Prayogik Rasayan

Hesperidin and Polycystic Ovary Syndrome (PCOS): Molecular Protection Beyond Conventional Therapy

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Abstract

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine–metabolic disorder driven by complex interactions between ovarian dysfunction, insulin resistance, chronic inflammation, oxidative stress, and gut microbial dysbiosis. Current therapies address isolated symptoms and are often associated with adverse effects, prompting interest in bioactive natural compounds with multi-target potential. Hesperidin (HSP), a citrus flavanone widely investigated for its antioxidant, anti-inflammatory, metabolic, and immunomodulatory properties, has gained attention as a candidate for PCOS management. This review synthesizes experimental evidence demonstrating that HSP improves ovarian morphology, supports follicular development, modulates sex-steroid and gonadotropin profiles, and enhances oocyte developmental competence. HSP additionally attenuates oxidative injury, inflammatory cascades, and apoptosis in ovarian and metabolic tissues through regulation of Nrf2, NF-κB, Bax/Bcl-2, and caspase pathways. Metabolically, HSP improves insulin signaling, glucose tolerance, and lipid profiles, while suppressing hepatic lipogenesis and promoting fatty acid oxidation. Recent studies further highlight its capacity to modify gut microbial composition, strengthen mucosal barrier function, increase short-chain fatty acid production, and reduce endotoxin-driven inflammation. Together, the findings indicate that HSP engages multiple mechanistic axes relevant to PCOS pathophysiology. However, clinical validation remains limited, underscoring the need for human trials to establish therapeutic applicability.

Keywords: PCOS, Hesperidin, Oxidative Stress, Insulin Resistance, Inflammation, Apoptosis, gut-biota

1. Introduction

PCOS is a complex endocrine condition marked by disrupted gonadotropin dynamics, elevated androgen levels, chronic anovulation, and ovaries containing multiple cystic follicles. It is frequently accompanied by metabolic disturbances, most notably insulin resistance (IR) (Hajam, *et al*., 2024). Estimates suggest that PCOS affects roughly 6–20% of women, with symptoms commonly appearing during early adolescence (Witchel, *et al*., 2019). Individuals with PCOS face higher risks of abnormal glucose metabolism of glucose and lipids, type 2 diabetes, endometrial malignancies, cardiovascular complications, and adverse gestetional outcomes besides exerting significant burden on reproductive, metabolic, and psychological aspects (Witchel, *et al*., 2019). Although the underlying mechanisms of PCOS are still not fully understood, current findings emphasize the involvement of HPO axis, chronic oxidative stress and inflammation, insulin resistance, adipose tissue abnormalities and altered gut biota in pathophysiology of PCOS (Singh, *et* al., 2023). At present, no universally accepted therapeutic guideline exists for PCOS (Teede, *et* al., 2018; Escobar-Morreale, 2018). As PCOS is not fully curable, management relies on symptom specific pharmacotherapy, primarily hormonal agents, though these frequently cause side effects. Anti-androgens improve hirsutism and ovulation (De Leo *et al*., 1998; Moghetti, *et al*., 1994) but may induce hepatotoxicity (Castelo-Branco, *et al*., 2009). Combined oral contraceptives regulate cycles and lower androgen excess (Mendoza, *et al*., 2014), yet long term use increases risks of IR, thrombosis (Gronich, *et al*., 2011), and menopausal concerns (Belisle & Love, 1986). Clomiphene citrate treats anovulatory infertility but can overstimulate the
ovaries, leading to multiple gestations (Brown & Farquhar, 2016). Thiazolidinediones enhance insulin sensitivity although it might cause weight gain and fluid retention (Legro, *et al*., 2013). Spironolactone reduces hirsutism (Tremblay, 1986) but often results in breakthrough bleeding (Sabbadin, *et al*., (2016).

In view of the constraints of current targeted treatments, naturally derived bioactive compounds have drawn growing interest for their therapeutic versatility (Malik, *et al*., 2024). These molecules often influence hormonal pathways and, being sourced from plants, microbes, or animal products, typically show good safety profiles. Many natural agents possess multiple biological activities, enabling them to act on various pathological processes simultaneously, an advantage in multifactorial condition like PCOS. When used alongside standard pharmacotherapies, they may enhance treatment outcomes, reduce adverse effects, and lower dependence on conventional drugs (Ataabadi *et al*., 2017; Yang *et al*., 2018; Rudic *et al*., 2022)

Hesperidin (HSP) is a citrus-derived bioflavonoid, a di-phenolic polyphenol with the molecular formula $C_{28}H_{34}O_{15}$, widely distributed in vegetables, herbs, legumes, and fruits. Its name originates from “hesperidium,” the characteristic fruit type of citrus species (Li & Schluesener2017). In plants, HSP

functions as a secondary metabolite contributing to defense against microbial pathogens such as fungi and bacteria (Del Río, *et al*., 2004). Sweet oranges (*Citrus sinensis*) and tangelos are among the richest natural sources and are commonly used for HSP extraction, although recent evidence indicates that it can also be produced synthetically (Binkowska, 2020). This classical dietary polyphenol, HSP exhibits diverse biological activities, including antioxidant, anti-inflammatory, antitumor, anticancer, antidiabetic, anti-allergic, antiulcer and neuro-protective effects (Al-Rikabi, *et* al., 2020; Welbat, *et al*., 2020; Ahmadi & Shadboorestan, 2016; Xiong, *et* al., 2019; Hanchang *et* al., 2019).

The pharmacokinetics of HSP involve gut microbiota mediated cleavage of the rutinoside group post-citrus ingestion, yielding hesperetin aglycones with low-to-moderate bioavailability due to extensive conjugation, though exhibiting excellent safety profiles (Li, *et al*., 2008; Sivaslioglu, & Goktas2024). HSP exhibits multi-target, multi-pathway actions across key pathological processes associated with PCOS, positioning it as a promising therapeutic candidate. The growing body of evidence on the effect of HSP in PCOS and related metabolic–reproductive disturbances provide a mechanistic foundation and expands future directions for PCOS management.

2. Mechanistic role of hesperidin in regulating PCOS associated pathophysiology

2.1. Effect of HSP on ovarian morphology, hypothalamic–pituitary–ovarian (HPO) axis and fertility

Ovulatory dysfunction is the most prevalent reproductive abnormality in PCOS, contributing to nearly 75% of cases and representing the leading cause of anovulatory infertility (Homburg, 2004). Although its exact mechanisms remain incompletely defined, Impaired folliculogenesis in PCOS arises largely from disruptions in the HPO axis, where altered gonadotropin and sex-steroid secretion impede normal folliclar maturation (Cadagan, *et al*., 2016). Granulosa cells are essential for oocyte support through glycolysis, show atresia, hypertrophy, and degeneration, leading to arrested follicular development and anovulation (Franks & Hardy, 2010).

Studies found HSP to restores ovarian structure and improves ovulatory competence in experimentally induced ovo-toxicity and letrozole-induced PCOS models by preserving follicular architecture, reducing follicular atresia, and promoting orderly progression through primary, secondary, preantral, and antral stages, ultimately expanding the functional ovarian reserve (Shoorei *et al*., 2019; Zarein *et al*., 2023; Taheri *et al*., 2021; Andhalkar *et al*., 2021).

An *in vitro* study by Shoorei *et al*., reported HSP (50 µmol/L) to improve follicle survival (P<0.01), enhanced antrum formation (P<0.001), and greater metaphase II oocyte yield (P<0.05) in 3D alginate cultures of preantral follicles. HSP induced dose-dependent increases in follicular diameter and elevated proliferating cell nuclear antigen (PCNA) immunoreactivity, suggesting accelerated granulosa cell proliferation and maturation (Shoorei *et al*., 2019).

Consistent with *in vitro* findings, HSP significantly increased primary, secondary, and antral follicle numbers while markedly lowering atretic follicle counts in malathion-exposed mice. These effects were accompanied by restored corpus luteum formation and improved stromal integrity, indicating restored ovarian histoarchitecture and improved functionality (Zarein *et al*., 2023; Talebi *et al*., 2024).

HSP also found to re-establishes homeostasis of HPO axis. In malathion treated animals, HSP restored the normal level of serum estradiol (E2), progesterone (P4), FSH, and LH (P<0.001) and normalized the LH/FSH ratio. These hormonal corrections corresponded with upregulated FSH receptor (FSHR) expression in granulosa cells (Zarein *et al*., 2023). Another study showed, in letrozole induced PCOS rats, HSP restored LH:FSH ratio levels, normalized the serum level of E2 and P4, beside showing anti-androgenic effect and attenuated polycystic ovarian morphology by increasing antral follicles and decreasing atretic and cystic follicles (P<0.05) (Andhalkar *et al*., 2021).

A recent finding by Shoorei *et al*., demonstrated, HSP (50 µmol/L) to improve *in vitro* fertilization (IVF) success (P < 0.05), with significantly greater progression to the 2-cell, 4-cell, morula, and blastocyst stages following fertilization with epididymal spermatozoa in 3D alginate hydrogel cultures of isolated preantral mouse follicles. Post-fertilization analyses showed that HSP-treated metaphase II oocytes displayed improved pronuclear formation, symmetrical blastomere cleavage, and more consistent cavitation patterns. These developmental advantages corresponded with dose-dependent increases in follicular diameter and improved zona pellucida structure, indicating enhanced cytoplasmic maturation and developmental competence (Shoorei *et al*., 2019).

Earlier mid-20th-century claims that phosphorylated hesperidin impaired fertility through hyaluronidase inhibition are not supported by contemporary evidence. Modern studies instead demonstrate that native HSP at physiologically beneficial concentrations (≈50 µmol/L) supports cumulus–oocyte complex expansion and acrosomal function, rather than impairing them (Shoorei *et al*., 2019). Although. to date, no human clinical trials have directly evaluated the effect of HSP on controlled ovarian stimulation outcomes, oocyte yield, embryo quality, implantation, or live birth rates.

2.2. Ameliorative effect HSP on oxidative, inflammation and apoptosis

The pathogenesis of PCOS is critically driven by oxidative stress, chronic low-grade inflammation, and granulosa cell apoptosis, which collectively disrupt folliculogenesis and HPO axis regulation (Ouyang *et al*., 2025). Elevated reactive oxygen species (ROS) in PCOS ovaries impairs granulosa cell steroidogenesis, accelerates follicular atresia via Bax upregulation and Bcl-2 downregulation, and exacerbates IR, while NF-κB-mediated TNF-α/IL-6 release promotes hyperandrogenemia and cyst formation (Liu *et al*., 2025). This vicious cycle amplifies apoptosis through caspase-3/9

activation and mitochondrial dysfunction, reducing ovarian reserve and ovulatory competence (Wang *et al*., 2025)

HSP exhibits potent antioxidative activity by scavenging ROS, suppressing lipid peroxidation, and enhancing endogenous antioxidant defences. This includes upregulation of key antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and replenishing reduced glutathione (GSH), thereby restoring redox homeostasis (Tirkey *et al*., 2005; Adefegha *et* al., 2017; Chen *et al*., 2024a).

In experimentally induced pleurisy by carrageenan, oral administration of HSP (80 mg/kg for 21 days) significantly decreased pleural exudate formation, leukocyte infiltration, and myeloperoxidase (MPO) activity. These improvements were paralleled by reductions in ROS fluorescence, along with restoration of non-protein sulfhydryl (NPSH) groups and δ-aminolevulinic acid dehydratase (δ-ALAD) activity, biomarkers typically suppressed during acute oxidative injury (Adefegha *et* al., 2017).

Mechanistically, HSP activates the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway, which promotes transcription of antioxidant enzymes, while concurrently suppressing NADPH oxidase 4 (NOX4) via upregulation of sirtuin 1 (SIRT1). This dual modulatory action has been demonstrated in nickel-induced hepatorenal toxicity models, where HSP reduced malondialdehyde (MDA) accumulation, inhibited apoptotic cell death, and enhanced SOD, CAT, and GPx activities (Ji *et al*., 2024).

HSP mitigates chronic inflammation primarily through suppression of NF-κB signaling and downstream pro-inflammatory cytokines, including TNF-α and IL-6, thereby limiting neutrophil activation, chemotaxis, and tissue infiltration. In toxin- or drug-induced organ injury models, such as cyclophosphamide hepatotoxicity and metal or drug induced nephrotoxicity, HSP significantly downregulated NF-κB and p65 activation and reduced transcription and translation of TNF-α and IL-6, which translated into attenuated inflammatory cell infiltration and improved tissue architecture (Subramanian *et al*., 2015; Zhou *et al*., 2019). Similarly, in models of nanoparticle or bleomycin induced lung and brain injury, HSP reduced oxidative–inflammatory signaling by inhibiting IκBα degradation, decreasing NF-κB nuclear translocation, and concomitantly lowering pro-inflammatory cytokines, supporting its role as a systemic anti-inflammatory modulator (Zhou *et a*l., 2019; Al-Rikabi *et al*., 2020).

In malathion-induced ovarian toxicity models, HSP restored ovarian histoarchitecture by downregulating pro-apoptotic markers such as Bax and NF-κB and upregulating the expression of the anti-apoptotic protein Bcl-2. Additionally, HSP modulated key microRNAs, including miR-129-3p and miR-96-5p, contributing to the attenuation of inflammation-associated granulosa cell apoptosis (Talebi *et al*., 2024).

Evidence from cyclophosphamide- and irradiation-induced ovarian injury further demonstrates the role of HSP in preserving granulosa and theca cell integrity, reducing activation of caspase-3 and caspase-9, and limiting follicular atresia by exerting antioxidative and anti-apoptotic effects (Chen *et al*., 2024b). At the molecular level, HSP suppresses apoptotic signaling by modulating Bax/Bcl-2 ratio, inhibiting caspase activation, and reducing PARP cleavage, which are hallmark events for initiating and executing apoptosis. HSP also suppresses transcription factors like specificity protein 1 (Sp1), which modulates cell proliferation and survival genes, contributing further to its anti-apoptotic effect (Aggarwal *et al*., 2020). In dihydrotestosterone exposed granulosa cell models, hesperidin reduced intracellular ROS, decreased pro-apoptotic signaling, and maintained cell viability even under experimental JAK2 activation or PI3K inhibition, indicating that its protective effect involves fine tuning of these pathways rather than nonspecific antioxidant action (Zhang *et al*., 2025a). By restoring PI3K/AKT signaling and restraining aberrant JAK2/STAT3 activation, HSP attenuates ROS driven inflammatory responses and apoptosis in granulosa cells, thereby linking its systemic antioxidant and anti-inflammatory properties to localized ovarian protection and improved follicular survival in PCOS (Zhang *et al*., 2025a).

These mechanisms highlight multi-targeted approach of HSP to protect ovarian follicles from oxidative stress, inflammation and apoptosis, thereby maintaining follicular viability and improving ovarian function.

2.3. Effect of HSP on IR and glucose homeostasis

Approximately **50–70% of women with PCOS exhibit** IR **(IR) (**Legro *et al*., 2013). The resulting hyperinsulinemia disrupts follicular growth by impairing glucose uptake and reducing glycolytic energy production in granulosa cells. Excess insulin also elevates circulating androgens by stimulating LH release through the insulin receptors and by suppressing sex hormone–binding globulin (SHBG) synthesis. Moreover, IR contributes to dyslipidemia by downregulating lipid droplet associated proteins in adipocytes **(**Houston *et al*., 2025). Thus, IR serves as a central pathological link between the reproductive and metabolic disturbances characteristic of PCOS.

HSP ameliorates IR and restores glycemic balance predominantly in high-fat diet (HFD)–induced obesity and hyperglycemia models, with progressive reductions in fasting blood glucose, random blood glucose, circulating insulin, and improved homeostatic model assessment for IR (HOMA-IR), while not inducing hypoglycemia in normoglycemic controls (Peng *et al*., 2021; Rehman *et al*., 2020). At the molecular level, HSP found to enhances insulin signaling by activating the insulin receptor/phosphoinositide-dependent kinase-1 (PDK1) pathway in adipocytes and hepatocytes, increasing IR phosphorylation and PDK1 phosphorylation, resulting in an 11–61% dose-dependent enhancement of glucose uptake in 2-deoxyglucose assays, independent of changes in total IR or PDK1 protein expression (Peng *et al*., 2021).

In high-glucose–exposed LO2 hepatocytes, HSP restored insulin sensitivity by promoting AKT/GSK3β phosphorylation, upregulating glucose transporters expression including GLUT2/GLUT4 and insulin receptor substrate-1 (IRS1), while enhancing antioxidant defenses (SOD/GPx) and reducing ROS and MDA levels thereby improving mitochondrial redox status and normalizing glucose metabolic flux via boosted

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glucokinase and suppressed glucose-6-phosphatase/PEPCK (Tian *et al*., 2021). Concurrently HSP found to correct hyperglycemia and androgen excess, in experimentally induced PCOS in animal model, supporting its utility in IR-dominant PCOS phenotypes (Andhalkar *et al*., 2021). However, a clinical trial demonstrated modest glycemic improvements, with meta-analytic evidence showing a nonsignificant reduction in fasting plasma glucose (FPG) across 8 RCTs (Shams-Rad *et al*., 2020).

2.5. Effect of HSP on dyslipidemia and obesity

Epidemiological data indicate that 38–88% of women with PCOS are overweight or obese (Barber *et al*., 2019). Excess adiposity increases lipolysis and circulating free fatty acids (FFA), impairing insulin-dependent glucose uptake and contributing to IR. Obesity further drives adipocyte hypertrophy, cell death, and elevated pro-inflammatory cytokine production (Guilherme *et al*., 2008). This metabolic dysregulation manifests as dyslipidemia, characterized by elevated triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and reduced high-density lipoprotein cholesterol (HDL-C) in 70% of PCOS patients, exacerbating cardiovascular risk through atherogenic lipid profiles and impaired reverse cholesterol transport (Wild *et al*., 2011).

HSP improves dysregulated lipid metabolism and mitigates obesity in HFD induced hyperlipidemia and non-alcoholic fatty liver disease (NAFLD) models by lowering circulating TC, TG, and LDL-C, reducing hepatic lipid deposition, and elevating HDL-C in rodent models, alongside significant body weight reduction and decreased fat mass (Xiong *et al*., 2019; Liu *et al*., 2024; Morshedzadeh *et al*., 2023). Consistently HSP showed corrective effect on dyslipidemia in cadmium chloride exposed rats and also found with a hepatoprotective effect (Aja *et al*., 2020). These effects are mediated by suppression of de novo lipogenesis, downregulating the transcription and translation of SREBP-1c, ACC, and FAS and enhancement of fatty acid β-oxidation via upregulation of PPAR-α and CPT-1, reducing hepatic lipid accumulation, VLDL secretion, and adiposity (Mosqueda-Solís *et al*., 2018; Liu *et al*., 2024).

Mechanistically, HSP activates the AMPK pathway, leading to ACC phosphorylation and reduced malonyl-CoA, thereby relieving inhibition of CPT-1 and promoting mitochondrial fatty acid oxidation. HSP further modulates lipid transport by regulating transcripts such as RBP, H-FABP, and C-FABP, contributing to reduced VLDL output and diminished LDL oxidation via boosted PON-1 activity while suppressing obesogenic gut microbiota shifts (Wang *et al*., 2011; Liu *et al*., 2024).

Clinical meta-analyses similarly show modest yet significant reductions in TC and TG at doses ≥500 mg/day over 4-12 weeks across 12 RCTs, while serum LDL-C and HDL-C appear variable (5-15% inconsistent gains), with body weight effects remaining understudied in humans indicating dose- and duration-dependent benefits in dyslipidemic individuals (Heidari *et al*., 2025).

2.6. Effect of HSP on gut-biota

The human gut harbors approximately 10^{14} microorganisms, predominantly Firmicutes and Bacteroidetes (Faith *et al*., 2013). In PCOS, both α- and β-diversity are reduced, accompanied by disturbances in the Firmicutes/Bacteroidetes ratio (Hanna *et al*., 2025). Such dysbiosis compromises intestinal barrier integrity, facilitating LPS translocation into circulation, which promotes chronic inflammation, IR, and obesity (Ghosh *et al*., 2020). Altered gut microbiota can also disrupt gut–brain axis signaling, including GABA pathways, contributing to excessive GnRH and LH secretion (Yao *et al*, 2015). Thus, gut microbial imbalance is a key pathogenic factor in PCOS development and progression.

HSP reported to significantly enhance microbial α-diversity, enriches beneficial commensals such as *Lactobacillus* spp., and reduces pathobionts under conditions of HFD induced dysbiosis or xenobiotic injury (Liu *et al*., 2024; Yang *et al*., 2024). In healthy and HFD-fed rodents, HSP increases the proportion of IgA-coated bacteria, elevates intestinal secretory IgA levels, expands $TCR\alpha\beta^{+}$ lymphocyte populations in mesenteric lymph nodes, and strengthens gut-associated lymphoid tissue (GALT), reflecting an immunomodulatory, prebiotic effect (Estruel-Amades *et al*., 2019).

These microbial and immune changes are accompanied by marked restoration of intestinal barrier integrity through upregulation of tight-junction proteins such as ZO-1 and occludin, reduced gut permeability, and attenuation of circulating inflammatory cytokines including TNF-α, IL-6, and IL-1β (Liu *et al*., 2024; Wang *et al*., 2025). Crucially, fecal microbiota transplantation (FMT) from HSP-treated donors to naïve HFD fed mice recapitulates the metabolic improvements and decreased systemic inflammation (Liu *et al*., 2024). Beyond obesity, HSP and its aglycone hesperetin also rectify microbial dysbiosis and attenuate IL-17 and TLR4/NF-κB-driven inflammatory injury in models of irinotecan-induced mucositis, colitis, and other epithelial barrier disruptions, further highlighting its role in maintaining mucosal immune tolerance and epithelial resilience (Zhang *et al*., 2025b; Wang *et al*., 2024; Ran *et al*., 2024). *In vitro* anaerobic fermentation studies show that hesperidin and related flavanones significantly alter microbial metabolic outputs including enhanced short-chain fatty acid (SCFA) synthesis—while interacting synergistically with dietary fibers such as RG-I pectins to modulate community structure and improve microbial fermentation efficiency (Pan et al., 2023; Wu et al., 2024). Related compounds such as neohesperidin similarly mitigate HFD induced colitis and rebalance SCFA producing bacteria (Lu et al., 2025), suggesting conserved microbiota-targeted activity across citrus flavanones. Collectively, these findings support hesperidin as a microbiota-mediated therapeutic candidate capable of restoring eubiosis, strengthening intestinal barrier function, and reducing endotoxin-induced inflammatory signaling—mechanisms directly linked to LPS-driven metabolic inflammation, IR, and ovarian dysfunction central to PCOS pathophysiology. Despite strong preclinical support, human trials evaluating the microbiome-modulatory effects of HSP in PCOS populations are lacking, representing a key translational opportunity.

3. Conclusion

Collective evidence positions hesperidin as a biologically versatile compound capable of intervening at several critical nodes of PCOS pathophysiology. By simultaneously mitigating oxidative stress, inflammatory activation, metabolic dysfunction, and granulosa-cell apoptosis, while also improving folliculogenesis and hormone homeostasis, HSP addresses both reproductive and metabolic features of the disorder in a manner unmatched by most current pharmacotherapies. The growing recognition of the gut–ovarian axis in PCOS further elevates the significance of HSP's microbiota-modulating actions, including restoration of microbial diversity, tightening of epithelial barrier function, and suppression of LPS-mediated systemic inflammation. These convergent effects suggest that HSP may function not merely as an adjunctive antioxidant but as a multi-axis regulator capable of influencing the endocrine, metabolic, and immune pathways that sustain PCOS.

Nevertheless, the majority of evidence arises from in vitro and animal models. Translation into clinical practice will require rigorous human studies that define optimal dosing, bioavailability enhancing formulations, pharmacokinetics, and long-term safety. While preliminary findings are promising, establishing HSP as a therapeutic option for PCOS will depend on closing these translational gaps through well-designed clinical investigations.

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5. References

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