REVIEW
Integrative Medicine Discovery 2025;9:e25008. https://doi.org/10.53388/IMD202509008

Classic Chinese herbal formula Guizhi-Fuling Wan: a complementary treatment for polycystic ovary syndrome

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Competing interests

The authors declare no conflicts of interest.

Acknowledgments

This work was supported by funds from the Natural Science Foundation of Shandong Province (No. ZR2020MH346; No. ZR2021MH003) and the National Natural Science Foundation of China (No. 81273667).

Peer review information

Integrative Medicine Discovery thanks Ye Zhao and another anonymous reviewer for their contribution to the peer review of this paper.

Abbreviations

PCOS, polycystic ovary syndrome; GFW, Guizhi-Fuling Wan; GFC, Guizhi-Fuling capsule; IL-1β, interleukin-1 beta; TNF-α, tumor necrosis factor-α; NF-κB, nuclear factor kappa-B; IR, insulin resistance; LPS, lipopolysaccharide; IL-6, interleukin-6; ECM, extracellular matrix.

Citation

Yang N, Su RL, Zhang N, et al. Classic Chinese herbal formula Guizhi-Fuling Wan: a complementary treatment for polycystic ovary syndrome. *Integr Med Discov*. 2025;9:e25008. doi: 10.53388/IMD202509008.

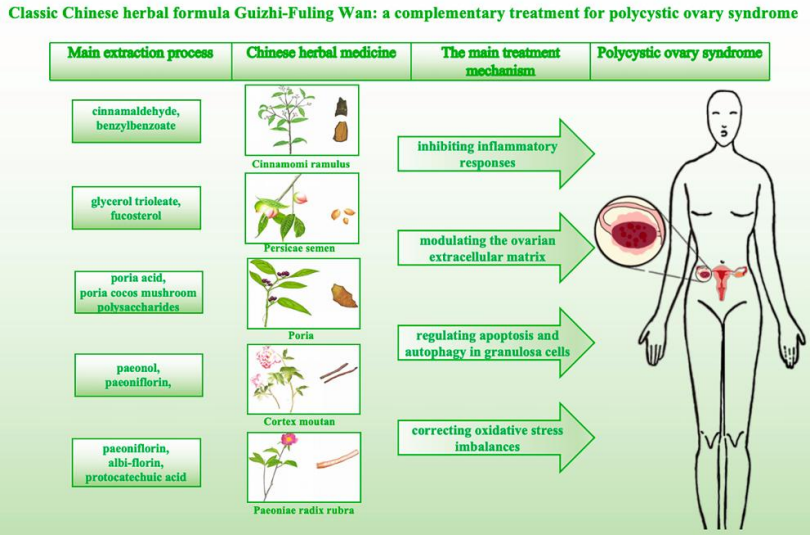
Executive editor: Xin-Yue Zhang.

Received: 20 October 2024; **Revised:** 05 March 2025; **Accepted:** 17 March 2025; **Available online:** 20 March 2025.

Abstract

Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder that poses a significant threat to women's health. As a classical traditional Chinese medicine (TCM) formulation, Guizhi-Fuling Wan (GFW) has a good application prospect in the complementary treatment of PCOS. This study aimed to systematically summarize the traditional efficacy and pharmacological composition of the Chinese medicines contained in GFW and evaluate the clinical efficacy and safety of their active ingredients in the complementary treatment of PCOS. A growing number of studies have demonstrated that GFW is effective at complementally treating PCOS through various mechanisms, including inhibiting inflammatory responses, modulating the intraovarian extracellular matrix, regulating apoptosis and autophagy in granulosa cells, and correcting oxidative stress imbalances. In addition, the GFW has been shown to be effective in treating the complications of PCOS. However, there are several problems, and future work should focus on elucidating the efficacy, safe dosage, and safety of different dosage forms of GFW, increasing the toxicological value of traditional Chinese medicine, and confirming the safety of the combination of GFW with Western medicine for the treatment of PCOS.

Keywords: Guizhi-Fuling Wan; polycystic ovary syndrome; clinical application; therapeutic mechanisms; safety evaluation



Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder and a major cause of infertility in women of reproductive age. It is a complex endocrine disorder characterized by various endocrinological features such as hyperandrogenism, hyperluteinizing hormone, insulin resistance, hyperinsulinism, and metabolic syndrome [1]. Irregular menstrual cycle, sporadic ovulation, infertility, polycystic ovarian changes, obesity, hirsutism are the main clinical manifestations of PCOS, and are easily complicated by type II diabetes, cardiovascular disease, endometrial cancer, depression and other diseases [2, 3]. This condition significantly affects the quality of life for women, with a global prevalence of 20% among women of reproductive age [4]. Due to the high prevalence of PCOS, it has become a major global public health concern. The etiology of PCOS remains unclear; genetics and environmental factors have been implicated in the pathogenesis of this disease [5, 6]. The ovary is widely recognized as the main organ affected by PCOS [7], and alterations in ovarian morphology and dysfunction affect fertility in patients with PCOS [8]. First-line prescription drugs for the clinical treatment of PCOS include oral contraceptives to treat irregular menstruation [9], anti-androgen therapy to treat hyperandrogenemia, aromatase inhibitors to induce ovulation, and insulin sensitizers to improve metabolic functions [10, 11]. Although these treatments have certain beneficial effects on PCOS-related symptoms, patients still experience adverse effects, such as obesity, ovarian hyperstimulation syndrome, and endometrial hyperplasia, which are caused by long-term dependence on medication and cannot be ignored [12–14]. Therefore, it has become a challenge for clinicians and researchers to improve the therapeutic efficacy for the treatment of PCOS effectively.

Given the multi-component, multi-target, and multi-action characteristics of Chinese herbal compounds [15], they can show unique advantages and greater prospects in the prevention and treatment of the disease. A domestic medicine, traditional Chinese medicine, has a rich history dating back centuries for clinical practices in China. PCOS belongs to the category of “infertility” in traditional Chinese medicine. Generally, infertility is caused by the disharmony of “Yin” and “Yang” in the human body and by the imbalance of “Qi” and blood, which leads to the slow operation of blood in the human body; ultimately, blood stasis occurs, and the accumulation of excessive stasis in the uterus leads to disorders of the menstrual cycle and infertility, which is a kind of “Stasis of Blood Syndrome”; therefore, blood stasis is at the core of disease occurrence [16, 17].

Guizhi-Fuling Wan (GFW) was first reported in Zhong-Jing Zhang’s book “*Jingui Yaolue*” in the Eastern Han Dynasty (25–220 C.E.) and was later included in the Chinese Pharmacopeia Commission [18]. GFW consists of *Cinnamomi Ramulus* (*Cinnamomum cassia* Presl), *Poria* (*Poria cocos* (Schw.) Wolf), *Paeoniae Radix Rubra* (*Paeonia lactiflora* Pall.), *Moutan Cortex* (*Paeonia suffruticosa* Andr.), and *Persicae Semen* (*Prunus persica* (L.) Batsch). The plant names have been checked with MPNS (http://mpns.kew.org) and the medicinal source is *Pharmacopoeia of China* (2015). And GFW has shown efficacy in removing “Blood Stasis” and “Warming and Activating Meridian”. Originally used to treat the restlessness of pregnancy due to a mass, the GFW now offers significant therapeutic benefits for “Blood Stasis” in patients with gynecological illnesses. GFW has been used in Chinese medical practice for thousands of years to treat gynecological illnesses. In recent years, the good efficacy of GFW in the complementary treatment of PCOS has been confirmed by a large number of basic studies and clinical trials, and the mechanism of action of GFW in the complementary treatment of PCOS has also been further investigated [19]. However, these research results have not been updated and summarized in a timely manner. In this paper, we review the traditional efficacy and pharmacological composition of the Chinese medicines contained in GFW, as well as the clinical efficacy and safety evaluation of their active ingredients in treating and complementally treating PCOS. In addition, we provide an in-depth discussion of the related therapeutic mechanisms to understand the protective effects of GFW on PCOS and explore new ideas for further clinical treatment of this disease.

Materials and methods

Plant material

GFW consists of *Cinnamomi Ramulus* (*Cinnamomum cassia* Presl), *Poria* (*Poria cocos* (Schw.) Wolf), *Paeoniae Radix Rubra* (*Paeonia lactiflora* Pall.), *Moutan Cortex* (*Paeonia suffruticosa* Andr.), and *Persicae Semen* (*Prunus persica* (L.) Batsch). The plant names have been checked with MPNS (http://mpns.kew.org) and the medicinal source is *Pharmacopoeia of China* (2015).

Methods

The data were retrieved from the China National Knowledge Infrastructure (https://www.cnki.net/), WanFang Data (https://www.wanfangdata.com.cn/), PubMed (https://pubmed.ncbi.nlm.nih.gov/), SpringerLink (https://link.springer.com/), Web of Science (Science Citation Index Expanded sub-database) (http://apps.webofknowledge.com/), and Google Scholar (https://scholar.google.com). Only information published in Chinese or English was considered in this review. The keywords used in the search included “Polycystic ovary syndrome”, “PCOS”, “Guizhi-Fuling”, “Clinical application”, “Therapeutic mechanism’, “Chemical composition”, “Quality control”, “Pharmacokinetics”, “Pharmacodynamics”, “Activity”, “Adverse reactions” and various combinations of these terms. The search dates ranged from 1 January 2000 to 28 February 2025. The inclusion criteria were chemical composition, quality control, pharmacokinetic studies, pharmacological properties, adverse effects of GFW, clinical applications, therapeutic mechanisms, and safety evaluation of GFW for the treatment of PCOS; the exclusion criteria were incomplete data, letters to the editor, posters, and conference abstracts.

Classic Chinese herbal formula GFW

The Chinese herbal compound GFW is a traditional formula for treating gynecological diseases with “Blood Stasis”. GFW is critical in improving blood circulation, harmonizing “Qi” and blood, and “Warming the Meridians” [20]. The sources, medicinal components, harvest time flavor, “Meridian Tropism”, therapeutic effects, traditional uses, active ingredients, and extraction processes of the five herbs in GFW are reviewed in this paper (Table 1) [18].

According to various studies and *Jingui Yaolue*, the various components of the GFW formula are *Cinnamomi Ramulus*, *Persicae Semen*, *Poria*, *Paeoniae Radix Rubra*, and *Moutan Cortex*. *Cinnamomi Ramulus* is pungent and sweet in taste, warm in nature, and can warm and promote blood circulation to remove “Blood Stasis”. It is used as the “Monarch Drug” in GFW and is often used to treat amenorrhea due to “Blood Cold”, “Wind-Cold” [21].

Persicae Semen has the effect of promoting blood circulation and removing “Blood Stasis” and has been used to treat dysmenorrhea, amenorrhea, and “Blood Stasis” mass in the uterus for a long time in ancient China [22]. *Poria* is sweet and light in taste and neutral in nature, and has the effects of “Invigorating the Spleen” and “Eliminating Phlegm”. Therefore, in GFW, *Persicae Semen* and *Poria* are “Ministerial Drugs” [23].

And *Paeoniae Radix Rubra* is a bitter taste in medicinal properties. It can dissipate “Blood Stasis”, “Regulate Menstruation”, and “Nourish Blood”. It is widely used for eye redness, swelling, and pain, and liver depression [24]. And *Moutan Cortex* can “Disperse Blood Clots” and “Remove Blood Stasis”, which is widely used in irregular menstruation”, amenorrhea, and traumatic injury. Thus, *Paeoniae Radix Rubra* and *Moutan Cortex* are “Adjuvant Drugs” in GFW [25]. Besides, in GFW, the combination of *Cinnamomi Ramulus* and *Paeoniae Radix Rubra* reflects the combination of “Yin” and “Yang”, while the combination of *Poria* and *Moutan Cortex* reflects the harmonization of “Qi” and blood: these five herbs work together to activate blood circulation and remove “Blood Stasis”.

Pharmacological study of the active components of GFW

GFW comprises several active ingredients, four of which (pachymic acid, albiflorin, amygdalin, and cinnamic acid) were simultaneously determined using microwave-assisted extraction coupled with hydrophilic interaction liquid chromatography-tandem mass spectrometry [26]. In addition, gallic acid, amygdalin, albiflorin, paeoniflorin, paeonol, cinnamic acid, and pachymic acid, the seven active ingredients of Guizhi-Fuling capsule (GFC), were determined using microwave-assisted extraction combined with ultra performance liquid chromatography tandem mass spectrometry [27]. Furthermore, the ultra-high performance supercritical fluid chromatography method was employed to measure the content of six analytes, namely, paeonol, coumarin, cinnamic alcohol, cinnamic acid, paeoniflorin, and amygdalin in GFC and tablet samples [28]. The active ingredients of GFC, cinnamic acid, and paeonol were determined using the high-performance liquid chromatographic method [29]. Another study utilized high-performance liquid chromatography method with photodiode array detector method to identify galloylpaeoniflorin, paeoniflorin, mudanpioside C, and benzoylpaeoniflorin which are common components of moutan cortex and *Paeoniae Radix Rubra* in GFW [30]. In addition, 48 volatile components, including four acetophenones, three fatty acid esters, 13 phenylpropanoids, and 19 sesquiterpenes, along with 70 non-volatile components, including six acetophenones, 12 galloyl glucoses, 31 monoterpene glycosides, three phenols, and 12 triterpene acids were identified using gas chromatography–mass spectrometry with automated mass spectral deconvolution and identification system and rapid-resolution liquid chromatography coupled with electrospray ionization quadrupole time-of-flight tandem mass spectrometry [31]. A recent study identified 219 compounds, such as cinnamaldehyde, α-methylcinnamicaldehyde, and anethol, contained in GFW [32]. The chemical components isolated from GFW likely have potential applications in treating PCOS (Figure 1).

Table 1 Traditional application of five Chinese herbs in GFW

Chinese Materia Medica	***Cinnamomi Ramulus***	***Persicae Semen***	***Poria***	***Moutan Cortex***	***Paeoniae Radix Rubra***
Origin	*Cinnamomum cassia* Presl	*Prunus persica* (L.) Batsch or *Prunus davidiana* (Carr) Franch.	*Poria cocos* (Schw.) Wolf	*Paeonia suffruticosa* Andr.	*Paeonia lactiflora* Pall. or *Paeonia veitchii* Lynch
Medicinal parts	Dry twigs	Dry mature seeds	Dry sclerotia	Dry root barks	Dry roots
Harvest time	Spring and summer	After fruit ripens	7–9 months	Autumn	Spring and autumn
Flavor and meridian tropism	Pungent and sweetish taste, warm property, heart, lung, “Bladder Meridian”.	Sweetish and bitter taste, flat property, heart, liver, “Large Intestine Meridian”.	Sweetish and mild taste, flat property, heart, lung, spleen, “Kidney Meridian”.	Pungent and bitter taste slightly cold properties, heart, liver, “Kidney Meridian”.	Bitter taste, slightly cold property, “Liver Meridian”.
Efficacy	Relieving sweating and relieving muscles, “Warming the Meridians”, helping “Yang” to transform “Qi”.	Activating blood circulation and removing “Blood Stasis”, “Moistening Intestines” and relieving constipation, relieving cough and asthma.	“Clearing Dampness” and promoting diuresis, strengthening the spleen, and nourishing the heart.	Removing heat to cool blood, activating blood circulation, and removing “Blood Stasis”.	“Removing Heat to Cool Blood”, removing “Blood Stasis”, and relieving pain.
Traditional uses	Treatment of “Wind-cold” and cold, “Cold Abdominal Pain”, “Blood-Cold Menstruation”, paralysis and pain in joints, phlegm, edema, palpitation, renal mass.	Treatment of menorrhagia, painful menstruation, abdominal mass, suppurative lung disease, acute appendicitis, fall injury, constipation, cough, asthma.	Treatment of edema, little urine, phlegm, dizziness and palpitation, “Spleen Deficiency”, loose stools, diarrhea, restlessness, palpitation, and insomnia.	Treatment of “Febrile Virulent Maculae”, hematemesis and epistaxis, “Night Fever and Early Coolness”, sweatless bone vapor, menorrhagia and dysmenorrhea, carbuncles and sores, fall injury.	Treatment of “Febrile Virulent Maculae”, hematemesis and epistaxis, red eyes and swelling pain, “Liver Depression” and dysmenorrhea, menorrhagia, abdominal mass and pain, fall injury, carbuncles, and sores.
Usage and dosage	3–10 g	5–10 g	10–15 g	6–12 g	6–12 g
Effective ingredients	Cinnamaldehyde, benzyl benzoate,	Glycerol trioleate, fucosterol	*Poria* acid, *Poria cocos* mushroom polysaccharides	Paeonol, paeoniflorin	Paeoniflorin, albi-florin, protocatechuic acid
Main extraction process	Microwave extraction, ethanol extraction, etc.	Ethanol extraction, ultrasonic assistance, etc.	Ultrasonic assistance, microwave extraction, etc.	Steam distillation, supercritical fluid extraction, ultrasonic assistance, etc.	Steam distillation, ethanol extraction, etc.
Reference	*Pharmacopoeia of China* (ChP) (2020) [18]				

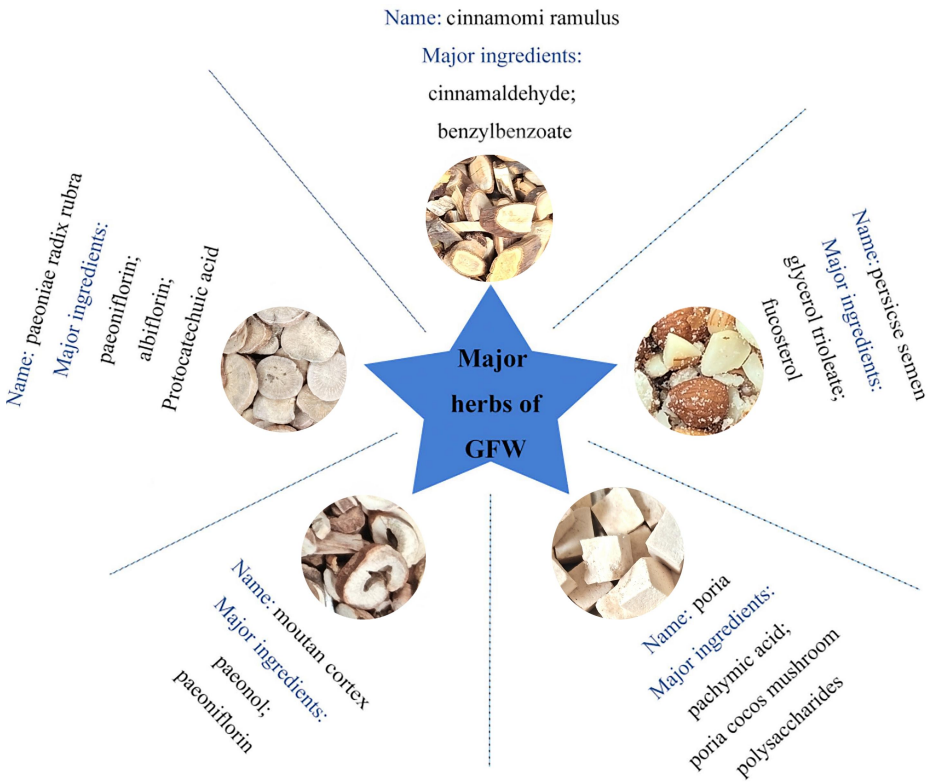


Figure 1 Five traditional Chinese medicines isolated from GFW are used to treat the active ingredients of PCOS. GFW, Guizhi-Fuling Wan.

Cinnamomi Ramulus

Cinnamomi Ramulus is one of the early herbal medicines in Chinese history, first recorded in *Shennong Bencao Jing*. *Cinnamomi Ramulus* contains volatile oil (0.69%) and pharmacological components, such as cinnamaldehyde, benzyl benzoate, cinnamyl acetate, β-cadinene, calamenene, and coumarin [21]. Cinnamaldehyde, the main constituent of *Cinnamomi Ramulus*, increased vasodilatation [26], significantly improved blood rheology in a rat model of "Blood Stasis", improved "Blood Stasis" and showed anticoagulant properties [33]. It has been reported that cinnamaldehyde and other volatile oils relieved the pain by inhibiting the frequency and amplitude of uterine contractions in mice [34]. Cinnamaldehyde inhibits toll-like receptor 4 expression and attenuates the inflammatory response by reducing the production of inflammatory cytokines (interleukin-1 beta (IL-1β), tumor necrosis factor-α (TNF-α), etc.) released by activating the nuclear factor kappa-B (NF-κB) pathway [35, 36]. Another study revealed that cinnamaldehyde (cinnam) has an anti-inflammatory effect by reducing prostaglandin synthesis by inhibiting COX-2 [37], which can be targeted to treat chronic inflammation in patients with PCOS. In addition, cinnamaldehyde has been shown to lower blood glucose levels by *GLUT4* gene expression levels in mouse skeletal muscle [38]. This upregulation enhances antioxidant defense against reactive oxygen species generated in hyperglycemic conditions, thereby protecting pancreatic β-cells and producing hypoglycemic effects [39], exhibiting therapeutic effects for insulin resistance (IR) symptoms in PCOS.

Furthermore, the therapeutic application of *Cinnamomi Ramulus* has shown favorable outcomes in clinical studies. The combination of *Cinnamomi Ramulus* and *Poria* increased the dissolution rate of cinnamaldehyde by about three times, further improving blood circulation and activating the meridian effects of *Cinnamomi Ramulus* [40, 41]. Another study showed that the anticoagulant effect of *Cinnamomi Ramulus* was enhanced by the combination of *Cinnamomi Ramulus* and *Persicae Semen* [42].

Persicae Semen

Persicae Semen was first reported in *Shennong Bencao Jing*. *Persicae Semen* is a commonly used herb for improving blood circulation and removing "Blood Stasis". *Persicae Semen* contains various nutrients and bioactive compounds. The main chemical components are fatty acids, glycosides, sterols and their glycosides, flavonoids and their glycosides, proteins, and amino acids [43]. Research has indicated that the compounds present in *Persicae Semen* possess blood circulation-promoting properties. Notably, the triglyceride found in *Persicae Semen* has exhibited anticoagulant activity [22]. Additionally, the aqueous extract of peach kernel, bitter amygdalin, and peach kernel fatty oil all exhibit varying degrees of inhibition on platelet aggregation [44]. Ethyl acetate extract of *Persicae Semen* showed significant antithrombotic effects [45]. Further studies revealed that *Persicae Semen* extract rockweed sterols inhibited the proliferation and cell cycle progression of ovarian cancer cells by regulating the expression of peroxiredoxin III and modulating multiple signaling pathways involved in cell proliferation [46, 47], thereby inhibiting the progression of ovarian cancer. Furthermore, animal experiments revealed that the combination of *Persicae Semen* and *Paeoniae Radix Rubra* (1:1) significantly improved blood flow in a rat model of acute "Blood Stasis", and the combination treatment improved blood circulation [48].

Poria

Poria was first reported in *Shennong Bencao Jing*, and is also documented later in *Bencao Tu Jing*, *Bencao Jing Jizhu*, *Tangye Bencao*, and other publications. Since ancient times, *Poria* has been used to treat a variety of diseases, and its chemical composition and pharmacological activity have been extensively studied. *Poria* mainly contains two different types of compounds: polysaccharides (β-cocosanoid, rhamnose, xylose, mannose, galactose, etc.) and triterpenoids (acetyl poric acid, poric acid, 3β-hydroxy woolly steroid trienoic acid, etc.) [23]. *Poria* acid has been reported to exert anticancer effects by inducing apoptosis via the suppression of TRIM29 expression [49]. Furthermore, the extract from *Poria cocos* and its triterpenes have shown the ability to improve insulin sensitivity, leading to a reduction in blood glucose levels. Triterpenoids can also inhibit the expression of inducible nitric oxide synthase and COX-2 by downregulating NF-κB and playing an anti-inflammatory role [50], they can also inhibit nitric oxide

production in lipopolysaccharide-activated RAW 264.7 mouse macrophages, with the compounds poricoic acid A and poricoic acid C being the most active [51]. Another study showed that total triterpenes of *Poria* modulated the levels of numerous neurotransmitters, inhibited the HPA (hypothalamic-pituitary-adrenal) axis, and inactivated the NLRP3 pathway, exerting antidepressant effects [52], which in turn alleviated depression symptoms in PCOS patients.

Moutan Cortex

Moutan Cortex was first reported in *Shennong Bencao Jing* and regarded as a superior medicine; *Moutan Cortex* has been widely used since the Han Dynasty in China. *Moutan Cortex* clears heat, activates blood circulation, and removes "Blood Stasis"; it has also been extensively studied in the field of pharmacology in recent years. Chemical constituents of *Moutan Cortex* include paeoniflorin, paeonol, oxypaeoniflorin, gallic acid, etc. [25]. Paeonol and paeoniflorin are the main active ingredients of peony bark in activating blood circulation and removing "Blood Stasis" [53]. Paeonol protected endothelial cells against oxidized low-density lipoprotein-induced vascular injury by downregulating miR-21 expression, inhibiting TNF-α release [54], which induced anti-atherosclerotic effects. Furthermore, paeonol acted as an inhibitor of calcium channels preventing the influx of external Ca^{2+} and the efflux of intracellular Ca^{2+}, causing the dilation of blood vessels [55]. It has also been shown that paeonol ameliorated lipopolysaccharide (LPS)-induced endometritis in a mice model by inhibiting NF-κB signaling pathway and reducing the secretion of inflammatory cytokines [56]. In addition, paeonol significantly suppressed the transcription of *PEPCK* gene, thereby suppressing the gluconeogenic activity [57]. Paeonol has demonstrated the ability to inhibit glucose uptake in BBMV (intestinal brush border membrane vesicles) and stimulate glycogen synthesis in liver cells. These collective effects contribute to the regulation of glucose metabolism [58], ultimately resulting in reduced blood glucose levels. The decoction of *Paeoniae Radix Rubra* and *Moutan Cortex* together increased the dissolution of active ingredients, improved blood circulation, and removed "Blood Stasis" [59].

Paeoniae Radix Rubra

Paeoniae Radix Rubra first appeared in *Shennong Bencao Jing* and is clinically used as a "blood activator"; it is usually used for the treatment of "Hepatic Depression" and dysmenorrhea, menorrhagia, bruises, and other clinical symptoms. *Paeoniae Radix Rubra* contains paeoniflorin, oxy-paeoniflorin, benzoylpaooniflorin, albi-florin, and other chemical components [24]. Paeoniflorin, pentagalloylglucose, paeonolactone glucoside, and protocatechuic acid have been reported to exert inhibitory effects on thrombosis, and their antithrombotic effects were mediated by regulating the expression of vascular endothelial growth factors, improving blood flow, and increasing anticoagulant effects [60]. In addition, ethanolic extract of *Paeoniae Radix Rubra* promoted vasodilation through endothelium-dependent diastolic function, activation of Ca^{2+} activated K^+ channels (K Ca), stimulation of ATP-sensitive potassium channels, regulation of the Akt/eNOS/NO/cGMP pathway, and inhibition of L-type calcium channels [61]. In recent years, several studies have confirmed that ethanol extract of *Paeoniae Radix Rubra* enhanced glucose-mediated insulin secretion and effectively reduced blood glucose levels [62], which showed therapeutic effects for IR symptoms in PCOS. Moreover, paeoniflorin has been found to modulate the expression of thermogenic genes via the AMPK and PI3K/AKT pathways. This leads to the activation of brown adipocyte differentiation, ultimately contributing to the improvement of obesity [63], this applies to obese PCOS patients. Paeoniflorin exhibited antidepressant effects by reducing oxidative stress and upregulating the expression of nerve growth factor [64], which is beneficial for patients with PCOS complicated by depression.

Clinical studies on PCOS prevention and treatment with GFW

Recent studies have confirmed the superior therapeutic efficacy of GFW in the treatment of PCOS and related complications, and it is worth promoting the clinical application of GFW for PCOS (Table 2) [65–70]. Clinical trials compared the therapeutic efficacy of ethinylestradiol cycloproterone and GFW combined with ethinylestradiol cycloproterone for the treatment of PCOS. The data from the trial showed that GFW combined with ethinylestradiol cycloproterone was more effective than ethinylestradiol cycloproterone, with overall effective rates of 86.67% and 62.50%, respectively. The combination of the two drugs increased the efficacy of the therapy, improving sex hormone levels, reducing serum endolipin and high-sensitivity C-reactive protein levels, and increasing ovulation and pregnancy rates [65]. Another clinical report also described the clinical efficacy of GFC in patients with PCOS. The efficacy of GFC combined with clomiphene was better than clomiphene-alone treatment. The combination group was more effective in protecting ovarian reserve, improving ovarian function, and correcting abnormalities in sex hormone secretion [66]. In addition, GFW, in combination with a variety of other treatments, has been widely used in the clinical treatment of PCOS and related complications. A clinical trial showed that a combination of GFW, ethinyl estradiol cyproterone, and clomiphene citrate was more effective than western medicine alone. After 6 months of continuous treatment, patients showed significant improvements in serum sex hormones levels, psychological status, and pregnancy outcomes (pregnancy rate and full-term delivery rate) within 1 year after completing the treatment [67]. Patients with PCOS often present with IR. A controlled trial showed that GFW combined with ethinylestradiol cycloproterone and metformin significantly improved hemodynamic stability, alleviated clinical manifestations of hirsutism and acne, increased ovulation and pregnancy rates, and effectively reduced miscarriage rates in PCOS patients with IR [68]. The results of clinical trials by Li-Shan Huang also showed that the combination of GFC with acupuncture and exercise showed better clinical efficacy in treating PCOS, significantly reducing the secretion of insulin and sex hormones, improving the body mass index of patients; moreover, no serious adverse effects were found [69]. According to another study, GFW combined with ethinyl estradiol cyproterone tablets and letrozole was significantly more effective than ethinyl estradiol cyproterone tablets combined with letrozole, and then after three consecutive months of treatment, the luteinizing hormone and testosterone levels of the patients were significantly improved, which increased the fertilization rate, eugenic embryo rate, and pregnancy rate of patients [70]. A systematic evaluation and meta-analysis also showed that GFW adjuvant therapy can improve the ovulation and pregnancy rates of PCOS patients [71]. In conclusion, many clinical trials have shown that GFW, as an adjuvant therapy to Western medicine, can enhance treatment efficacy and has fewer side effects than Western medicine alone (oral contraceptives, ovulation promoters, insulin sensitizers, etc.). Additionally, GFW, as a complementary alternative therapy for the treatment of PCOS, is a therapy that deserves to be promoted in the clinic.

Mechanism of GFW in the treatment of PCOS

GFW inhibits inflammatory response

The active ingredient composition of GFC significantly inhibited the release of IL-1β, TNF-α and prostaglandin E_2 from LPS-stimulated macrophages and suppressed the expression of IL-1β and mouse membrane-bound prostaglandin E synthase 1, coordinated immune-inflammatory networks, elicited protective immune responses and exerted anti-inflammatory effects [72]. In addition, salvinorin, the active ingredient in GFW, exerts anti-inflammatory effects by inhibiting the release of prostaglandin E_2 and interleukin-6 (IL-6) [73]. GFW showed several therapeutic benefits: regulating the structure of intestinal flora, increasing the relative abundance of *Alloprevotella*, upregulated short-chain fatty acids, and alleviating systemic inflammation by reducing the release of inflammatory factors (such as IL-6), and improving IR [74, 75].

Table 2 Clinical studies on PCOS prevention and treatment with GFW

No.	Group	Medication	Number of people	Age (average age)	Effective number	The medication time	Main outcome indicators	Inclusion time	Site	Ref.
1.	Observation group	In the control group, add GFW (twice a day, 10 pills each one).	45	20–35 (27.49 ± 6.11)	39 (86.67%)	3 months	The serum visfatin, hs-CRP, LH, TT, LH/FSH, FINS, SHBG, FPG	June 2014 to May 2015	Department of Reproductive Infertility, Xuzhou Maternal and Child Health Clinic, Jiangsu Province.	[65]
	Control group	Start taking ethinylestradiol cycloproterone tablets on the fifth day of menstruation, once a day, 1 pill at a time.	32	20–36 (27.85 ± 6.18)	20 (62.5%)		/			
2.	Observation group	In the control group, add GFC (twice a day, 10 pills each one).	53	21–39 (28.54 ± 5.02)	38 (71.7%)	4 menstrual cycles	FSH, T, E_2, sinusoidal follicle count	September 2015 to September 2018	Department of Obstetrics and Gynecology, Yucheng Maternal and Child Health Hospital, Shandong Province, China.	[66]
	Control group	Oral clomiphen, once a day, 1 pill at a time.	53	23–38 (27.93 ± 3.21)	35 (66.04%)		/			
3.	Observation group	In the control group, add GFW (twice a day, 9 pills each).	48	23–37 (30.6 ± 4.2)	40 (79.17%)	6 menstrual cycles	FSH, LH, E_2, T, SAS, SDS	February 2012 to February 2016	Department of Gynecology, Foshan Hospital of Traditional Chinese Medicine.	[67]
	Control group	Oral ethinylestradiol cycloproterone tablets (once a day, 1 pill at a time) for three months on the fifth day of menstruation, followed by oral clomiphene for five days, once a day, 1 pill at a time.	48	22–38 (29.4 ± 4.7)	29 (60.42%)		/			

Table 2 Clinical studies on PCOS prevention and treatment with GFW (*continued*)

No.	Group	Medication	Number of people	Age (average age)	Effective number	The medication time	Main outcome indicators	Inclusion time	Site	Ref.
4.	Observation group	In the control group, add GFW (twice a day, 9 pills each).	55	21–39 (30.8 ± 6.9)	49 (89.09%)	3 menstrual cycles	FINS, LH, FSH, E_2, FBG, A_2, T, HOMA-IR, ISI, TC, TG, HDL-C, LDL-C, BMI; ISI; WHR	August 2014 to June 2015	Department of Obstetrics, First People's Hospital, Mutual Aid Lane, Chengzhong District, Xining City, Qinghai Province.	[68]
	Control group	Oral metformin (3 times a day, 1 pill each one) and ethinylestradiol cycloproterone tablets (twice a day, 1 pill each one).	55	21–37 (29.8 ± 6.6)	45 (81.82%)		/			
5.	Observation group	Oral metformin (3 times a day, 1 pill each one) and GFC (3 times a day, 5 pills each one), acupuncture treatment combined with exercise.	55	20–33 (26.43 ± 3.51)	44 (80%)	6 menstrual cycles	FINS, LH, FSH, E_2, HOMA-IR, T, BMI	November 2013 to November 2016	Affiliated Hospital of Fujian University of Chinese Medicine.	[69]
	Control group	Oral metformin (3 times a day, 1 pill each one) and GFC (3 times a day, 5 pills each one), acupuncture treatment.	55	21–32 (26.72 ± 3.41)	33 (60%)		/			
6.	Observation group	GFW (2 times a day, 6 pills each one), ethinyl estradiol cyproterone tablets (once a day, 1 pill at a time) and letrozole (once a day, 1 pill at a time).	53	25–29 (27.04 ± 1.13)	51 (96.23%)	3 menstrual cycles	LH, FSH, E_2, A_2, T	September 2020 to December 2022	The First Affiliated Hospital of Henan University of Traditional Chinese Medicine, Henan Province, China.	[70]
	Control group	Ethinylestradiol cycloproterone tablets (once a day, 1 pill at a time) combined with letrozole (once a day, 1 pill at a time).	53	25–29 (27.35 ± 1.08)	41 (77.36%)		/			

GFW, GuiZhi-FuLing Wan; GFC, Guizhi-Fuling capsule; SHBG, sex hormone binding globulin; LH, luteinizing hormone; TT, total testosterone; T, testosterone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; FPG, fasting plasma glucose; FINS, fasting insulin; hs-CRP, high-sensitivity C-reactive protein; SAS, self-rating anxiety scale; SDS, self-rating depression scale; A_2, androstenedione; TC, total cholesterol; TG, total triglycerides; HDL-C, high density lipoprotein; LDL-C, low-density lipoprotein; HOMA-IR, insulin resistance index; ISI, insulin sensitivity index; BMI, body mass index; WHR, waist-hip ratio; E_2, estradiol.

GFW regulates the ovarian extracellular matrix

Matrix metalloproteinases and specific tissue inhibitors have important physiological roles in ovulation by regulating the degradation and reconstruction of extracellular matrix (ECM) components in the ovary; conversely, they are also involved in the pathological process leading to ovulation disorders in PCOS [76, 77]. Research has shown that GFW treatment significantly reduced the expression level of MMP-9, which was abnormally high in the ovary of PCOS rats; GFW treatment elevated the expression level of TIMP-1, which was abnormally low in the ovary of PCOS rats. Overall, GFW decreased the MMP-9/TIMP-1 ratio in PCOS rats, presumably by inhibiting the secretion of LH, blocking the action of androgen in target tissues, restoring physiological ECM degradation and remodeling activities in the ovary, and stimulating ovulation through positive feedback [78].

GFW regulates apoptosis and autophagy in granulosa cells

Autophagy, a self-degradative process, plays a key role in the pathogenesis of PCOS. The development of PCOS is associated with the hyperactivation of autophagy in ovarian cells, causing the breakdown of the ovarian structure, leading to ovulation disorders [79, 80]. Research demonstrated that GFW regulated the PI3K/Akt/mTOR signaling pathway, inhibited excessive autophagy in ovarian granulosa cells in PCOS rats, improved ovarian function, reduced IR, and restored ovulation rate [81]. Further study revealed that increased GFW levels in the serum inhibited the progression of autophagy in ovarian granulosa cells of PCOS mice through the H19/miR-29b-3p pathway and acted as a protective agent for ovarian granulosa cells [82]. In addition, GFW significantly reduced the number of apoptosis-positive granulosa cells, downregulated the expression of apoptosis-related proteins (cleaved-PARP, cleaved-Caspase3, and cleaved-Caspase9) in granulosa cells, and simultaneously downregulated the expression of autophagy-related proteins (Beclin1 and LC3II) to inhibit excessive apoptosis and autophagy in granulosa cells and to improve the microenvironment and function of granulosa cells to promote follicle development and ameliorate ovulation disorders in PCOS-IR rats [83].

GFW corrects oxidative stress imbalance

Research has demonstrated that oxidative stress plays a significant role in the molecular pathogenesis of PCOS , and that oxidative stress accelerates the onset and progression of PCOS by triggering negative effects such as poor follicular development and decreased oocyte quality [84, 85]. When used in combination with metformin, GFW has been shown to more effectively inhibit oxidative stress than metformin monotherapy in PCOS patients. Additionally, GFW has been shown to increase insulin receptorsubstrate-1 and insulin receptorsubstrate-2 expression and insulin sensitivity by inhibiting oxidative stress [86]. Another trial demonstrated that combining GFW with clomiphene was more effective than using clomiphene alone in treating PCOS and alleviating oxidative and antioxidant imbalances in the body [87]. In addition, combination treatment with GFW and rosiglitazone suppressed inflammation and oxidative stress in the serum and ovarian tissues of PCOS rats by modulating the PI3K/AKT/NF-κB and Nrf2/HO-1 pathways more efficiently than monotherapy by a mechanism that may be related to the increase in the expression of HO-1, PI3K P85, and Nrf2, as well as the p-AKT/AKT ratio, and the decrease in the expression of NF-κB p65 [88].

In conclusion, GFW has been found to effectively treat PCOS through various mechanisms, including inhibiting inflammatory responses, modulating the ovarian extracellular matrix, regulating apoptosis and autophagy in granulosa cells, and correcting oxidative stress imbalances. Figure 2 and Table 3 [72, 74, 78, 81, 82, 88] illustrate these mechanisms of action. Recent studies have shown that GFW combined with Western medicine is significantly more effective than Western medicine alone and that the combination significantly affects oxidative stress imbalances [88, 89]. However, it remains to be explored how the mechanism of action of GFW alone differs from that of Western drugs alone, whether the combination of GFW and Western drugs is simply a superimposition of efficacy mechanisms, and what additional therapeutic mechanisms are involved in the combination of GFW and Western drugs.

GFW treats PCOS complications

The common complications of PCOS include cardiovascular disease, metabolic disease, cancer, and psychiatric disorders [3, 89]. Animal experiments showed that GFW promoted apoptosis of cancer cells in tumor-bearing mice in vivo, with a tumor suppression rate of 38.93% and an apoptosis rate of 17.79%, and the antitumor effect of GFW was mediated by the upregulation of P21 (Waf1/Cip1) expression and downregulation of survivin expression [90]. In addition, both paeoniflorin and total triterpenes of *Poria cocos*, which are the active ingredients of GFW, exerted antidepressant effects [52, 64], alleviating depressive symptoms in PCOS patients.

GFW side effects and contraindications

There is no record of side effects of this formula in pills and soups in ancient medical records, suggesting that this formula is relatively safe for clinical use [91]. Clinical trials have found that individual patients who take the capsule dose mainly have mild gastrointestinal reactions such as nausea and vomiting, although changing to take it after meals

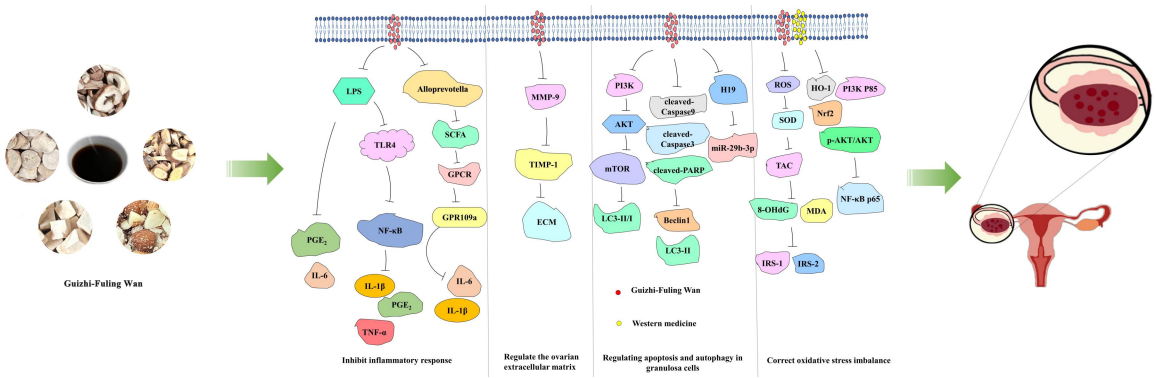


Figure 2 The main mechanism of GFW in the treatment of PCOS. LPS, lipopolysaccharide; PGE_2, Prostaglandin E_2; IL-6, interleukin-4; TLR-4, toll Like Receptor 4; NF-κB, nuclear factor kappa-B; IL-1β, interleukin-1 beta; TNF-α, tumor necrosis factor- α; SCFA, short-chain fatty acid; GPCR, G protein-coupled receptor; GPR109a, G protein-coupled receptor 109a; IL-6, interleukin-6; IL-1β, interleukin-1 beta; TIMP-1, tissue inhibitor of metalloproteinas-1; ECM, extracellular matrix; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; mTOR, mammalian target of rapamycin; LC3-II/I, light chain 3-II/I; ROS, reactive oxygen species; SOD, super oxide dismutase; TAC, total antioxidant capacity; 8-OHdG, 8-hydroxy-2 deoxyguanosine; MDA, malondialdehyde; IRS-1, insulin receptorsubstrate-1; IRS-2, insulin receptorsubstrate-2; HO-1, heme oxygenase-1; Nrf2, NF erythroid-2 related factor 2.

Table 3 The mechanism of action of GFW in the treatment of PCOS

Traditional Chinese medicine	Application	Animal or cell model	Name and dosage of the medication	Effect and mechanism	Reference
GFC	In vitro	Mouse macrophage cell line RAW 264.7.	The cultured cells were divided into 5 groups and added to 12. 5, 25, 100, 200, 400 mg/L 50, 100, 200, 400 mg/L of GFC and active ingredient combination.	GFC and active ingredient combination can inhibite the release of IL-1β, TNF-α and PGE_2 from LPS-stimulated macrophages.	[72]
GFW	In vivo	Six-week-old specific-pathogen free level female Sprague Dawley rats. Letrozole sodium carboxymethylcellulose (CMC-na) solution combined with high-fat emulsion administration in PCOS-IR rat models.	GFW by gavage at low, medium, and high doses of 0.31, 0.62, and 1.24 g/kg, respectively, and were administered once a day by gavage continuously for 36 days.	GFW increases the relative abundance of Alloprevotella and decreases the relative abundance of Ruminococcaceae UCG-003 and Lachnospiraceae UCG-008. GFW can reduce the release of HS-CPR, IL-6, and TNF-α to alleviate the systemic inflammatory state.	[74]
GFW	In vivo	Adults specific-pathogen free level female Sprague Dawley rats. Medial femoral subcutaneous insulin injection and HCG in PCOS rat models.	GFW by gavage at low and high doses of 1.16 and 2.33 g/kg, respectively, and were administered once a day by gavage continuously for 35 days.	GFW can regulate the levels of MMP-9 and TIMP-1 in serum and ovarian tissues of rats, and restore ovarian ECM function.	[78]
GFW	In vivo	Eight-week-old female Sprague Dawley rats. Letrozole injection combined with intragastric high-fat emulsion in PCOS rat models.	GFW by gavage at low, medium, and high doses of 0.31, 0.62, and 1.24 g/kg, respectively, and were administered once a day by gavage continuously for 30 days.	GFW inhibited granulosa cell autophagy and promoted follicular development to attenuate ovulation disorder in PCOS-IR rats. This was associated with the activation of the PI3K/AKT/mTOR signaling pathway.	[81]
GFW	In vivo	Six-week-old BALB/c mices. Letrozole injection combined with intragastric high-fat emulsion in PCOS mice models.	70.2 mg/kg GFW suspension was administered twice a day for 3 days.	GFW drug-containing serum inhibits autophagy in ovarian granulosa cells of PCOS mice by regulating the H19/miR-29b-3p pathway.	[82]
GFW	In vivo	Six-week-old specific-pathogen free level female Sprague Dawley rats. Letrozole injection combined with high-fat suspension in PCOS mice models.	GFW by gavage at low, medium, and high doses of 0.31, 0.62, and 1.24 g/kg, respectively, and were administered once a day by gavage continuously for 30 days.	*Poria cocos* pills significantly reduced the number of apoptosis-positive cells in granulosa cells of PCOS-IR rats, down-regulated the expression of apoptosis-related proteins such as cleaved-PARP, cleaved-Caspase3, cleaved-Caspase9, etc., and, at the same time, down-regulated the expression of autophagy-related proteins, Beclin1, LC3II, to inhibit granulosa cell excessive apoptosis and autophagy.	[88]

PCOS, polycystic ovary syndrome; GFC, Guizhi-Fuling capsule; GFW, GuiZhi-FuLing Wan; RAW264.7 cells, mouse monocyte macrophage leukemia cells; IL-1β, interleukin-1 beta; TNF-α, tumor necrosis factor α; PGE_2, Prostaglandin E_2; LPS, lipopolysaccharide; IR, insulin resistance; HS-CPR, hypersensitive C-reactive protein; IL-6, interleukin-6; MMP-9, matrix metalloproteinase-9; TIMP-1, tissue inhibitor of metalloproteinas-1; ECM, extracellular matrix; PI3K/AKT/mTOR, phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin.

can significantly reduce the gastrointestinal tract stimulation, but it also suggests that the development of new dosage forms of the traditional formula should be considered in a comprehensive manner [92]. In addition, some studies have shown that the clinical efficacy of GFC combined with ethinyl estradiol cyproterone tablets and metformin in the treatment of patients with PCOS is significant, and there is no increase in adverse effects [93].

Since GFW has the effect of promoting blood circulation, it should be used with caution by the elderly and the physically weak, and prohibited for use by pregnant women. In addition, it should be prohibited to drink alcohol and eat cold, greasy and spicy food during the period of taking the medicine [91].

GFW dosage forms

Currently, GFW has been made into various dosage forms, such as decoction, concentrated pills, honey pills, and capsules, etc. In addition, 27 potentially biologically active compounds were initially identified from concentrated extracts of GFW, including monoterpene glycosides, myristyl glycosides, acetophenone, phenyl allyl

compounds, and triterpenoids. After the identification, different dosages of each component of GFW were evaluated, and the results showed that the GFW capsule dosage form was more effective compared to both the honey pill and concentrate pill, which was attributed to the small daily intake of GFW and higher concentrations of the major active compounds in GFW [94]. One study indicated that the efficacy of GFW can be affected by changes in dosage form, resulting in a change in composition and efficacy [95]. The use of GFW pills has been found to be more effective than decoction because certain GFW ingredients, such as bitter amygdalin in *Persicae Semen*, can be easily decomposed by oxidation in water. Additionally, pills made with honey help protect against moisture, decrease the contact area of drug components with air, and enhance the compatibility of herbal medicines for greater efficacy [96]. The volatile components of Guizhi-Fuling Pills, Guizhi-Fuling Tablets, and Guizhi-Fuling Capsules were analyzed using headspace solid phase microextraction combined with gas chromatography-mass spectrometry, which revealed that *Cinnamomi Ramulus* was powdered, paeonol was extracted from *Moutan Cortex*, and other herbs were prepared according to the capsule preparation method to maintain a high level of each major active ingredient in the resulting preparation [97]. For the treatment of PCOS, different dosage forms of GFW have their own characteristics, and in general, capsules are superior to pills and tablets. However, finding the dosage form preparation method that maximizes the efficacy of GFW remains a major issue for future research.

Conclusions and future perspectives

In this review, we extracted evidence about GFW and PCOS from clinical studies and animal experiments in recent years, and not only systematically summarized the traditional efficacy and pharmacological composition of the Chinese medicines contained in GFW, but also firstly summarized the mechanism of action and safety evaluation of the active ingredients of GFW in the treatment and regulation of PCOS. GFW can effectively treat PCOS through multiple mechanisms, including inhibiting inflammatory responses, modulating the ovarian extracellular matrix, regulating apoptosis and autophagy in granulosa cells, and correcting oxidative stress imbalances. In addition, the GFW has been shown to be effective in treating the complications of PCOS. In conclusion, numerous experimental and clinical trials have provided substantial evidence supporting the notable effectiveness of GFW in managing PCOS.

However, there are still some limitations in this paper, and due to the limited databases searched, it was not possible to include all the articles related to this topic over the last fifteen years. Based on the results of the current study, we found that there are still some deficiencies of current research on GFW as a potential new treatment for patients with PCOS. Firstly, some bioactive compounds in GFW are likely to be overlooked and existing studies are insufficient to provide conclusive evidence on their potential pharmacological mechanisms. Therefore, comprehensive network pharmacology and experimental studies of other pharmacologically active components of GFW should be conducted. Secondly, toxicology studies on GFW reported no adverse effects in rats at a dose of 2,000 mg/kg/d [98, 99]. In order to minimize the occurrence of side effects, the safe doses of different dosage forms of GFW should be fully validated in the future. Third, whether the combination of herbal compounded GFW with western drugs increases the incidence of adverse reactions deserves further evaluation.

In addition, GFW is often used as an “Adjunctive Therapy” to Western medicine in clinical treatment, and further exploration of its unique therapeutic mechanism is highly important for improving the therapeutic efficacy of the combination of Chinese and Western medicine. In modern science and technology, the inclusion of bioinformatics, high-throughput sequencing, and high-performance liquid chromatography increasingly contribute to the in-depth study of understanding the mechanisms of GFW for the treatment of PCOS. Therefore, to assess the role of GFW and other herbal compounds for the prevention and complementary treatment of PCOS, people should continue to employ advanced methods, develop the experimental and clinical research, explore the active pharmaceutical components in GFW, and continuously search for new effective ingredients and action targets to provide theoretical basis for clinical treatment of PCOS. Simultaneously, we are actively advancing the research and development of the classical Chinese medicine formula GFW with the aim of preserving Chinese medicine culture, facilitating the modernization of Chinese medicine, and enhancing public health.

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