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Review Article

Modes of action of traditional Chinese medicine for diabetic infertility: from molecular pathways to clinical evidence

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Abstract: Diabetes-associated infertility results from interconnected immunometabolic, oxidative, inflammatory, and endocrine disturbances that impair reproductive function in both sexes. Conventional therapies address individual symptoms but often fail to target this systemic, immune-mediated complexity. This narrative review summarizes preclinical and clinical evidence on the role of Traditional Chinese Medicine (TCM) in managing diabetic infertility, with a focus on immune-endocrine interactions, cytokine modulation, and inflammatory signaling. TCM interventions - including single-herb extracts, multi-herb formulations, and non-pharmacological approaches such as acupuncture and mind-body interventions-enhance insulin sensitivity, suppress pro-inflammatory cascades (NF-κB, TNF-α, IL-6), and regulate key immunometabolic pathways such as PI3K/Akt and AMPK. Mechanistic studies have also demonstrated improved nitric oxide bioavailability, endothelial function, and mitochondrial protection in gametogenic cells. They further show stabilization of hypothalamic-pituitary-gonadal and immune signaling, along with modulation of the gut-microbiota-immune axis. These immunomodulatory effects contribute to better spermatogenesis, semen quality, ovulation, endometrial receptivity, implantation, and pregnancy outcomes, particularly in individuals with insulin resistance or polycystic ovary syndrome. Overall, TCM shows promise as an adjunctive immunomodulatory strategy for diabetic infertility, supported by preliminary evidence of reproductive benefits. However, current evidence remains limited, and well-designed multicenter, immunology-informed clinical trials are required to confirm its efficacy.

Keywords: Diabetic infertility, immunometabolism, immune-endocrine crosstalk, traditional chinese medicine, herbal medicine, acupuncture, inflammation, reproductive immunology

Introduction

Diabetes and infertility increasingly intersect as major global health concerns, imposing substantial physiological, psychological, and economic burdens. In 2021, an estimated 537 million adults aged 20-79 years were living with diabetes worldwide, a number projected to reach 783 million by 2045 - a 46% increase [1]. Meanwhile, infertility affects approximately 10-15% of couples globally, with male factors contributing to 40-60% of cases [2, 3]. Among men with type 2 diabetes mellitus (T2DM), infertility occurs in 35-51%, far exceeding the prevalence in the general population [4].

Diabetic infertility is a multifactorial reproductive disorder arising from chronic hyperglycemia and its downstream metabolic and inflammatory consequences. Persistent hyperglycemia elevates reactive oxygen species (ROS), promotes advanced glycation end-products (AGEs), activates inflammatory cascades, and induces mitochondrial and endoplasmic reticulum (ER) stress [5]. In men, these alterations impair sperm motility, increase DNA fragmentation, and disrupt endocrine homeostasis, often aggravated by immune-mediated testicular injury [6]. In women, insulin resistance (IR), oxidative stress, and hormonal imbalance

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impair folliculogenesis, reduce endometrial receptivity, and disturb ovulation, frequently presenting as polycystic ovary syndrome (PCOS) [7].

Although diabetic infertility and PCOS share core features such as IR, oxidative stress, and low-grade inflammation, they remain distinct entities. In PCOS, neuroendocrine dysregulation - characterized by elevated gonadotropin-releasing hormone (GnRH) pulse frequency, an increased LH/FSH ratio, and ovarian hyperandrogenism - occurs typically without overt hyperglycemia [8]. By contrast, diabetic infertility results primarily from systemic metabolic dysfunction rather than primary ovarian pathology.

Conventional treatments - including glycemic control, hormone therapy, and assisted reproductive technologies (ART) - address individual symptoms but rarely target the systemic immunometabolic complexity of diabetic infertility. These interventions also impose significant financial, emotional, and physiological burdens [9].

Traditional Chinese Medicine (TCM) provides a holistic, multimodal approach that integrates metabolic, endocrine, inflammatory, and reproductive regulation. Its modalities - including herbal medicine, acupuncture, moxibustion, and lifestyle modification - have demonstrated complementary effects. Herbal formulations improve glycemic control via PI3K/Akt and AMPK pathways and may alleviate reproductive dysfunctions [10, 11]. In women with PCOS, TCM reduces insulin and lipid levels, enhances ovulation, and improves pregnancy outcomes with fewer adverse effects than conventional therapies [12]. Acupuncture has been reported to modulate GnRH secretion, increase uterine blood flow, and improve semen quality while lowering miscarriage risk; clinical trials indicate enhanced outcomes when combined with ART [13].

Recent metabolomics-based studies have begun to elucidate the molecular mechanisms underlying TCM efficacy. These analyses show modulation of amino acid metabolism, energy and fatty acid utilization, ketone body turnover, and tricarboxylic acid cycle (TCA) cycle activity following TCM interventions in diabetic models, suggesting a mechanistic link between metabolic restoration and reproductive recovery [14].

Despite these promising findings, current evidence remains fragmented - largely based on small-scale or observational studies - with limited connection between molecular mechanisms and clinical outcomes such as live birth. Encouragingly, a randomized, waitlist-controlled trial is underway to evaluate Chinese herbal medicine for male-factor infertility, reflecting growing recognition of this research gap [15].

To date, no comprehensive review has integrated mechanistic and clinical evidence regarding TCM's role in diabetic infertility. This review aims to fill that gap by summarizing how diabetes disrupts reproductive function at molecular and systemic levels, critically evaluating TCM-based interventions - including herbal medicine, acupuncture, and lifestyle therapies - and proposing evidence-informed strategies that integrate traditional and conventional approaches to improve fertility outcomes in individuals with diabetes.

Methods

A narrative review design was employed to synthesize experimental and clinical evidence on the therapeutic mechanisms of TCM interventions - including herbal formulations, acupuncture, moxibustion, animal-derived preparations, and mind-body practices - in diabetic infertility. A comprehensive literature search was conducted in PubMed, Scopus, Web of Science, Embase, CNKI, and SinoMed databases for studies published between January 2000 and May 2025. The search strategy combined the following keywords and their synonyms: "Traditional Chinese Medicine", "herbal medicine", "acupuncture", "moxibustion", "Qigong", "Tai Chi", "diabetes mellitus", and "infertility". Eligible studies include peer-reviewed preclinical (*in vivo/in vitro*), clinical (randomized or observational), *in silico* (network pharmacology), and systematic review or meta-analysis investigations on molecular, physiological, or reproductive effects of TCM in diabetic infertility, either in affected individuals or corresponding animal models. Non-peer-reviewed papers, commentaries, and unrelated studies were excluded. For each study, key data - including study type, model, intervention, and mechanistic outcomes - were extracted and summarized narratively to integrate heterogeneous findings. The collected evidence was qualitatively analyzed to identify recurring molecular and physiological mechanisms linking metabolic regulation, oxidative balance, inflammation, and reproductive function. These insights were synthesized into a conceptual framework illustrates how TCM interventions converge to restore fertility under diabetic conditions.

Diabetes and male infertility

In men, diabetes-mainly through IR and hyperglycemia - induces metabolic and oxidative disturbances along the reproductive axis, ultimately impairing fertility [5]. IR disrupts the hypothalamic-pituitary-gonadal (HPG) axis by reducing GnRH release, lowering pituitary responsiveness, and decreasing LH and FSH secretion. It also impairs Leydig cell function, while hyperinsulinemia further reduces Leydig responsiveness to LH [16]. At the testicular level, altered glucose transporter expression in Sertoli and germ cells limits lactate production, compromising the energy supply required for spermatogenesis [17]. Hyperglycemia activates AGE - receptor for advanced glycation end products (RAGE), polyol, and PKC pathways, which increase mitochondrial reactive ROS, inhibit glycolytic enzymes, and promote oxidative damage to testicular tissue and sperm DNA [16]. These insults, together with ER stress and dysregulated autophagy, weaken the blood-testis barrier (BTB), trigger germ-cell apoptosis, and impair sperm motility and morphology [16]. Mitochondrial dysfunction - manifested as structural abnormalities, membrane potential loss, reduced ATP synthesis, and mitochondrial DNA deletions - further lowers sperm count and motility [18]. MicroRNAs such as miR-30c and miR-141 regulate genes involved in mitochondrial and energy metabolism in Sertoli cells; their dysregulation compromises spermatogenesis [19, 20]. Chronic inflammation characterized by elevated TNF-α, IL-1β, and IL-6 suppresses steroidogenic enzyme activity and reduces sperm quality, while endothelial dysfunction and diminished nitric oxide (NO) bioavailability contribute to erectile dysfunction (ED) [21]. Excess ROS damages sperm DNA, lipids, and proteins, leading to fragmentation, lipid peroxidation, and impaired ATP synthesis, all of which reduce motility and fertilization potential [22, 23]. ROS overproduction also inhibits the PI3K/Akt/mechanistic target of rapamycin (mTOR) pathway, enhancing autophagy through p62 degradation and nuclear factor erythroid 2-related factor 2 (Nrf2) suppression, thereby weakening antioxidant defenses and disrupting BTB integrity [24]. Oxidative injury induces ER stress, which activates the protein kinase RNA-like endoplasmic reticulum kinase (PERK)/eukaryotic initiation factor 2 alpha (eIF2α), Inositol-requiring enzyme 1 (IRE1), and activating transcription factor 6 (ATF6) pathways and triggers CHOP-, JNK-, and caspase-12-mediated germ-cell apoptosis. AGE-induced oxidative and ER stress in Leydig cells further impairs steroidogenesis [25]. Additional mechanisms include altered CatSper channel function, which disrupts sperm hyperactivation, and endothelial dysfunction marked by reduced endothelial nitric oxide synthase (eNOS)/NO signaling and elevated endothelin-1 (ET-1), aggravating ED [26]. Diabetes also disturbs zinc homeostasis-essential for antioxidant defense, DNA stability, and sperm maturation-thereby further compromising sperm quality [27]. Together, these neuroendocrine, metabolic, inflammatory, mitochondrial, and vascular disturbances form an interconnected pathophysiological network underlying diabetes-associated male infertility (**Figure 1**).

Diabetes and female infertility

In women, diabetes impairs fertility through central, ovarian, endometrial, and systemic mechanisms. Centrally, insulin deficiency in type 1 diabetes reduces leptin and kisspeptin signaling, disrupting GnRH pulsatility and leading to hypogonadotropic hypogonadism [28-30]. In T2DM, obesity-related IR suppresses leptin signaling and blunts GnRH and LH release, resulting in anovulation. Altered adipokine profiles and mild hypercortisolism further destabilize the HPG axis [8]. At the ovarian level, IR impairs folliculogenesis, oocyte quality, and endometrial receptivity [31]. Hyperinsulinemia overstimulates theca cells, leading to androgen excess typical of PCOS [32]. Baculescu et al. (2025) showed that hyperinsulinemia enhances androgen synthesis, thereby disrupting ovulation and follicular development [33]. Reduced AMP-activated protein kinase (AMPK) activity in granulosa cells lowers mitochondrial efficiency and glucose uptake, limiting the energy available for oocyte maturation [34]. Hyperglycemia-

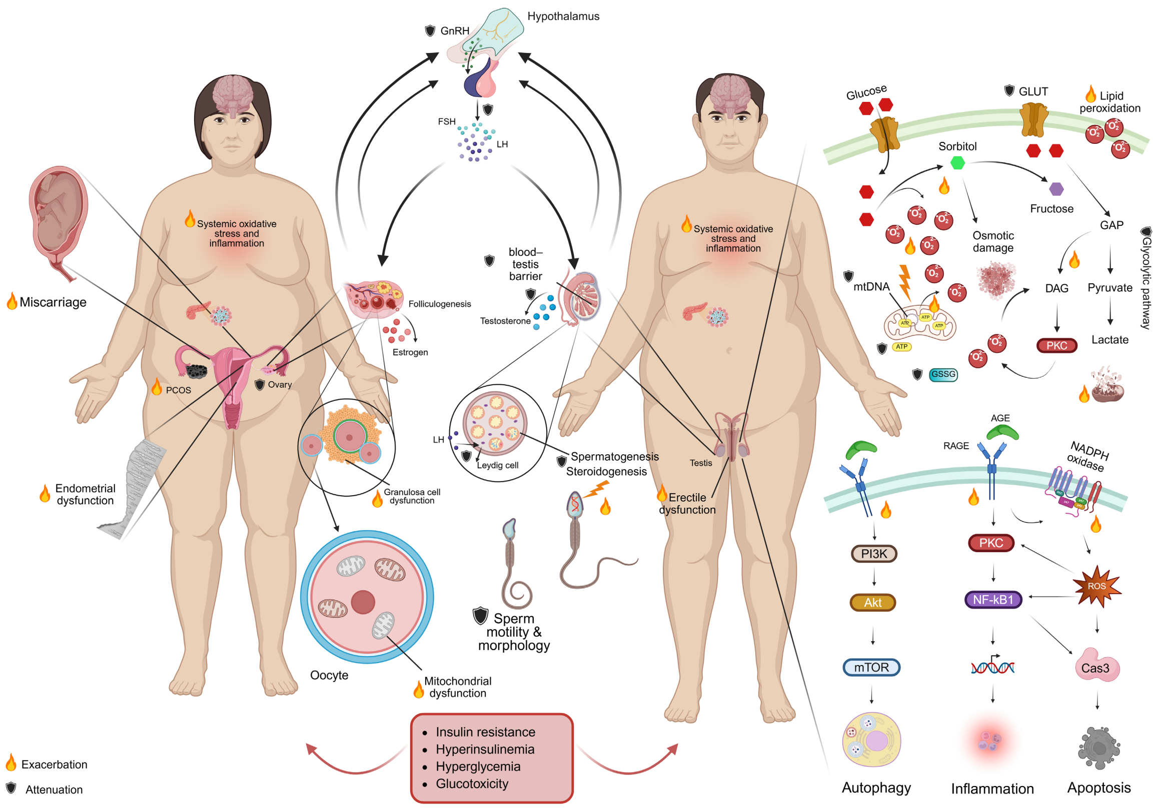

Figure 1. Diabetes-induced mechanisms underlying infertility. Chronic hyperglycemia and glucotoxicity trigger oxidative stress and inflammation, disrupting the HPG axis and damaging reproductive tissues. In females, these changes exacerbate PCOS features, endometrial dysfunction, granulosa cell loss, and oocyte mitochondrial damage, increasing miscarriage risk. In males, metabolic stress impairs Leydig cell steroidogenesis, compromises the blood-testis barrier, and disrupts spermatogenesis, leading to reduced sperm quality and erectile dysfunction. At the molecular level, AGE-RAGE and PKC signaling, ROS accumulation, and NF-κB activation promote inflammation, apoptosis, and autophagy imbalance. IR, insulin resistance; HPG, hypothalamic-pituitary-gonadal; PCOS, polycystic ovary syndrome; BTB, blood-testis barrier; AGE, advanced glycation end product; RAGE, receptor for AGE; PKC, protein kinase C; PI3K, phosphoinositide 3-kinase; ROS, reactive oxygen species; NF-κB, nuclear factor kappa B; DAG, diacylglycerol; GAP, glyceraldehyde-3-phosphate; mtDNA, mitochondrial DNA; GLUT, glucose transporter; GSK3β, glycogen synthase kinase 3 beta; Cas3, caspase-3.

induced upregulation of miR-93 and miR-223 further inhibits AMPK signaling, decreasing oocyte competence [35].

Endometrial dysfunction arises from downregulation of glucose transporter type 4 (GLUT4), which compromises glucose handling and decidualization [31]. Accumulated ROS exacerbate granulosa-cell injury and follicular atresia [36]. Park et al. (2020) reported that oxidative stress activates NF-κB, inducing follicular apoptosis and reducing oocyte viability [37]. Persistent oxidative stress coupled with IL-6-mediated inflammation diminishes endometrial receptivity and contributes to implantation failure [38]. Activation of the AGE-RAGE pathway amplifies oxidative injury. Sopasi et al. demonstrated that this mechanism compromises oocyte integrity and reproductive potential [39].

Beyond ovarian and endometrial impairment, diabetes affects tubal and uterine function through endometriosis progression, pelvic inflammation, and autonomic neuropathy, which together disrupt tubal peristalsis [40]. Diabetic endometrium may also exhibit hyperplasia, abnormal bleeding, edema, and aberrant angiogenesis, increasing the risk of infertility and malignancy [40]. Implantation failure has been linked to abnormal integrin expression, reduced pinopode formation, and dysregulated LIF (leukemia inhibitory factor)/IGF-1 (insulin-like growth factor 1)/Beclin-1 signaling. Maternal hyperinsulinemia also activates the mTOR path-

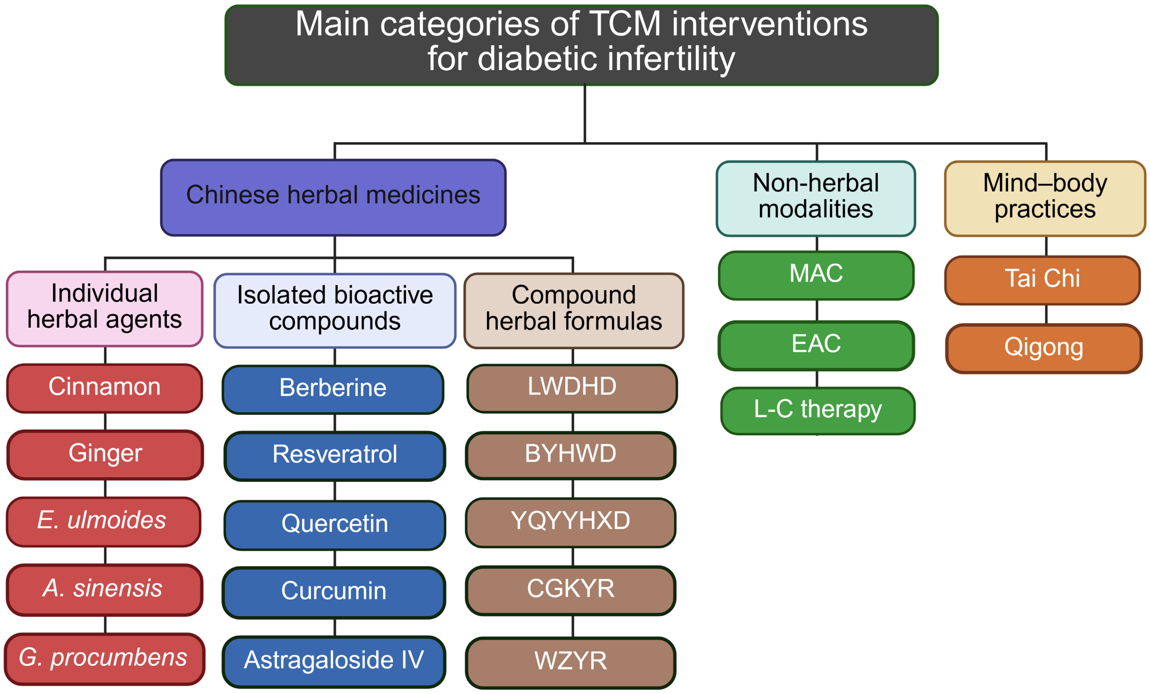

Figure 2. Categories of TCM interventions for diabetic infertility. TCM strategies are grouped into individual herbal agents, isolated bioactive compounds, compound herbal formulas, non-herbal modalities, and mind-body practices. TCM, Traditional Chinese Medicine; LWDHD, Liuwei Dihuang Decoction; BYHWD, Buyang Huanwu Decoction; YQYYHXD, Yiqi Yangyin Huoxue Decoction; CGKYR, Chaige Kangyi Recipe; WZYR, Wuzi Yanzong Recipe; MAC, manual acupuncture; EAC, electroacupuncture; L-C therapy, leech-centipede therapy.

way, impairing decidualization and trophoblast invasion [31]. Additional factors such as excessive AMPK activation in type 1 diabetes, IFN-γ upregulation, and defective spiral-artery remodeling further reduce endometrial receptivity and increase pregnancy loss [41]. Hyperglycemia exerts embryotoxic effects through DNA damage, O-GlcNAcylation, and growth arrest in preimplantation embryos [42]. Also, circadian disruption caused by prediabetes or shift work alters leptin-insulin dynamics, GnRH signaling, and endometrial gene expression, worsening reproductive outcomes [43]. At the clinical level, diabetic neuropathy, vasculopathy, and psychosocial stress contribute to reduced libido and arousal, further decreasing fertility potential [43] (**Figure 1**).

Principles and applications of TCM in managing diabetic infertility

TCM views diabetic infertility as a manifestation of Yin-Yang imbalance and Qi deficiency, which in biomedical terms correspond to oxidative stress, hormonal dysregulation, and chronic inflammation. Through its herbal and non-herbal modalities (**Figure 2**), it aims to restore systemic homeostasis and counteract reproductive injury associated with chronic hyperglycemia [12]. Experimental evidence supporting this framework derives from well-established diabetic animal models, including streptozotocin (STZ)-induced β-cell injury, leptin receptor-deficient (db/db) mice, and high-fat diet (HFD) combined with STZ administration to mimic T2DM. For reproductive analogs, letrozole-, dehydroepiandrosterone (DHEA)-, and dihydrotestosterone (DHT)-induced PCOS models have been widely used to investigate ovarian dysfunction under IR conditions. Clinical studies have primarily focused on women with PCOS - with or without IR - and men with T2DM-associated ED, reflecting overlapping yet distinct manifestations of diabetic reproductive impairment.

Herbal medicine

Herbal medicine represents the core therapeutic approach in managing diabetic infertility. By regulating both glucose metabolism and reproductive hormones, herbal formulations target the metabolic-endocrine interface underlying infertility in diabetes. This dual modulation corrects hyperglycemia-induced oxidative and inflammatory stress while supporting gonadal function, establishing herbal therapy as both a metabolic stabilizer and a fertility restorer within this framework.

Individual herbal agents

As key modulators of metabolic and endocrine balance, several herbs counteract IR and hormonal dysregulation that impair fertility (**Table 1**). *Cinnamon (Cinnamomum spp.)* provides the strongest and most consistent evidence linking metabolic regulation to reproductive recovery. In alloxan-induced diabetic rats, cinnamon bark powder (80 mg/kg/day for four weeks) improved glycemic control, enhanced antioxidant defense, and restored sperm motility. In another experiment, the aqueous bark extract (500 mg/kg/day for six weeks) elevated serum testosterone and preserved seminiferous architecture, confirming testicular protection under diabetic stress. A pilot randomized controlled trial (RCT) in forty-five women with PCOS treated with cinnamon powder (1.5 g/day for six months) improved menstrual cyclicity and ovulation despite minimal change in fasting glucose and insulin sensitivity [44-46]. Cinnamon therefore restores reproductive function by improving insulin sensitivity, reducing inflammation, and re-establishing hormonal and oxidative equilibrium.

Comparable effects are seen with *Glycyrrhiza glabra* and *Angelica sinensis*, which target the ovarian-metabolic axis. In estradiol-induced PCOS rats, *Glycyrrhiza* extract (100 mg/kg/day for six weeks) normalized sex-steroid profiles and stimulated folliculogenesis, while *Angelica sinensis* (2-8 g/kg/day for four weeks) in letrozole plus HFD models improved glucose-lipid metabolism, restored ovarian morphology, and rebalanced the gut microbiota [47, 48]. These botanicals converge on a gut-ovarian regulatory axis aligning metabolic homeostasis with hormonal equilibrium. Supporting this mechanism, *White tea (Camellia sinensis)* used as the sole drinking fluid for two months in STZ-diabetic male rats enhanced insulin sensitivity, reduced oxidative stress, and improved sperm motility and viability [49]. These findings suggest that rebalancing metabolic function and oxidative stability is central to restoring fertility under diabetic conditions.

Beyond metabolic regulation, several botanicals directly protect gonadal tissues from hyperglycemic injury. *Ginger (Zingiber officinale)* (100-400 mg/kg/day for four to eight weeks) increased testosterone, improved sperm viability, and restored ovarian steroidogenic gene expression in diabetic rats [50, 51]. Similarly, *Dioscorea zingiberensis* (125-250 mg/kg/day for ten weeks) activated the Nrf2/HO-1 pathway, reinforced the BTB, and enhanced spermatogenesis [52]. In female PCOS models, *Crocus sativus (saffron)* petal extract (50-600 mg/kg/day for fifteen days, intraperitoneal) reduced TNF-α, IL-6, and oxidative stress while repairing ovarian histoarchitecture in testosterone-induced mice [53]. These data confirm that oxidative and barrier injuries are reversible through antioxidant and anti-inflammatory mechanisms, reinforcing gametogenic resilience under metabolic stress.

Some herbs primarily enhance male reproductive recovery through interconnected vascular and metabolic mechanisms. *Gynura procumbens* demonstrates consistent efficacy across preclinical models, where treatment (50-1000 mg/kg/day for two to four weeks) lowered blood glucose, increased sperm count and libido, and improved implantation rates in untreated females [54-56]. Similarly, in STZ-induced diabetic rats, *Eucommia ulmoides* leaf extract administered for sixteen weeks improved insulin sensitivity and erectile function via activation of NO-cGMP and Akt-eNOS signaling [57]. These findings indicate that vascular remodeling and endothelial repair operate synergistically with metabolic restoration to re-establish male reproductive competence.

Building on this vascular-metabolic interaction, certain herbs further engage androgenic signaling to enhance male reproductive recovery. *Tribulus terrestris* exemplifies this dual mechanism. In a twelve-week randomized trial involving 180 men, it improved International Index of Erectile Function (IIEF) scores and sexual satisfaction, while a smaller thirty-day study showed no clear advantage over placebo. Complementary preclinical studies demonstrated reduced glucose, higher testosterone, and improved sperm morphology and motility [58-60].

Table 1. Main effects and mechanisms of individual botanicals in TCM for diabetic infertility

Herbal species	TCM-based mechanism	Main anti-diabetic effect	Main anti-infertility effect	Study model/ population	Key herbal part	Ref.
Cinnamon (*Ceylon cinnamon*)	Warms & tonifies kidney yang; disperses cold & alleviates pain (abdominal, waist/knees); promotes blood & Qi circulation; warms middle burner & treats cold abdomen/stomach pain; alleviates dysmenorrhea & menstrual pain	↓ FPG/fasting insulin; ↓ HOMA-IR; improved lipids; ↑ glucose uptake; ↑ IRS-1/PI3K interaction; insulin-sensitizing & antioxidant effects; ↓ NF-κB/TNF-α; PI3K/IRS-1 signaling	Women: ↑ menstrual frequency/cyclicity, ↑ ovulation; Men: ↑ sperm count/motility/viability; ↑ testosterone, LH, FSH; ↓ IGF-1/IGFBP-1 (PCOS mice)	Diabetic rats, PCOS women	Bark (inner/outer), whole cinnamon powder, leaf & bud essential oils	[44-46]
Eucommia ulmoides	Nourishes liver & kidneys; strengthens tendons & bones; calms the fetus; relieves lumbar & knee pain; treats osteoporosis; used traditionally for hypertension, hyperglycemia/diabetes, obesity	Improved glucose tolerance & insulin resistance; antioxidant (↑ SOD, GSH-Px; ↓ MDA)	Restored endothelial/EF; ↑ NO/cGMP; Akt-eNOS pathway; penile endothelial integrity	Diabetic Rats	Leaf & bark extract	[57]
Female Ginseng (*Angelica sinensis)*	Tonifies & invigorates blood; regulates menstruation & relieves menstrual pain (irregular menses, amenorrhea, dysmenorrhea); moistens the intestines to relieve constipation when blood is deficient; disperses cold & harmonizes blood stagnation pains	Improved insulin resistance; ↓ dyslipidemia	Restored estrous cycle; improved ovarian histopathology; hormonal profile regulation	Diabetic rats	Root/Radix (dried root) & root aqueous extract	[48]
Ginger (*Zingiber officinale*)	Pungent, enters lung, spleen, stomach channels; disperses wind-cold (common cold, chills), warms middle & stops vomiting (especially cold stomach), expels cold phlegm & stops cough; relieves seafood poisoning; strengthens digestion & appetite; dried ginger rescues collapse of yang in severe cold	↓ FBG; ↑ serum insulin; ↑ HOMA-β; antioxidant/anti-inflammatory; ↓ NF-κB/TNF-α; ↑ TAC/SOD/GPx/CAT	↑ sperm count/motility/viability; ↑ testosterone, LH, FSH; preserved seminiferous tubules; anti-apoptotic effects; ↑ PCNA & AR	PCOS mice models	Root/Rhizome	[50, 51]
Gynura procumbens	Clears heat & resolves toxicity; stops bleeding & reduces swelling; strengthens & tonifies; expels wind & dampness	Antihyperglycemic effects	Restored spermatogenesis; ↑ testosterone, LH, FSH; ↑ sperm count & morphology; ↑ implantation; ↑ CRISP1, CES5A, ZPBP, PEBP1 → improved sperm maturation, capacitation & sperm-egg interaction	Diabetic rats	Leaf extract (aqueous/ethanolic)	[54-56]
Licorice (*Glycyrrhiza glabra*)	Tonifies spleen Qi, harmonizes & moderates harsh medicines; clears toxins & alleviates spasms; relieves cough & expels phlegm; protects gastrointestinal lining & treats mild stomach ulceration; diminishes pain & soothes muscle spasm	↑ Insulin; ↓ cholesterol/TG/LDL-C; ↑ HDL-C; antioxidant + anti-inflammatory; ↓ TNF-α/IL-1β/IL-4/IL-6/IL-10; ↑ SOD/CAT/GPx/GSH	Restored folliculogenesis; ↓ cystic/atretic follicles; ↑ corpus luteum; hormonal rebalance; progesterone ↑; androgens ↓	Diabetic rats	Root/Radix (dried root) & root extract	[47]
Pucture-vine (*Tribulus terrestris*)	Calms liver & anchors yang (for liver-yang rising causing headache, dizziness or vertigo); dredges liver Qi & disperses stagnation (for flank/chest distension, insufficient lactation, irregular menstruation); dispels wind-heat & brightens eyes (for red, swollen, painful eyes with tearing or visual disturbance); dispels wind & stops itching (in skin lesions, urticaria, eczema)	↓ Blood glucose; antioxidant & anti-apoptotic effects (↓ Caspase-3/9, ↑ Bcl-2/Bax)	Mixed clinical results: ↑ IIEF or no benefit, in diabetic rats ↑ sperm count, motility, morphology, testosterone; endothelial NO pathway (↑ eNOS, ↑ NO, ↑ cGMP); androgenic/erectogenic activity; improved smooth muscle/collagen balance	Diabetic Rats, male patients with sexual dysfunction	Aerial parts, fruits, & roots	[58-60]
Saffron (*Crocus sativus*)	Invigorates blood & dispels stasis; cools blood & clears heat; detoxifies & reduces swelling; calms the mind & relieves melancholy; unblocks channels & alleviates pain	↑ antioxidant enzymes (GSH, GST); ↓ inflammatory cytokines (TNFα, IL-1β, IL-6, IL-18, CRP); ↓ NF-κB/NF-κB p65; ↑ IκB expression	↑ FSH; ↓ LH, testosterone & estrogen; restores ovarian follicle development; improves steroidogenic enzymes; restores estrogen negative feedback	Male patients	Petals	[53]

White tea (*Camellia sinensis*)	Clears inner heat & detoxifies; moistens lungs & relieves dryness; calms spirit, reduces anxiety; supports memory & protects nerves; helps lower blood pressure & blood lipids; suitable for damp-heat constitutions	Improved glucose tolerance & insulin sensitivity; ↓ lipid/protein oxidation; ↑ FRAP	Restored sperm concentration, motility, viability; normalized morphology; anti-oxidant effects → testicular/epididymal protection	Male patients	Leaves & young buds/shoots	[49]
Yellow ginger (*Dioscorea zingiberensis*)	Clears lung heat & relieves cough; promotes diuresis & unblocks urinary strangury; resolves toxicity & reduces swelling; alleviates rheumatic low-back pain; treats early-stage sores/abscesses & pyogenic skin infections; relieves pain from contusions & sprains; treats insect (bee/bug) stings	↓ MDA & 8-OHdG; ↑ SOD; restored GSH/T-GSH, Nrf2-HO-1-NQO1 activation	Improved testicular morphology; ↑ sperm count; ↓ abnormal forms; ↑ ZO-1 → restored BTB	Diabetic mice	Rhizome (underground part)	[52]

Abbreviations: ↑, Increase; ↓, Decrease; TCM, Traditional Chinese Medicine; DZEE, Dioscorea zingiberensis ethanol extract; EULE, Eucommia ulmoides leaf extract; NS, Not specified; RCT, Randomized controlled trial; IIEF, International Index of Erectile Function; LH, Luteinizing hormone; FSH, Follicle-stimulating hormone; CRISP1, Cysteine-rich secretory protein 1; CES5A, Carboxylesterase 5A; ZPBP, Zona pellucida binding protein; PEBP1, Phosphatidylethanolamine-binding protein 1; MDA, Malondialdehyde; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; SOD, Superoxide dismutase; GSH, Glutathione; T-GSH, Total glutathione; Nrf2, Nuclear factor erythroid 2-related factor 2; HO-1, Heme oxygenase 1; NQO1, NAD(P)H quinone oxidoreductase 1; ZO-1, Zonula occludens-1; NO, Nitric oxide; cGMP, Cyclic guanosine monophosphate; Akt, Protein kinase B; eNOS, Endothelial nitric oxide synthase; FPG, Fasting plasma glucose; HOMA-IR, Homeostatic model assessment of insulin resistance; IRS-1, Insulin receptor substrate-1; PI3K, Phosphoinositide 3-kinase; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; TNF-α, Tumor necrosis factor alpha; IGF-1, Insulin-like growth factor 1; IGFBP-1, Insulin-like growth factor-binding protein 1; PCOS, Polycystic ovary syndrome; WEA, Water extract of Angelica sinensis; FRAP, Ferric reducing antioxidant power; TG, Triglyceride; LDL-C, Low-density lipoprotein cholesterol; HDL-C, High-density lipoprotein cholesterol; CAT, Catalase; GPx, Glutathione peroxidase; IL-1β, Interleukin-1 beta; IL-4, Interleukin-4; IL-6, Interleukin-6; IL-10, Interleukin-10; FBG, Fasting blood glucose; HOMA-β, Homeostatic model assessment of β-cell function; PCNA, Proliferating cell nuclear antigen; AR, androgen receptor; TAC, Total antioxidant capacity; GST, Glutathione S-transferase; CRP, C-reactive protein; IκB, Inhibitor of nuclear factor kappa B; BTB, Blood-testis barrier; EF, Erectile function; Bcl-2, B-cell lymphoma 2; Bax, Bcl-2-associated X protein; Caspase-3/9, Cysteine-aspartic proteases 3 and 9.

Table 2. Main anti-diabetic and reproductive mechanisms of isolated bioactive compounds in diabetic infertility

Bioactive agent	TCM-based mechanism	Main anti-diabetic effect	Main anti-infertility effect	Study model/ population	Botanical source	Ref.
Astragaloside IV	Tonifies Qi & raises Yang; strengthens spleen & lung; secures exterior, stops sweating; promotes urination, reduces edema; generates fluids, nourishes Blood; resolves pus, heals sores	↓ Oxidative stress; anti-apoptotic *in vivo*; pro-apoptotic *in vitro* KGN cells	Improved ovarian morphology & fertility potential; PPARγ signaling; granulosa cell protection	Diabetic mice; PCOS rats	Dried root (Radix Astragali) of *Astragalus membranaceus*	[89, 90]
Berberine	Clear heat & damp, treat *xiao ke* (wasting-thirst/diabetes), & resolve damp-heat in the lower jiao linked to reproductive disorders	↓ BMI, FPG, FINS, HOMA-IR; improved lipids; AMPK/PI3K-Akt-GLUT4 activation	↑ Ovulation, pregnancy, live birth; ↓ LH, testosterone; improved ovarian morphology; HPO axis regulation	PCOS rats & women	Rhizome (dried root/rhizome) of *Coptis chinensis* (Huang Lian), & also from the bark of *Phellodendron* species (Huang Bai)	[61-67]
Betaine	Tonifies liver & kidney, nourishes yin & essence, brightens eyes; cools blood & stops bleeding; clears heat, generates fluids, harmonizes Stomach; calms Heart & Shen, relieves irritability, stops sweating, alleviates dysentery	↓ ROS, ↓ MDA; ↑ SOD/CAT; improved insulin sensitivity; ↓ TC/TG; antioxidant; PI3K/Akt signaling; osmolyte & methyl donor role	Restored testicular/ovarian morphology; improved estrous cycle, ovulation, embryo development	Diabetic mice, PCOS women	Fruit of *Lycium barbarum* (Goji), leaves of *Spinacia oleracea* (spinach), root &/or leaves of *Beta vulgaris* (beet), various *Amaranthus* species (amaranth), & the grain of *Triticum aestivum* (wheat)	[84, 86-88, 177]
Catalpol	Clears heat & cools the blood; nourishes Yin & replenishes essence; treats heat-entering Ying/Blood, Yin-deficiency signs (dry mouth, night sweats), blood deficiency (anemia), dizziness, tinnitus, soreness of loins & knees	↑ Insulin sensitivity via AMPK/IRS1/GLUT4; ↓ NF-κB; antioxidant; PI3K/Akt/mTOR activation; suppression of RAGE/NOX4/NF-κB	Restored spermatogenesis; ↓ apoptosis; restored sex hormones	Diabetic mice; PCOS rats; PCOS granulosa cells	Root of *Rehmannia glutinosa*	[91, 178, 179]
Crocin	Nourishes & invigorates blood; resolves blood stasis; used for pain from stasis, dysmenorrhea, amenorrhea, & emotional depression.	↓ Blood glucose; antioxidant; ↓ oxidative stress	↑ testosterone; ↑ sperm count/motility; improved testis histology; some IVF benefit; antioxidant & anti-apoptotic (↓ Bax/caspase, ↑ Bcl-2)	Diabetic rats, subjects with metabolic syndrome, PCOS rats, diabetic mice	Stigmas of *Crocus sativus L.* flowers	[85, 180, 181]

Cryptotanshinone	Same as *Salvia miltiorrhiza*	↓ HMGB1/TLR4/NF-κB; ↑ GLUT4/PI3K/AKT2 → improved insulin resistance; anti-inflammatory; insulin signaling activation	Restored estrous cycle; improved follicles; ↓ testosterone, LH, estradiol (E2)	Diabetic mice, PCOS rats	Root of *Salvia miltiorrhiza* (Danshen)	[182, 183]
Curcumin	Invigorates blood; promotes Qi; regulates menses; relieves pain; reduces swelling	↓ BMI, FPG, FINS, HOMA-IR; improved lipids; ↑ antioxidant enzymes; PPARγ activation; SIRT1/PGC-1α; anti-inflammatory effects	↓ FAI, ↓ LH/FSH; possible reproductive hormone regulation	PCOS women	Rhizome (underground stem/rootstock) of *Curcuma longa*	[68, 69, 184]
DNLP	Nourishing Yin, clearing heat & generating fluids; treating Yin-deficiency manifestations such as dry mouth/throat, thirst, weakness	↓ FBG, ↓ HOMA-IR	↑ Sperm count, motility, viability; improved testicular histology; ↑ PCNA, ↑ SIRT1; anti-apoptotic	Diabetic rats	The root of *Astragalus membranaceus* & *Panax ginseng*; stems, leaves, flowers, & roots from *Dendrobium nobile*	[185]
Ginsenosides (Rg3, Rb1)	Powerfully tonifies Yuan-Qi; strengthens spleen & lung; generates fluids & alleviates thirst; benefits heart-Qi & calms the shen	↓ ROS; improved antioxidant capacity	↓ Granulosa cell apoptosis; restored ovarian reserve; anti-apoptotic (↑ Bcl-2/Bax); mitochondrial protection	KGN cells, diabetic rats	Root of *Panax ginseng*	[93, 94]
GSTT	Same as *Tribulus terrestris* (see **Table 1**)	↑ eNOS; ↑ NO/cGMP; endothelial protection; antioxidant, endothelial NO pathway	Improved EF; ↑ ICP; better smooth muscle/collagen balance; ↓ apoptosis	Diabetic rats	Fruits of *Tribulus terrestris* (puniculate porrect fruit) — the aerial reproductive part of the plant	[79]
Icariin	Tonifies kidney Yang, strengthens bones & sinews, dispels wind-damp, enhances sexual function	Improved glucose homeostasis; antioxidant; anti-apoptotic	Preserved spermatogenesis; improved testis morphology	Diabetic mice	Dried stems & leaves of *Epimedium* spp	[82]
LBP	Tonifies Liver & Kidney, nourishes Yin & essence, brightens eyes, moistens Lung, promotes fertility	↓ Oxidative stress; ↑ SOD/GSH; ↓ apoptosis; antioxidant, anti-apoptotic (↑ Bcl-2/Bax, ↓ caspase-3)	Preserved spermatogenesis, ↑ sperm quality	Diabetic rats & mice	Dried fruit of *Lycium barbarum* (wolfberry/goji berry)	[80, 81]
Morroniside	Nourishing liver & kidney; arresting seminal emission & sweat; treating kidney-deficiency with symptoms such as dizziness, tinnitus, soreness of loins & knees	PI3K/Akt/mTOR; Nrf2 activation	Improved granulosa cell viability, ↓ apoptosis	PCOS granulosa cells	Fruit (Corni Fructus) of *Cornus officinalis*	[92]
Pachymic acid	Strengthens spleen, drains damp & promotes urination, calms heart & shen	Improved insulin resistance; anti-inflammatory; HMGB1/RAGE suppression	Improved ovarian function (PCOS)	PCOS rats	Sclerotium of *Poria cocos*	[95]
PNS	Stops bleeding & disperses blood-stasis; treats bleeding (nose, lung, stomach, urine), trauma bruises, chest/abdominal pain from stasis	↑ SOD; endothelial protection; antioxidant; vascular protection	↑ EF	Diabetic rats	Roots (especially the *taproot/rhizome*) of the *Panax notoginseng*	[77]
Puerarin	Releases exterior, relieves muscle stiffness; generates fluids & alleviates thirst; raises Yang & stops diarrhea; promotes eruption in measles	↓ HOMA-IR, FINS, TG/LDL; ↑ HDL; endocrine modulation	↓ LH; ↓ LH/FSH; ↓ testosterone	PCOS women	Root of *Pueraria lobata*	[72]
Quercetin	Tonifies kidney; nourish yin; clear heat; invigorate blood; & enhance fertility	↓ FBG, ↓ insulin, ↓ HOMA-IR; improved lipid/antioxidant status; ↑ adiponectin; PI3K/Akt activation; antioxidant (↑ SOD, CAT)	↓ testosterone, LH; improved ovarian morphology & folliculogenesis	Diabetic rats, PCOS women	Leaves of *Ginkgo biloba*, *Morus alba*, *Cuscuta chinensis*, *Epimedium* species, & *Sophora japonica*	[73, 74]

Resveratrol	Clear heat & toxins, invigorate blood, nourish Yin & kidney, tonify Qi & blood, & support reproductive health	↓ FPG; ↓ insulin resistance; restored IGF-1; improved metabolic profile; SIRT2 ↑; glycolysis enzyme regulation; mitochondrial biogenesis	↓ testosterone, ↓ LH; improved folliculogenesis, oocyte/embryo quality, live birth	PCOS women & rats, PCOS granulosa cells	Skin of *Vitis vinifera* (grape), root of *Polygonum cuspidatum* (Japanese knotweed), fruit of *Morus alba* (mulberry), & seeds of *Arachis hypogaea* (peanut)	[70, 71, 186-189]
Tanshinones	Invigorates blood & dispels stasis; relieves pain; clears heat & eases irritability; cools blood; reduces swelling & resolves sores; regulates menses	↓ BMI, TG, TC; ↑ HDL; metabolic improvement	↑ Ovulation & pregnancy; ↓ LH, ↓ testosterone; hormonal regulation	PCOS women	Dried root (radix) of *Salvia miltiorrhiza* (Danshen)	[75, 76, 190, 191]

Abbreviations: ↑, Increase; ↓, Decrease; LBP, Lycium barbarum polysaccharides; DNLP, Dendrobium nobile Lindl polysaccharides; PNS, Panax notoginseng saponins; GSTT, Tribulus terrestris saponins; EF, erectile function; ICP, Intracavernosal pressure; BMI, body mass index; FINS, fasting insulin; FAI, free androgen index; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; HMGB1, high mo-bility group box 1; TLR4, toll-like receptor 4; E2, estradiol; CAT, catalase; IGF-1, insulin-like growth factor 1; SIRT2, sirtuin 2; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PPARγ, peroxisome proliferator-activated receptor gamma; KGN cells, human granulosa cell line KGN; PCNA, proliferating cell nuclear antigen; AMPK, AMP-activated protein kinase; GLUT4, Glucose transporter type 4; mTOR, Mechanistic target of rapamycin; RAGE, Receptor for advanced glycation end products; NOX4, NADPH oxidase 4; HPO axis, Hypothalamic-pituitary-ovarian axis; ROS, Reactive oxygen species.

The combined evidence indicates that *Tribulus* enhances reproductive recovery through dual modulation of androgen signaling and endothelial function. Together, individual herbal agents lay the mechanistic foundation for reversing diabetic infertility through targeted, system-wide regulation (Table S1).

Isolated bioactive compounds

The antidiabetic and fertility-enhancing actions of individual herbs arise from one or more active phytochemicals that have been experimentally validated in diverse infertility models. These bioactive molecules act independently or in concert, engaging overlapping signaling pathways that regulate metabolism, oxidative balance, and gonadal recovery. Through modulation of PI3K/Akt, Nrf2/HO-1, and NF-κB pathways, they collectively restore endocrine and reproductive homeostasis (**Table 2**).

Berberine, an isoquinoline alkaloid from *Coptidis Rhizoma*, exemplifies this integrative action. In preclinical PCOS models induced by letrozole and HFD, oral berberine (100-400 mg/kg/day for four weeks) activated the PI3K-Akt-GLUT4 axis, enhanced insulin sensitivity, and normalized ovarian morphology. Multiple RCTs involving 80-120 women with PCOS (0.3-0.5 g three times daily for 3-4 months) further demonstrated reduced homeostatic model assessment of insulin resistance (HOMA-IR) and androgen levels, along with improved ovulation and live birth rates compared with placebo or metformin. These consistent findings indicate that metabolic stabilization translates directly into endocrine and fertility recovery [61-67]. Similar cross-pathway effects are observed with polyphenolic compounds, which mitigate oxidative and mitochondrial stress - two hallmarks of reproductive dysfunction. Curcumin (500-1500 mg/day for 6-12 weeks) improved insulin sensitivity and antioxidant capacity in pilot clinical trials involving women with PCOS [68, 69]. Resveratrol (20 mg/kg/day in PCOS rats; 400-1500 mg/day in small clinical studies) lowered testosterone, LH, and dehydroepiandrosterone sulfate (DHEAS), while promoting sirtuin 1/peroxisome proliferator-activated receptor gamma coactivator 1-alpha (SIRT1/PGC-1α) - mediated mitochondrial biogenesis and improving oocyte quality [70, 71]. Likewise, quercetin (30 mg/kg/day in rats; 1 g/day for 12 weeks in PCOS patients) normalized estrous cycles, alleviated insulin resistance, and enhanced ovarian steroidogenesis. Also, Puerarin (150 mg/day for three months) produced similar clinical benefits, improving menstrual regularity and reducing hyperinsulinemia [72-74]. Together, these polyphenols highlight how redox balance and insulin signaling act in concert to restore oocyte quality through mitochondrial repair and metabolic realignment.

Terpenoid derivatives from *Salvia miltiorrhiza*, particularly tanshinones and cryptotanshinone, extend these protective effects by suppressing high-mobility group box 1/toll-like receptor 4/nuclear factor kappa-B (HMGB1/TLR4/NF-κB) signaling. This inhibition alleviates ovarian inflammation and lipid imbalance, both major contributors to PCOS pathology. In preclinical models, terpenoids restored folliculogenesis and normalized hormonal profiles, while three-month clinical regimens (1 g three times daily; n ≈ 60-90 PCOS patients) improved lipid metabolism and reduced LH, adrenocorticotropic hormone (ACTH), and testosterone levels. These outcomes position terpenoids as dual modulators of inflammation and endocrine balance [75, 76]. In male reproductive dysfunction, saponins and vascular regulators play complementary roles by promoting endothelial repair and maintaining erectile function. In diabetic rat models, *Tribulus terrestris* saponins (40 mg/kg/day for four weeks) enhanced NO-cGMP signaling and cavernosal pressure, *Panax notoginseng* saponins (50-150 mg/kg/day) improved the Bcl-2/Bax ratio and vascular integrity, and *Ganoderma lucidum* β-glucans preserved mitochondrial function while reducing fibrosis [77-79]. Clinical observations in men with diabetic ED supported these findings, reporting improved erectile performance and endothelial responsiveness. Maintaining nitric oxide bioavailability and vascular remodeling thus emerges as a fundamental mechanism underlying erectile and testicular recovery in diabetes.

Beyond vascular regulation, polysaccharides and flavonoids protect testicular tissue by preserving mitochondrial stability and antioxidant defense. In STZ-induced diabetic mice, *Lycium barbarum* polysaccharides (100-200 mg/kg/day for 6-8 weeks) enhanced sperm motility, strengthened the BTB, and prevented germ-cell apoptosis [80, 81]. Similarly, icariin (40-80 mg/kg/day for 11 weeks) activated AMPK-Nrf2 signaling to restore BTB integrity, while *Dendrobium nobile* polysaccharides (400 mg/kg/day for six weeks) elevated SIRT1 and PCNA expression, promoting spermatogenesis [82]. Also, Crocin (15-60 mg/kg/day for 2-4 weeks) reduced ROS and ER stress, restored gonadal morphology, and improved sperm and hormonal parameters in diabetic rodents, whereas betaine (200-800 mg/kg/day *in vivo*; 5 mM in granulosa and Leydig cell assays) produced comparable antioxidative and steroidogenic benefits [83-88]. These convergent findings emphasize that mitochondrial protection and redox stability are essential to sustaining spermatogenic capacity under diabetic stress.

On the ovarian side, glycosides such as astragaloside IV (20-80 mg/kg/day subcutaneous or 50 mg/kg oral) also support metabolic and reproductive recovery. They improve insulin resistance, restore estrous cycles, and activate PPARγ-dependent autophagy in diabetic female mice and small clinical cohorts [89, 90]. Catalpol (50 mg/kg/day for four weeks) and morroniside further strengthen these antioxidative defenses through SIRT1/Nrf2 activation, reducing oxidative injury and apoptosis in ovarian tissues [91, 92]. Pachymic acid (8-33 mg/kg/day) suppresses HMGB1/RAGE/NF-κB signaling and normalizes endocrine indices, while ginsenosides Rg3 and Rb1 maintain mitochondrial potential and granulosa-cell viability in both animal and *in vitro* models [93-95]. Together, these glycosides act through interrelated mechanisms-autophagy induction, oxidative stress reduction, and mitochondrial preservation - to maintain ovarian structure and hormonal balance under diabetic conditions. Overall, these structurally diverse molecules - including alkaloids, polyphenols, terpenoids, saponins, polysaccharides, and glycosides - form an interconnected biochemical network. Acting across metabolic and endocrine pathways, they reestablish vascular, hormonal, and redox stability, thereby defining the molecular framework of fertility restoration in diabetes (Table S2).

Compound herbal formulas

Compound herbal formulas represent the most validated TCM approach for diabetic infertility, acting synergistically across vascular, metabolic, and gonadal axes to restore endothelial integrity, oxidative balance, and hormonal regulation. Restoring vascular health is particularly critical in male diabetic infertility, where endothelial injury and NO depletion drive ED, and herbal prescriptions targeting vascular repair reestablish NO signaling and oxidative stability (**Table 3**).

In controlled clinical studies, oral Yishen Huoxue Decoction (12 weeks) improved erectile-function scores, raised NO and superoxide dismutase (SOD), and lowered endothelin-1 and malondialdehyde (MDA) levels in men with diabetic ED. Also, corroborative preclinical findings showed enhanced penile eNOS/cGMP signaling and improved blood flow, confirming NO-mediated endothelial recovery [96, 97]. Yiqi Yangyin Huoxue Decoction, in men with T2DM-ED, increased IIEF-5 scores and testosterone while lowering LH and E_2, suggesting improved erectile function via hormonal regulation [98]. Likewise, a four-month controlled clinical trial involving seventy diabetic men found that Buyang Huanwu Decoction enhanced erectile tone and testosterone, while complementary animal models demonstrated eNOS-cGMP activation and reduced cavernosal apoptosis, indicating that microvascular remodeling underlies its clinical efficacy [99]. These convergent clinical and experimental data indicate that vascular formulas act primarily through NO-eNOS preservation and microcirculatory repair to reverse endothelial dysfunction.

Further evidence from both pilot clinical and preclinical studies supports the vascular-restorative role of antioxidant-activating formulas. Oral Yougui Pill (9g for eight weeks) achieved efficacy comparable to tadalafil but with fewer side effects, while diabetic rat models showed activation of Nrf2-HO-1 signaling and reduced endothelial apoptosis, linking antioxidant defense to vascular recovery [100-102]. Similarly, Qianlie Shutong Capsule (with α-lipoic acid) improved endothelial integrity and NO bioavailability in middle-aged men after eight weeks, and preclinical analogs such as Yiyuan Qiwei Pills and Tianjing Tongluo Decoction enhanced eNOS expression and normalized sex-hormone profiles in diabetic rats [103-106]. The consistent upregulation of NO-related pathways across these formulations underscores

Table 3. Main effects and mechanisms of compound herbal formulas in diabetic infertility

Herbal compound	TCM-based mechanism	Main anti-diabetic effect	Main anti-infertility effect	Study model/ population	Herbal composition	Ref.
ABR+SV	Regulates blood-stasis; strengthens liver & kidney; relieves lumbar-knee soreness & weakness; moves blood & resolves menstrual disorders; promotes lactation	↓ Blood glucose; ↑ insulin/ glucagon	Improved EF; improved penile histology; ↑ eNOS; ↓ VEGFA/ACE; ↓ Caspase-3	Diabetic rats with ED	*Achyranthes bidentata* Blume (ABR) 15 g, *Gypsophila vaccaria* (L.) Sm. (SV) 10 g	[112]
BSHXD	Tonifies kidney, strengthens sinews & bones; activates blood & stops pain. Used for post-injury weakness of kidney/Yin: loins/knees soreness & weakness, especially lower back; tongue pale, white coating; pulse thin & weak	↑ PI3K/AKT signaling	↑ ICP; improved EF; ↓ apoptosis & fibrosis; anti-apoptotic; anti-fibrotic	Diabetic rats with ED	*Rehmannia glutinosa* (Gaertn.) DC. (Shudi) 15 g, *Cornus officinalis* Siebold & Zucc. (Shanzhuyu) 12 g, *Dioscorea oppositifolia* L. (Shanyao) 12 g, *Paeonia lactiflora* Pall. (Baishao) 12 g, *Ligusticum chuanxiong* Hort. (Chuanxiong) 10 g, *Angelica sinensis* (Oliv.) Diels (Danggui) 10 g, *Cuscuta chinensis* Lam. (Tusizi) 15 g, *Eucommia ulmoides* Oliv. (Duzhong) 15 g, *Psoralea corylifolia* L. (Buguzhi) 12 g, *Carthamus tinctorius* L. (Honghua) 10 g	[111]
BSHZF	Strengthens spleen & kidney, transforms turbidity & clears toxins; used for PCOS with kidney deficiency + phlegm-dampness, & chronic renal failure with spleen-kidney weakness & damp-turbid accumulation	↓ FBG; ↓ FINS; improved insulin resistance; gut microbiota modulation	↓ testosterone; improved ovarian morphology; improved estrous cycle; ↑ SCFA bacteria; ↓ LPS/ TNF-α	PCOS rats	*Cuscuta chinensis* Lam. (Tusizi) 15 g, *Lycium barbarum* L. (Gouqizi) 15 g, *Pinellia ternata* (Thunb.) Makino, praeparata cum alumine (Qing Banxia) 8 g, *Angelica sinensis* (Oliv.) Diels (Danggui) 15 g, *Poria cocos* (Schw.) Wolf (Fuling) 15 g, *Salvia miltiorrhiza* Bunge (Danshen) 20 g, *Cyperus rotundus* L. (Xiangfu) 10 g, *Ligusticum chuanxiong* Hort. (Chuanxiong) 10 g, *Paeonia lactiflora* Pall. (Baishao) 15 g, *Glycyrrhiza uralensis* Fisch. (Gancao) 6 g, *Citrus reticulata* Blanco (Qingpi) 6 g, *Coix lacryma-jobi* L. var. *ma-yuen* (Roman.) Stapf (Yiren) 20 g, *Plantago asiatica* L. (Cheqianzi) 10 g, *Platycodon grandiflorus* (Jacq.) A.DC. (Jiegeng) 10 g, *Patrinia scabiosifolia* Fisch. ex Trevir. (Baijiangcao) 20 g, *Benincasa hispida* (Thunb.) Cogn., exocarpium (Dongguapi) 30 g	[127]
Bushen-based decoctions	Tonifies the kidney (Yin or Yang) & strengthens bones & marrow; used in patterns of Kidney-deficiency with Blood-stasis to treat osteoporosis, lumbar-knee weakness, diminished ovarian reserve, & menopausal syndrome	Improved insulin resistance; ↓ BMI; ↓ glucose/ lipids	↑ Pregnancy; improved perfusion & receptivity; ↓ LH/testosterone; hormonal modulation; improved ovarian blood flow	PCOS women	Bushen Quyu Huatan decoction, Bushen Jianpi decoction, Shugan Bushen decoction, Bushen Huoxue Cupailuan decoction, Bushen Huoxue Culuan Prescription, Bushen Tiaochong decoction, Bushen Huatan fang	[125, 126]
BYHWD	Tonifies Qi & activates blood; treats hemiplegia, mouth-&-eye deviation, speech impairment post-stroke; improves neurological recovery in cerebral small vessel disease & peripheral nerve injury; addresses conditions of Qi-deficiency with blood-stasis.	NS	↑ EF; ↑ IIEF-5; ↑ QoL; hormonal rebalance; endothelial & oxidative stress regulation	Diabetic patients with ED	*Astragalus membranaceus* (Fisch.) Bunge (Huangqi), *Angelica sinensis* (Oliv.) Diels (Danggui), *Paeonia lactiflora* Pall. (Red Peony, Paeoniae Radix Rubra), *Ligusticum chuanxiong* Hort. (Chuanxiong), *Prunus persica* (L.) Batsch (Peach Kernel, Taoren), *Carthamus tinctorius* L. (Safflower, Honghua), *Pheretima aspergillum* (E. Perrier) (Earthworm, Dilong)	[99]
CFDT/ CFDTD/ MCDD	Dries damp; transforms phlegm; moves Qi; treats phlegm-dampness syndrome with irregular menstruation, PCOS; obesity, vaginal discharge; alleviates abdominal distension; improves insulin resistance & follicular development.	↓ HOMA-IR; ↓ FBG; improved insulin signaling; ↓ inflammation; PI3K/AKT activation; ASK1/JNK inhibition; NF-κB modulation	↑ Pregnancy & ovulation; improved receptivity & ovarian morphology	Patients with delayed menstruatio; PCOS women	*Atractylodes lancea* (Thunb.) DC. (Cangzhu), *Cyperus rotundus* L. (Xiangfu), *Citrus reticulata* Blanco, pericarpium (Chenpi), *Pinellia ternata* (Thunb.) Makino, praeparata (Banxia), *Poria cocos* (Schw.) Wolf (Fuling), *Glycyrrhiza uralensis* Fisch. (Gancao), *Citrus aurantium* L. (Zhiqiao), *Magnolia officinalis* Rehder & E.H.Wilson (Houpo), *Arisaema heterophyllum* Blume, praeparata (Tiannanxing), *Alisma orientale* (Sam.) Juz. (Zexie).	[115-117, 136-138, 192]

CGKYR	Modern formulation without classical TCM basis	↓ Insulin resistance; PI3K/Akt activation; ↓ NF-κB	Improved decidualization; improved endometrium; better pregnancy outcomes; IL-6/STAT3 pathway; Th17/Treg balance; trophoblast invasion	RPL patients with insulin resistance	*Bupleurum chinense* DC. (Chaihu), *Scutellaria baicalensis* Georgi (Huangqin), *Citrus aurantium* L. (Zhike), *Pueraria lobata* (Willd.) Ohwi (Gegen), *Codonopsis pilosula* (Franch.) Nannf. (Dangshen), *Zingiber officinale* Roscoe (Shengjiang), *Atractylodes lancea* (Thunb.) DC. (Cangzhu), *Paeonia lactiflora* Pall. (Baishao), *Pinellia ternata* (Thunb.) Makino (Banxia), *Cinnamomum cassia* (L.) J.Presl (Rougui), *Alisma orientale* (Sam.) Juz. (Zexie)	[139]
Cuscuta-Salvia herb pair	Nourishes liver & kidney Yin; secures essence; activates blood to remove stasis; treats kidney-deficiency symptoms such as weak, sore loins/knees, tinnitus, dizziness; regulates menstruation, alleviates abnormal uterine bleeding & miscarriage threats; clears blood stasis & promotes menstrual flow	Regulated PI3K-Akt, MAPK; IL-6, AKT1, VEGFA targets	Improved ovarian morphology; improved follicle development	PCOS mice	*Semen Cuscutae* + *Radix Salviae*	[128]
DXP/Xiaoyao-based	Soothes liver qi; strengthens spleen; nourishes blood; treats liver-Qi stagnation with spleen deficiency: depression, emotional disturbance, functional dyspepsia, menstrual irregularity, post-stroke mood disorders	↓ FINS; ↓ HOMA-IR; improved insulin resistance	Ovulation; ↑ pregnancy rates; anti-inflammatory; metabolic modulation	PCOS women	*Astragalus membranaceus* (Fisch.) Bunge (Huangqi) 120 g, *Angelica sinensis* (Oliv.) Diels (Danggui) 6 g, *Paeonia lactiflora* Pall. (Chishao) 4.5 g, *Pheretima aspergillum* (Dilong) 3 g, *Ligusticum chuanxiong* Hort. (Chuanxiong) 3 g, *Carthamus tinctorius* L. (Honghua) 3 g, *Prunus persica* L. (Taoren) 3 g	[130, 131]
DZSD	Modern formulation without classical TCM basis	↓ Insulin resistance (HOMA-IR); ↓ plasma cardiotrophin-1; improved glucose-lipid metabolism; insulin-sensitizing; anti-inflammatory effects	Improved ovulation; ↑ clinical & biochemical pregnancy; improved menstrual cycle & hormone; modulation of HPO axis; endocrine regulation	PCOS women	*Atractylodes chinensis* (Cangzhu) 12 g, *Pinellia ternata* (Banxia) 12 g, *Angelica sinensis* (Danggui) 12 g, *Atractylodes macrocephala* (Baizhu) 10 g, *Poria cocos* (Fuling) 10 g, *Alisma orientale* (Zexie) 10 g, *Ligusticum chuanxiong* (Chuanxiong) 10 g, *Cyperus rotundus* (Xiangfu) 9 g, *Glycyrrhiza uralensis* (Gancao) 9 g	[129]
FXJC	Modern formulation without classical TCM basis	↓ AGEs; ↓ Ang II; RAAS modulation; endothelial protection	Improved EF; synergy with tadalafil	Diabetic patients with ED	*Curculigo orchioides* Gaertn. (Xianmao), *Cynomorium songaricum* Rupr. (Suoyang), *Epimedium brevicornu* Maxim. (Yinyanghuo), *Psoralea corylifolia* L. (Buguzhi)	[109, 110]
GFW	Tonifies kidney & liver Yin; used for kidney-Yin deficiency with symptoms: weak, sore loins & knees; tinnitus; night sweats; dry mouth/throat; seminal leakage; internal heat signs; red tongue, thin rapid pulse.	↓ HOMA-IR; ↓ TNF-α; ↓ IL-6; PI3K/AKT/mTOR regulation	↓ testosterone, ↓ LH; improved ovulation & ovarian morphology; gut microbiota-inflammation axis	PCOS rats	*Cinnamomum cassia* (Ramulus Cinnamomi/Guizhi) 15 g, *Poria cocos* (Fuling) 15 g, Semen Persicae (Taoren) 15 g, *Paeonia lactiflora* (Chishao) 15 g, Cortex Moutan (Mudanpi) 15 g	[118, 119]
GHYSJ	Nourishing kidney essence & replenishing Qi & Yin; treating dizziness, memory loss, insomnia, fatigue & weakness	↓ FBG; ↓ ROS/MDA; ↑ Nrf2/HO-1, GPX4; antioxidant; anti-ferroptosis	↑ Sperm count; ↑ motility; ↑ testosterone	Diabetic rats	*Panax ginseng* C.A. Mey. (Renshen), *Astragalus membranaceus* (Fisch.) Bunge (Huangqi), *Epimedium brevicornu* Maxim. (Yinyanghuo), *Polygonatum sibiricum* Redouté (Huangjing), *Lycium barbarum* L. (Gouqi), *Cuscuta chinensis* Lam. (Tusizi), *Ligustrum lucidum* W.T. Aiton (Nvzhenzi), *Lonicera japonica* Thunb. (Jinyinhua), *Paeonia lactiflora* Pall. (Baishao), *Rosa laevigata* Michx. (Jinyingzi), *Glycyrrhiza uralensis* Fisch. (Gancao).	[143]
Ginger + Cinnamon combo	Warms middle burner & disperses cold; warms stomach & relieves gastric pain; promotes digestion; warms meridians & stops pain in cold patterns.	Synergistic ↓ glucose; ↑ insulin; antioxidant; ↑ SIRT1; ↓ NF-κB/TNF-α	Synergistic ↑ sperm count, motility, testosterone; anti-apoptotic	Diabetic rats	Ginger (*Zingiber officinale*) 1 g/L, Cinnamon (*Cinnamomum zeylanicum*) 1 g/L	[144, 145]
HXTLQWD	Activates blood & dredges the collaterals; dispels blood stasis & calms wind; used for patterns of collateral obstruction with stasis-related pain or numbness	Antioxidative stress (↓ PKC)	Improved EF (human & animal); endothelial rescue; NO pathway	Diabetic rats & patients with ED	*Astragalus membranaceus* (Fisch.) Bunge (Huangqi), *Angelica sinensis* (Oliv.) Diels (Danggui), *Ligusticum chuanxiong* Hort. (Chuanxiong), *Salvia miltiorrhiza* Bunge (Danshen), *Paeonia lactiflora* Pall. (Baishao), *Carthamus tinctorius* L. (Honghua), *Prunus persica* (L.) Batsch (Taoren)	[107, 108]

Kuntai capsule	Nourishes Yin & clears heat; calms the mind & relieves irritability; tonifies heart & kidney; treats menopausal symptoms, diminished ovarian reserve/ovarian insufficiency; regulates reproductive hormones & enhances ovarian & uterine health	↓ BMI; ↓ FPG; ↓ insulin resistance; improved lipids; insulin sensitizing	↓ LH; ↓ testosterone	PCOS women	*Rehmannia glutinosa*, *Coptis chinensis*, *Paeonia* (*Paeonia lactiflora/Paeonia alba*), *Scutellaria baicalensis*, *Equus asinus* (donkey-hide gelatin, Ejiao), & *Poria cocos*	[124]
LDP	Tonifies liver-Yin & kidney-Yin; used for Yin-deficiency signal patterns: weak, sore loins & knees; tinnitus; night sweats; dry throat/mouth; frequent/clear urination; dizziness & fatigue	↓ HOMA-IR; improved glucose-lipid metabolism; PI3K/AKT inhibition; FoxO1a activation	↑ Pregnancy rate; improved ovarian morphology	PCOS women & rats	Rehmanniae Radix Praeparata: Corni Fructus: Dioscoreae Rhizoma: Alismatis Rhizoma: Moutan Cortex: *Poria cocos* = 8:4:4:3:3:3 (by weight)	[120, 121, 123]
QLST capsule	Clears heat & drains dampness; resolves blood-Stasis; used in TCM for chronic prostatitis & prostate hyperplasia with damp-heat & stasis: frequent/urgent urination, dribbling, perineal or lower abdominal discomfort	↓ MDA; ↓ ET-1; ↑ NO; ↑ SOD; ↑ GSH; antioxidative stress; NO pathway	Improved EF	Diabetic patients with ED	*Hedyotis diffusa* Willd. (Baihuasheshecao), *Scutellaria baicalensis* Georgi (Huangqin), *Plantago asiatica* L. (Cheqianzi), *Polygonum cuspidatum* Siebold & Zucc. (Huzhang), *Curcuma longa* L. (Jianghuang), *Glycyrrhiza uralensis* Fisch. (Gancao)	[103, 106]
RR-CO	Nourishes kidney-Yin & liver-Yin; treats kidney-yin deficiency with loins/knees soreness & weakness; used for tinnitus, frequency of urination, seminal emission, & other symptoms of Yin deficiency	↓ FBG; ↑ GLP-1; improved gut microbiota	Improved sperm/testis morphology; ↑ testosterone; gut-testis axis regulation; GLP-1R upregulation	Diabetic mice	*Rehmannia glutinosa* (Gaertn.) DC. 25 g, *Cornus officinalis* Siebold & Zucc. 15 g	[122]
STP	Tonifies kidney-essence & secures the fetus; used for threatened or recurrent miscarriage with kidney deficiency signs; sense of lower abdominal dragging, weak loins & knees, dizziness, tinnitus	Improved insulin resistance; antioxidant; anti-inflammatory	↑ Progesterone; improved endometrial blood flow; ↑ pregnancy; progestogenic effects	Recurrent spontaneous abortion women	*Semen Cuscutae (Tu Si Zi)* 20 g, *Dipsacus asper* (Xu Duan) 30 g, *Ligustrum lucidum* (Nu Zhen Zi) 10 g, *Parasitic Loranthus* (Sang Ji Sheng) 20 g, *Colla Corii Asini* (Ass-hide Gelatin) 30 g	[135]
TJTLD	Modern formulation without classical TCM basis	↑ eNOS; inhibition of RhoA/ROCK	Improved EF; ↑ sexual hormones; endothelial rescue via NO pathway	Diabetic rats with ED	*Epimedium brevicornu* Maxim. 15 g, *Rehmannia glutinosa* (Gaertn.) DC. 10 g, *Hirudo nipponica* Whitman 10 g, *Cyathula officinalis* K.C.Kuan 10 g	[105]
WYZR	Nourishes kidney jing; secures seminal emission; strengthens loins & knees; treats impotence, premature ejaculation, dribbling urine, & male sterility	↓ Blood glucose, ↓ ER stress	Preserved spermatogenesis; ↓ DNA oxidative damage; improved sperm quality; NO-cGMP activation; ↓ caspase-3 (anti-apoptotic); hormone regulation	PCOS rats, Diabetic mice & rats	*Lycium barbarum* (Fructus Lycii, Gouqizi), *Cuscuta chinensis* (Semen Cuscutae, Tusizi), *Rubus idaeus* (Fructus Rubi, Fupenzi), *Schisandra chinensis* (Fructus Schisandrae, Wuweizi), *Plantago asiatica* (Semen Plantaginis, Cheqianzi)	[140-142]
Yiyuan qiwei Pill	Modern formulation without classical TCM basis	NS	↑ nNOS activity; ↑ EF; reduced corpus cavernosum damage; NO-cGMP activation; endothelial repair	Diabetic rats with ED	*Rehmannia glutinosa* Praeparata (Shudihuang) 25 g, *Cistanche deserticola* (Roucongrong) 20 g, Cornu Cervi (LuRong) 20 g, *Rehmannia glutinosa* (Shengdi) 15 g, *Eucommia ulmoides* (Duzhong) 15 g, *Cuscuta chinensis* (Tusizi) 15 g, *Psoralea corylifolia* (Buguzhi) 15 g, *Cynomorium songaricum* (Suoyang) 15 g, *Lycium barbarum* (Gouqizi) 15 g, *Epimedium brevicornu* (Yinyanghuo) 15 g, *Panax ginseng* (Renshen) 15 g, *Achyranthes bidentata* var. (Niuxi) 15 g, *Asparagus cochinchinensis* (Tian dong) 15 g, Hippocampus (Seahorse) 1 pair, *Bombyx mori* larva (Can'e) 10 g, *Pantala flavescens* (Qingting) 9 g, Nine-aroma insect (Jiuxiangchong) 9 g, Amber (HuPo) 8 g, *Syzygium aromaticum* (Dingxiang) 8 g, *Amomum villosum* (Sharen) 8 g, Costus root (Mu Xiang) 9 g	[104]

Yougui pill/ Yougui Wan	Warms kidney-Yang; restores Ming-men fire; fortifies essence & blood; treats impotence, low sperm count, cold limbs, lumbar-knee weakness; reverses menopausal atrophy; enhances immune function; reduces glucocorticoid-induced apoptosis	Antioxidant	Improved EF vs placebo; ↑ testosterone; Nrf2-HO-1 activation; anti-oxidative stress	Diabetic rats with ED; ED patients; female rats with sexual dysfunction	Radix Rehmanniae Praeparata (Shu Di Huang), Radix Aconiti Lateralis Praeparata (Fu Zi), Cinnamomi Cortex (Rou Gui), Rhizoma Dioscoreae (Shan Yao), Fructus Corni (Shan Zhu Yu), Semen Cuscutae (Tu Si Zi), Fructus Lycii (Gou Qi), Cervi Cornus Colla (Lu Jiao Jiao), Eucommiae Cortex (Du Zhong), Radix Angelicae Sinensis (Dang Gui)	[100-102, 193]
YQYYHXD	Tonifies Qi & nourishes Yin; activates blood circulation; used for Qi-Yin deficiency with blood stasis pattern (e.g. in type II diabetes to reduce proteinuria, improve renal function; in IPF to lower fibrosis; in ischemic stroke to ameliorate symptoms)	Adjunct glycemic support	↑ Testosterone; ↓ LH, ↓ estradiol; improved EF; HPG-axis balance	Diabetic patients with ED	*Astragalus membranaceus*, *Pseudostellaria heterophylla*, *Rehmannia glutinosa*, *Cornus officinalis*, *Dioscorea opposita* (or *oppositifolia*), *Epimedium brevicornu*, *Ligusticum chuanxiong*, *Carthamus tinctorius*, *Paeonia lactiflora*, *Cyathula officinalis*, *Ophiopogon japonicus*, *Cuscuta chinensis*	[98]
YSHXD	Tonifies kidney & nourishes essence; invigorates Blood & dispels stasis; strengthens sinews/bones & relieves lumbar-knee soreness; indicated for Kidney-deficiency with Blood-stasis patterns (e.g., post-trauma convalescence, chronic lumbago/weakness)	NS	Improved EF (↑ IIEF-5, EQS); ↓ ET-1; ↑ NO; antioxidative stress; endothelial protection	ED patients	*Rheum palmatum* (Rhei Radix et Rhizoma, Da Huang), *Angelica sinensis* (Angelica sinensis Radix, Dang Gui), *Achyranthes bidentata* (Achyranthes bidentata Radix, Niu Xi), *Salvia miltiorrhiza* (Salvia miltiorrhiza Radix et Rhizoma, Dan Shen), *Panax notoginseng* (Notoginseng Radix et Rhizoma, San Qi), *Carthamus tinctorius* (Carthami Flos, Hong Hua), *Astragalus membranaceus* (Astragali Radix, Huang Qi)	[96, 97]
ZYP	Modern formulation without classical TCM basis	Improved insulin resistance; ↓ oxidative stress; anti-inflammatory; antioxidant	↑ Implantation; ↑ pregnancy; ↑ live birth; improved endometrium	Infertile & PCOS women	Cortex, Morindae Officinalis Radix, Cervi Cornu Degelatinatum, Codonopsis Radix, Atractylodis Macrocephalae Rhizoma, Asini Corii Colla, Lycii Fructus, Rehmanniae Radix Praeparata, Polygoni Multiflori Radix Praeparata, Artemisiae Argyi Folium, Amomi Fructus.	[132-134]
ZYZY	Modern formulation without classical TCM basis	NS	Improved EF; synergy with sildenafil; sexual confidence; QoL improvement	Diabetic patients with ED	*Rehmannia glutinosa* (Gaertn.) DC. 20 g, *Reynoutria multiflora* (Thunb.) Moldenke 18 g, *Lycium barbarum* L. 18 g, *Dioscorea oppositifolia* L. 15 g, *Broussonetia papyrifera* (L.) L'Hér. Ex Vent. 15 g, *Dendrobium nobile* Lindl. 15 g, *Ligustrum lucidum* W.T.Aiton 15 g, *Epimedium brevicornu* Maxim. 10 g, *Cuscuta chinensis* Lam. 10 g, *Cervus nippon* Temminck 10 g, *Rosa laevigata* Michx. 10 g, *Albizia julibrissin* Durazz 8 g	[113, 114]

Abbreviations: ↑, Increase; ↓, Decrease; WYZR, Wuzi Yanzong recipe; YSHXD, Yishen Huoxue Decoction; YQYYHXD, Yiqi Yangyin Huoxue Decoction; BYHWD, Buyang Huanwu Decoction; EF, Erectile function; QoL, Quality of life; nNOS, Neuronal nitric oxide synthase; TJTLD, Tianjing Tongluo Decoction; BMI, Body mass index; IR, Insulin resistance; CFDT, Cangfu Daotan Decoction; CFDTD, Cangfu Daotan Decoction (variant); MCDD, Modified Cangfu Daotan Decoction; AKT1, RAC-alpha serine/threonine-protein kinase 1; VEGFA, Vascular endothelial growth factor A; HXTLQWD, Huoxue Tongluo Qiwei Decoction; GFW, Guizhi Fuling Wan; FXJC, Fufang Xuanju Capsule; AGEs, Advanced glycation end products; Ang II, Angiotensin II; RAAS, Renin-angiotensin-aldosterone system; QLST, Qianlie Shutong Capsule; LDP, Liuwei Dihuang Pill; ICP, Intracavernosal pressure; PNS, Panax notoginseng saponins; ABR+SV, Achyranthes bidentata root + Semen vaccariae; BSHXD, Bushen Huoxue Decoction; BSHZF, Bu Shen Hua Zhuo formula; GHYSJ, Guhan Yangsheng Jing; ROS, Reactive oxygen species; GPX4, Glutathione peroxidase 4; DZSD, Danxi Zhishitan Decoction; CT-1, Cardiotrophin-1; CGKYR, Chaige Kangyi Recipe; STAT3, Signal transducer and activator of transcription 3; Th17/Treg, T-helper 17 cells/Regulatory T cells; DXP, Danzhi Xiaoyao Pill; SIRT1, Sirtuin 1; RR-CO, Radix Rehmanniae - Cornus Officinalis; GLP-1, Glucagon-like peptide-1; GLP-1R, Glucagon-like peptide-1 receptor; STP, Shoutai Pill; ZYP, Zishen Yutai Pill; ZYZY, Ziyin Zhuangyang Capsule; ACE, Angiotensin-converting enzyme; ASK1, Apoptosis signal-regulating kinase 1; JNK, c-Jun N-terminal kinase; MAPK, Mitogen-activated protein kinase; ET-1, Endothelin-1; PKC, Protein kinase C; RhoA, Ras homolog family member A; ROCK, Rho-associated protein kinase; AKT2, RAC-beta serine/threonine-protein kinase 2; SCFA, Short-chain fatty acids; LPS, Lipopolysaccharide; HPG axis, Hypothalamic-pituitary-gonadal axis; FoxO1a, Forkhead box O1; IIEF-5, International Index of Erectile Function-5; EQS, Erection Quality Score; ED, Erectile dysfunction.

endothelial activation and redox stabilization as shared mechanisms driving functional recovery.

Both preclinical and small clinical data further demonstrate the capacity of Huoxue Tongluo Qiwei Decoction to preserve endothelial ultrastructure and increase intracavernosal pressure following eight weeks of therapy, directly mapping microstructural repair to hemodynamic improvement [107, 108]. In combined interventions, Fufang Xuanju Capsule with tadalafil produced superior erectile and vascular outcomes compared to tadalafil alone, consistent with inhibition of AGEs and Ang II signaling [109, 110]. Complementary preclinical studies on Bushen Huoxue Decoction and *Achyranthes bidentata* plus *Semen vaccariae* Granules confirmed enhanced NO-cGMP signaling, improved vascular elasticity, and reduced apoptosis under hyperglycemic stress [111, 112]. Moreover, RCTs of Ziyin Zhuangyang Capsule (Shisanwei) reported improved erectile scores, normalized testosterone, and elevated NO, suggesting dual restoration of endothelial and androgenic function [113, 114]. Collectively, these findings support that vascular-targeted herbal prescriptions rebuild endothelial tone and restore erectile performance through overlapping antioxidative and NO-mediated mechanisms.

Beyond vascular repair, compound formulas that regulate metabolic and ovarian axes play a pivotal role in restoring female fertility disrupted by diabetes and PCOS. Cangfu Daotan Decoction, tested in both preclinical models and small clinical cohorts (~3 months), improved insulin sensitivity, suppressed ASK1/JNK and NF-κB/LCN-2 signaling, and restored folliculogenesis and uterine perfusion [115-117]. Guizhi Fuling Pill acted through PI3K/Akt/mTOR activation, lowering TNF-α and IL-6 while protecting granulosa cells from apoptosis, and preclinical results indicated improved IR and ovarian morphology [118, 119]. In human RCTs involving 80-120 participants (8-12 weeks), Liuwei Dihuang Pill enhanced IRS-1/FoxO1a signaling and improved ovulation and pregnancy rates, while the *Rehmanniae glutinosa-Cornus officinalis* herb pair increased GLP-1 secretion and enriched butyrate-producing gut microbiota, linking metabolic-microbial modulation with reproductive improvement [120-123]. These findings collectively highlight metabolic-hormonal crosstalk as a major determinant of ovarian repair.

Further evidence from a double-blind RCT (1.2 g/day for three months) showed that Kuntai Capsule lowers body mass index (BMI), fasting insulin, and testosterone while improving ovulation, providing robust clinical validation of its endocrine and metabolic regulatory effects [124]. In obese PCOS women, Bushen Quyu Huatan and Bushen Tiaochong Decoctions modulated leptin/adiponectin balance and improved ovarian perfusion, yielding pregnancy rates above 70% [125, 126]. In STZ-induced diabetic rat models, Bu Shen Hua Zhuo Formula inhibited TLR4/NF-κB signaling and remodeled gut microbiota toward short-chain-fatty-acid producers, linking inflammation control to ovarian restoration [127]. Similarly, Danxi Zhishitan Decoction improved ovarian function and insulin sensitivity under metabolic stress, while *Cuscuta-Salvia* Formula activated PI3K-Akt/MAPK signaling to sustain granulosa-cell viability and enhance endometrial receptivity [128, 129]. Danzhi Xiaoyao regimens further normalized ovulation by modulating inflammatory and hypothalamic-pituitary signaling [130, 131]. These interrelated mechanisms demonstrate how adipokine regulation, microbial rebalancing, and neuroendocrine stability collectively restore ovarian function under diabetic stress.

Formulas promoting uterine receptivity and implantation complete this therapeutic cascade. In two multicenter RCTs enrolling over two thousand IVF patients, Zishen Yutai Pill (5 g TID) significantly improved implantation and live-birth rates without added adverse effects [132-134]. In PCOS women with kidney-deficiency syndrome, combining Zishen Yutai Pill with Bushen Tiaojing Decoction for three cycles improved ovulation (90%) and pregnancy rates (76%), while reducing LH and testosterone levels [134]. A systematic meta-analysis of twelve RCTs confirmed that Shoutai Pill reduced miscarriage and increased live-birth rates [135]. Similarly, Modified Cangfu Daotan Decoction and Bu Shen Hua Zhuo Formula promoted follicular maturation and endometrial receptivity via metabolic-microbiome crosstalk [127, 136-138]. In IR contexts, Chaige Kangyi Recipe improved endometrial receptivity through IL-6/vascular endothelial growth factor

(VEGF) modulation, aligning angiogenesis with implantation success [139]. These uterine-targeted regimens demonstrate that local vascular, endocrine, and immune mechanisms cooperate to enhance conception and early gestational stability.

At the gonadal level, herbal combinations preserve spermatogenic function and testicular microcirculation under oxidative stress. In preclinical diabetic models, Wuzi Yanzong Recipe reduced ER stress and germ-cell apoptosis, activated NO-cGMP signaling, and maintained testicular structure, while aging models confirmed its capacity to prevent seminiferous degeneration [140-142]. Guhan Yangsheng Jing limited ferroptosis by restoring GPX4/xCT expression and reducing lipid peroxidation, linking mitochondrial protection to sperm viability [143]. The *Radix rehmanniae-Cornus officinalis* pair further increased GLP-1-mediated gut-testis communication, improving spermatogenesis through metabolic repair [122]. Similarly, the Ginger-Cinnamon combination reduced oxidative and inflammatory injury in diabetic rat testes, improving sperm motility and testosterone levels [144, 145]. Collectively, these findings indicate that gonadal-protective formulas sustain spermatogenic integrity and redox equilibrium under metabolic stress (Table S3).

Non-herbal TCM modalities

Acupuncture

Acupuncture modulates neuroendocrine and metabolic signaling across the hypothalamic-pituitary-ovarian (HPO) and insulin pathways, integrating systemic and reproductive regulation, which is relevant to diabetic and PCOS-related infertility.

In women with PCOS, RCTs (8-12 weeks) consistently reported improved insulin sensitivity, lower BMI and HOMA-IR, and reduced LH and testosterone with normalization of the LH/FSH ratio [146-148]. These outcomes indicate restored hypothalamic-pituitary feedback and endocrine homeostasis. Corresponding reproductive improvements-enhanced follicular growth, greater endometrial thickness, and higher ovulation and pregnancy rates-confirm that hormonal normalization translates into measurable fertility gains.

Combined protocols pairing electroacupuncture (EA) with Chinese herbal medicine or clomiphene citrate achieved superior ovulation and conception rates compared with single therapy [149], illustrating how neuromodulatory stimulation enhances ovarian responsiveness when integrated with pharmacologic or herbal regimens. In obese women, 12-week abdominal acupuncture achieved metabolic and menstrual benefits comparable to metformin [150], supporting its potential as a non-pharmacologic insulin sensitizer. Animal studies using letrozole-, DHEA-, or DHT-induced PCOS models showed that low-frequency EA restored estrous cyclicity and ovarian morphology, improved glucose uptake, and normalized gonadotropins through modulation of GnRH, insulin receptor, and connexin-43 expression [151]. These mechanisms link autonomic regulation with ovarian recovery. When combined with metformin, EA further improved glucose tolerance and ovarian structure, underscoring its dual metabolic-reproductive role. Microbiome analyses also revealed increased *Agathobacter* and decreased *Erysipelatoclostridium* after EA [152], suggesting that gut-brain-ovarian signaling may partly mediate its systemic effects. Overall, acupuncture synchronizes central endocrine control with peripheral metabolic and ovarian signaling, providing a mechanistic rationale for its adjunctive use in diabetic and PCOS-associated infertility (**Tables 4** and S4).

Moxibustion

Moxibustion, a thermal therapy employing *Artemisia vulgaris*, promotes reproductive recovery under metabolic stress through vascular and inflammatory regulation. In PCOS rat models, it preserved granulosa-cell integrity, enhanced ovarian blood flow, and modulated gut-metabolite interactions by suppressing TNF-α, IL-6, and NF-κB activity-evidence of restored ovarian microcirculation and reduced cytokine-driven atresia [153]. Small RCTs (6-12 weeks, n = 60-100) mirrored these effects in humans, reporting improved ovulation, menstrual regularity, and pregnancy rates, particularly when moxibustion was combined with acupuncture or herbal therapy [154, 155]. These combined protocols also increased integrin αvβ3 and VEGF expression, improving uterine perfusion and endometrial receptivity. Such findings sug-

Table 4. Effects of non-herbal TCM modalities in diabetic infertility

TCM modality	TCM-based mechanism	Main anti-diabetic effect	Main anti-infertility effect	Study model/ population	Intervention component	Ref.
EAC	Modern technique without classical TCM basis	↓ BMI, ↓ fasting insulin, ↓ HOMA-IR; ↑ ISI; improved insulin sensitivity & glucose tolerance	Restored estrous cyclicity & ovarian morphology; ↓ LH, ↓ testosterone; ↑ E2, FSH, SHBG; ↑ ovulation & pregnancy	PCOS rats & women	Needling at ST29 (Guilai) & SP6 (Sanyinjiao)/(≈2-10 Hz)	[151, 194, 195]
Leech-Centipede granules	Breaks up blood stasis & opens collaterals; used for menstruation blocked by blood stasis, trauma bruising, & painful numbness in limbs	↓ Blood glucose; ↑ insulin & glucagon; antioxidant (↑ SOD, ↓ MDA); ↓ NF-κB/ICAM-1/LOX-1; endothelial protection	↑ EF; improved endothelial morphology & penile hemodynamics; endothelial protection	Diabetic rats with ED	*Hirudo* spp. (leech, whole dried body), *Scolopendra* spp. (centipede, whole dried body)	[156]
MAC	Elevates Qi; opens the collaterals & relaxes sinews; treats low back/leg pain; numbness; stiffness in joints; clears meridian blockages caused by cold-damp or blood-stasis	Improved insulin sensitivity; ↓ HOMA-IR, FBG, fasting & 2 h insulin; ↓ BMI & WHR; improved glucolipid metabolism; regulation of HPO axis; metabolic modulation; possible gut microbiota effects; neuroendocrine stress regulation	↑ Ovulation & pregnancy rates; improved menstrual regularity; ↓ LH, ↓ testosterone, ↓ LH/FSH; ↑ E2; improved endometrial thickness & ovarian histology; hormonal balancing compared to OCP; improved ovarian/endometrial environment	PCOS women	Needling at RN4 (Guanyuan), EX-CA1 (Zigong), ST29 (Guilai), ST36 (Zusanli), SP6 (Sanyinjiao), RN6 (Qihai), RN12 (Zhongwan), ST25 (Tianshu), KI3 (Taixi), KI6 (Zhaohai), LR3 (Taichong), SP10 (Xuehai), PC6 (Neiguan), DU20 (Baihui)	[196, 197]
MAC + moxibustion	Warm meridians; stimulate qi & blood flow; dispel cold & damp; relieve joint & low back pain, numbness; improve digestion; ease menstrual discomfort	↓ BMI; ↓ fasting insulin; improved insulin resistance; endocrine regulation	↑ Pregnancy & ovulation; ↓ miscarriage; ↓ LH, ↓ LH/FSH; ↓ Testosterone; generally mild AEs	PCOS women	Needling at RN4 (Guanyuan), EX-CA1 (Zigong), ST29 (Guilai), ST36 (Zusanli), SP6 (Sanyinjiao), RN6 (Qihai), RN12 (Zhongwan), ST25 (Tianshu), KI3 (Taixi), KI6 (Zhaohai), LR3 (Taichong), SP10 (Xuehai), PC6 (Neiguan), DU20 (Baihui), SP9 (Yinlingquan), GB26 (Daimai), SP3 (Taibai), Qihai, PiShu, ShenShu, TianShu, BL32 (Ciliao), BL20 (Pishu), BL23 (Shenshu)	[155]

Abbreviations: ↑, Increase; ↓, Decrease; EAC, electroacupuncture; MAC, manual acupuncture; ISI, insulin sensitivity index; AEs, adverse events; OCP, oral contraceptive pill; WHR, waist-to-hip ratio; 2h-PBG, 2-hour postprandial blood glucose; ICAM-1, intercellular adhesion molecule 1; LOX-1, lectin-like oxidized low-density lipoprotein receptor-1; SHBG, Sex hormone-binding globulin; RN, EX-CA, ST, SP, KI, LR, PC, DU, GB, BL: Standard WHO acupuncture meridian point prefixes (e.g., RN = Ren, ST = Stomach, SP = Spleen, KI = Kidney, LR = Liver, PC = Pericardium, DU = Governing vessel, GB = Gallbladder, BL = Bladder).

gest that moxibustion restores fertility by rebalancing ovarian and uterine vascular dynamics through coordinated anti-inflammatory and pro-angiogenic mechanisms, offering a simple, low-cost adjunct for metabolic infertility (**Tables 4** and S4).

Leech-Centipede granules

Leech-Centipede Granules (LCG), derived from *Hirudo* and *Scolopendra*, exhibit vasoprotective activity in diabetic ED, a key vascular cause of male infertility. In STZ-diabetic rats (4-6 weeks, oral), LCG upregulated eNOS-cGMP signaling, enhanced cavernosal blood flow, and reduced fibrosis [156]. Concomitant downregulation of LOX-1, PKCβ, TNF-α, and IL-6, along with lower collagen deposition, indicated integrated antioxidant and anti-inflammatory remodeling of the endothelium. These molecular and histological changes restore erectile capacity under hyperglycemic stress, identifying LCG as a mechanistically coherent but still preclinical candidate for vascular repair in diabetic infertility (**Tables 4** and S4).

Mind-body practices

Mind-body exercises such as Tai Chi and Qigong engage shared metabolic, vascular, and neuroendocrine pathways relevant to both diabetes and infertility.

A meta-analysis of RCTs in T2DM showed significant reductions in fasting glucose and HOMA-IR, confirming improvements in insulin signaling and glycemic regulation [157]. Another systematic review of RCTs in inflammatory conditions showed reduced C-reactive protein (CRP), IL-6, and TNF-α levels with enhanced antioxidant enzyme activity, suggesting systemic anti-inflammatory and redox stabilization [158]. Similarly, a meta-analysis of Tai Chi and Qigong in hypertension found increased nitric oxide and reduced ET-1, indicating endothelial repair and vascular relaxation [159]. Neuroendocrine trials support these mechanisms: a Tai Chi RCT in older women normalized cortisol and improved heart-rate variability, implying stabilization of HPG balance [160]. These physiological effects mirror PCOS pathology, where oxidative stress and gut dysbiosis impair steroidogenesis and ovulation [161, 162]. Consistently, a meta-analysis of mind-body interventions (mainly Tai Chi and Qigong) in women with PCOS showed reductions in BMI, testosterone, and insulin resistance, alongside improved quality-of-life scores [163]. In men, a single-arm study of 92 infertile participants found that a three-month Qigong program improved sperm concentration and motility, achieving a 27% spontaneous pregnancy rate - demonstrating direct reproductive benefit via metabolic and vascular repair [164].

Overall, Tai Chi and Qigong act as low-cost, non-pharmacologic interventions that enhance glycemic control, vascular homeostasis, and endocrine stability, highlighting their potential as adjunctive therapies for diabetic infertility.

Challenges of TCM in managing diabetic infertility

Despite promising evidence, translating this approach into standardized care for diabetic infertility faced several challenges. The first involves variability in quality and authenticity among multi-herb formulations. DNA-metabarcoding studies revealed species substitution and adulteration, while ongoing surveillance continues to identify heavy-metal and microbial contamination-issues that complicate dosage determination and reduce reproducibility [165]. Although the European Medicines Agency-Herbal Medicinal Products Committee (EMA-HMPC) guidelines specify standards for identity testing, chemical markers, and contaminant limits, their implementation remains inconsistent across regions and product categories [166]. The second challenge relates to the limited clinical evidence base (**Table 5**). Despite the Consolidated Standards of Reporting Trials for Chinese Herbal Medicine 2017 (CONSORT-CHM 2017) framework, RCTs involving herbal medicine and acupuncture continue to show heterogeneity in syndrome differentiation, small sample sizes, incomplete reporting, and inadequate blinding-factors that weaken effect estimates [167, 168]. A third concern involves herb-drug interactions, which present potential risks in diabetes management. For example, goldenseal reduced metformin exposure by approximately 25% in controlled trials, whereas berberine co-administration enhanced glycemic lowering. These findings highlighted both potential benefits and risks, emphasizing the need for prospective pharmacokinetic monitoring [169]. Safety and pharmacovigilance

Table 5. Summary of clinical studies evaluating TCM interventions for diabetic infertility

Intervention	Study type	Number	Population summary	Fertility endpoints
Berberine	5 RCTs + 1 prospective cohort	1,682	Women with PCOS ± IR	Pregnancy rate, ovulation rate, menstrual regularity, hormones, metabolic indices
Cinnamon supplements	RDBPCT	45	Women with PCOS	Menstrual cyclicity, ovulation rate
Tribulus terrestris	2 RDBPCTs	210	Men with mild to moderate ED	Sexual function (IIEF scores, satisfaction, desire)
Curcumin	3 RDBPCTs	192	Overweight/obese women with PCOS	Hormonal and metabolic indicators related to fertility (LH, LH/FSH, testosterone, IR)
Modified Yougui Pill	RCT	74	Women with PCOS	LH, LH/FSH, testosterone, E_2, menstrual and ovulatory function
Puerarin	RCT	51	Obese and non-obese women with PCOS	Menstrual regularity, testosterone, SHBG
Quercetin	RDBPCT	84	Women with PCOS	testosterone, LH, SHBG
Resveratrol	2 RCTs + 1 meta-analysis of 4 RCTs	300	Women with PCOS	Oocyte/embryo quality, pregnancy rate, sex hormones
Tanshinone	4 RCTs	≈ 220	Women with PCOS with hyperandrogenism or metabolic disorders	Testosterone, LH, ACTH, GH, ovulatory function
Bushen Quyu Huatan Decoction	RCT	148	Women with PCOS-related infertility	Pregnancy rate, ovulation rate, LH, LH/FSH, testosterone
Bushen Tiaochong Decoction	RCT	147	Obese women with PCOS	E_2, LH, FSH, LH/FSH, endometrial receptivity
BYHWD	RCT	70	Men with diabetic ED	IIEF-5, sexual and life quality
CFDT	6 RCTs	≈ 440	Women with PCOS or infertility	Pregnancy rate, ovulation rate, endometrial thickness, LH, FSH, testosterone
DXP	RCT	60	Women with PCOS	Ovulation rate, pregnancy rate, LH, testosterone
Xiao Yao San	Meta-analysis of 19 RCTs	1,588	Women with PCOS	Pregnancy rate, ovulation rate, LH/FSH, testosterone, E_2
DZSD	RCT	92	Women with PCOS	Pregnancy rate, ovulation rate, LH, FSH, E_2
FXJC + LDP	RCT	60	Men with T2DM-ED	IIEF-5, erectile function
FXJC	RCT	80	Men with T2DM-ED	IIEF-5, erectile hardness, satisfaction
HXTLQWD	RCT	66	Men with T2DM-ED	IIEF-5, erectile function
Kuntai Capsule	RDBPCT	100	Women with PCOS	LH, LH/FSH, testosterone, menstrual regularity
LDP + Xiaoyao San	Observational study	16	Women with PCOS	Ovulation rate, pregnancy rate, LH, LH/FSH, testosterone
QLST	2 RCTs	136	Men with T2DM-ED	IIEF-5, erectile function
STP	Meta-analysis of 12 RCTs	916	Pregnant women with URSA	Early pregnancy loss, live birth rate
Yougui Pill	RCT	42	Men with T2DM-ED	IIEF-5, erectile function
YSHXD	2 RCTs	200	Men with T2DM-ED	IIEF-5, EQS, erectile function
ZYP	3 RCTs	2,425	Women with infertility due to PCOS or decreased ovarian reserve, including IVF/IUI patients	Pregnancy rate, live birth, ovulation rate, implantation, LH, FSH, E_2, testosterone, ovarian and endometrial indices
ZYZY	2 RCTs	180	Men with T2DM-ED	IIEF-5, erectile function, sexual satisfaction
EAC	RCT	84	Women with PCOS	Testosterone, menstrual frequency
MAC	2 RCTs (sham-controlled)	170	Women with PCOS-related infertility	Pregnancy rate, ovulation rate, LH, FSH, testosterone, LH/FSH
MAC + moxibustion	Meta-analysis of 25 RCTs	1,991	Women with PCOS	Pregnancy rate, ovulation rate, miscarriage rate, sex hormones

Abbreviations: RDBPCT, Randomized Double-Blind Placebo-Controlled Trial; ACTH, Adrenocorticotropic Hormone; GH, Growth Hormone.

represent another key priority, especially among reproductive-age populations. Known toxicities such as aristolochic acid-induced nephropathy and urothelial cancer underscore the importance of validated sourcing and continuous post-marketing surveillance [170]. Finally, regulatory heterogeneity-ranging from the EU registration system to WHO-documented regional frameworks - continues to hinder international comparability and the integration of clinical trials [171, 172]. These barriers explain the scarcity of adequately powered studies specifically addressing diabetic infertility and highlight essential priorities: adopting pharmacopoeial-grade standardized products, designing CONSORT-compliant RCTs with core fertility outcomes, predefining herb-drug interaction monitoring, and implementing transparent multi-region pharmacovigilance systems.

Future opportunities: epigenetics, artificial intelligence (AI), and standardization

Emerging research provides new directions for advancing this field in diabetic infertility. Epigenetic studies in T2DM have revealed reproducible DNA methylation and chromatin patterns associated with insulin signaling and inflammation, offering mechanistic targets and potential biomarkers for future trials [173]. Human and animal data indicate that glycemic control mitigates oocyte-level epigenetic damage, whereas maternal diabetes induces heritable methylation changes that influence fertility outcomes [174]. At the endometrial level, epigenetic regulation of AGE-RAGE signaling and impaired embryo-endometrium communication highlightthe need for disease-specific reproductive endpoints in upcoming studies [40]. AI applications may accelerate these advances by integrating clinical, omics, and pharmacological data to identify bioactive compounds, optimize formulations, and improve product quality control. However, challenges such as inconsistent datasets, limited model interpretability, and the absence of prospective validation still restrict broader implementation [175]. Among emerging innovations, standardization offers the most immediate translational benefit. International frameworks - including ISO/TC 249, EMA/HMPC, and WHO regulatory guidelines - provide harmonized criteria for herbal identity, marker compounds, and contaminant thresholds. Aligning future research with these standards will facilitate multicenter collaboration and enhance consistency in reporting fertility outcomes such as ovulation, menstrual regularity, and pregnancy rates [172, 176].

Conclusion

This narrative review evaluated the therapeutic potential of TCM in managing diabetes-related infertility - a disorder characterized by intertwined metabolic, oxidative, inflammatory, and hormonal disturbances that impair the HPG axis and reproductive tissues. Evidence from preclinical and clinical studies indicates that interventions based on this system - including isolated compounds, multi-herb formulations, and non-herbal modalities such as acupuncture - enhance fertility by improving insulin sensitivity, reducing oxidative stress, regulating hormonal balance, and preserving mitochondrial and gonadal function (**Figure 3**). Clinical findings have shown improved sperm quality and sexual function in diabetic men, alongside enhanced ovulation and pregnancy rates in women with IR or PCOS. Among isolated compounds, berberine, resveratrol, and quercetin demonstrate consistent though preliminary human evidence, while most other agents remain supported mainly by preclinical data. Nevertheless, small sample sizes, heterogeneous formulations, and limited reporting of definitive endpoints-particularly live birth-restrict translational certainty. Safety concerns, including herb-drug interactions and variability in product quality, further emphasize the need for stringent regulatory and pharmacovigilance oversight. Future research should prioritize large, multicenter RCTs employing standardized formulations, validated products, core fertility outcomes, and structured safety monitoring. Integrating omics technologies and AI-based analytical approaches may further elucidate underlying mechanisms and support precision applications. Despite current limitations, TCM offers a scientifically grounded, holistic, and multi-target framework that complements conventional therapies and represents a promising direction for restoring fertility in diabetes.

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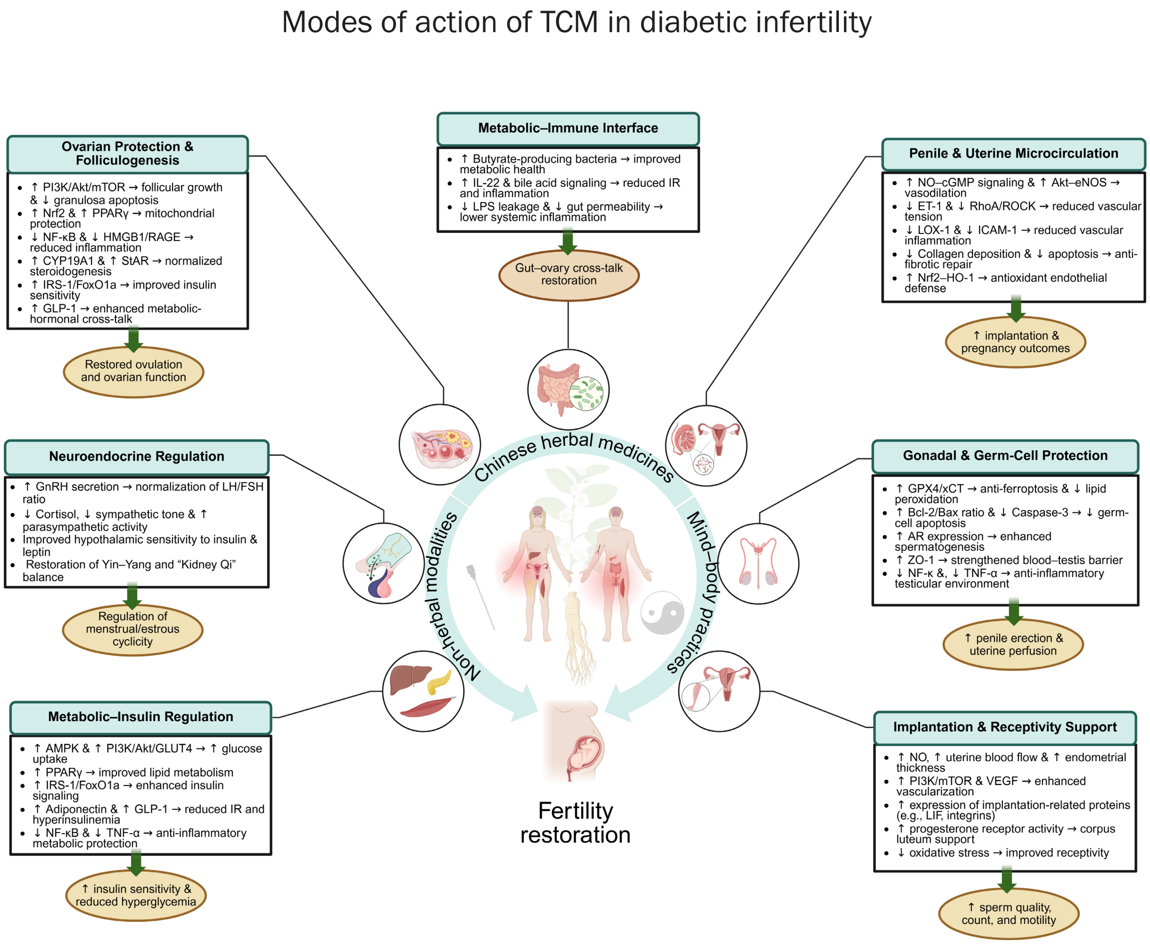

Figure 3. Integrated mechanistic framework of TCM restoring metabolic and reproductive balance in diabetic infertility. Diverse TCM modalities converge on shared metabolic, antioxidant, vascular, gonadal, and neuroendocrine pathways, collectively enhancing insulin sensitivity, alleviating oxidative and inflammatory stress, and restoring reproductive function.

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Disclosure of conflict of interest

None.

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References

[1] Magliano D, Boyko E and committee IDAtes. Global picture [Internet]. Place: International Diabetes Federation; 2021 Available from: https://www.ncbi.nlm.nih.gov/books/NBK581940.

[2] Agarwal A, Mulgund A, Hamada A and Chyatte MR. A unique view on male infertility around the globe. Reprod Biol Endocrinol 2015; 13: 37.

[3] Leslie S, Soon-Sutton T and Khan M. Male Infertility [Internet]. Place: StatPearls Publishing; 2024 Available from: https://www.ncbi.nlm.nih.gov/books/NBK562258.

[4] Fan C, Zhang J and Qiu D. Causal relationship between genetically predicted type 2 diabetes mellitus and male infertility. Front Endocrinol (Lausanne) 2024; 15: 1357279.

[5] Huang R, Chen J, Guo B, Jiang C and Sun W. Diabetes-induced male infertility: potential mechanisms and treatment options. Mol Med 2024; 30: 11.

[6] Wang SC, Wang SC, Li CJ, Lin CH, Huang HL, Tsai LM and Chang CH. The therapeutic effects of traditional chinese medicine for poor semen quality in infertile males. J Clin Med 2018; 7: 239.

[7] Qi YB, Yi P and Fu XH. Research progress on insulin resistance in polycystic ovary syndrome. Reprod Dev Med 2025; 9.

[8] Su P, Chen C and Sun Y. Physiopathology of polycystic ovary syndrome in endocrinology, metabolism and inflammation. J Ovarian Res 2025; 18: 34.

[9] Di Carlo C, Cimini C, Belda-Perez R, Valbonetti L, Bernabò N and Barboni B. Navigating the intersection of glycemic control and fertility: a network perspective. Int J Mol Sci 2024; 25: 9967.

[10] Wen S, Zhang H, Huang X, Wang C, Dong M, Wang C, Xu C, Yuan Y, Li Y, Zhou L and Yuan X. The therapeutic effect and mechanism of traditional chinese medicine in type 2 diabetes mellitus and its complications. Diabetes Metab Syndr Obes 2025; 18: 1599-1627.

[11] Ni Y, Wu X, Yao W, Zhang Y, Chen J and Ding X. Evidence of traditional Chinese medicine for treating type 2 diabetes mellitus: from molecular mechanisms to clinical efficacy. Pharm Biol 2024; 62: 592-606.

[12] Jiang X, Wang Y, Hua Y, Tang H and Li H. Mechanisms of traditional Chinese medicine regulating polycystic ovary syndrome through gut microbiota: a review. Front Endocrinol (Lausanne) 2025; 16: 1610869.

[13] Zhang L, Bao B, Wang X, Tong S, Wen H and Liu B. Acupuncture in the treatment of male infertility: a review. Integr Med Res Nephrol Androl 2024; 11: e23-00028.

[14] Huang Y, Lu J, Zhao Q, Chen J, Dong W, Lin M and Zheng H. Potential therapeutic mechanism of traditional chinese medicine on diabetes in rodents: a review from an NMR-based metabolomics perspective. Molecules 2022; 27: 5109.

[15] Wen Q, Xu H, Zou H, Wang P, Xing X, Chen Y, Zhu Q, Chen Y, Tan M, Zhang M, Pan T, Chen Y, Wang Y and Wu S. The effect of Chinese herbal medicine on male factor infertility: study protocol for a randomized controlled trial. Front Endocrinol (Lausanne) 2024; 15: 1418936.

[16] Zhang W, Tong L, Jin B and Sun D. Diabetic testicular dysfunction and spermatogenesis impairment: mechanisms and therapeutic prospects. Front Endocrinol (Lausanne) 2025; 16: 1653975.

[17] Estermann MA, Sheheen J, Grimm SA, Tezak B, Chen YY, Morita T, Yao HHC and Capel B. Glycogen metabolism in mouse embryonic Sertoli cells sustains the germ line through the lactate shuttle. bioRxiv 2025; [preprint]: doi:10.1101/2025.1107.1123.666216.

[18] Vahedi Raad M, Firouzabadi AM, Tofighi Niaki M, Henkel R and Fesahat F. The impact of mitochondrial impairments on sperm function and male fertility: a systematic review. Reprod Biol Endocrinol 2024; 22: 83.

[19] Nicholls PK, Harrison CA, Walton KL, McLachlan RI, O'Donnell L and Stanton PG. Hormonal regulation of sertoli cell micro-RNAs at spermiation. Endocrinology 2011; 152: 1670-1683.

[20] Senousy MA, Shaker OG, Gamal A, Aboraia NM and Ayeldeen G. Serum expression signature of TUG1, MALAT1, miR-483, and miR-141 and their targets TGF-β1 and STAT3 in severe male factor infertility. Sci Rep 2025; 15: 18529.

[21] Liu D, Qin Z, Yi B, Xie H, Liang Y, Zhu L, Yang K and Zhang H. Inflammatory cytokine profiles in erectile dysfunction: a bidirectional Mendelian randomization. Front Immunol 2024; 15: 1342658.

[22] Wang Y, Fu X and Li H. Mechanisms of oxidative stress-induced sperm dysfunction. Front Endocrinol (Lausanne) 2025; 16: 1520835.

[23] Fleming SD and Thomson LK. The oxidative stress of human sperm cryopreservation. Antioxidants (Basel) 2025; 14: 402.

[24] Kong X, Wang X, Xia Q, Hu Q, Yu W, Huang Q, Li J, Wang C, Lin Z, Liu Y, Qi Y, Tan X, Zheng B and Yu J. Unveiling the nexus between environmental exposures and testicular damages: revelations from autophagy and oxidative stress imbalance. Cell Death Discov 2025; 11: 258.

[25] Rahmani M, Tavalaee M, R Drevet J and Nasr-Esfahani MH. Role of endoplasmic reticulum stress in the male reproductive system. Cell J 2023; 25: 437-446.

[26] Hwang JY. Analysis of Ca(2+)-mediated sperm motility to evaluate the functional normality of the sperm-specific Ca(2+) channel, CatSper. Front Cell Dev Biol 2024; 12: 1284988.

[27] Akbari H, Elyasi L, Khaleghi AA and Mohammadi M. The effect of zinc supplementation on improving sperm parameters in infertile diabetic men. J Obstet Gynaecol India 2023; 73: 316-321.

[28] Zaimi M, Michalopoulou O, Stefanaki K, Kazakou P, Vasileiou V, Psaltopoulou T, Karagiannakis DS and Paschou SA. Gonadal dysfunction in women with diabetes mellitus. Endocrine 2024; 85: 461-472.

[29] Sridhar A, Khan D and Moffett RC. The impact of diabetes and obesity on fertility and the po-

tential role of gut hormones as treatment. Diabet Med 2023; 40: e15230.
[30] Mączka K, Stasiak O, Przybysz P, Grymowicz M and Smolarczyk R. The impact of the endocrine and immunological function of adipose tissue on reproduction in women with obesity. Int J Mol Sci 2024; 25: 9391.
[31] Lei R, Chen S and Li W. Advances in the study of the correlation between insulin resistance and infertility. Front Endocrinol (Lausanne) 2024; 15: 1288326.
[32] Rambaran N and Islam MS. Decoding androgen excess in polycystic ovary syndrome: roles of insulin resistance and other key intraovarian and systemic factors. World J Diabetes 2025; 16: 108789.
[33] Baculescu N, Radian S, Manda D, Serban CG, Niculescu DA, Gheorghiu ML, Grigorescu F and Poiana C. Stimulated hyperinsulinemia is independently associated with higher serum DHEAS in PCOS: a retrospective study. J Clin Med 2025; 14: 6246.
[34] Yang W, Wang L, Wang F and Yuan S. Roles of AMP-activated protein kinase (AMPK) in mammalian reproduction. Front Cell Dev Biol 2020; 8: 593005.
[35] Xiang J, Shen X, Zhang Y, Zhu Q, Yin H and Han S. MiR-223 inhibits proliferation and steroid hormone synthesis of ovarian granulosa cell via the AKT signaling pathway by targeting CRIM1 in chicken. Poult Sci 2024; 103: 103910.
[36] Moustakli E, Stavros S, Katopodis P, Skentou C, Potiris A, Panagopoulos P, Domali E, Arkoulis I, Karampitsakos T, Sarafi E, Michaelidis TM, Zachariou A and Zikopoulos A. Oxidative stress and the NLRP3 inflammasome: focus on female fertility and reproductive health. Cells 2025; 14: 36.
[37] Park JH, Park SA, Lee YJ, Joo NR, Shin J and Oh SM. TOPK inhibition accelerates oxidative stress-induced granulosa cell apoptosis via the p53/SIRT1 axis. Int J Mol Med 2020; 46: 1923-1937.
[38] Kaltsas A, Zikopoulos A, Moustakli E, Zachariou A, Tsirka G, Tsiampali C, Palapela N, Sofikitis N and Dimitriadis F. The silent threat to women's fertility: uncovering the devastating effects of oxidative stress. Antioxidants (Basel) 2023; 12: 1490.
[39] Sopasi F, Spyropoulou I, Kourti M, Vasileiadis S, Tripsianis G, Galazios G and Koutlaki N. Oxidative stress and female infertility: the role of follicular fluid soluble receptor of advanced glycation end-products (sRAGE) in women with endometriosis. Hum Fertil (Camb) 2023; 26: 1400-1407.
[40] Jackuliak P, Jankovský M, Kovářová M, Voller J, Feitscherová C and Varga I. Impact of hyperglycaemia on cellular microenvironment and function of endometrium and uterine tube: scoping review focused on infertility in diabetic women. Front Cell Dev Biol 2025; 13: 1582039.
[41] Zhu Y, Liu X, Xu Y and Lin Y. Hyperglycemia disturbs trophoblast functions and subsequently leads to failure of uterine spiral artery remodeling. Front Endocrinol (Lausanne) 2023; 14: 1060253.
[42] Brown HM, Green ES, Tan TCY, Gonzalez MB, Rumbold AR, Hull ML, Norman RJ, Packer NH, Robertson SA and Thompson JG. Periconception onset diabetes is associated with embryopathy and fetal growth retardation, reproductive tract hyperglycosylation and impaired immune adaptation to pregnancy. Sci Rep 2018; 8: 2114.
[43] Xie L, Huang D, Zha X, Wei C, Dong J, Zheng H, Xu Z, Wu J and Lai P. The role of circadian rhythm-related genes in type 2 diabetes from a multi-omics perspective. J Glob Health 2025; 15: 04227.
[44] Al-Shawabk M and Aljamal A. Effect of cinnamon administration on fertility of normal and diabetic male rats. Pak J Nutr 2019; 18: 491-495.
[45] AL-Khamas AJ. Effect of cinnamon zeylanicum bark water extract on male diabetic albino rats fertility. Basrah J Vet Res 2018; 17: 123-135.
[46] Kort DH and Lobo RA. Preliminary evidence that cinnamon improves menstrual cyclicity in women with polycystic ovary syndrome: a randomized controlled trial. Am J Obstet Gynecol 2014; 211: 487, e481-486.
[47] Kandeel WA, Farag SA, Ali HM and Ashry M. Hormonal, inflammatory modulatory and antioxidant effects of glycyrrhiza glabra l extract in polycystic ovary syndrome-modeled rats. Iran J Toxicol 2025; 19: 52-61.
[48] Gao Y, Mo S, Cao H, Zhi Y, Ma X, Huang Z, Li B, Wu J, Zhang K and Jin L. The efficacy and mechanism of Angelica sinensis (Oliv.) Diels root aqueous extract based on RNA sequencing and 16S rDNA sequencing in alleviating polycystic ovary syndrome. Phytomedicine 2023; 120: 155013.
[49] Tomás GDC. Male fertility and type 2 diabetes mellitus: effect of white tea [dissertation]. Place: Universidade da Beira Interior (Portugal); 2013.
[50] Nassiri M, Khaki A, Ahmadi-Ashtiani H, Rezazadeh S, Rastgar H and Gharachurlu S. Effects of ginger on spermatogenesis in streptozotocin-induced diabetic rat. J Med Plants 2009; 8: 118-124.
[51] Fallah Raoufi M, Mokhlesabadi Farahani T, Mousavi Sadr Jadidi ES and Moradi Gardeshi T. Protective effects of ginger extract on oxida-

tive stress and steroidogenesis-related genes in the ovary of streptozotocin -induced diabetic rats. Int J Med Lab 2023; 10: 254-263.
[52] Zhou J, Xi Y, Zhang J, Tang J, Zhou X, Chen J, Nie C, Zhu Z and Ma B. Protective effect of Dioscorea zingiberensis ethanol extract on the disruption of blood-testes barrier in high-fat diet/streptozotocin-induced diabetic mice by upregulating ZO-1 and Nrf2. Andrologia 2020; 52: e13508.
[53] Moshfegh F, Zafar Balanejad S, Shahrokhabady K and Attaranzadeh A. Investigating the effect of crocus sativus (Saffron) petal hydro-alcoholic extract on ovarian follicle, inflammatory markers, and antioxidant enzymes in mice model of polycystic ovary syndrome. J Reprod Infertil 2022; 23: 18-25.
[54] Hassan Z, Yam MF, Ahmad M and Yusof APM. Antidiabetic properties and mechanism of action of Gynura procumbens water extract in streptozotocin-induced diabetic rats. Molecules 2010; 15: 9008-9023.
[55] mat noor M and Radzuan N. Anti-hyperglycemic effect of gynura procumbens methanolic extract on fertility and libido of induced diabetic male rats. Sains Malaysiana 2012; 41: 1549-1556.
[56] Akmar K and mat noor M. Gynura procumbens leaf improves blood glucose level, restores fertility and libido of diabetic-induced male rats. Sains Malaysiana 2017; 46: 1471-1477.
[57] Fu H, Bai X, Le L, Tian D, Gao H, Qi LX and Hu KP. Eucommia ulmoides oliv. leaf extract improves erectile dysfunction in streptozotocin-induced diabetic rats by protecting endothelial function and ameliorating hypothalamic-pituitary-gonadal axis function. Evid Based Complement Alternat Med 2019; 2019: 1782953.
[58] Kamenov Z, Fileva S, Kalinov K and Jannini EA. Evaluation of the efficacy and safety of Tribulus terrestris in male sexual dysfunction-A prospective, randomized, double-blind, placebo-controlled clinical trial. Maturitas 2017; 99: 20-26.
[59] Santos CA Jr, Reis LO, Destro-Saade R, Luiza-Reis A and Fregonesi A. Tribulus terrestris versus placebo in the treatment of erectile dysfunction: a prospective, randomized, double blind study. Actas Urol Esp 2014; 38: 244-248.
[60] Ghanbari A, Moradi M, Raoofi A, Falahi M and Seydi S. Tribulus terrestris hydroalcoholic extract administration effects on reproductive parameters and serum level of glucose in diabetic male rats. Int J Morphol 2016; 34: 796-803.
[61] Zhang N, Liu X, Zhuang L, Liu X, Zhao H, Shan Y, Liu Z, Li F, Wang Y and Fang J. Berberine decreases insulin resistance in a PCOS rats by improving GLUT4: dual regulation of the PI3K/AKT and MAPK pathways. Regul Toxicol Pharmacol 2020; 110: 104544.
[62] An Y, Sun Z, Zhang Y, Liu B, Guan Y and Lu M. The use of berberine for women with polycystic ovary syndrome undergoing IVF treatment. Clin Endocrinol (Oxf) 2014; 80: 425-431.
[63] Wang L, Kong Y and Ren Y. Therapeutic effect of berberine combined with diformin for women with polycystic ovary syndrome and insulin resistance. J Zhejiang Chin Med Univ 2011; 35: 713-715.
[64] Li X, Kuang H, LUO Y and Chen Q. Clinical observation of berberine in intervening insulin resistance of polycystic ovary syndrome. J Guangzhou Univ Tradit Chin Med 2017; 172-177.
[65] Li H and Yu J. Effect of Berberine combined with letrozole on ovulation induction in women with PCOS. J Pract Obstet Gynaecol 2016; 3: 84-85.
[66] Wu XK, Wang YY, Liu JP, Liang RN, Xue HY, Ma HX, Shao XG and Ng EH; Reproductive and Developmental Network in Chinese Medicine. Randomized controlled trial of letrozole, berberine, or a combination for infertility in the polycystic ovary syndrome. Fertil Steril 2016; 106: 757-765, e751.
[67] Li L, Li C, Pan P, Chen X, Wu X, Ng EH and Yang D. A single arm pilot study of effects of berberine on the menstrual pattern, ovulation rate, hormonal and metabolic profiles in anovulatory chinese women with polycystic ovary syndrome. PLoS One 2015; 10: e0144072.
[68] Jamilian M, Foroozanfard F, Kavossian E, Aghadavod E, Shafabakhsh R, Hoseini A and Asemi Z. Effects of curcumin on body weight, glycemic control and serum lipids in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. Clin Nutr ESPEN 2020; 36: 128-133.
[69] Heshmati J, Golab F, Morvaridzadeh M, Potter E, Akbari-Fakhrabadi M, Farsi F, Tanbakooei S and Shidfar F. The effects of curcumin supplementation on oxidative stress, Sirtuin-1 and peroxisome proliferator activated receptor γ coactivator 1α gene expression in polycystic ovarian syndrome (PCOS) patients: a randomized placebo-controlled clinical trial. Diabetes Metab Syndr 2020; 14: 77-82.
[70] Liang A, Zhang W, Wang Q, Huang L, Zhang J, Ma D, Liu K, Li S, Chen X, Li S and Lei X. Resveratrol regulates insulin resistance to improve the glycolytic pathway by activating SIRT2 in PCOS granulosa cells. Front Nutr 2023; 9: 1019562.
[71] Liang A, Huang L, Liu H, He W, Lei X, Li M, Li S, Liang H, Chen G, Tang J, Chen F, Cao X, Wang Y, Shen X and Chen X. Resveratrol improves follicular development of PCOS rats by regulating

the glycolytic pathway. Mol Nutr Food Res 2021; 65: e2100457.
[72] Li W, Hu H, Zou G, Ma Z, Liu J and Li F. Therapeutic effects of puerarin on polycystic ovary syndrome: a randomized trial in Chinese women. Medicine (Baltimore) 2021; 100: e26049.
[73] Rezvan N, Moini A, Janani L, Mohammad K, Saedisomeolia A, Nourbakhsh M, Gorgani-Firuzjaee S, Mazaherioun M and Hosseinzadeh-Attar MJ. Effects of quercetin on adiponectin-mediated insulin sensitivity in polycystic ovary syndrome: a randomized placebo-controlled double-blind clinical trial. Horm Metab Res 2017; 49: 115-121.
[74] Jahan S, Abid A, Khalid S, Afsar T, Qurat Ul A, Shaheen G, Almajwal A and Razak S. Therapeutic potentials of quercetin in management of polycystic ovarian syndrome using letrozole induced rat model: a histological and a biochemical study. J Ovarian Res 2018; 11: 26.
[75] Su J, Xue H, Fan X and Cheng Y. Effect of tanshinone on glucose metabolism in patients with polycystic ovary syndrome. Med J Natl Def Forces Northwest China 2015; 36: 610-612.
[76] Wang M, Xue H and Zhong J. Effect of tanshinone pretreatment combined with ovulation induction therapy on pregnancy outcomes in patients with polycystic ovary syndrome and metabolic disorders. Chin Clin Res 2016; 29.
[77] Li H and Gou X. Antiapoptotic effects of panax notoginseng saponins on erectile function in diabetic rats with erectile dysfunction. J Chongqing Med Univ 2013; 38: 1325-1330.
[78] Yao X, Yuan Y, Jing T, Ye S, Wang S and Xia D. Ganoderma lucidum polysaccharide ameliorated diabetes mellitus-induced erectile dysfunction in rats by regulating fibrosis and the NOS/ERK/JNK pathway. Transl Androl Urol 2022; 11: 982-995.
[79] Zhang H, Tong WT, Zhang CR, Li JL, Meng H, Yang HG and Chen M. Gross saponin of Tribulus terrestris improves erectile dysfunction in type 2 diabetic rats by repairing the endothelial function of the penile corpus cavernosum. Diabetes Metab Syndr Obes 2019; 12: 1705-1716.
[80] Shi GJ, Zheng J, Wu J, Qiao HQ, Chang Q, Niu Y, Sun T, Li YX and Yu JQ. Beneficial effects of Lycium barbarum polysaccharide on spermatogenesis by improving antioxidant activity and inhibiting apoptosis in streptozotocin-induced diabetic male mice. Food Funct 2017; 8: 1215-1226.
[81] Lei X, Huo P, Wang Y, Xie Y, Shi Q, Tu H, Yao J, Mo Z and Zhang S. Lycium barbarum polysaccharides improve testicular spermatogenic function in streptozotocin-induced diabetic rats. Front Endocrinol (Lausanne) 2020; 11: 164.
[82] Lu CS, Wu CY, Wang YH, Hu QQ, Sun RY, Pan MJ, Lu XY, Zhu T, Luo S, Yang HJ, Wang D and Wang HW. The protective effects of icariin against testicular dysfunction in type 1 diabetic mice Via AMPK-mediated Nrf2 activation and NF-κB p65 inhibition. Phytomedicine 2024; 123: 155217.
[83] Nikbakht-Jam I, Khademi M, Nosrati M, Eslami S, Foroutan-Tanha M, Sahebkar A, Tavalaie S, Ghayour-Mobarhan M, Ferns GAA, Hadizadeh F, Tabassi SAS, Mohajeri SA and Emamian M. Effect of crocin extracted from saffron on pro-oxidant-anti-oxidant balance in subjects with metabolic syndrome: a randomized, placebo-controlled clinical trial. Eur J Integr Med 2016; 8: 307-312.
[84] Jiang YP, Yang JM, Ye RJ, Liu N, Zhang WJ, Ma L, Zheng P, Niu JG, Liu P and Yu JQ. Protective effects of betaine on diabetic induced disruption of the male mice blood-testis barrier by regulating oxidative stress-mediated p38 MAPK pathways. Biomed Pharmacother 2019; 120: 109474.
[85] Elham MN, Yasmin M, Mohammed M and Mohammed MS. Effect of crocin on letrozole-induced polycystic ovarian syndrome. Med J Cairo Univ 2019; 87: 5237-5243.
[86] Samie KA, Tabandeh MR and Afrough M. Betaine ameliorates impaired steroidogenesis and apoptosis in mice granulosa cells induced by high glucose concentration. Syst Biol Reprod Med 2020; 66: 400-409.
[87] Abnosi MH, Tabandeh MR and Mosavi-Aroo F. Corrigendum to: betaine ameliorates high glucose-induced oxidative stress in granulosa cells. Reprod Fertil Dev 2023; 35: 492.
[88] Tabandeh MR, Davoodi E, Bayati V and Dayer D. Betaine regulates steroidogenesis, endoplasmic reticulum stress response and Nrf2/HO-1 antioxidant pathways in mouse Leydig cells under hyperglycaemia condition. Arch Physiol Biochem 2024; 130: 768-778.
[89] Ren X, Wen Y, Yu L, Tian J and Lei A. Astragaloside IV relieves reproductive damage in diabetic female mice by inhibiting the apoptosis of follicular granulosa cells. Adv Vet Med 2021; 42: 65-71.
[90] Wen M, Chen W, Zhou Q and Dou X. Astragaloside IV regulates autophagy-mediated proliferation and apoptosis in a rat model of PCOS by activating the PPARγ pathway. Iran J Basic Med Sci 2022; 25: 882-889.
[91] Jiao N, Chen Y, Zhu Y, Wang W, Liu M, Ding W, Lv G, Lu J, Yu B and Xu H. Protective effects of catalpol on diabetes mellitus-induced male reproductive damage via suppression of the AGEs/RAGE/Nox4 signaling pathway. Life Sci 2020; 256: 116736.

[92] Ma Y, Hao G, Lin X, Zhao Z, Yang A, Cao Y, Zhang S, Fan L, Geng J, Zhang Y, Chen J, Song C, He M and Du H. Morroniside protects human granulosa cells against H(2)O(2)-induced oxidative damage by regulating the Nrf2 and MAPK signaling pathways. Evid Based Complement Alternat Med 2022; 2022: 8099724.
[93] Tang Z, Jiang W, Li X, Huang Q, Zhao H and Lai H. Protective effects of ginsenoside Rb1 on cyclophosphamide-induced premature ovarian failure in rats. Chin J Histochem Cytochem 2014; 23: 63-60.
[94] Zhou P, Pei WD, Sun YF, Yu Y and Jin D. The protective effect of ginsenoside Rg3 on oxidative stress injury induced by H_2O_2 in KGN cell. Tianjin Medical Journal 2021; 49: 920-916.
[95] Tang H, Li LX, Hua Y, Jiang XM, Zhang SW and Fu JR. Improvement effects of poria acid on insulin resistance in rats with polycystic ovary syndrome and its mechanism. China Pharm 2024; 35: 57-62.
[96] Li Y, Paine M and Zhu X. Clinical observation on yishen huoxue decoction combined with hypoglycemic therapy for type 2 diabetic erectile dysfunction. Liaoning J Tradit Chin Med 2011; 38: 2227-2228.
[97] Zhang L and Qiu R. Effect of yishen huoxue decoction combined with thioctic acid on serum of Hcy,NO,ET-1 and oxidative stress in patients with type 2 diabetes mellitus with erectile dysfunction. J Liaoning Univ Tradit Chin Med 2017; 19: 199-202.
[98] Cao Y, Cao A and Zhang X. Influence of Yiqi yangyin huoxue TCM on sex hormone level of type II diabetic erectile dysfunctional patients. Journal of Zhejiang Chinese Medical University 2011; 35: 152-151.
[99] Yang H, Yao L and Xu Z. The efficacy of buyang huanwu decoction on diabetic erectile dysfunction. Mod Chin Doctors 2021; 59: 130-133.
[100] Zhai X, Ge M and Zhao J. Clinical study of Yougui Pill in the treatment of diabetic erectile dysfunction with syndrome of deficiency of kidney yin and yang. Shanghai J Tradit Chin Med 2020; 54: 61-63.
[101] Zhai X, Tan M, Ge M, Wan Z and Xu D. Effect of Yougui Pill on oxidative stress of corpus cavernosum tissue in rats with diabetic erectile dysfunction. Acad J Shanghai Univ Tradit Chin Med 2022; 36: 227-231.
[102] Wang Y, Shi C, Yu W, Jiao W and Shi G. Efficacy of Yougui pill combined with Buzhong Yiqi decoction in alleviating the sexual dysfunction in female rats through modulation of the gut microbiota. Pharm Biol 2022; 60: 46-55.
[103] Guo JH. Effects of Qianlieshutong capsule combined with α-lipoic acid on serum homocysteine, nitric oxide and oxidative stress products in middle-aged and elderly patients with type 2 diabetes and erectile dysfunction. Chin J Gerontol 2016; 36: 4476-4478.
[104] Wang D, Zhang S, Jiang X, Lü X, Zhu T and Lin J. Mechanism of action of Yiyuanqiwu pills in treating diabetic erectile dysfunction in rats. Chin J Exp Tradit Med Form 2022; 28: 77-84.
[105] Shang J, Sheng W, Li X, Mu J, He X and Liu H. Effects of tianjing tongluo decoction and its disassembled formulae on sex hormones and the expression of penile cavernosa eNOS enzyme in diabetic rats with erectile dysfunction. Mod Tradit Chin Med Materia Med-World Sci Technol 2019; 21: 547-552.
[106] He G and Hao C. Effects of qianlieshutong capsule and α-lipoic acid on middle-aged and elderly patients with type 2 diabetes and erectile dysfunction. Chin Sexol 2018; 27: 28-31.
[107] Sun S, Wang J, Xu S, Zhou H, Li H, Zhou Y, Bao B, Deng S, Wang S and Wang B. Clinical observation on Huoxue Tongluo Qiwei decoction combined with low-dose tadalafil in the treatment of erectile dysfunction in diabetic patients with blood stasis and kidney deficiency. Shizhen Tradit Chin Med 2021; 32: 124-126.
[108] Li X, Feng JL, Chen ZL, Bao BH, Dai HH, Meng FC, Deng S, Wang B, Li HS and Wang JS. Mechanism by which Huoxue Tongluo Qiwei Decoction improves the erectile function of rats with diabetic erectile dysfunction. J Ethnopharmacol 2022; 283: 114674.
[109] Jiang C, Cao Z, Chen Q, Luo Y, Wang K, Xu L and Dai Y. Observation on the efficacy of Fufang Xuanju Capsule combined with tadalafil in the treatment of diabetic erectile dysfunction. J Bengbu Med Coll 2016; 41: 1323-1325.
[110] You C, Wu Q, Wang X and Yang X. Effects of Fufang Xuanju Capsule on AGEs and Ang II in patients with type 2 diabetic erectile dysfunction and its clinical efficacy. Chin Sexol 2017; 26: 93-96.
[111] Yue Z, Ma W, Qin M, Liu B, Ke M and Wang C. Mechanism of bushen huoxue recipe in treating diabetic erectile dysfunction in rats. J Beijing Univ Tradit Chin Med 2015; 38: 462-466.
[112] Wang JS, Feng JL, Dai HH, Chen ZL, Li X, Bao BH, Deng S, Meng FC, Zhao Q, Xu HS, Wang B and Li HS. Potential mechanism of achyranthis bidentatae radix plus semen vaccariae granules in the treatment of diabetes mellitus-induced erectile dysfunction in rats utilizing combined experimental model and network pharmacology. Pharm Biol 2021; 59: 545-554.
[113] Wu Q, You C and Dai N. Clinical curative effect observation of Ziyin Zhuangyang capluse in treating type 2 diabetic erectile dysfunction. Clin J Tradit Chin Med 2015; 27: 1601-1604.

[114] Yang H and Dai N. Clinical observation of shisanwei Ziyin Zhuangyang capsule combined sildenafi l in treating diabetic erectile dysfunction (yin and yang defi ciency syndrome). Clin J Tradit Chin Med 2017; 29: 248-250.
[115] Ding CF, Wang CY, Yang X, Zheng RH, Yan ZZ and Chen WQ. Effect of modified cangfu daotan decoction in improving endometrial receptivity in infertility patients with polycystic ovarian syndrome. Zhongguo Zhong Xi Yi Jie He Za Zhi 2014; 34: 1297-1301.
[116] Wan J. Effect of Cangfu daotan decoction on hormone level and lipid metabolism in patients with obese polycystic ovary syndrome. Shaanxi J Tradit Chin Med 2017; 38: 219-221.
[117] Wei I, Hua Y, Zhang Y and Zhang X. Effect of cangfu Daotan decoction combined with western medicine on sex hormone and insulin resistance in patients with polycystic ovary syndrome. World J Integr Chin West Med 2020; 165: 15124-15127.
[118] Liu M, Zhu H, Zhu Y and Hu X. Guizhi Fuling Wan reduces autophagy of granulosa cell in rats with polycystic ovary syndrome via restoring the PI3K/AKT/mTOR signaling pathway. J Ethnopharmacol 2021; 270: 113821.
[119] Zhu Y, Li Y, Liu M, Hu X and Zhu H. Guizhi Fuling Wan, Chinese herbal medicine, ameliorates insulin sensitivity in PCOS model rats with insulin resistance via remodeling intestinal homeostasis. Front Endocrinol (Lausanne) 2020; 11: 575.
[120] Qiu Z, Dong J, Xue C, Li X, Liu K, Liu B, Cheng J and Huang F. Liuwei Dihuang Pills alleviate the polycystic ovary syndrome with improved insulin sensitivity through PI3K/Akt signaling pathway. J Ethnopharmacol 2020; 250: 111965.
[121] Yan X, Ma SG, Lei Q and He TT. Effects of liuwei dihuang pills on endocrine metabolism in rats with polycystic ovary syndrome by inhibiting TGF-β1/SMAD signal pathway. Drug Eval Res 2022; 45: 2494-2500.
[122] Chen Y, Song S, Shu A, Liu L, Jiang J, Jiang M, Wu Q, Xu H and Sun J. The herb pair radix rehmanniae and cornus officinalis attenuated testicular damage in mice with diabetes mellitus through butyric acid/glucagon-like peptide-1/glucagon-like peptide-1 receptor pathway mediated by gut microbiota. Front Microbiol 2022; 13: 831881.
[123] Li CY. 16 cases of polycystic ovary syndrome treated with Liuwei Dihuang Wan combined with Xiaoyao Powder. Chinese Medicine Modern Distance Education of China 2015; 13: 33-34.
[124] Liang R, Liu Z, Li P, Fan P, Xu L, Sun X, Peng J, Peng X and Zhang M. Kuntai capsules improve glucolipid metabolism in patients with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. Medicine (Baltimore) 2019; 98: e16788.
[125] Mo Z, Li S and Chen Y. Effects of bushen quyu huatan decoction on ovarian function and pregnancy outcomes in patients with polycystic ovary-induced infertility. Chin J Tradit Chin Med 2019; 37: 2768-2771.
[126] Ma R, Wang X and Zhu X. Clinical efficacy of Bushen Tiaochong decoction in obesity patients with polycystic ovary syndrome and effect on endometrial receptivity. Chin J Exp Tradit Med Formulae 2018; 24: 188-192.
[127] Wang Y, Xiao H, Liu Y, Tong Q, Yu Y, Qi B, Bu X, Pan T and Xing Y. Effects of Bu Shen Hua Zhuo formula on the LPS/TLR4 pathway and gut microbiota in rats with letrozole-induced polycystic ovary syndrome. Front Endocrinol (Lausanne) 2022; 13: 891297.
[128] Zhang YY, Ma JX, Zhu YT, Wang YX, Chen WQ, Sun X, Zhang W, Wang CY and Ding CF. Investigation of the mechanisms and experimental verification of Cuscuta-Salvia in the treatment of polycystic ovary syndrome (PCOS) via network pharmacology. J Ovarian Res 2022; 15: 40.
[129] Wei M, Hu T, Qi T and Yi Y. TCM combined with low radiation terahertz waves in the treatment of polycystic ovarian syndrome patients: effects on plasma myocardial nutrient-1. J Radiat Res Appl Sci 2024; 17: 101067.
[130] Zhou X, Ma Q, Yan Z, Wang Y, Qin J, Tong T, Liang R, Li Y, Wang Y and Chen J. Efficacy and safety of Chinese patent medicine Xiao Yao San in polycystic ovary syndrome: a systematic review and meta-analysis. J Ethnopharmacol 2023; 313: 116517.
[131] Liu Y and Mao LH. Effect of danzhi xiaoyao pill on ovulation induction of polycystic ovarian syndrome patients of pathogenic fire derived from stagnation of gan-qi. Zhongguo Zhong Xi Yi Jie He Za Zhi 2013; 33: 1191-1195.
[132] Ma X, Cui H and Zhang F. Effects of Zishen Yutai Pills on ovarian reserve function and pregnancy outcomes in infertile patients. Shaanxi Tradit Chin Med 2019; 40: 198-200.
[133] Chen X and Yang D. Effect of Zishen Yutai Pills versus placebo in improving live birth rates in women undergoing fresh embryo transfer cycles: a randomized controlled clinical trial. Chin J Reprod Contracept 2022; 42: 1065-1074.
[134] Li Y, Wang Y and Xu D. Analysis of the efficacy of Zishen Yutai Pills on patients with polycystic ovary syndrome and infertility and its effect on hormone levels. Contemporary Medicine 2019; 25: 48-50.
[135] Li HF, Shen QH, Li XQ, Feng ZF, Chen WM, Qian JH, Shen L, Yu LY and Yang Y. The efficacy of

traditional chinese medicine shoutai pill combined with western medicine in the first trimester of pregnancy in women with unexplained recurrent spontaneous abortion: a systematic review and meta-analysis. Biomed Res Int 2020; 2020: 7495161.
[136] Zheng X, Hua Z and Ding C. Effects of modified Cangfu Daotan Decoction on reproductive endocrine function and glucose metabolism in patients with phlegm-dampness type polycystic ovary syndrome complicated with insulin resistance. Zhejiang J Integr Tradit Chin West Med 2013; 23: 88-91.
[137] Li X, Yang Q and Wang Q. Effects of Cangfu Daotan decoction combined with clomiphene on serum hormone level and endometri-al receptivity in patients with polycystic ovary syndrome combined with infertility. China Pharm 2017; 3698-3701.
[138] Yang D and Xia Y. 29 cases of late menstruation caused by hyperinsulinemia due to kidney deficiency and phlegm-dampness type treated with modified Cangfu Daotan Decoction. Shandong J Tradit Chin Med 2015; 34: 186-185.
[139] Wu J, Pan Y, Lu Y, Qian J, Zhang J, Xue Y, Xiao C, Qiu Y, Xie M and Li S. Exploring the mechanisms of Chaige Kangyi Recipe in treating recurrent pregnancy loss with insulin resistance. Sci Rep 2025; 15: 13866.
[140] Cao S, Renzeng CD, Li YP, Wu P, Tong L and Bao TY. Effects of Wuzi Yanzong recipe and its disassembled formulae on apoptosis of spermatogenic cell and NO cGMP pathway in diabetic rats with erectile dysfunction. Chin High Alt Med Biol 2018; 39: 112-117.
[141] Ma N, Zhao HX, Chen Q, You X, Ma QY, Yang SQ, Yuan D and Zhang CC. Protective effect of Wuzi Yanzong recipe on testicular DNA oxidative damage in natural ageing rats. Zhongguo Zhong Yao Za Zhi 2018; 43: 2985-2990.
[142] Zhao H, Ma N, Liu Z, Wang T, Yuan C, He Y, Dun Y, Zhou Z, Yuan D and Zhang C. Protective effect of Wuzi Yanzong recipe on testicular dysfunction through inhibition of germ cell apoptosis in ageing rats via endoplasmic reticulum stress. Andrologia 2019; 51: e13181.
[143] Fu X, Jing Y, Yang R, Zhu C, Tu Y, Hu Z, Sheng W, Jiao Q, Liu L, Zhang W and He Q. Guhan Yangsheng Jing mitigates oxidative stress and ferroptosis to improve reproductive damage in diabetic male rats. J Ethnopharmacol 2025; 347: 119746.
[144] Alrefaei GI, Almohaimeed HM, Algaidi SA, Almuhayawi MS, AbdAllah FM, Al-Abbas NS and Ayuob N. Cinnamon and ginger extracts attenuate diabetes-induced inflammatory testicular injury in rats and modulating SIRT1 expression. J Mens Health 2023; 19: 22-32.
[145] Khaki A, Khaki AA, Hajhosseini L, Golzar FS and Ainehchi N. The anti-oxidant effects of ginger and cinnamon on spermatogenesis dysfunction of diabetes rats. Afr J Tradit Complement Altern Med 2014; 11: 1-8.
[146] Duan F and Zeng K. 30 cases of phlegm-dampness polycystic ovary syndrome treated with thunder-fire moxibustion combined with acupuncture. Hunan J Tradit Chin Med 2015; 31: 78-79.
[147] Manneras L, Cajander S, Lönn M and Stener-Victorin E. Acupuncture and exercise restore adipose tissue expression of sympathetic markers and improve ovarian morphology in rats with dihydrotestosterone-induced PCOS. Am J Physiol Regul Integr Comp Physiol 2009; 296: R1124-R1131.
[148] Maliqueo M, Benrick A, Alvi A, Johansson J, Sun M, Labrie F, Ohlsson C and Stener-Victorin E. Circulating gonadotropins and ovarian adiponectin system are modulated by acupuncture independently of sex steroid or β-adrenergic action in a female hyperandrogenic rat model of polycystic ovary syndrome. Mol Cell Endocrinol 2015; 412: 159-169.
[149] Muharam R, Srilestari A, Mihardja H, Callestya LJ and Harzif AK. Combination of electroacupuncture and pharmacological treatment improves insulin resistance in women with polycystic ovary syndrome: double-blind randomized clinical trial. Int J Reprod Biomed 2022; 20: 289.
[150] Zheng YH, Wang XH, Lai MH, Yao H, Liu H and Ma HX. Effectiveness of abdominal acupuncture for patients with obesity-type polycystic ovary syndrome: a randomized controlled trial. J Altern Complement Med 2013; 19: 740-745.
[151] Feng Y, Johansson J, Shao R, Mannerås L, Fernandez-Rodriguez J, Billig H and Stener-Victorin E. Hypothalamic neuroendocrine functions in rats with dihydrotestosterone-induced polycystic ovary syndrome: effects of low-frequency electro-acupuncture. PLoS One 2009; 4: e6638.
[152] Wu T, Xu G, Hong X, Fan H, Zeng J, Liu Y, Hu J, Liang F, Yang J and Chen J. Acupuncture for hormonal readiness and gut microbiota in obese polycystic ovary syndrome: an open-label, randomized controlled trial. Front Endocrinol (Lausanne) 2024; 15: 1509152.
[153] Lin Y, Zeng H, Lin J, Peng Y, Que X, Wang L, Chen L and Bai N. Evaluating the therapeutic potential of moxibustion on polycystic ovary syndrome: a rat model study on gut microbiota and metabolite interaction. Front Cell Infect Microbiol 2024; 14: 1328741.
[154] Li K, Gao K, Ma Y and Yuyan W. Comparative observation on the efficacy of umbilical moxibustion with herbs and oral clomiphene on

ovulation in patients with polycystic ovary syndrome. J Clin Acupunct 2016; 32: 50-52.
[155] Li P, Peng J, Ding Z, Zhou X and Liang R. Effects of acupuncture combined with moxibustion on reproductive and metabolic outcomes in patients with polycystic ovary syndrome: a systematic review and meta-analysis. Evid Based Complement Alternat Med 2022; 2022: 3616036.
[156] Wang JS, Li X, Chen ZL, Feng JL, Bao BH, Deng S, Dai HH, Meng FC, Wang B and Li HS. Effect of leech-centipede medicine on improving erectile function in DIED rats via PKC signalling pathway-related molecules. J Ethnopharmacol 2021; 267: 113463.
[157] Sun Y, Li Q and Xue W. The effect of Tai Chi on glycemic control in type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. Front Endocrinol (Lausanne) 2025; 16: 1605253.
[158] Shu C, Feng S, Cui Q, Cheng S and Wang Y. Impact of Tai Chi on CRP, TNF-alpha and IL-6 in inflammation: a systematic review and meta-analysis. Ann Palliat Med 2021; 10: 7468-7478.
[159] Liu D, Yi L, Sheng M, Wang G and Zou Y. The efficacy of Tai Chi and Qigong exercises on blood pressure and blood levels of nitric oxide and endothelin-1 in patients with essential hypertension: a systematic review and meta-analysis of randomized controlled trials. Evid Based Complement Alternat Med 2020; 2020: 3267971.
[160] Campo RA, Light KC, O'Connor K, Nakamura Y, Lipschitz D, LaStayo PC, Pappas LM, Boucher KM, Irwin MR, Hill HR, Martins TB, Agarwal N and Kinney AY. Blood pressure, salivary cortisol, and inflammatory cytokine outcomes in senior female cancer survivors enrolled in a tai chi chih randomized controlled trial. J Cancer Surviv 2015; 9: 115-125.
[161] Yan H, Wang L, Zhang G, Li N, Zhao Y, Liu J, Jiang M, Du X, Zeng Q, Xiong D, He L, Zhou Z, Luo M and Liu W. Oxidative stress and energy metabolism abnormalities in polycystic ovary syndrome: from mechanisms to therapeutic strategies. Reprod Biol Endocrinol 2024; 22: 159.
[162] Huang F, Deng Y, Zhou M, Tang R, Zhang P and Chen R. Fecal microbiota transplantation from patients with polycystic ovary syndrome induces metabolic disorders and ovarian dysfunction in germ-free mice. BMC Microbiol 2024; 24: 364.
[163] Zhao K, Nie L, Ye X and Hu X. Effects of mind-body interventions on polycystic ovary syndrome: a comprehensive meta-analysis. J Ovarian Res 2024; 17: 154.
[164] Guo X. Qigong treatment of 92 cases of male infertility. China Naturopathy 2012; 20: 21-22.
[165] Zhou S, Zhou T, Zhang Y, Yang B, Niu J, Li W, Weitu Y, Long F, Liu Z and Zhou J. DNA metabarcoding unveils authenticity and adulteration in commercial Chinese polyherbal preparations: Renshen Jianpi Wan as a critical case study. Front Pharmacol 2025; 16: 1584065.
[166] (EMA) EMA. EMA/HMPC Guideline on quality of herbal medicinal products and traditional herbal medicinal products (Rev.3). Place: Government Agency; 2022. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/final-guideline-quality-herbal-medicinal-productstraditional-herbal-medicinal-products-revision-3_en.pdf.
[167] Cheng CW, Wu TX, Shang HC, Li YP, Altman DG, Moher D and Bian ZX; CONSORT-CHM Formulas 2017 Group. CONSORT extension for Chinese herbal medicine formulas 2017: recommendations, explanation, and elaboration. Ann Intern Med 2017; 167: 112-121.
[168] Liu T, Jiang L, Li S, Cheng S, Zhuang R, Xiong Z, Sun C, Liu B, Zhang H and Yan S. The blinding status and characteristics in acupuncture clinical trials: a systematic reviews and meta-analysis. Syst Rev 2024; 13: 302.
[169] Wang J, Bi C, Xi H and Wei F. Effects of administering berberine alone or in combination on type 2 diabetes mellitus: a systematic review and meta-analysis. Front Pharmacol 2024; 15: 1455534.
[170] Zhou Q, Jiang L, Su T, Liu G and Yang L. Overview of aristolochic acid nephropathy: an update. Kidney Res Clin Pract 2023; 42: 579-590.
[171] Commission EMAEE. Herbal medicinal products in the EU: legal framework and Traditional Herbal Medicinal Products registration (Directive 2004/24/EC). Place: Government Agency; 2025. Available from: https://www.ema.europa.eu/en/human-regulatory-overview/herbal-medicinal-products?utm.
[172] (WHO) WHO. WHO Global Report on Traditional and Complementary Medicine 2019. Place: Organization WH; 2019. Available from: https://www.who.int/publications/i/item/978924151536.
[173] Nadiger N, Veed JK, Chinya Nataraj P and Mukhopadhyay A. DNA methylation and type 2 diabetes: a systematic review. Clin Epigenetics 2024; 16: 67.
[174] Guo HY, Tang SB, Li LJ, Lin J, Zhang TT, Chao S, Jin XW, Xu KP, Su XF, Yin S, Zhao MH, Huang GA, Yang LJ, Shen W, Zhang L, Zhang CL, Sun QY and Ge ZJ. Gestational diabetes mellitus causes genome hyper-methylation of oocyte via increased EZH2. Nat Commun 2025; 16: 127.

[175] Li Y, Liu X, Zhou J, Li F, Wang Y and Liu Q. Artificial intelligence in traditional Chinese medicine: advances in multi-metabolite multi-target interaction modeling. Front Pharmacol 2025; 16: 1541509.
[176] (ISO) IOfS. ISO/TC 249 - Traditional medicine: committee scope and standards. Place: Standardization IOf; 2025. Available from: https://www.iso.org/committee/598435.html.
[177] Yin C, Zhang T and Li T. Betaine ameliorated placental dysfunction in polycystic ovary syndrome through attenuating oxidative stress and cell apoptosis. Maturitas 2025; 199.
[178] Zhao J, Tan Y, Feng Z, Zhou Y, Wang F, Zhou G, Yan J and Nie X. Catalpol attenuates polycystic ovarian syndrome by regulating sirtuin 1 mediated NF-κB signaling pathway. Reprod Biol 2022; 22: 100671.
[179] Yan J, Deng D, Wu Y, Wu K, Qu J and Li F. Catalpol protects rat ovarian granulosa cells against oxidative stress and apoptosis through modulating the PI3K/Akt/mTOR signaling pathway. Biosci Rep 2020; 40: BSR20194032.
[180] Khorasani MK, Ahangarpour A and Khorsandi L. Effects of crocin and metformin on methylglyoxal-induced reproductive system dysfunction in diabetic male mice. Clin Exp Reprod Med 2021; 48: 221-228.
[181] Roshankhah S, Jalili C and Salahshoor MR. Effects of crocin on sperm parameters and seminiferous tubules in diabetic rats. Adv Biomed Res 2019; 8: 4.
[182] Huang Y, Li W, Wang CC, Wu X and Zheng J. Cryptotanshinone reverses ovarian insulin resistance in mice through activation of insulin signaling and the regulation of glucose transporters and hormone synthesizing enzymes. Fertil Steril 2014; 102: 589-596, e584.
[183] Yang Y, Yang L, Qi C, Hu G, Wang L, Sun Z and Ni X. Cryptotanshinone alleviates polycystic ovary syndrome in rats by regulating the HMGB1/TLR4/NF-κB signaling pathway. Mol Med Rep 2020; 22: 3851-3861.
[184] Sohaei S, Amani R, Tarrahi MJ and Ghasemi-Tehrani H. The effects of curcumin supplementation on glycemic status, lipid profile and hs-CRP levels in overweight/obese women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled clinical trial. Complement Ther Med 2019; 47: 102201.
[185] Lei X, Huo P, Xie YJ, Wang Y, Liu G, Tu H, Shi Q, Mo ZC and Zhang S. Dendrobium nobile Lindl polysaccharides improve testicular spermatogenic function in streptozotocin-induced diabetic rats. Mol Reprod Dev 2022; 89: 202-213.
[186] Banaszewska B, Wrotyńska-Barczyńska J, Spaczynski RZ, Pawelczyk L and Duleba AJ. Effects of resveratrol on polycystic ovary syndrome: a double-blind, randomized, placebo-controlled trial. J Clin Endocrinol Metab 2016; 101: 4322-4328.
[187] Ortega I, Villanueva JA, Wong DH, Cress AB, Sokalska A, Stanley SD and Duleba AJ. Resveratrol reduces steroidogenesis in rat ovarian theca-interstitial cells: the role of inhibition of Akt/PKB signaling pathway. Endocrinology 2012; 153: 4019-4029.
[188] Ardehjani NA, Agha-Hosseini M, Nashtaei MS, Khodarahmian M, Shabani M, Jabarpour M, Fereidouni F, Rastegar T and Amidi F. Resveratrol ameliorates mitochondrial biogenesis and reproductive outcomes in women with polycystic ovary syndrome undergoing assisted reproduction: a randomized, triple-blind, placebo-controlled clinical trial. J Ovarian Res 2024; 17: 143.
[189] Ali Fadlalmola H, Elhusein AM, Al-Sayaghi KM, Albadrani MS, Swamy DV, Mamanao DM, El-Amin EI, Ibrahim SE and Abbas SM. Efficacy of resveratrol in women with polycystic ovary syndrome: a systematic review and meta-analysis of randomized clinical trials. Pan Afr Med J 2023; 44: 134.
[190] Zhang J, Xue H, Su J, Zuo Y, Fan X and Cheng Y. Clinical observation on the effect of tanshinone in the treatment of polycystic ovary syndrome with hyperandrogenism. Guangxi Med 2015; 37: 767-769.
[191] Wu M, Liu N and Han L. Effects of tanshinone capsules on lipid metabolism and hypothalamic-pituitary-adrenal axis in patients with polycystic ovary syndrome. Shandong Pharm 2016; 56: 96-94.
[192] Xu W, Tang M, Wang J and Wang L. Identification of the active constituents and significant pathways of Cangfu Daotan decoction for the treatment of PCOS based on network pharmacology. Evid Based Complement Alternat Med 2020; 2020: 4086864.
[193] Xu B, Li M, Chen C and Luo Y. Effects of tcm periodic therapy on sex hormone, glucose and lipid metabolism of patients with polycystic ovary syndrome. Chin J Inf Tradit Chin Med 2016; 35-38.
[194] Jedel E, Labrie F, Odén A, Holm G, Nilsson L, Janson PO, Lind AK, Ohlsson C and Stener-Victorin E. Impact of electro-acupuncture and physical exercise on hyperandrogenism and oligo/amenorrhea in women with polycystic ovary syndrome: a randomized controlled trial. Am J Physiol Endocrinol Metab 2011; 300: E37-E45.
[195] Feng Y, Johansson J, Shao R, Mannerås-Holm L, Billig H and Stener-Victorin E. Electrical and manual acupuncture stimulation affect oestrous cyclicity and neuroendocrine function in an 5α-dihydrotestosterone-induced rat poly-

cystic ovary syndrome model. Exp Physiol 2012; 97: 651-662.
[196] Pan W, Li FX, Wang Q, Huang ZQ, Yan YM, Zhao L and Shen XY. A randomized sham-controlled trial of manual acupuncture for infertile women with polycystic ovary syndrome. Integr Med Res 2022; 11: 100830.
[197] Pastore LM, Williams CD, Jenkins J and Patrie JT. True and sham acupuncture produced similar frequency of ovulation and improved LH to FSH ratios in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2011; 96: 3143-3150.

Table S1. Details of studies on individual herbal agents for diabetic infertility

Author/year	Study design	Population/model	Intervention		Sample size	Main anti-diabetic (metabolic) effect	Main anti-infertility (reproductive) effect
			Test (dose, route, duration)	Control			
Al-Shawabkeh, 2019	*In vivo*	Adult male Wistar rats with alloxan-induced diabetes	Cinnamon bark powder (80 mg/kg/d, oral, 4 wks)	Distilled water	40	↓ Blood glucose, ↑ antioxidant activity	↑ Testosterone, sperm motility & morphology; restored fertility in diabetic rats
Al-Khamas AJH, 2018	*In vivo*	Adult male albino rats with alloxan-induced diabetes	*Cinnamomum zeylanicum* bark water extract (500 mg/kg/d, oral, 6 wks)	Vehicle or untreated	24	↓ Blood glucose; ↑ pancreatic/hepatic antioxidant activity	↑ Testosterone; improved spermatogenesis & testicular histology; preserved seminiferous tubules; ↑ fertility
Kort, 2014	RDBPCT	Women with PCOS	Cinnamon powder (1.5 g/d, oral, 6 mo)	Placebo	45	No significant change in insulin resistance or serum androgens	Improved menstrual cyclicity & ovulatory function
Fu, 2019	*In vivo*	Male Sprague-Dawley rats with STZ-induced diabetes	*Eucommia ulmoides* leaf extract (180-730 mg/kg/d, oral, 16 wks)	Untreated	65	↑ Glucose tolerance and insulin sensitivity; ↓ oxidative stress	Restored HPG axis; ↑ GnRH, FSH, LH, testosterone; improved EF via NO-cGMP/Akt-eNOS pathways
Gao, 2023	*In vivo*	Female rats with HFD + letrozole-induced PCOS	*Angelica sinensis* extract (2-8 g/kg/d, oral, 4 wks)	Untreated	NR	↓ Insulin resistance; ↑ glucose-lipid metabolism	Restored estrous cycle; ↑ ovarian morphology; modulated gut microbiota
Nassiri, 2009	*In vivo*	Male Wistar rats with STZ-induced diabetes	*Zingiber officinale* extract (100 mg/kg/d, oral, 4 wks)	Untreated	40	↑ Antioxidant capacity; ↓ lipid peroxidation	↑ Sperm viability & motility
Fallah Raoufi, 2023	*In vivo*	Female rats with STZ-induced diabetes	*Zingiber officinale* extract (200-400 mg/kg/d, oral, 8 wks)	Untreated	NR	↓ Glucose; ↑ insulin, ↑ antioxidant enzymes (↓ MDA, ↑ GPx)	↑ Steroidogenic genes (StAR, 3β-HSD); normalized E_2, P_4, ↓ testosterone; protected ovarian tissue
Hassan, 2010	*In vivo* & *In vitro*	Male rats with STZ-induced diabetes	*Gynura procumbens* leaf extract (500 or 1000 mg/kg/d, oral, 14 d)	Untreated	20	↓ Fasting glucose; ↑ glucose tolerance and peripheral uptake; no β-cell change	NR
Mat Noor, 2012	*In vivo*	Male rats with STZ-induced diabetes	*Gynura procumbens* methanolic extract (50 or 300 mg/kg/d, oral, 30 d)	Untreated	60	↓ Blood glucose comparable to metformin	↑ Sperm count, motility, libido (↓ mounting latency; ↑ frequency)
Akmar, 2017	*In vivo*	Male rats with STZ-induced diabetes	*Gynura procumbens* leaf extract (~450 mg/kg/d, oral, 30 d)	Untreated	NR	↓ Blood glucose; improved glycemic control	Restored fertility and libido; ↑ sperm parameters and implantation sites
Kandeel, 2025	*In vivo*	Female Wistar rats with E_2-induced PCOS	*Glycyrrhiza glabra* extract (100 mg/kg/d, oral, 6 wks)	Untreated	40	Slight improvement in insulin regulation & metabolic profile	↓ FSH, LH, PRL, testosterone, E_2; ↑ P_4; improved folliculogenesis and antioxidant defense
Kamenov, 2017	RDBPCT	Men with mild-moderate ED	*Tribulus terrestris* extract (3×2 tablets/d, 12 wks)	Placebo	180	NR	↑ Sexual function (IIEF domains: desire, orgasm, satisfaction); improved overall EF
Santos, 2014	RDBPCT	Men with ED	*Tribulus terrestris* extract (800 mg/d, oral, 30 d)	Placebo	30	NR	No significant difference vs placebo; slight ↑ IIEF-5; testosterone unchanged
Ghanbari, 2016	*In vivo*	Male Wistar rats with STZ-induced diabetes	*Tribulus terrestris* hydroalcoholic extract (100-500 mg/kg, i.p., 2 wks)	Untreated	30	↓ Blood glucose; ↑ body weight	↑ Testosterone; improved sperm count, motility, morphology; restored seminiferous tubules
Moshfegh, 2022	*In vivo*	Female NMRI mice with testosterone-induced PCOS	*Crocus sativus* petal extract (50-600 mg/kg/d, i.p., 15 d)	Untreated	60	NR	↓ TNF-α, IL-1β, IL-6, IL-18, CRP; ↑ GSH, GST; improved ovarian morphology (↓ cystic follicles, ↑ corpus luteum)
Tomás, 2013	*In vivo*	Male Wistar rats with STZ-induced T2D	White tea substituted for drinking water (oral, ~2 mo)	Water	NR	↑ Glucose tolerance & insulin sensitivity; ↓ lipid/protein oxidation	↑ Sperm concentration, motility, viability; ↓ testicular oxidative stress
Zhou, 2020	*In vivo*	Male C57BL/6 mice with STZ-induced diabetes + HFD	*Dioscorea zingiberensis* extract (125-250 mg/kg/d, oral, 10 wks)	Untreated	32	↓ Oxidative stress (↓ MDA, 8-OHdG; ↑ SOD, GSH); activated Nrf2/HO-1/NQO1 pathway	Restored BTB integrity (↑ ZO-1); improved testicular morphology and sperm count; ↓ abnormal sperm

Abbreviations: ↑, Increase; ↓, Decrease; NR, Not reported; N/A, Not applicable; TCM, Traditional Chinese Medicine; PCOS, Polycystic ovary syndrome; ED, Erectile dysfunction; EF, Erectile function; STZ, Streptozotocin; HFD, High-fat diet; RDBPCT, Randomized double-blind placebo-controlled trial; RCT, Randomized controlled trial; HPG, Hypothalamic-pituitary-gonadal axis; GnRH, Gonadotropin-releasing hormone; FSH, Follicle-stimulating hormone; LH, Luteinizing hormone; PRL, Prolactin; E_2, Estradiol; P_4, Progesterone; T, Testosterone; NO, Nitric oxide; cGMP, Cyclic guanosine monophosphate; Akt, Protein kinase B; eNOS, Endothelial nitric oxide synthase; IR, Insulin resistance; HOMA-IR, Homeostatic model assessment of insulin resistance; β-cell, Beta cell; GPx, Glutathione peroxidase; MDA, Malondialdehyde; SOD, Superoxide dismutase; GSH, Glutathione; HO-1, Heme oxygenase 1; Nrf2, Nuclear factor erythroid 2-related factor 2; NQO1, NAD(P)H quinone oxidoreductase 1; ZO-1, Zonula occludens-1; BTB, Blood-testis barrier; T2D, Type 2 diabetes; IL-1β, Interleukin-1 beta; IL-6, Interleukin-6; IL-18, Interleukin-18; TNF-α, Tumor necrosis factor alpha; CRP, C-reactive protein; GST, Glutathione S-transferase; HK2, Hexokinase 2; LDHA, Lactate dehydrogenase A; SIRT2, Sirtuin 2; ATP, Adenosine triphosphate; DZE, *Dioscorea zingiberensis* ethanol extract; EULE, *Eucommia ulmoides* leaf extract; WEA, Water extract of *Angelica sinensis*; HOMA-β, Homeostatic model assessment of β-cell function; IIEF, International Index of Erectile Function; PGC-1α, Peroxisome proliferator-activated receptor-gamma coactivator 1-alpha.

Table S2. Details of studies on isolated bioactive compounds related to diabetic infertility

Author/ year	Study design	Population/model	Intervention		Sample size	Main anti-diabetic (metabolic) effect	Main anti-infertility (reproductive) effect
			Test (dose, route, duration)	Control			
Ren, 2021	*In vivo*	Female ICR mice with STZ-induced T1D	Astragaloside IV (50 mg/kg, oral, 1 wks)	Untreated	60	↓ ROS and oxidative stress in oocytes; ↑ glucose metabolism	↓ Granulosa-cell apoptosis; ↑ ovulation rate and oocyte maturation; restored follicular structure
Wen, 2022	*In vivo* + *in vitro*	Female SD rats with DHEA-induced PCOS; KGN granulosa cells	Astragaloside IV (20-80 mg/kg/d, SC, 20 d; 20-80 μg/mL *in vitro)*	Untreated	30	↓ Glucose, insulin, HOMA-IR; ↑ insulin sensitivity	Restored estrous cycle; ↓ LH, FSH, testosterone; ↑ autophagy (↑ LC3-II/I, Beclin-1; ↓ p62); activated PPARγ signaling
Zhang, 2020	*In vivo*	Female SD rats with letrozole + HFD-induced PCOS	Berberine (100-400 mg/kg/d, oral, 28 d)	Untreated	60	↓ Glucose, insulin, HOMA-IR; ↑ GLUT4, PI3K, p-AKT, IRS-1; ↓ p-p38MAPK, ERK; improved lipid profile	Restored estrous cyclicity and ovarian morphology (↓ cysts, ↑ corpus luteum); ↓ testosterone, LH; ↑ FSH, E_2; improved follicular development
An, 2014	RDBPCT	Infertile women with PCOS undergoing IVF	Berberine (500 mg TID, oral, 3 mo)	Placebo; metformin	150	↓ FBG, ↓ FINS, ↓ HOMA-IR; ↑ SHBG; effects > placebo, ≈ metformin	↑ Clinical pregnancy & live birth vs placebo; ↓ severe OHSS; better BMI/lipid profile & GI tolerance vs metformin
Wang, 2011	RCT	Women with PCOS and IR	Berberine (0.3 g TID + Metformin 0.5 g TID, oral, 3 mo)	Metformin	82	↓ FBG, FINS, HOMA-IR; improved lipids (↓ TG, TC) vs metformin	↑ Menstrual regularity, ovulation, pregnancy rate; ↓ LH, testosterone; ↑ E_2, P
Li, 2017	RCT	Women with PCOS and IR	Berberine (0.3 g TID, oral, 3 mo)	Metformin	60	↓ FINS, HOMA-IR, TC, TG, LDL-C; comparable to metformin	↓ LH, testosterone, LH/FSH; ↑ menstrual regularity and biphasic cycles; fewer GI side effects
Li, 2016	RDBPCT (multi-center)	Infertile women with PCOS	Letrozole + berberine (0.3 g TID, oral, 3 mo)	Letrozole + placebo; berberine + placebo; double placebo	644	↓ IR; improved metabolic profile	↑ Ovulation and live birth vs letrozole alone; enhanced ovulation induction and pregnancy outcomes
Wu, 2016	RDBPCT (multi-center)	Infertile women with PCOS	Letrozole (2.5-5 mg/d) + berberine (1.5 g/d, oral, ≤6 mo)	Letrozole alone; berberine alone	644	↓ IR and improved glucose metabolism; no synergistic effect with letrozole	↑ Live birth: no added fertility benefit from combination therapy
Li, 2015	Pilot clinical study	Anovulatory women with PCOS	Berberine (0.4 g TID, oral, 4 mo)	Untreated	102	↓ IR incidence, ↓ TC, TG, LDL-C; effect stronger in normal-weight subgroup	↑ Menstrual regularity, ↑ ovulation; no change in androgen levels
Jiang, 2019	*In vivo*	Male ICR mice with STZ-induced diabetes	Betaine (200-800 mg/kg/d, oral, 8 wks)	Untreated	40	↓ ROS, MDA; ↑ SOD, CAT, GSH; inhibited p38 MAPK phosphorylation	Restored testicular morphology; ↑ BTB proteins (ZO-1, Occludin, Claudin-11, Connexin-43); improved spermatogenesis
Abnosi, 2023	*In vitro*	Primary granulosa cells from female C57BL/6 mice	Betaine (5 mM, 24 h under high glucose ± FSH)	Normal glucose; high glucose without betaine	N/A	↓ NF-κB; ↑ Nrf2, Cat, Sod1, GPx; ↓ MDA; restored antioxidant defense	Restored E_2 and P_4 with FSH; improved steroidogenesis and prevented oxidative injury
Samie, 2020	*In vitro*	Granulosa cells from ovaries of immature female C57BL/6 mice	Betaine (5 mM, 24 h under high glucose ± FSH)	Normal glucose; high glucose without betaine	N/A	↑ Cell viability; ↓ Bax/Bcl2 & caspase-3; cytoprotective against hyperglycemia	↑ E_2 and P_4; ↑ StAR, 3β-HSD, Cyp11a1, Cyp19a1; enhanced granulosa cell function
Yin, 2025	Clinical + *in vivo*	Pregnant women with PCOS and DHT-induced PCOS mice	Betaine (NR); evaluated in mice and human placental metabolomics	Untreated	25 women, NR	↓ ROS & apoptosis in placenta; ↑ antioxidant balance	Restored pup number and birth weight; ameliorated placental dysfunction via anti-oxidative and anti-apoptotic effects
Tabandeh, 2024	*In vitro*	TM3 mouse Leydig cells under high-glucose ± HCG	Betaine (5 mM, 24 h)	Normal-glucose; high-glucose without betaine	N/A	↓ ER stress (ATF6, GRP78, CHOP, IRE1); ↓ ROS; ↑ Nrf2, HO-1; ↑ GSH/GSSG ratio	↑ Testosterone; ↑ LH receptor, StAR, P450scc, 3β-HSD; restored steroidogenesis

Zhao, 2022	*In vivo* + *in vitro*	DHEA-induced PCOS rats; KGN granulosa cells	Catalpol (50 mg/kg, oral, 4 wks, *in vivo*); (50 µg/mL, 48 h *in vitro*)	Untreated	40	↓ Body weight, ROS, MDA; ↑ SOD, CAT, GSH; activated SIRT1; inhibited NF-κB	↓ Testosterone, E_2, P_4; restored ovarian morphology and cycle; ↓ apoptosis; improved folliculogenesis via SIRT1/NF-κB
Yan, 2020	*In vitro*	Primary granulosa cells from immature Wistar rats	Catalpol (5-20 µM, 24 h; 2 h pretreatment before H_2O_2 150 µM)	Normal GCs; H_2O_2-only	N/A	↓ ROS, MDA; ↑ SOD, GSH-Px, viability; activated PI3K/Akt/mTOR	↓ Bax, caspase-9; ↑ Bcl-2; ↓ caspase-3; protection from oxidative apoptosis in GCs
Jiao, 2020	*In vivo* + *in vitro*	Male KK-Ay diabetic mice; GC-2 spermatocyte-derived cells	Catalpol (50-100 mg/kg/d, oral, 8 wks, *in vivo*); (0.1-10 µM, 1 h + 48 h AGEs *in vitro*)	Untreated; AGEs-only; aminoguanidine	30, N/A	↓ ROS, MDA; ↑ SOD; ↓ RAGE, Nox4, NF-κB p65; suppressed AGEs/RAGE/Nox4/NF-κB	↑ Testis/body weight, sperm count, testosterone, LH, FSH; ↓ apoptosis (Bax/Bcl-2); improved spermatogenesis and morphology
Roshankha, 2019	*In vivo*	Male Wistar rats with STZ-induced diabetes	Crocin (12.5-50 mg/kg/d, i.p., 28 d)	Untreated	64	↓ Blood glucose; antioxidant protection (↓ oxidative injury)	↑ Sperm count, motility, morphology, viability; restored seminiferous structure; ↑ fertility potential
Elham, 2019	*In vivo*	Female rats with letrozole-induced PCOS	Crocin (50 mg/kg/d, i.p., 6 wks)	Clomiphene	40	↓ Glucose, insulin, HOMA-IR, TC; restored metabolic profile	↓ Testosterone, FSH, LH; ↑ E_2; restored ovarian morphology; effect comparable to clomiphene
Khorasani, 2021	*In vivo*	Male NMRI mice with MGO-induced diabetes	Crocin (15-60 mg/kg/d, oral, 16 d); metformin (150 mg/kg/d (ref))	Untreated	70	↓ Glucose, insulin; ↑ SOD; ↓ MDA; improved redox balance	↑ Testosterone, sperm count; ↓ LH; normalized seminiferous structure
Huang, 2014	*In vivo* + *in vitro*	Female mice with DEX-induced ovarian IR	Cryptotanshinone (100 mg/kg/d, oral, 3 d; 300 nM *in vitro*, 3 d)	Saline + vehicle; DEX-only	60	↑ Glucose uptake; ↑ AKT2, GSK3β, GLUT4; restored insulin signaling; ↓ oxidative inhibition	↓ E_2, P; ↓ CYP11, CYP17; normalized steroidogenesis and ovulation in PCOS-like mice
Yang, 2020	*In vivo* + *in vitro*	Female SD rats with insulin + HCG-induced PCOS; IR GCs	Cryptotanshinone (27 mg/kg/d, oral, 3 wks, *in vivo*); (300 nM, 72 h, *in vitro)*	Untrated	60	↓ Body weight, glucose, TNF-α, HMGB1; ↓ NF-κB/TLR4; improved insulin sensitivity	↓ LH, testosterone, LH/FSH; ↑ FSH; restored follicles; ↓ cysts; improved ovulatory structure via HMGB1/TLR4/NF-κB
Sohaei, 2019	RDBPCT	Overweight/obese women with PCOS	Curcumin (500 mg BID, oral, 6 wks)	Placebo	60	↓ Insulin; ↑ QUICKI; ↓ HOMA-IR	NR
Jamilian, 2020	RDBPCT	Women with PCOS	Curcumin (500 mg/d, oral, 12 wks)	Placebo	60	↓ FPG, ↓ insulin, ↓ HOMA-IR, ↑ QUICKI, ↑ PPAR-γ & LDLR expression	NR
Heshmati, 2020	RDBPCT	Overweight/obese women with PCOS and impaired glucose tolerance	Curcumin (1500 mg/d, oral, 12 wks)	Placebo	72	↑ GPx, ↑ PGC-1α, ↑ SIRT1, ↑ oxidative defense	NR
Lei, 2022	*In vivo*	Male SD rats with HFD + STZ-induced diabetes	Dendrobium nobile polysaccharides (400 mg/kg/d, oral, 6 wks)	Metformin	24	↓ FBG, ↓ HOMA-IR, ↑ insulin; improved glucose homeostasis	↑ Sperm count/motility, ↑ PCNA, ↑ SIRT1; ↓ apoptosis; restored seminiferous structure
Tang, 2014	*In vivo*	Female Wistar rats with cyclophosphamide-induced POF	Ginsenoside Rb1 (25 mg/kg/d, oral, 4 wks)	Cyclophosphamide + saline	30	NR	↑ Bcl-2/Bax ratio; ↓ apoptosis; restored ovarian structure and folliculogenesis
Zhou, 2021	*In vitro*	Human granulosa (KGN) cells under oxidative stress	Ginsenoside Rg3 (10 mg/L, 24 h + H_2O_2 200 µM)	Untreated; H_2O_2-only	N/A	NR	↑ Cell viability, ↓ ROS, ↓ apoptosis, ↑ Bcl-2/BAX, ↓ Cyt C - protection from oxidative damage
Zhang, 2019	*In vivo*	Male SD rats with T2DM-induced ED (HFD + STZ)	*Tribulus terrestris* saponins (40 mg/kg/d, oral, 4 wks)	Sildenafil	30	↓ Glucose, ↓ LDL, ↑ insulin sensitivity	↑ ICP, eNOS, NO, cGMP; ↓ ROS, caspase-3/9; improved erectile and endothelial function
Lu, 2024	*In vivo*	Male C57BL/6J mice with STZ-induced T1DM	Icariin (40-80 mg/kg qod, oral, 11 wks)	Vehicle	104	Activated AMPK; ↑ SOD, CAT, GSH-Px; ↓ MDA, ROS, IL-6, TNF-α	↑ Testosterone, sperm count/motility, ↓ apoptosis; restored BTB proteins & spermatogenesis (lost in $Nrf2^{-/-}$)

Lei, 2020	*In vivo*	Male SD rats with HFD + STZ-induced diabetes	*Lycium barbarum* polysaccharides (100 mg/kg/d, oral, 6 wks)	Metformin	24	↓ Glucose, ↓ HOMA-IR, ↑ insulin	↑ Sperm number/motility, ↑ PCNA, ↑ SIRT1/HIF-1α; ↓ apoptosis; restored spermatogenesis
Shi, 2017	*In vivo*	Male C57BL/6J mice with STZ-induced diabetes	*Lycium barbarum* polysaccharides (100-200 mg/kg/d, oral, 8 wks)	Untreated	40	↓ FBG, ↑ insulin, ↑ SOD, CAT, GPx; ↓ MDA, ROS	↑ Testis weight, sperm count, motility; ↑ testosterone, FSH, LH; ↓ apoptosis; improved seminiferous morphology
Ma, 2022	*In vitro*	Human granulosa cells (from IVF patients)	Morroniside (1-50 μM, 24 h pretreatment + H_2O_2 600 μM, 24 h)	Untreated; H_2O_2-only	N/A	NR	↑ Viability, ↓ ROS/MDA; ↑ SOD, NQO1, T-AOC; ↓ apoptosis; activated Nrf2, inhibited p38/JNK - protection of GCs
Hong, 2024	*In vivo*	Female SD rats with letrozole-induced PCOS	Pachymic acid (8.33-33.3 mg/kg/d, oral, 4 wks)	Diane-35; rHMGB1	126	↓ FBG, ↓ FINS, ↓ HOMA-IR; inhibited HMGB1/RAGE/NF-κB; ↓ IL-1β, TNF-α	↑ FSH, ↓ LH/testosterone; improved ovarian morphology; restored follicles & endocrine balance
Li, 2013	*In vivo*	Male SD rats with STZ-induced diabetes	*Panax notoginseng* saponins (50-150 mg/kg/d, i.p., 4 wks)	Untreated	30	↓ Glucose; ↑ weight gain, improved metabolism	↑ ICP, Bcl-2/Bax ratio; ↓ apoptosis; improved erectile and smooth muscle function
Li, 2021	RCT	Women with PCOS and obesity	Diane-35 + metformin ± puerarin (150 mg/d, 3 mo)	Standard therapy (Diane-35 + metformin)	70	↓ FINS, ↓ HOMA-IR, ↓ TC, ↑ HDL-C, ↑ SOD, vitamin E	↓ Testosterone, ↑ SHBG; normalized menses; improved ovarian endocrine & hyperandrogenism
Rezvan, 2017	RDBPCT	Women with PCOS	Quercetin (1 g/d, oral, 12 wks)	Placebo	84	↑ Adiponectin; ↓ FBS, insulin, HOMA-IR; improved insulin sensitivity	↓ Testosterone, LH; ↑ SHBG (marginal); restored hormonal and metabolic balance in PCOS
Jahan, 2018	*In vivo*	Female SD rats with letrozole-induced PCOS	Quercetin (30 mg/kg/d + letrozole, oral, 21 d)	Metformin	24	↓ Glucose, cholesterol, TG, LDL/VLDL; ↑ HDL; ↑ SOD, CAT, GR → better redox balance	↓ Testosterone; ↑ P_4, E_2; restored estrous cycle; ↓ cysts; ↑ corpora lutea & folliculogenesis
Liang, 2022	*In vivo* + *in vitro*	Letrozole + HFD-induced PCOS rats; human KGN cells	Resveratrol (20 mg/kg/d, oral, 30 d, *in vivo*); (25 μM, *in vitro*)	untreated	24	↓ Glucose, insulin, HOMA-IR; ↑ insulin sensitivity via SIRT2 & IGF1/IGF1R signaling	↑ Glycolysis (HK2, LDHA, PKM2); ↑ GC viability; restored follicular morphology in PCOS
Liang, 2021	*In vivo*	Female SD rats with letrozole + HFD-induced PCOS	Resveratrol (20 mg/kg/d, oral, 30 d)	untreated	16	↓ Body wt, ↑ LDHA, HK2, ATP, lactate → restored glycolysis & IR	↓ Testosterone, LH, FSH; ↑ SIRT2; restored estrous cycle; ↑ follicles & CLs; ↓ cysts; normalized ovarian function
Banaszewska, 2016	RDBPCT	Women with PCOS	Resveratrol (1500 mg/d, oral, 3 mo)	Placebo	34	↓ Insulin, ↓ HOMA-IR, ↑ ISI; better glucose-insulin homeostasis	↓ Testosterone, ↓ DHEAS; no change in LH/FSH or BMI; improved hyperandrogenism
Ortega, 2012	*In vitro*	Theca-interstitial cells from immature female SD rats	Resveratrol (3-30 μM, 24 h ± LH/insulin)	Vehicle	N/A	↓ Insulin-induced Akt phosphorylation; ↓ PI3K/Akt signaling; ↓ glucose uptake & lipogenesis	↓ CYP17, StAR; ↓ P_4, A_4, Testosterone; balanced steroidogenesis; ↓ androgen excess
Ardehjani, 2024	Triple-blind RCT	Women with PCOS undergoing ICSI	Resveratrol (800 mg/d, oral, 60 d)	Placebo	48	↓ TOS, OSI; ↑ TAC, SIRT1, PGC-1α, mtDNA, ATP → improved mitochondrial function	↑ Oocyte maturity, ↑ high-quality embryos; ↑ ART quality outcomes
Ali Fadlalmola, 2023	Systematic review & meta-analysis of 4 RCTs	women with PCOS	Resveratrol (400-1500 mg/d, oral, 40 d-3 mo)	Placebo	218	No effect on insulin or lipids	↓ Testosterone, LH, DHEAS; No sig. effect on pregnancy rates; ↓ hyperandrogenism; hormonal normalization supports fertility
Zhang, 2015	RCT	Women with PCOS + hyperandrogenism	Tanshinone (1 g TID, oral, 3 mo)	Placebo	48	↓ TC, ↓ TG, ↓ LDL, ↑ HDL; no change in FBG or insulin	↓ Testosterone; stable BMI & menses; improved androgen profile & endocrine function

Wu, 2016	RCT	Women with PCOS	Diane-35 (2 mg cyproterone + 0.035 mg ethinylestradiol) + Tanshinone (1 g TID, oral, 3 mo)	Diane-35	72	↓ TG, TC, LDL-C; ↑ HDL-C; improved lipid metabolism & insulin sensitivity	↓ LH, ACTH, cortisol, UFC; ↑ GH; normalized HPA axis and endocrine balance, enhancing ovulatory potential
Su, 2015	RCT	Women with PCOS	Tanshinone capsule (oral, 3 mo)	Placebo	NR	↓ 1h-GLU, ↓ 2h-GLU; ↑ glucose clearance and insulin sensitivity; ↓ TC, TG; ↑ HDL-C	↓ Testosterone; improved reproductive endocrine balance and ovulatory potential
Wang, 2016	RCT	Women with PCOS + metabolic disorders and infertility	Tanshinone (1 g TID, oral, 3 mo); letrozole + FSH ovulation induction (3 cycles)	Placebo	60	↓ BMI, ↓ TC, ↓ TG; improved lipids and ↓ IR (via AMPK-PI3K pathway)	↓ LH, FSH, improved ovulation and endocrine profile

Abbreviations: T1D, Type 1 diabetes; TOS, Total oxidant status; OSI, Oxidative stress index; mtDNA, Mitochondrial DNA; ART, Assisted reproductive technology; ICSI, Intracytoplasmic sperm injection; OHSS, Ovarian hyperstimulation syndrome; BMI, Body mass index; GI, Gastrointestinal; SHBG, Sex hormone-binding globulin; QUICKI, Quantitative insulin sensitivity check index; PPARγ, Peroxisome proliferator-activated receptor gamma; LDLR, Low-density lipoprotein receptor; GLUT4, Glucose transporter type 4; PI3K, Phosphoinositide 3-kinase; p-AKT, Phosphorylated protein kinase B; IRS-1, Insulin receptor substrate-1; p38 MAPK, p38 mitogen-activated protein kinase; ERK, Extracellular signal-regulated kinase; LC3-II/I, Microtubule-associated protein 1A/1B-light chain 3 ratio; Beclin-1, Autophagy marker protein; p62, Sequestosome-1 protein; ATF6, Activating transcription factor 6; GRP78, Glucose-regulated protein 78; CHOP, C/EBP homologous protein; IRE1, Inositol-requiring enzyme 1; RAGE, Receptor for advanced glycation end products; Nox4, NADPH oxidase 4; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; Caspase-3/9, Cysteine proteases 3 and 9; CYP11, Cytochrome P450 family 11 enzymes; CYP17, Cytochrome P450 17α-hydroxylase; CYP19A1, Aromatase enzyme gene; CYP11A1 (P450scc), Cytochrome P450 side-chain cleavage enzyme; StAR, Steroidogenic acute regulatory protein; 3β-HSD, 3-beta-hydroxysteroid dehydrogenase; Cyp11a1, Cytochrome P450 family 11 subfamily A member 1; Cyp19a1, Cytochrome P450 family 19 subfamily A member 1; HIF-1α, Hypoxia-inducible factor 1-alpha; HMGB1, High-mobility group box 1; TLR4, Toll-like receptor 4; GSK3β, Glycogen synthase kinase 3 beta; AKT2, Protein kinase B isoform 2; DHEA, Dehydroepiandrosterone; DHT, Dihydrotestosterone; DEX, Dexamethasone; GCs, Granulosa cells; AGEs, Advanced glycation end products; ISI, Insulin sensitivity index; TC, Total cholesterol; TG, Triglycerides; LDL/VLDL, Low/very-low-density lipoprotein; AMPK, AMP-activated protein kinase; PI3K/Akt/mTOR, Phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin pathway; POF, Premature ovarian failure; UFC, Urinary free cortisol; ACTH, Adrenocorticotropic hormone; GH, Growth hormone; HPA, Hypothalamic-pituitary-adrenal axis; A_4, Androstenedione; PKM2, Pyruvate kinase M2; CLs, Corpora lutea.

Table S3. Details of studies on compound herbal formulas for diabetic infertility

Author/year	Study design	Population/model	Intervention		Sample size	Main anti-diabetic (metabolic) effect	Main anti-infertility (reproductive) effect
			Test (dose, route, duration)	Control			
Wang, 2021	*In vivo* + network pharmacology	Male SD rats with STZ-induced diabetes & apomorphine-induced ED	Achyranthis bidentatae radix + Semen vaccariae granules (2.5 g/kg/d, oral, 8 wks)	Deionized water	18	↓ Glucose; ↑ insulin; ↓ glucagon; ↑ eNOS; improved vascular endothelium	↑ EF; ↑ eNOS; ↓ CASP3, ACE, VEGFA; restored NO signaling and penile structure
Yue, 2015	*In vivo*	Male SD rats with STZ-induced diabetes	Bushen Huoxue Recipe (3 or 6 g/kg/d, oral, 8 wks)	Saline	40	↓ Glucose; ↑ insulin sensitivity; improved body weight	↑ ICP, ICP/MAP; ↑ AKT, p-AKT; ↓ apoptosis in corpus cavernosum; ↓ collagen ratio; improved EF
Wang, 2022	*In vivo*	Female SD rats with letrozole-induced PCOS	Bu Shen Hua Zhuo Formula (4.5-18 g/kg/d, oral, 28 d)	Letrozole; metformin	30	↓ FBG, ↓ FINS, ↓ LPS, ↓ TLR4/NF-κB; improved metabolism & inflammation	↓ Testosterone, restored ovarian morphology; ↓ cysts, ↑ corpora lutea; normalized ovulation; ↑ Lactobacillus & SCFA species
Mo, 2019	RCT	Women with PCOS-related infertility	Bushen Quyu Huatan Decoction (150 mL BID × 20 d/cycle, oral, 3 cycles) + clomiphene (50 mg/d, oral, 5 d)	Clomiphene	148	NR	↑ Pregnancy rate; ↑ ovulation & menstrual regularity; no AE increase, ↓ LH, ↓ LH/FSH, ↓ testosterone; improved ovarian blood flow (↑ PSV, PI; ↓ RI)
Ma, 2018	RCT	Obese women with PCOS	Bushen Tiaochong Decoction (1 dose/day, mL, oral, 3 mo) + Diane-35 + letrozole	Diane-35 + letrozole	147	↓ BMI, ↓ leptin, ↓ visfatin, ↑ adiponectin; improved glucose/lipid metabolism & ↓ IR	↑ E_2; ↓ LH, ↓ FSH, ↓ LH/FSH; ↑ endometrial thickness, PI; efficacy; improved receptivity
Yang, 2021	RCT	Men with diabetic ED	Buyang Huanwu Decoction (1 dose/d, oral, 4 mo)	Vitamin B1 + standard diabetes therapy	70	Improved glucose metabolism via endocrine regulation	↓ E_2, FSH, LH, PRL; ↑ testosterone, ↑ IIEF-5; ↑ WHOQOL-BREF; efficacy; improved erectile & sexual function
Ding, 2014	RCT	Women with PCOS infertility	Modified CFDTD (100 mL BID, oral, D5-+10 Ov, ×3 cycles) + CC + HMG + HCG	CC + HMG + HCG	160, 195, 298	↓ HOMA-IR; ↑ UCP2 expression; improved glucose & lipid metabolism	↑ Endometrial thickness; ↓ PI, RI; ↑ Pregnancy rate; improved receptivity & uterine flow

Wan, 2017	RCT	Obese PCOS women	Modified CFDTD (1 dose/d, oral, 3 mo)	Clomiphene	80	↓ TC, TG, LDL-C; ↑ HDL-C; improved lipid metabolism; fewer AEs	↓ LH, FSH, testosterone; significant hormonal improvement; restored ovulatory function
Wei, 2020	RCT	Women with PCOS	CFDTD (1 dose/d, oral, 3 mo) + Diane-35 + Metformin	Diane-35 + Metformin	90	↓ HOMA-IR, TC, TG, LDL-C; ↑ HDL-C; marked metabolic improvement	↓ LH, testosterone, PRL; ↑ E_2, FSH; improved ovulation & hormonal balance
Xu, 2020	Network pharmacology	Bioinformatic PCOS targets (TCMSP, GeneCards, OMIM, STRING)	CFDTD (Atractylodes, Cyperus, Pinellia, Poria, Citrus, etc.)	N/A	N/A	Regulation of PI3K-Akt, MAPK, AGE-RAGE, and IR pathways	Modulated VEGFA, ESR1, AR, HIF1A; improved angiogenesis, folliculogenesis & steroidogenesis
Zheng, 2013	RCT	Women with PCOS + IR	Modified CFDTD, decoction (1 dose/d BID, oral, 3 mo)	Metformin	60	↓ FPG, insulin, HOMA-IR; ↓ BMI; similar efficacy to metformin, fewer GI AEs	NR
Li, 2017	RCT	Women with PCOS infertility	CFDTD (400 mL BID, oral, 3 mo) + Clomiphene 50 mg/d	Clomiphene	116	Indirect metabolic benefit (improved HOMA-IR)	↑ E_2, ↓ LH, ↑ endometrial thickness, ↓ PI/RI; ↑ pregnancy
Yang, 2015	RCT	Women with hyperinsulinemia & delayed menstruation	Modified CFDTD (1 dose/d, oral, 3 mo)	Metformin	58	↓ FINS; improved insulin sensitivity; fewer GI AEs	Menstrual recovery; restored cycles & ovulation; improved ovarian symptoms
Wu, 2025	Integrative pharmacology + *in vitro*	RPL patients with IR + human decidual stromal cells	100 μg/mL, in vitro, 24 h	Pioglitazone; untreated	N/A	↓ IR via PI3K/Akt & JAK2/STAT3; ↓ oxidative stress; ↑ insulin sensitivity	↑ IL-6 mRNA; ↑ decidual cell proliferation; improved implantation & reduced miscarriage risk
Zhang, 2022	*In vivo* + network pharmacology	Female C57BL/6 mice with letrozole-induced PCOS	Cuscuta-Salvia formula (0.1 mL/10 g, oral, 30 d)	Metformin	24	↓ Body wt, glucose AUC; ↑ p-AKT, MAPK; improved insulin sensitivity	↓ AR, CYP17A1, CYP19A1; ↑ VEGFA, FSHb; restored follicular morphology & hormone balance
Liu, 2013	RCT	Women with PCOS + IR & anovulatory infertility	Danzhi Xiaoyao Pill (6 g BID, oral, ×3 cycles) + Metformin + Cyproterone; ± Letrozole/HMG	Metformin + Cyproterone	60	↓ FINS; Improved IR without BMI change	↓ LH, testosterone; ↑ ovulation, ↑ pregnancy; improved endometrial receptivity
Zhou, 2023	Meta-analysis of 19 RCTs	Women with PCOS	Xiao Yao San & variants (varied dose, oral, 3 mo) ± Western drugs (Met, clomiphene citrate, Diane-35)	Western medicine alone	1,588	↓ FPG, FINS, HOMA-IR; improved lipids (↓ TC, TG, LDL; ↑ HDL)	↑ ovulation, ↑ pregnancy; ↓ LH/FSH, ↓ testosterone; improved cycle & ovarian morphology
Wei, 2024	RCT	Women with PCOS	Danxi Zhishitan Decoction (NR, oral, 3 mo) + terahertz therapy + Metformin 500 mg TID	Metformin	92	↓ HOMA-IR, ↓ CT-1, ↓ T; ↑ E_2; improved insulin & lipid metabolism	↓ LH, ↑ FSH, E_2; ↑ pregnancy; ↑ total efficacy; improved ovulation & receptivity
You, 2017	RCT	Men with T2DM-ED	Fufang Xuanju Capsule + Liuwei Dihuang Pill (NR, oral, 3 mo)	Liuwei Dihuang Pill	60	↓ AGEs, ↓ Ang II; improved endothelial/glucose indices	↑ IIEF-5; better sexual function; no significant AEs
Jiang, 2016	RCT	Men with T2DM-ED	Fufang Xuanju Capsule (NR, oral, 1 mo) + tadalafil (10 mg)	Tadalafil	80	Indirect endothelial/NO improvement (herbal NO-cGMP support)	↑ IIEF-5 (notably in moderate ED); ↑ total efficacy
Liu, 2021	*In vivo*	Female SD rats with letrozole + HFD PCOS	Guizhi Fuling Wan (0.31-1.24 g/kg/d, oral, 30 d); ± LY294002	Metformin	84	↓ FPG, ↓ FINS, ↓ HOMA-IR; PI3K/AKT/mTOR activation	↓ LH, testosterone, LH/FSH; ↑ P, E_2; ↑ mature follicles/CL; ↓ cysts/atretic follicles
Zhu, 2020	*In vivo*	Female SD rats with letrozole + HFD PCOS	Guizhi Fuling Wan (0.31-1.24 g/kg/d, oral, 35 d)	Metformin	72	↓ FPG/FINS/HOMA-IR; ↓ IL-6, TNF-α, hs-CRP; microbiota modulation	Restored cycles; ↓ testosterone; improved ovarian morphology; efficacy ≈ metformin
Fu, 2025	*In vivo*	Male SD rats with HSHF + STZ-induced diabetes	Guhan Yangsheng Jing (0.432-1.728 g/kg/d, oral, 4 wks)	Untreated metformin; vitamin E	72	↓ FBG, ↓ MDA/Fe^{2+}/LPO; ↑ SOD/GSH/GPX4/xCT; ↑ Nrf2/HO-1; ↓ ROS/ferroptosis	↑ Sperm count/motility; ↑ testosterone, FSH; ↓ LH; improved testes histology; ↓ apoptosis
Alrefaei, 2023	*In vivo*	Male SD rats with STZ-induced diabetes	Ginger (500 mg/kg/d); Cinnamon (100 mg/kg/d); combo (oral, 6 wks)	Metformin	36	↓ FBG; ↑ insulin, ↑ HOMA-β; ↓ HOMA-IR; ↑ TAC (combo ≈ metformin)	↑ testosterone; restored seminiferous structure; ↓ TUNEL; ↑ PCNA & AR; ↓ TNF-α/NF-κB; ↑ SIRT1

Khaki, 2014	*In vivo*	Male Wistar rats with STZ-induced diabetes	Ginger (100 mg/kg, oral, 8 wk); Cinnamon (75 mg/kg, oral, 8 wk); combo (100 + 75 mg/kg, oral, 8 wk)	Saline	80	↓ Glucose; ↑ insulin; ↑ SOD/GPx/CAT/TAC; ↓ MDA	↑ Sperm count/motility/viability; ↑ testosterone, LH, FSH; improved testicular morphology
Sun, 2021	RCT	Men with T2DM-ED	Huoxue Tongluo Qiwei Decoction (5 mg/d BID, oral, 4 wks) + tadalafil	Tadalafil	66	Maintained glycemic control; improved microcirculation/endothelium	↑ IIEF-5; ↑ total efficacy; ↓ TCM symptom score
Li, 2022	*In vivo*	Male SD rats with diabetes	HTQD (3.33-13.34 g/kg/d, oral, 8 wks); tadalafil	Untreated	60	↓ FBG/FINS/HOMA-IR; ↑ eNOS/NO; ↓ MDA; ↑ SOD/GSH-Px	↑ ICP/MAP; ↑ cGMP; restored CC structure; ↓ collagen; ↑ smooth muscle & VEGF
Liang, 2019	RDBPCT	Women with PCOS	Heyan Kuntai Capsules (4 caps TID, oral, 6 mo)	Placebo	100	↓ BMI/WHR; ↓ FPG/2hG; ↓ FINS/2hINS; ↓ HOMA-IR; ↑ ISI; improved lipids	↓ LH, LH/FSH, testosterone; ↑ menstrual regularity; indirect ovulatory benefit
Qiu, 2020	*In vivo*	Female SD rats with letrozole + HFD PCOS	Liuwei Dihuang Pills (1.2-3.6 g/kg/d, oral, 21 d)	Untreated	50	↓ FBG/FINS/HOMA-IR; ↑ PI3K/Akt; ↓ p-IRS1 (S307)	↑ FSH/E_2; ↓ LH/testosterone; ↑ FSHR & Cyp19a1; improved ovarian morphology & CL formation
Yan, 2022	*In vivo*	Female SD rats with letrozole + HFD PCOS	LWDH (50 mg/kg/d, oral, 10 d); ± SRI-011381	Metformin	60	↓ TGF-β1/SMAD2/3; efficacy ≈ metformin	Normalized sex hormones; restored ovarian/uterine morphology; ↓ cysts; improved follicular structure & function
Cuiyun, 2015	Prospective clinical observational study	Women with PCOS	*Liuwei Dihuang Wan* + *Xiaoyao San* decoction (NR, oral, 6 mo)	None (single-arm)	16	↓ Obesity, acne; balanced endocrine-metabolic status	↓ Testosterone, ↓ LH, ↓ LH/FSH; improved BBT, ovulation & pregnancy; regularized cycles; improved endometrial receptivity
He, 2018	RCT	Men with T2DM + ED	Qianlie shutong capsule (3 caps TID, oral, 3 wks) + α-lipoic acid	α-lipoic acid alone	82	↓ Hcy, MDA, ET-1; ↑ NO, NOS, GSH-Px, SOD; enhanced antioxidant & endothelial function	↑ IIEF-5; improved penile hemodynamics & rigidity; higher recovery rate
Jinghua, 2016	RCT	Men with T2DM + ED	Qianlie shutong capsule (3 caps TID, oral, 3 wks) + α-lipoic acid	α-lipoic acid alone	54	↓ Hcy, MDA, ET-1; ↑ NO, NOS, SOD, GSH-Px; improved antioxidant capacity	↑ IIEF-5; improved erectile rigidity & vascular response
Chen, 2022	*In vivo*	Male C57BL/6J mice with HFD + STZ-induced diabetes	*Radix Rehmanniae-Cornus Officinalis* extract (8 g/kg/d, oral, 8 wks)	Metformin	50	↓ FBG, ↓ HOMA-IR; ↑ GLP-1/GLP-1R, ↑ butyrate, ↓ IL-6/TNF-α; improved gut microbiota (↑ *Lactobacillus*, *Bifidobacterium*)	↑ Testosterone, LH, FSH; ↓ testicular apoptosis (↓ Bax, ↑ Bcl-2); restored spermatogenesis & seminiferous structure; ↑ GLP-1R in testes
Shang, 2019	*In vivo*	Male SD rats with STZ-induced DMED	Tianjing Tongluo Decoction (9.3 g/kg/d, oral, 30 d), Decoction I (7.2 g/kg/d, oral, 30 d), Decoction II (2.1 g/kg/d, oral, 30 d), 30 d	Tadalafil	60	↓ Blood glucose; improved insulin sensitivity; ↑ endothelial NO synthesis	↑ Testosterone; ↑ eNOS in corpus cavernosum; improved penile microcirculation and EF
Cao, 2018	*In vivo*	Male SD rats with STZ-induced DMED	Wuzi Yanzong Recipe (1.08 g/kg/d, oral, 30 d) and disassembled sub-formulas	Water	100	↓ Blood glucose; ↑ NOS activity (iNOS, cNOS); ↑ cGMP; restored NO-cGMP signaling	↑ ICP/MAP ratio; ↓ spermatogenic cell apoptosis; improved tubular histology
Ma, 2018	*In vivo*	Male SD rats with natural ageing	Wuzi Yanzong Recipe (1-4 g/kg/d, oral, 4 mo)	Untreated	40	↑ SOD; ↓ MDA in testes; improved oxidative defense & redox homeostasis	↓ 8-OHdG; ↑ Nrf2, HO-1, NQO1; ↓ APE1, OGG1, XRCC1; protected spermatogenic DNA & delayed testicular aging
Zhao, 2019	*In vivo*	Male SD rats with natural ageing	Wuzi Yanzong Recipe (1 or 4 g/kg/d, oral, 4 mo)	Untreated	40	NR	↓ E2; ↑ testosterone; restored testis weight and ER/redox balance; ↑ sperm count & viability; ↓ germ cell apoptosis; improved tubule structure and morphology
Wang, 2022	*In vivo*	Male SD rats with STZ-induced DMED	Yiyuan Qiwei Pill (1.5-6 g/kg/d, oral, 2 mo)	Saline	65	↓ Glucose, ↓ AGEs; ↑ endothelial function	↑ ICP, NO, cGMP; ↑ nNOS & NOS expression; ↓ PDE5; improved penile structure and erection

Zhai, 2020	RCT	Men with T2DM-ED	Yougui Pill (9 g TID, oral, 8 wks)	Placebo + Tadalafil	42	Maintained stable glycemia; regulated oxidative & neurovascular status	↑ IIEF-5, efficacy; ↑ EF with mild AEs only
Zhai, 2022	*In vivo*	Male SD rats with STZ-induced DMED	Yougui Pill (9 g/kg/d, oral, 8 wks)	Untreated	30	↓ MDA; ↑ SOD, GSH-Px; no change in glucose	↑ Erection frequency; ↓ latency; ↓ endothelial apoptosis; ↑ eNOS, Nrf2, HO-1
Wang, 2022	*In vivo*	Female SD rats with OVX-induced sexual dysfunction	Yougui Pill + Buzhong Yiqi Decoction (3.6 mL/d, oral, 4 wks)	Sham and OVX + estradiol benzoate	24	Restored gut microbiota (↑ Proteobacteria, ↓ Romboutsia/Lactobacillus); balanced amino-acid/fat metabolism	↑ E_2 & cAMP; restored estrous cycle; improved sexual behavior & vaginal maturity
Xu, 2016	RCT	Women with PCOS	Modified Yougui Pill (200-300 mL QD, oral, 3 cycles) + Diane-35	Diane-35 alone	74	↓ Glucose and lipids; improved metabolic profile vs control	↓ LH, LH/FSH, testosterone; ↑ E_2; improved menstrual regularity, ovulation, & clinical efficacy
Cao, 2011	Prospective (pre-post clinical) study	Men with T2DM-ED	Yiqi Yangyin Huoxue Decoction (1 dose/d, oral, 12 wks)	Self-control	40	Maintained normal FPG & 2h-PG; no hepatic/renal AEs	↑ IIEF-5; ↑ testosterone; ↓ LH, E_2; ↑ response rate → enhanced EF
Li, 2011	RCT	Men with T2DM-ED	Yishen Huoxue Decoction (NR, oral, 12 wks) + standard therapy	Standard therapy only	84	Glycemia within targets; improved microcirculation	↑ IIEF-5, EQS, efficacy; ↑ erectile hardness & satisfaction
Zhang, 2017	RCT	Men with T2DM-ED	Yishen Huoxue Decoction (NR, oral, 3 mo) + α-Lipoic Acid	α-Lipoic Acid alone	116	↓ Hcy, ET-1, MDA; ↑ NO, SOD, GSH-Px; ↓ oxidative stress	↑ IIEF-5, EQS & sexual satisfaction; ↑ efficacy
Li, 2020	Systematic review & meta-analysis of 12 RCTs	Pregnant women with URSA	Shoutai Pill (1 dose/day, oral, 12-20 wk) + standard Western therapy	Western therapy alone	916	↓ Serum D-dimer; improved microcirculation	↓ Early pregnancy loss; ↑ Live birth rate; improved pregnancy outcomes
Ma, 2019	RCT	Infertile women with diminished ovarian reserve undergoing IUI	Zishen Yutai Pill (5 g TID, oral, 3 cycles) + folic acid + vitamin E	Folic acid + vitamin E	60	NR	↓ FSH, ↑ E_2, ↑ LH; improved ovarian blood flow (↓ RI, PI; ↑ PSV); ↑ Pregnancy rate; ↑ Live birth rate; improved ovulation and ovarian reserve
Chen, 2022	RDBPCT	Women undergoing IVF/ICSI fresh embryo transfer	Zishen Yutai Pill (5 g TID, oral, 1 cycle)	Placebo	2265	NR	↑ Live birth rate; ↑ Implantation and clinical pregnancy rates; no difference in miscarriage or adverse events
Li, 2019	RCT	Women with PCOS-related infertility	Zishen Yutai Pill (5 g TID, oral, 3 mo) + cyproterone-ethinylestradiol	Cyproterone-ethinylestradiol alone	100	NR	↓ Testosterone, LH, FSH; ↓ LH/FSH ratio; improved endocrine balance; ↑ Total efficacy; improved ovulation, conception, and menstrual regularity
Wu, 2015	RCT	Men with T2D-ED	Ziyin Zhuangyang Capsule (varied dose, oral, 8 wk) + standard glycemic control	Liuwei Dihuang Decoction + standard glycemic control	60	Stable glycemic control	↑ IIEF-5 score, total efficacy; improved EF without adverse effects
Yang, 2017	RCT	Men with T2D-ED	Shisanwei Ziyin Zhuangyang Capsule (3 caps TID, oral, 4 wk) + Sildenafil	Sildenafil	120	Improved metabolic regulation; no hepatic or renal toxicity	↑ IIEF-5; ↑ sexual satisfaction; ↓ TCM score; significant EF and QoL improvement

Abbreviations: ACE, Angiotensin-converting enzyme; VEGFA, Vascular endothelial growth factor A; VEGF, Vascular endothelial growth factor; ICP, Intracavernosal pressure; MAP, Mean arterial pressure; LPS, Lipopolysaccharide; SCFA, Short-chain fatty acid; PSV, Peak systolic velocity; PI, Pulsatility index; RI, Resistance index; UCP2, Uncoupling protein 2; CFDTD, Modified Cangfu Daotan Decoction; CC, Clomiphene citrate; HMG, Human menopausal gonadotropin; HCG, Human chorionic gonadotropin; TCMSP, Traditional Chinese Medicine Systems Pharmacology database; GeneCards, GeneCards database; OMIM, Online Mendelian Inheritance in Man; STRING, Search Tool for the Retrieval of Interacting Genes/Proteins; ESR1, Estrogen receptor 1; HIF1A, Hypoxia-inducible factor 1-alpha (gene); JAK2, Janus kinase 2; STAT3, Signal transducer and activator of transcription 3; RPL, Recurrent pregnancy loss; URSA, Unexplained recurrent spontaneous abortion; AUC, Area under the curve; FSHβ, Follicle-stimulating hormone beta subunit; FSHR, Follicle-stimulating hormone receptor; LY294002, PI3K inhibitor LY294002; hs-CRP, High-sensitivity C-reactive protein; HSHF, High-sugar high-fat; GPX4, Glutathione peroxidase 4; xCT, Cystine/glutamate antiporter (SLC7A11); LPO, Lipid peroxides; DMED, Diabetes mellitus-associated erectile dysfunction; T2DM-ED, Type 2 diabetes mellitus-associated erectile dysfunction; nNOS, Neuronal nitric oxide synthase; PDE5, Phosphodiesterase type 5; iNOS, Inducible nitric oxide synthase; cNOS, Constitutive nitric oxide synthase; GLP-1, Glucagon-like peptide-1; GLP-1R, GLP-1 receptor; OVX, Ovariectomized; cAMP, Cyclic adenosine monophosphate; WHOQOL-BREF, World Health Organization Quality of Life-BREF; EQS, Erectile quality score; Hcy, Homocysteine; ET-1, Endothelin-1; NOS, Nitric oxide synthase; BBT, Basal body temperature; Ang II, Angiotensin II; SD, Sprague-Dawley; MAPK, Mitogen-activated protein kinase; rHMGB1, Recombinant high-mobility group box 1; p-IRS1 (S307), Phosphorylated insulin receptor substrate-1 at Ser307; TGF-β1, Transforming growth factor beta 1; SMAD2/3, Mothers against decapentaplegic homologs 2 and 3; ALA, Alpha-lipoic acid; D5-+10 Ov, Day 5 to +10 of ovulation cycle; TCM, Traditional Chinese Medicine.

Table S4. Details of studies on non-herbal TCM modalities for diabetic infertility

Author/year	Study design	Population/ Model	Intervention: Test (dose, route, duration)	Intervention: Control	Sample size	Main anti-diabetic (metabolic) effect	Main anti-infertility (reproductive) effect
Feng, 2009	*In vivo*	Female Wistar rats with DHT-induced PCOS	Low-frequency electroacupuncture (2 Hz, 15-25 min/d, topical, 4-5 wks)	Untreated	24	Improved insulin sensitivity; normalized AR-GnRH signaling	Restored estrous cyclicity; ↓ AR and GnRH expression → normalized HPO axis and ovulation recovery
Jedel, 2011	RCT (3-arm)	Women with PCOS	Low-frequency electroacupuncture (2 Hz, topical, 16 wks)	Exercise/Untreated	74	↓ DHEAS, ↓ androgen metabolites; ↑ VO_2max	↓ Total testosterone, ↓ free testosterone, ↓ acne, ↑ menstrual frequency; EA > exercise for ovulation restoration
Feng, 2012	*In vivo*	Female Wistar rats with DHT-induced PCOS	Low-frequency electroacupuncture (2 Hz, topical, 4-5 wks) or manual acupuncture (topical, 4-5 wks)	Untreated	24	Improved insulin sensitivity (reported previously)	EA ↓ serum testosterone; both EA and manual ↑ P; EA restored oestrous cycle in 88%; manual in 62%; EA acted via opioid receptor modulation (Oprk1, Oprm1); manual affected steroid receptor genes (Esr2, Pgr, Kiss1r) → normalized ovulatory function
Wang, 2021	*In vivo*	Male SD rats with STZ-induced diabetic ED	Leech-Centipede medicine (0.15-0.6 g/kg/d, oral, 8 wks)	Untreated or tadalafil & PKC inhibitor	36	↓ Blood glucose, ↑ insulin; ↓ MDA, ↑ SOD; improved oxidative and endothelial status	↑ EF; improved penile structure; ↓ PKCβ, NF-κB, ICAM-1 → restored endothelial integrity
Pan, 2022	RCT	Infertile women with PCOS	Manual acupuncture (2×/wk, topical, 3 mo) + herbal decoction (syndrome-based)	Sham (acupuncture + same herbs)	86	no significant change in HOMA-IR	↓ E_2, testosterone, P, LH, LH/FSH; ↑ pregnancy rate; ↑ ovulation; ↓ PCOS and TCM scores; improved menstrual regularity & hormonal balance
Pastore, 2011	RDBSCT	Women with oligo-/anovulatory PCOS	True acupuncture (EA + manual, 12 sessions, topical, 8 wks)	Sham acupuncture (non-penetrating)	84	No significant change in glucose or HbA1c; ↓ fasting insulin correlated with ↑ ovulation	Both ↓ LH/FSH and improved menstrual frequency; ovulation similar; minor ↑ pregnancy
Li, 2022	Systematic review and meta-analysis of 25 RCTs	Women with PCOS	Acupuncture (3×/wk, topical, 3 mo) + moxibustion (3×/wk, topical, 3 mo,) ± basic treatment	Basic treatment alone	1991	↓ Fasting insulin, ↓ BMI → improved insulin sensitivity	↓ LH, ↓ LH/FSH, ↓ testosterone; ↑ pregnancy, ↑ ovulation, ↓ miscarriage; normalized sex hormones and ovarian morphology

Abbreviations: EA, Electroacupuncture; AR, Androgen receptor; GnRH, Gonadotropin-releasing hormone; HPO axis, Hypothalamic-pituitary-ovarian axis; VO_2max, Maximal oxygen consumption; Oprk1, Opioid receptor kappa 1; Oprm1, Opioid receptor mu 1; Esr2, Estrogen receptor beta; Pgr, Progesterone receptor; Kiss1r, Kisspeptin receptor; PKC, Protein kinase C; PKCβ, Protein kinase C beta; ICAM-1, Intercellular adhesion molecule-1; HbA1c, Hemoglobin A1c; RDBSCT, Randomized double-blind sham-controlled trial.