

Study on the Mechanism and Application Prospect of Guizhi Fuling Wan in Improving Insulin Resistance in Polycystic Ovary Syndrome

Yiduo Zheng*

Zhejiang Chinese Medical University, No. 260 Baichuan Street, Fuyang District, Hangzhou, Zhejiang Province, China

**Corresponding author: Yiduo Zheng.*

Abstract

Polycystic ovary syndrome (PCOS) represents a prevalent endocrine and metabolic disorder among reproductive-aged women, with insulin resistance (IR) serving as a pivotal factor in its pathophysiology. Current Western medical approaches primarily target symptomatic relief; however, they are often associated with notable adverse effects, high recurrence rates, and drug dependency. Guizhi Fuling Wan, a classical traditional Chinese medicinal formula known for its blood-activating and stasis-resolving properties, has recently demonstrated considerable therapeutic promise in managing gynecological conditions. This review systematically synthesizes available theoretical insights and literature to delineate the mechanistic actions, pharmacodynamic constituents, and clinical application prospects of Guizhi Fuling Wan in ameliorating IR associated with PCOS. Accumulating evidence suggests that this formula may enhance insulin sensitivity and mitigate PCOS-related metabolic disturbances through multifaceted mechanisms, including modulation of the PI3K/Akt/mTOR signaling cascade, suppression of autophagy in ovarian granulosa cells, and attenuation of inflammatory responses and oxidative stress. Nevertheless, the current body of evidence predominantly derives from animal studies, with a conspicuous paucity of robust clinical data. Future investigations should prioritize high-quality clinical trials to validate its therapeutic efficacy, elucidate its pharmacodynamic underpinnings, and assess its synergistic potential when co-administered with conventional drugs, thereby offering novel perspectives for integrated traditional Chinese and Western medicine strategies in PCOS management.

Keywords

Guizhi Fuling Wan, polycystic ovary syndrome, insulin resistance, classic prescription, mechanism of action, clinical application

1. Introduction

Polycystic ovary syndrome (PCOS) is a complex endocrine disease characterized by hyperandrogenemia, ovulatory dysfunction and polycystic ovarian morphology, affecting approximately 5%-20% of women of childbearing age worldwide [1]. Insulin resistance (IR) is an important pathological basis of PCOS, and about 50%-70% of patients have IR, which leads to compensatory hyperinsulinemia and aggravates ovarian dysfunction and metabolic disorders. Insulin resistance occurs not only in classic target tissues (liver, adipose

tissue, muscle) but also locally in the ovary, and may affect follicular development and androgen synthesis through abnormal PI3K/Akt pathway [2].

At present, commonly used clinical drugs such as metformin can improve insulin sensitivity, but they have gastrointestinal adverse reactions, weak improvement effect on hyperandrogenemia, limited long-term efficacy and high recurrence rate, making it difficult to comprehensively regulate the overall metabolic state of PCOS patients [3]. Traditional Chinese medicine (TCM) has the advantage of multi-target regulation. Therefore, exploring a safe and effective TCM treatment scheme with comprehensive regulatory effects has important clinical significance.

Guizhi Fuling Wan, a classical formula first documented in the Synopsis of the Golden Chamber, comprises five herbal ingredients: Cinnamomi Ramulus, Poria Cocos, Persicae Semen, Moutan Cortex, and Paeonia Radix. Renowned for its actions in invigorating blood circulation, dispersing blood stasis, resolving masses, and softening nodules, this prescription has long been employed in traditional Chinese medicine to address gynecological conditions associated with blood stasis patterns. In recent years, its therapeutic potential has garnered growing interest in the management of endometriosis, uterine leiomyomas, and related disorders. However, its application specifically targeting insulin resistance in polycystic ovary syndrome (PCOS) remains in an early exploratory phase. The present review systematically examines available literature and integrates theoretical reasoning to elucidate the putative mechanisms through which Guizhi Fuling Wan may counteract insulin resistance in PCOS, while also forecasting its clinical utility. This effort aims to furnish a theoretical foundation and practical guidance for the integration of traditional Chinese and Western medicine in the holistic management of PCOS.

2. Theoretical Basis

2.1 Definition and Pathogenesis of PCOS

According to the Rotterdam criteria, the diagnosis of PCOS requires at least two of the following three conditions: ovulatory dysfunction, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology on ultrasound [4]. The pathogenesis of PCOS is extremely complex, driven not by a single factor but by the interaction and mutual causation of genetic susceptibility, intrauterine environment, lifestyle factors and core endocrine and metabolic disorders.

Epidemiological and genetic studies have demonstrated a marked familial aggregation of PCOS, with first-degree female relatives exhibiting a substantially higher risk compared to the general population. Compelling evidence from twin studies further substantiates the predominant role of genetic predisposition, as the concordance rate in monozygotic twins (approximately 70%) far exceeds that in dizygotic twins (around 30%). At the pathophysiological level, insulin resistance and its consequent compensatory hyperinsulinemia are considered pivotal in the onset and progression of PCOS. This metabolic aberration not only disrupts ovarian function, leading to follicular developmental arrest, but also significantly elevates the long-term risk of metabolic disorders by amplifying inflammatory responses and oxidative stress.

2.2 TCM Connotation and Modern Pharmacology of Guizhi Fuling Wan

In traditional Chinese medicine (TCM), polycystic ovary syndrome is conventionally classified under patterns such as “intermingled phlegm and blood stasis” or “kidney deficiency with blood stasis,” with the core pathogenesis characterized by disharmony between qi and blood coupled with endogenous blood stasis. Guizhi Fuling Wan, as a canonical formula for activating blood circulation and resolving stasis, is believed to ameliorate the “blood stasis” status by regulating qi and blood, dispersing stagnation, and unblocking the collaterals, thereby restoring the physiological functions of the Chong and Ren meridians. The formula comprises five herbal ingredients working in concert: Cinnamomi Ramulus warms and promotes blood flow, Poria Cocos fortifies the spleen and drains dampness, Persicae Semen and Moutan Cortex invigorate blood circulation and eliminate stasis, while Paeonia Radix enriches the blood and soothes the liver. Collectively, these components achieve the therapeutic objectives of activating blood flow, dispersing stasis, and harmonizing the dynamic equilibrium of qi and blood.

2.3 Theoretical Basis of Guizhi Fuling Wan in Treating Insulin Resistance in PCOS

Guizhi Fuling Wan is composed of equal proportions of Cinnamomi Ramulus, Poria Cocos, Moutan Cortex, Persicae Semen and Paeonia Radix. Modern research has identified more than 15 active metabolites from the prescription, mainly including monoterpene glycosides such as paeoniflorin, paeonol and benzoylpaeoniflorin, as well as triterpenoids such as pachymic acid and dehydro-pachymic acid. These active components mediate the pharmacological effects of the prescription by acting on inflammatory signaling pathways, antioxidant response systems and immune regulation targets.

In recent years, many experimental studies have suggested that Guizhi Fuling Wan may alleviate PCOS-related metabolic abnormalities by improving insulin signal transduction and inhibiting local ovarian inflammation and autophagy. For example, animal experiments have shown that this prescription can significantly reduce fasting insulin levels in PCOS model rats, improve insulin sensitivity, and regulate the expression of adipokines such as adiponectin, providing preliminary theoretical support for the clinical application of Guizhi Fuling Wan in PCOS.

3. Literature Review

3.1 Records of Guizhi Fuling Wan in Treating Gynecological Diseases in Ancient TCM Classics

Guizhi Fuling Wan was first recorded in Synopsis of Golden Chamber: Pulse Syndrome and Treatment of Pregnant Women, which is indicated for “women with chronic abdominal masses, vaginal bleeding for less than three months after amenorrhea”. Later generations of physicians expanded its application to various gynecological blood stasis syndromes such as abdominal masses, dysmenorrhea and amenorrhea, highlighting its compatibility characteristics of “removing blood stasis without damaging healthy qi”. PCOS patients often present with delayed menstruation, amenorrhea, infertility and other symptoms, which are mostly classified into blood stasis syndrome in TCM differentiation. Therefore, this prescription has good theoretical adaptability in the treatment of PCOS.

3.2 Modern Mechanism Research of Guizhi Fuling Wan in Improving Insulin Resistance in PCOS

Existing studies have confirmed that Guizhi Fuling Wan may improve insulin resistance in PCOS patients through the following pathways:

1) Regulating Insulin Signaling Pathway

Studies have shown that Guizhi Fuling Wan can activate the PI3K/Akt/mTOR signaling pathway, increase the phosphorylation level of insulin receptor substrate (IRS), enhance the efficiency of insulin signal transduction, and then promote the uptake and utilization of glucose by peripheral tissues [8]. The activation of this pathway is closely related to cell survival and metabolic regulation, and may be one of the core mechanisms by which Guizhi Fuling Wan improves insulin resistance.

2) Inhibiting Autophagy of Ovarian Granulosa Cells

The autophagy level of ovarian granulosa cells in PCOS patients is abnormally elevated, which is closely related to follicular development disorders. Guizhi Fuling Wan can reduce excessive autophagy of ovarian granulosa cells by restoring the balance of autophagy-related signaling pathways, thereby protecting ovarian function [9]. This effect may be related to the regulation of mTOR pathway and the expression of autophagy-related proteins.

3) Improving Inflammatory Response and Oxidative Stress

Guizhi Fuling Wan has both anti-inflammatory and antioxidant activities, which can reduce the levels of inflammatory factors such as tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6), and alleviate the low-grade inflammatory state related to insulin resistance [10]. At the same time, its active components can scavenge oxygen free radicals, enhance the activity of antioxidant enzymes, and relieve the damage caused by oxidative stress to the body.

4. Discussion

4.1 Feasibility and Effectiveness of Guizhi Fuling Wan in Treating PCOS

A comprehensive meta-analysis encompassing 16 randomized controlled trials with a cumulative sample size of 1,385 PCOS patients was conducted to compare the clinical outcomes of Guizhi Fuling Wan combined with conventional Western medicine versus Western medicine monotherapy. The pooled results demonstrated that the combination regimen yielded significantly superior ovulation rates (RR=1.24, 95% CI: 1.15–1.34) and pregnancy rates (RR=1.53, 95% CI: 1.38–1.69) relative to Western medicine alone. Regarding endocrine and metabolic parameters, the combined therapy group exhibited marked reductions in follicle-stimulating hormone (FSH), total testosterone, luteinizing hormone (LH), and homeostatic model assessment for insulin resistance (HOMA-IR), with a standardized mean difference for total testosterone of -1.07 95. In contrast, estradiol (E2) levels and miscarriage rates did not differ significantly between the two groups. The meta-analytic findings support that adjunctive Guizhi Fuling Wan effectively enhances both ovulation and pregnancy rates in PCOS patients, potentially through the modulation of sex hormone profiles and the amelioration of insulin resistance.

Based on the existing research evidence, Guizhi Fuling Wan has shown good potential in improving insulin resistance in PCOS. Its multi-target and holistic regulatory characteristics meet the therapeutic needs of the complex pathogenesis of PCOS. Especially for blood stasis-type PCOS patients complicated with obesity, dyslipidemia and irregular menstruation, this prescription can exert comprehensive conditioning advantages. However, the current clinical research evidence is limited, and its exact clinical efficacy still needs to be further verified by high-quality studies.

4.2 Application Prospect of Integrated Traditional Chinese and Western Medicine Treatment

In recent years, integrated traditional Chinese and Western medicine treatment of PCOS has gradually become a research hotspot. The combined use of Guizhi Fuling Wan with Western medicines such as metformin can exert synergistic therapeutic effects: on the one hand, it improves insulin sensitivity, and on the other hand, it regulates endocrine and metabolic disorders, reducing the dosage and adverse reactions of Western medicine. For example, a clinical study showed that adjuvant treatment with Guizhi Fuling Wan can significantly improve the ovulation rate and pregnancy rate of PCOS patients complicated with insulin resistance.

4.3 Future Research Directions

1) Conducting High-Quality Clinical Studies

Rigorously designed, large-sample, randomized, double-blind, placebo-controlled clinical trials should be carried out to systematically evaluate the efficacy of Guizhi Fuling Wan in improving insulin resistance, reproductive function, and metabolic profiles in PCOS patients, along with long-term safety monitoring and assessment.

2) Deepening Mechanistic Investigations

Modern technologies including systems pharmacology, metabolomics, and proteomics should be integrated to comprehensively profile the pharmacodynamic material basis and multi-target network regulatory mechanisms of Guizhi Fuling Wan, thereby identifying its key intervention targets and core signaling pathways in PCOS.

3) Exploring Individualized Therapeutic Regimens

Prescription-syndrome correspondence studies should be conducted across different TCM syndrome types of PCOS (e.g., kidney deficiency with blood stasis type, phlegm-dampness intermingled type) to facilitate precision medicine. The incorporation of syndrome-based quantitative scoring scales may aid in establishing a treatment evaluation framework grounded in syndrome differentiation, thereby providing objective evidence for stratified clinical decision-making

4) Dosage Form Improvement and Standardization Construction

Develop modern dosage forms that are convenient to take and quality-controllable (such as formula granules, capsules), and formulate corresponding quality control standards to ensure the stability and reproducibility of clinical medication.

4.4 Limitations and Challenges of Existing Research

Current research on Guizhi Fuling Wan in the treatment of PCOS still has many shortcomings:

1) Shallow Research Level

Most studies are limited to animal experiments, with a small number of clinical randomized controlled trials and small sample sizes. There is a lack of large-sample, multi-center high-quality clinical studies, making it difficult to draw definitive research conclusions.

2) Incompletely Elucidated Mechanism of Action

Although existing studies have suggested that multiple signaling pathways are involved in its pharmacological effects, the specific action targets, pharmacodynamic material basis and network regulation mechanism still need in-depth exploration. The application of new technologies such as systems pharmacology and metabolomics needs to be further strengthened.

3) Insufficient Compatibility and Dosage Form Optimization

The traditional dosage form of Guizhi Fuling Wan is pills, and decoctions, capsules and other dosage forms are also commonly used in modern clinical practice. However, there is a lack of systematic comparative research on the impact of different dosage forms on efficacy. In addition, there is a lack of research on compatibility optimization for different TCM syndromes of PCOS.

5. Conclusion

As a classic TCM prescription, Guizhi Fuling Wan has potential therapeutic value in improving insulin resistance in PCOS. It may exert curative effects through multiple mechanisms, including regulating PI3K/Akt/mTOR and other signaling pathways, inhibiting autophagy of ovarian granulosa cells, and reducing inflammatory response and oxidative stress. Current research is mainly experimental, and clinical evidence is insufficient. In the future, the integration of clinical and basic research should be strengthened to promote the standardized and individualized application of Guizhi Fuling Wan in the treatment of PCOS, and actively explore the synergistic effect of its combined treatment with Western medicine, so as to provide safer and more effective treatment options for PCOS patients.

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Conflicts of Interest

The authors declare no conflict of interest.

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