally documented in Jingyue's Complete Works by the Ming Dynasty physician Zhang Jingyue, is renowned for its dual capacity to "tonify Yang within Yin", reinforce Kidney Qi, and regulate menstruation by nourishing Blood. Designed for women with concurrent Qi-Blood deficiency, menstrual irregularities, and infertility, this formula has been extolled by later physicians as the quintessential prescription for menstrual regulation and fertility enhancement. Recent advancements in modern research methodologies have expanded its therapeutic scope in gynecological disorders. This review systematically summarizes clinical progress in applying Yulinzhu for reproductive endocrine diseases, including hypomenorrhea, amenorrhea, polycystic ovary syndrome (PCOS), and premature ovarian insufficiency (POI). From a mechanistic perspective integrating network pharmacology predictions and experimental validation, we elucidate its modulation of multiple signaling pathways—HIF-1, SIRT1/TERT, mTOR, FOXO3a, and SIRT1-FoxO1—to improve ovarian microenvironment, delay ovarian aging, and mitigate oxidative stress damage. Evidence indicates that Yulinzhu exerts therapeutic effects via a "multi-component, multi-target, multi-pathway" regulatory network. Future studies should prioritize high-quality clinical trials to further delineate its pharmacodynamic material basis and molecular mechanisms, thereby facilitating the modernization and clinical translation of this classical formula.*

Keywords: Yulinzhu Decoction, Gynecological diseases, Ovarian function, Network pharmacology, Mechanism of action, Research advances.

1. Introduction

The Yulinzhu Decoction was first documented in Jingyue's Complete Works·Volume 51 by the Ming Dynasty physician Zhang Jingyue, who asserted: "For women presenting with concurrent Qi and Blood deficiency, menstrual irregularities, and infertility, the modified Yulinzhu formula demonstrates exceptional therapeutic efficacy". This sophisticated prescription integrates two classical formulas: Siwu Decoction (comprising *Angelicae Sinensis Radix*, *Rehmanniae Radix Praeparata*, *Paeoniae Radix Alba*, and *Chuanxiong Rhizoma*) for blood nourishment and menstrual regulation, and Sijunzi Decoction (containing *Ginseng Radix et Rhizoma*, *Atractylodis Macrocephalae Rhizoma*, *Poria*, and *Glycyrrhizae Radix et Rhizoma Praeparata cum Melle*) for Qi reinforcement and spleen fortification. These are synergistically combined with *Cuscutae Semen* and *Eucommiae Cortex* to warm and tonify the Liver and Kidney, *Cervi Cornus Degelatinatum* for essence replenishment and marrow nourishment, and a minimal quantity of *Zanthoxyli Pericarpium* to activate the Governor Vessel. This dual mechanism ensures abundant essence-blood and unobstructed Chong-Ren Meridians, epitomizing Zhang Jingyue's therapeutic principle: "To effectively tonify Yin, one must seek Yang within Yin". Dysfunction in these systems—manifesting as Kidney deficiency with essence depletion, Liver stagnation with blood stasis, or spleen deficiency with Qi weakness—leads to menstrual disorders, infertility, and amenorrhea. Yulinzhu's primary focus on Kidney-tonification and essence replenishment, with secondary attention to Liver-Spleen regulation and Qi-Blood modulation, aligns perfectly with the "dual deficiency-stasis pathology" characteristic of gynecological disorders. Its demonstrated efficacy in ovarian function improvement,

pregnancy rate enhancement, and menstrual cycle regulation stems from this multidimensional approach. Recent advances in pharmacognosy and molecular biology have shifted research paradigms from traditional efficacy descriptions to mechanistic explorations at cellular and molecular levels. Concurrently, clinical applications have expanded significantly. This review systematically examines: Clinical progress in treating gynecological diseases and Mechanistic insights through network pharmacology predictions and multi-pathway experimental validations. The findings aim to provide evidence-based guidance for clinical practice and inspire future investigations into this classical formulation.

2. Clinical Applications of Yulinzhu Decoction in Gynecological Diseases

2.1 Infertility

Infertility is a prevalent reproductive health issue among women of childbearing age. According to the World Health Organization (WHO), approximately 17.5% of adults worldwide (~1/6 of the population) suffer from infertility [1]. In China, the age-standardized prevalence of infertility exceeds the global average and continues to rise. Traditional Chinese Medicine (TCM) Gynecology (10th Edition) defines infertility as the failure to conceive after one year of regular, unprotected intercourse while cohabiting with a partner. Zhang Jingyue originally formulated Yulinzhu Decoction for "women with concurrent Qi-Blood deficiency, menstrual irregularities, and infertility", embodying the therapeutic philosophy: "To tonify the Kidney, first replenish Blood; to replenish Blood, first regulate Qi. "Clinical studies confirm that Yulinzhu exerts significant efficacy in treating various infertility etiologies: Anovulatory Infertility: Wang Yun et al.

[2] treated 50 patients with modified Yulinzhu Decoction, observing 72% pregnancy rates within 9 months and 94% ovulation restoration rates. Thin Endometrial Infertility: Zheng Ruijun [3] administered Yulinzhu plus tailored herbs to 30 patients over 3-12 ovulatory cycles, achieving 17 pregnancies and 9 cases of endometrial improvement (≥ 7 mm), with an 86.7% total efficacy rate. Diminished Ovarian Reserve (DOR): Tang Huizhen et al. [4] combined menstruation-regulating and fertility-promoting acupuncture with Yulinzhu, significantly enhancing high-quality embryo counts, fertilization rates, and cumulative pregnancy rates compared to controls. PCOS-Related Infertility: Lou Xueli et al. [5] integrated Yulinzhu with Guizhi Fuling Wan and clomiphene, demonstrating superior ovulation rates, pregnancy rates, endometrial thickness/pattern improvement, and hormonal regulation (reduced leptin and IGF-1 levels) versus clomiphene monotherapy. Kidney Deficiency-Type Infertility: Prof. Wang Peijuan [6] applied “State-Target Differentiation” theory, targeting “Kidney deficiency” as the constitutional state, menstrual disorders and lumbar weakness as symptom targets, and ovarian function/endometrial receptivity as objective markers. Modified Yulinzhu effectively regulated Chong-Ren Meridians, yielding remarkable outcomes.

2.2 Hypomenorrhea

Hypomenorrhea is clinically characterized by regular menstrual cycles but markedly reduced menstrual volume ($<50\%$ of normal baseline or total volume <20 mL) or shortened duration (≤ 2 days, sometimes only spotting). Its pathogenesis involves both deficiency patterns (e.g., essence-blood depletion or Chong-Ren Meridian insufficiency) and excess patterns (e.g., Cold stagnation, Phlegm obstruction, or Blood stasis). As stated in Fu Qingzhu’s Gynecology, “Menstruation originates from the Kidney” [7], implying that Kidney Qi abundance is pivotal for normal menstruation. Kidney deficiency-induced Chong-Ren Meridian insufficiency often underlies hypomenorrhea. Clinical Evidence for Yulinzhu: Yang Yuting et al. [8] treated 30 patients with Kidney-deficient hypomenorrhea using modified Yulinzhu plus intradermal acupuncture. After 3 months, the cure rate reached 50%, with a 90% total efficacy rate. The treatment group exhibited significantly increased endometrial thickness versus controls. Jiang Han et al. [9] administered modified Yulinzhu to 35 patients with menstrual disorders due to diminished ovarian reserve (DOR), observing reduced serum FSH and FSH/LH ratios, elevated E2 levels, and restored regular menstrual cycles.

2.3 Amenorrhea

Amenorrhea, first documented in The Yellow Emperor’s Inner Canon, is also termed “menstrual block” or “absent menses”. Secondary amenorrhea refers to the cessation of menstruation for ≥ 3 cycles or 6 months after menarche. Its etiology aligns with TCM’s deficiency-excess dichotomy: Excess patterns: Cold congelation, Blood stasis, or Phlegm-dampness accumulation. Deficiency patterns: Essence-blood insufficiency or Qi-Blood deficiency [10]. Kidney-Liver dysfunction and Qi-Blood stagnation are predominant in secondary amenorrhea [11]. Prof. Deng Weiming [12] emphasized Yulinzhu’s suitability for

“Blood-exhaustion amenorrhea” caused by spleen-Kidney dual deficiency and Chong-Ren Meridian collapse. After 3 menstrual cycles of modified Yulinzhu therapy, patients with 2-year amenorrhea resumed regular menses. Kim Kyung-Lee et al. [13] augmented Yulinzhu with Codonopsis Radix, Cyperi Rhizoma, Corydalis Rhizoma, Cervi Cornus Pantotrichum, and Placenta Hominis, treating 24 amenorrhea patients. Outcomes: Cure (restored cycles): 13 cases (54.2%), Effective (menses within 35-60 days): 7 cases (29.1%), Total efficacy rate: 83%.

2.4 Polycystic Ovary Syndrome (PCOS)

Polycystic ovary syndrome (PCOS) is the most prevalent endocrine-metabolic disorder among reproductive-aged women, characterized by menstrual irregularities, hyperandrogenism, polycystic ovarian morphology, and metabolic dysfunction. Globally, PCOS affects 8%-13% of women [14-15], with a 7.8% prevalence (~24 million cases) in China [16]. TCM Pathogenesis & Treatment Rationale PCOS is attributed to spleen-Kidney deficiency compounded by Phlegm-dampness and Blood stasis. Yulinzhu Decoction demonstrates multi-target efficacy by: Tonifying spleen-Kidney function, Resolving dampness-stasis pathology, Restoring hypothalamic-pituitary-ovarian (HPO) axis homeostasis Clinical Evidence. Wang Jie et al. [17] combined Yulinzhu with letrozole in 49 PCOS infertility patients for 3 months: Total efficacy: 91.84% (vs. 75.51% in controls), Regulated hormones: \downarrow LH/FSH, \uparrow E2, Improved endometrial receptivity. He Wenli [18] treated 54 Kidney deficiency-Blood stasis PCOS cases with Yulinzhu + Diane-35 for 12 weeks: 90.74% efficacy rate, \downarrow IGF-1 and androgens, \uparrow ovulation rates. Sun Xin et al. [19] integrated Yulinzhu with Chaihu Shugan San in 30 Liver-Qi stagnation PCOS patients: 84.62% efficacy after 3 months, \downarrow Androgens, restored menstrual cyclicity.

2.5 Premature Ovarian Insufficiency (POI) & Premature Ovarian Failure (POF)

POF is defined as ovarian dysfunction before age 40, marked by hypoenestrogenism, elevated gonadotropins (FSH >25 IU/L), and amenorrhea/infertility [20]. POI represents its early-stage continuum. Therapeutic Advantages of Yulinzhu.

While Western medicine lacks definitive treatments [21], TCM—particularly Yulinzhu—modulates: Ovarian reserve markers (AMH, AFC), HPO axis feedback, Mitochondrial function in granulosa cells. Dong Xiaoying et al. [23] treated 28 spleen-Kidney Yang-deficient POF patients with Yulinzhu + Climen for 2 months: 92.86% efficacy, \downarrow FSH/LH, \uparrow E2, Li Shanxia et al. [24] randomized 60 POI patients to Yulinzhu vs. hormone replacement therapy (HRT): Yulinzhu outperformed HRT in: \downarrow FSH/LH, \uparrow E2/AMH, \uparrow Antral follicle count (AFC) and endometrial thickness. Wei Maolin et al. [25] demonstrated in POI rats: Yulinzhu \uparrow AMH/E2 more effectively than Yangjing Zhongyu Decoction, Innovative Combinatorial Therapies. Li Yang et al. [26] applied “Yulin Yangchao” protocol (Yulinzhu + specialized acupuncture) based on “Yangming Meridian Decline at Age 35” theory: Superior to herbs-alone in: Menstrual recovery (\downarrow FSH, \uparrow E2/AMH), Ovarian reactivation (\uparrow AFC), Symptom relief (TCM syndrome scores).

3. Modern Research on the Mechanism of Action of Yulinzhu

3.1 Multi-target Targeting Characteristics Revealed by Network Pharmacology

Network pharmacology provides a crucial tool for elucidating the complex mechanism of action of Yulinzhu. Ruan Xin et al. [27] screened the blood-soluble active components of the five core herbs—*Cuscuta chinensis*, *Eucommia ulmoides*, *Rehmannia glutinosa*, *Angelica sinensis*, and *Panax ginseng*—in Yulinzhu using the TCMSP database, identifying key active compounds such as quercetin, kaempferol, β -sitosterol, and stigmasterol. They predicted 103 potential target points associated with POIs, with critical targets including AKT1, CAV1, ESR1, and RHOA, which are involved in biological processes such as cell proliferation, estrogen signaling, and cell signaling. Another study [28] identified 172 active components, 3,444 drug targets, and 223 shared target genes related to POF in Yulinzhu, with key targets including RELA, TP53, STAT3, FOS, MAPK1, and MAPK3. Molecular docking demonstrated strong binding affinity between the core components and these critical targets. These studies suggest that Yulinzhu exerts its therapeutic effects through a “multi-component multi-target multi-pathway” network regulatory mechanism. Recent studies published in the *Journal of Ethnopharmacology* [29-31] employed LC-MS/MS technology to characterize 93 active components in Yulinzhu and constructed a “component-target-pathway” network using network pharmacology, revealing ESR1 as the core therapeutic target, with the estrogen signaling pathway and stem cell pluripotency pathway being the key pathways of action. Molecular docking and surface plasmon resonance experiments confirmed that kaempferol and quercetin are the active components in Yulinzhu with the strongest binding affinity to ESR1 (binding energies of -6.82 kcal/mol and -6.95 kcal/mol, respectively; KD values of 1.15 μ M and 2.25 μ M, respectively). Further validation using an ESR1 gene knockout *Drosophila* model demonstrated that ESR1 knockout prevented Yulinzhu from reversing abnormal hormone levels and reduced expression of reproductive stem cell markers, confirming that ESR1 serves as the key mediator in the pharmacological action of Yulinzhu.

3.2 Modulation of the HIF-1 Signaling Pathway Improves the Ovarian Hypoxic Microenvironment.

Based on KEGG pathway enrichment analysis, Ruan Xin et al. [27, 32] found that the core targets of Yulinzhu were significantly enriched in the hypoxia-inducible factor-1 (HIF-1) signaling pathway. Animal experiments demonstrated that Yulinzhu intervention reduced HIF-1 α protein expression levels in ovarian tissues of POI model rats and improved serum hormone levels. HIF-1 α is a key transcription factor involved in cellular sensing and adaptation to hypoxic conditions, playing critical roles in ovarian follicle development, luteal formation, and atresia. The local hypoxic microenvironment in the ovaries can lead to granulosa cell apoptosis and follicular developmental disorders. Yulinzhu ameliorates ovarian hypoxia by modulating the HIF-1 pathway, which may represent one of its key mechanisms for protecting ovarian function.

3.3 Modulation of the SIRT1/TERT Pathway to Delay Ovarian Aging

Ovarian aging is closely associated with telomere shortening and mitochondrial dysfunction. Recent studies [33] have demonstrated that Yulinzhu can modulate the silencer-of-transcription factor 1 (SIRT1)/telomerase reverse transcriptase (TERT) pathway to improve ovarian function in naturally aging rats. Experimental results showed that after Yulinzhu intervention, the number of follicles at all levels increased, while atretic follicles decreased in the ovarian tissues of aging rats; serum AMH levels improved; levels of superoxide dismutase (SOD) and glutathione (GSH) in ovarian tissues increased; malondialdehyde (MDA) levels decreased; telomerase activity elevated; FSHR and ER expression were upregulated; and the expression of SIRT1 and TERT proteins increased. SIRT1 is involved in cellular aging, oxidative stress, and energy metabolism; TERT, as the catalytic subunit of telomerase, is crucial for maintaining telomere length and delaying cellular aging. By upregulating the SIRT1/TERT pathway, Yulinzhu enhances antioxidant capacity and delays the progression of ovarian aging.

3.4 Intervention of the FOXO3a Pathway to Mitigate Oxidative Stress Damage

Oxidative stress is one of the key mechanisms underlying ovarian dysfunction. The accumulation of reactive oxygen species (ROS) can lead to granulosa cell apoptosis, impaired oocyte quality, and accelerated follicular atresia. Oxidative stress triggers the dephosphorylation of formin protein O3a (FOXO3a), which inhibits cell proliferation and induces apoptosis, thereby participating in the regulation of primordial follicle development initiation. Yang Zhen et al. [34] demonstrated through animal experiments that intervention with Yulinzhu reduced FOXO3a protein expression in ovarian tissues of POI model mice while increasing the expression of peroxisome proliferator-activated receptor γ co-activator-1 α (PGC-1 α). These findings indicate that Yulinzhu modulates redox reactions by downregulating oxidative stress-inducing factors and upregulating antioxidant factors, thereby improving oocyte mitochondrial function and promoting follicular development.

3.5 Regulation of the SIRT1-FoxO1 Pathway-Mediated Autophagy

Autophagy plays a critical role in maintaining ovarian function. The SIRT1-FoxO1 pathway is one of the primary pathways regulating cellular autophagy, where FoxO1 modulates the expression of autophagy-related proteins, and SIRT1 plays a pivotal role in autophagy by deacetylating FoxO1. Activation of the SIRT1/FoxO1 pathway can inhibit autophagy and improve ovarian function during natural aging [35]. Research by He Xiaolan et al. [36] demonstrated that after intervention with Yulinzhu, the expression of SIRT1 and FoxO1 in ovarian tissues of POF model rats significantly increased, while the levels of Ac-FoxO1 protein markedly decreased. Additionally, the levels of autophagy-related factors (LC3B, beclin-1, Atg5, Atg7) and the LC3-II/LC3-I ratio were reduced, whereas p62 levels increased. These findings suggest that Yulinzhu may inhibit autophagy in POF rat ovarian tissues by regulating the SIRT1/FoxO1 pathway.

3.6 Regulation of the mTOR Signaling Pathway to Promote Follicular Development

The mammalian rapamycin target protein (mTOR) pathway is closely associated with follicular growth, development, and proliferation. Specifically, mTORC1 mediates cellular quality control and protein synthesis, while mTORC2 is involved in cell survival and proliferation. Dong Xiaoying et al. [37], by establishing an immunogenic POI mouse model, demonstrated that Yulinzhu can upregulate mTOR and AKT protein levels in ovarian tissues of model rats, effectively activate the mTOR signaling pathway, and exhibit significant effects in promoting follicular development and improving the follicular microenvironment.

3.7 Regulation of Hormone Receptor Expression to Enhance Ovarian Responsiveness

The regulatory effect of Yulinzhu on hormone receptors has also attracted attention. Studies have demonstrated that Yulinzhu upregulates the expression of FSHR and ER in ovarian tissues of aged rats [33]. FSHR is the receptor through which FSH acts on granulosa cells, and its expression level directly influences ovarian responsiveness to gonadotropins; ER mediates the biological effects of estrogen and participates in processes such as follicular development and endometrial proliferation. By upregulating FSHR and ER expression, Yulinzhu enhances ovarian sensitivity to endocrine signals, thereby improving follicular development and ovulation function.

3.8 Regulation of the Hypothalamic-Pituitary-Adrenal Axis to Improve Metabolic Disorders

Studies have revealed that the mechanism by which liver qi stagnation and emotional disturbances contribute to polycystic ovary syndrome (PCOS) is associated with activation of the hypothalamic-pituitary-adrenal (HPA) axis. Overactivation of the HPA axis can lead to lipid metabolism disorders, subsequently inducing ovarian dysfunction. Zhang Li et al. [38] employed Yueju Wan combined with Yulin Zhu Tang to treat PCOS-related infertility patients, randomly assigning 100 patients into a control group and an observation group, with 50 cases in each group. The results showed that the clinical overall efficacy rate in the observation group was 90.0%, significantly higher than the 76.0% in the control group. The observation group demonstrated superior outcomes in improving TCM syndrome scores, lipid metabolism indicators, HPA axis-related parameters, and ovulation indicators compared to the control group. The study indicates that adjunctive therapy with Yueju Wan and Yulin Zhu Tang effectively alleviates symptoms in PCOS-related infertility patients, improves ovarian function, and regulates lipid metabolism levels and HPA axis dysfunction.

4. Discussion and Prospects

As a classic gynecological formula with a long history of clinical application, Yulinzhu has demonstrated promising efficacy in recent years for treating conditions such as oligomenorrhea, amenorrhea, PCOS, POI/POF, and infertility. Based on existing research, the mechanisms by which Yulinzhu improves ovarian function can be summarized as

follows: (1) Enhancement of the local ovarian microenvironment (through regulation of the HIF-1 and mTOR pathways); (2) Delay of cellular aging (through regulation of the SIRT1/TERT pathway); (3) Modulation of autophagy and reduction of oxidative stress injury (through regulation of the SIRT1-FoxO1 and FOXO3a pathways); (4) Regulation of sex hormone receptor expression (upregulation of FSHR and ER); (5) Promotion of reproductive stem cell regeneration via ESR1-mediated pathways (through regulation of estrogen signaling and stem cell pluripotency pathways). Recent studies have elucidated novel mechanisms by which Yulinzhu improves ovarian reserve function from the perspective of reproductive stem cell regeneration, providing new insights into the scientific rationale of the “tonifying the kidneys and replenishing essence” theory [29-31].

However, current research still has the following limitations: First, clinical studies are predominantly small-sample, single-center studies, lacking large-sample randomized controlled trials, and the level of evidence needs improvement. Second, mechanistic studies are primarily based on network pharmacology predictions, with experimental validation focusing mainly on individual pathways, while interactions between pathways remain insufficiently investigated. Third, the relationship between the “multi-component” and “multi-target” characteristics of traditional Chinese formulas remains unclear, and research on their pharmacodynamic mechanisms requires further exploration. Fourth, clinical efficacy evaluation metrics primarily focus on hormone levels and pregnancy outcomes, with inadequate attention paid to deeper indicators such as endometrial receptivity, oocyte quality, and mitochondrial function.

Future research should be deepened in the following aspects: First, conduct multicenter, large-sample, randomized controlled trials to accumulate high-quality clinical evidence. Second, integrate multi-omics technologies such as network pharmacology, metabolomics, transcriptomics, and proteomics to systematically elucidate the action network of Yulinzhu. Third, combine modern reproductive biology techniques to investigate its mechanisms of action in depth from perspectives including follicular development, granulosa cell function, mitochondrial dynamics, and reproductive stem cell regeneration. Fourth, explore the scientific implications of the “formula-syndrome correspondence,” identify the specific diseases and target populations for which Yulinzhu is most effective, and promote personalized treatment. Fifth, strengthen clinical research on the combination of Yulinzhu with traditional Chinese medicine therapies such as acupuncture and acupoint thread embedding, and explore optimized integrated Chinese-Western medical treatment regimens.

In summary, Yulinzhu, as a representative formula for “dual supplementation of qi and blood and simultaneous regulation of the kidneys and spleen,” holds broad application prospects in gynecological reproductive disorders. Deepening its modern research is of great significance for unlocking the value of this classical formula, enriching the theoretical framework of Traditional Chinese Medicine (TCM) gynecology, and serving clinical practice.

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