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Review Article

Resveratrol in the Management of Polycystic Ovary Syndrome: Molecular Mechanisms, Pharmacological Effects, and Clinical Evidence

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ABSTRACT

Polycystic Ovary Syndrome (PCOS) is a complex endocrine and metabolic disorder characterized by hyperandrogenism, ovulatory dysfunction, insulin resistance, chronic inflammation, and oxidative stress, which collectively contribute to reproductive and metabolic complications in women of reproductive age. Current therapeutic strategies primarily provide symptomatic management and are often associated with adverse effects and limited long-term efficacy, necessitating the development of safer and multi-targeted treatment approaches. Resveratrol (RV), a naturally occurring polyphenolic compound, has gained considerable attention owing to its diverse pharmacological properties, including antioxidant, anti-inflammatory, insulin-sensitizing, anti-obesity, cardioprotective, and anti-hyperandrogenic activities. This review comprehensively summarizes the chemistry, pharmacokinetics, safety profile, molecular mechanisms, and therapeutic potential of RV in PCOS. Emerging evidence indicates that RV modulates key signaling pathways, including SIRT1/AMPK, PI3K/Akt, NF-κB, and Nrf2, thereby improving insulin sensitivity, suppressing androgen synthesis, attenuating oxidative stress and inflammation, and restoring ovarian function. Furthermore, preclinical and clinical studies have demonstrated its beneficial effects on hormonal regulation, metabolic parameters, follicular development, and reproductive outcomes in PCOS. Despite its promising therapeutic potential, the clinical application of RV remains limited by poor oral bioavailability, rapid metabolism, and the lack of standardized therapeutic regimens. Advances in novel drug delivery systems and well-designed clinical investigations are required to optimize its therapeutic efficacy and establish its role in evidence-based PCOS management. Overall, RV represents a promising multi-target natural therapeutic candidate for addressing the complex pathophysiology of PCOS and improving both reproductive and metabolic health outcomes.

Keywords: Alternative therapy, Cardioprotective, Polycystic ovary syndrome, Resveratrol, Women's health.

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INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is one of the most common endocrine and metabolic disorders affecting women of reproductive age, with an estimated prevalence of 8-13% according to the Rotterdam diagnostic criteria (Ndefo *et al*., 2013). It is characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology, resulting in reproductive, metabolic, and psychological complications that substantially impair quality of life. In addition to menstrual irregularities, infertility, hirsutism, and acne, women with PCOS are at increased risk of insulin resistance, obesity, type 2 diabetes mellitus, dyslipidemia, cardiovascular disease, and endometrial cancer (Lin *et al*., 2013).

According to the Rotterdam consensus criteria, PCOS is diagnosed by the presence of at least two of the following: oligo- or anovulation, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology after excluding related endocrine disorders. These criteria classify PCOS into four phenotypes with varying reproductive and metabolic manifestations (Liao *et al*., 2021).

Although the precise pathophysiology of PCOS remains incompletely understood, increasing evidence indicates that the syndrome results from complex interactions among genetic susceptibility, environmental factors, insulin resistance, chronic low-grade inflammation mediated by oxidative stress and Nuclear Factor Kappa B (NF-κB) signaling (Cooney and Dokras, 2018; McFarland, 2012). Hyperinsulinemia enhances ovarian androgen

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production and disrupts follicular development, while chronic inflammation and oxidative stress further aggravate ovarian dysfunction, ultimately contributing to anovulation and infertility (Szydlarska *et al.*, 2017). These interconnected mechanisms make PCOS a multifactorial disorder requiring therapeutic strategies that target multiple pathological pathways rather than individual symptoms (Dewailly *et al.*, 2006; McLuskie and Newth, 2017).

Current management of PCOS primarily relies on lifestyle modification, combined oral contraceptives, insulin sensitizers (e.g., metformin), ovulation-inducing agents, and anti-androgen therapies (Guastella *et al.*, 2010; Pehlivanov and Orbetzova, 2007). While these approaches improve reproductive and metabolic outcomes, they are frequently associated with gastrointestinal disturbances, hormonal adverse effects, limited long-term efficacy, or recurrence of symptoms following treatment discontinuation. Consequently, there is growing interest in identifying safer, multi-target therapeutic agents derived from natural products (Gluszak *et al.*, 2012; Kar, 2013).

Among naturally occurring phytochemicals, Resveratrol (RV) has attracted considerable attention because of its broad pharmacological activities, including antioxidant, anti-inflammatory, insulin-sensitizing, anti-obesity, cardioprotective, and anti-hyperandrogenic properties (Manzoor *et al.*, 2019). Experimental and emerging clinical evidence suggests that RV modulates several signaling pathways implicated in PCOS, including Sirtuin 1/AMP-Activated Protein Kinase Signaling Pathway (SIRT1/AMPK), Phosphoinositide 3-Kinase/Protein kinase B signaling pathway (PI3K/Akt), NF-κB, and oxidative stress-related pathways, thereby improving insulin sensitivity, reducing androgen synthesis, attenuating inflammation, and restoring ovarian function. Its pleiotropic pharmacological activities make it an attractive candidate for targeting the multifactorial pathogenesis of PCOS (Okoth *et al.*, 2020).

This review comprehensively summarizes the pharmacological properties, molecular mechanisms, pharmacokinetics, and therapeutic potential of RV in PCOS. It critically discusses evidence from preclinical and clinical studies, highlights current limitations, and identifies future research directions required for the successful clinical translation of RV in PCOS management. Despite its promising biological activities, the clinical application of RV is limited by poor aqueous solubility, rapid metabolism, and low oral bioavailability, highlighting the need for improved delivery strategies and further clinical investigation.

METHODOLOGY

Literature was searched in PubMed, Scopus, Web of Science and Google Scholar using keywords including "Resveratrol", "PCOS", "Polycystic ovary syndrome", "oxidative stress", "inflammation", and "insulin resistance". English-language articles published up to 2025 were included. Original research, clinical studies and systematic reviews were considered.

Resveratrol: Chemistry and Biological Significance

Chemical Classification

Resveratrol (3,5,4′-trihydroxystilbene; RV) is a naturally occurring non-flavonoid polyphenolic compound belonging to the stilbene family of phytochemicals (Galiniak *et al.*, 2019). It is synthesized by numerous plant species as a phytoalexin in response to environmental stressors, including ultraviolet radiation, microbial infection, oxidative stress, and physical injury (Breuss *et al.*, 2019; Salehi *et al.*, 2018). Owing to its diverse pharmacological activities, RV has attracted considerable attention in biomedical research over the past few decades. It exhibits antioxidant, anti-inflammatory, insulin-sensitizing, cardioprotective, neuroprotective, and anti-apoptotic properties that contribute to its therapeutic potential in several chronic disorders (Bhattacharya *et al.*, 2023; Meng *et al.*, 2020). Furthermore, its ability to modulate multiple cellular signaling pathways has established RV as a promising natural bioactive compound for the management of metabolic and reproductive diseases (Meng *et al.*, 2023; Walle, 2011).

Natural Occurrence

RV is naturally present in more than seventy plant species and is widely distributed in various dietary and medicinal sources (Li *et al.*, 2016; Wang *et al.*, 2011). It is predominantly found in grapes (*Vitis vinifera*), blueberries, cranberries, mulberries, peanuts, soybeans, pistachios, pomegranate seeds, dark chocolate, and red wine (Burns *et al.*, 2002; Keylor *et al.*, 2015; Marques *et al.*, 2009). Among medicinal plants, *Polygonum cuspidatum* (Japanese knotweed or Itadori) is considered one of the richest commercial sources of RV and is extensively utilized for its pharmaceutical extraction (Francioso *et al.*, 2014). The concentration of RV varies considerably among natural sources owing to differences in plant species, environmental conditions, cultivation practices, and post-harvest processing. The widespread occurrence of RV in commonly consumed foods has contributed significantly to its recognition as a safe and therapeutically valuable phytochemical (Hsu *et al.*, 2014; Kulkarni and Cantó, 2015).

Cis- and Trans-Isomers of RV

RV exists naturally in two geometric isomeric forms, namely cis-RV and trans-RV. Among these, trans-RV is the more stable and biologically active isomer and accounts for the majority of the reported therapeutic effects (Rauf *et al.*, 2017). Structurally, RV comprises two aromatic phenolic rings linked by an ethylene bridge, conferring potent antioxidant properties and enabling interactions with multiple intracellular signaling pathways (Cvejic *et al.*, 2010; Lim and Koffas, 2010; Sanders *et al.*, 2000). Exposure to ultraviolet light and certain environmental conditions may induce the isomerization of trans-RV to the cis

form, potentially affecting its biological activity and stability. Consequently, trans-RV remains the preferred form employed in most experimental and clinical investigations (Chan *et al.*, 2019; Chiva-Blanch *et al.*, 2011; Jeandet *et al.*, 1992).

Biological Significance and Therapeutic Relevance in PCOS

The biological significance of RV lies in its pleiotropic ability to regulate oxidative stress, inflammation, mitochondrial function, apoptosis, and cellular metabolism. Numerous studies have demonstrated that RV modulates key molecular pathways, including SIRT1/AMPK, PI3K/Akt, NF-κB, and Nuclear Factor erythroid 2-related factor 2 signaling pathway (Nrf2), thereby exerting antioxidant, anti-inflammatory, insulin-sensitizing, and cytoprotective effects (Romero-Pérez *et al.*, 1996; Vang *et al.*, 2011). These multi-target mechanisms are particularly relevant to PCOS, a multifactorial endocrine disorder characterized by insulin resistance, hyperandrogenism, chronic inflammation, oxidative stress, and impaired follicular development (Goldberg *et al.*, 2003). Emerging evidence suggests that RV can simultaneously improve insulin sensitivity, suppress androgen biosynthesis, attenuate inflammatory responses, and promote normal ovarian function. The ability of RV to target multiple pathological pathways involved in PCOS highlights its considerable therapeutic potential and provides a strong rationale for its continued investigation in preclinical and clinical settings (Table 1) (Gambini *et al.*, 2015).

Therapeutic Dose, Pharmacokinetics and Safety Profile of RV

Dietary Sources and Therapeutic Dose of RV

RV is present in a variety of dietary sources, including red grapes, blueberries, cranberries, peanuts, mulberries, soybeans, pistachios, pomegranate seeds, dark chocolate, and red wine (Walle *et al.*, 2004). Among these, *Polygonum cuspidatum* (Japanese knotweed) is recognized as one of the richest natural sources and is extensively utilized for the commercial extraction of RV (Kaldas *et al.*, 2010). The concentration of RV varies considerably among food products depending on plant species, geographical conditions, cultivation practices, and processing methods. Red grapes contain approximately 92-1604 mg/kg of RV, whereas red wine contains 0.361-1.972 mg/L. Similarly, peanuts contain 0.03-0.14 mg/g, dark chocolate contains approximately 350 mg/kg, and Itadori tea provides approximately 68 mg/100 mL of RV (Vitrac *et al.*, 2003). Despite its widespread occurrence in natural products, achieving therapeutically relevant concentrations through dietary intake alone remains challenging (Almeida *et al.*, 2009; Goldberg *et al.*, 2003). Figure 1 illustrates the sources and dosing range of RV.

The therapeutic dose of RV has primarily been established through preclinical investigations and clinical dose-escalation studies. Human clinical trials have demonstrated that daily doses ranging from several hundred milligrams to 5 g are generally well tolerated over short-term administration. Low-dose supplementation (8 mg/day) has been associated with improvements in cardiovascular risk factors, whereas doses between 500 and 1000 mg/day are commonly employed in metabolic and inflammatory disorders (Herr *et al.*, 2015). Furthermore, short-term administration of up to 2 g/day has demonstrated an acceptable safety profile in healthy individuals. Although high-dose supplementation has been utilized in clinical studies, an optimal therapeutic dose for specific disease conditions, including PCOS, has not yet been established. Consequently, further dose-optimization studies are warranted to determine the most effective and safe therapeutic regimen for long-term clinical applications (Bahramrezaie *et al.*, 2019; Ortega *et al.*, 2012).

Pharmacokinetics of RV

RV exhibits favorable intestinal absorption but relatively poor systemic bioavailability due to rapid metabolism and extensive first-pass conjugation. Following oral administration, approximately 70-75% of RV is absorbed through passive diffusion and transporter-mediated mechanisms in the gastrointestinal tract. Figure 2 shows the pharmacokinetics of RV. Nevertheless, only trace amounts of unmetabolized RV are detected in systemic circulation because it undergoes rapid biotransformation within intestinal epithelial cells and the liver (Banaszewska *et al.*, 2016).

Absorption

Orally administered RV is rapidly absorbed from the gastrointestinal tract and reaches peak plasma concentrations within approximately 30-60 min following administration. Despite its efficient absorption, its limited aqueous solubility and extensive metabolism substantially reduce the concentration of free RV available for therapeutic activity. Consequently, pharmacological effects are thought to arise from both the parent compound and its biologically active metabolites (Wang *et al.*, 2020).

Distribution

Following absorption, RV is distributed to various tissues, including the liver, kidneys, heart, adipose tissue, and reproductive organs. Experimental studies have demonstrated its ability to accumulate within metabolically active tissues and modulate multiple intracellular signaling pathways involved in inflammation, oxidative stress, and mitochondrial function. The extensive tissue distribution of RV contributes to its broad spectrum of biological activities (Chen *et al.*, 2022).

Metabolism

RV undergoes rapid phase II metabolism in the intestine and liver through glucuronidation and sulfation reactions mediated primarily by Uridine Diphosphate Glucuronosyl Transferases

(UGTs) and Sulfotransferases (SULTs). Major circulating metabolites include RV-3-O-glucuronide, RV-4′-O-glucuronide, and RV sulfates, which may contribute substantially to its pharmacological effects. However, rapid metabolic conversion significantly limits circulating concentrations of free RV following oral administration (Ortega *et al.*, 2012).

Bioavailability Limitations

Poor aqueous solubility, rapid metabolism, extensive first-pass conjugation, and relatively short plasma half-life collectively contribute to the low oral bioavailability of RV. These pharmacokinetic limitations represent one of the major challenges hindering its successful clinical translation. Consequently, numerous formulation strategies, including nanoparticles, liposomes, phytosomes, polymeric micelles, and nanofiber-based delivery systems, are currently being explored to improve its stability, enhance systemic exposure, and achieve sustained therapeutic effects (Brenjian *et al.*, 2020; Ghowsi *et al.*, 2018; Marti *et al.*, 2017).

Safety and Toxicity Profile of RV

RV possesses a favorable safety profile and is generally well tolerated in both experimental models and human clinical studies. Short-term supplementation at doses ranging from several hundred milligrams to 5 g/day has demonstrated minimal toxicity in healthy individuals. The most frequently reported adverse effects include mild gastrointestinal disturbances, such as nausea, abdominal discomfort, diarrhea, and bloating, particularly at higher doses. Importantly, no serious treatment-related toxicities have been consistently reported in clinical investigations involving short-term administration (Ortega *et al.*, 2012).

Although RV exhibits low toxicity, long-term safety data remain limited, particularly in individuals with chronic metabolic disorders requiring prolonged therapeutic intervention. Moreover, variability in dosage regimens among clinical studies has hindered the establishment of standardized therapeutic recommendations. Future investigations focusing on dose optimization, improved delivery systems, and long-term clinical outcomes are therefore essential for the successful clinical translation of RV in PCOS management (Marti *et al.*, 2017).

Molecular Mechanisms of RV In PCOS

Regulation of Hyperandrogenism

Hyperandrogenism represents one of the principal pathological hallmarks of PCOS and contributes significantly to anovulation, follicular arrest, and metabolic dysfunction. Excessive androgen production by ovarian theca cells is frequently associated with hyperinsulinemia and dysregulated steroidogenic signaling pathways. Elevated insulin levels potentiate luteinizing hormone-mediated androgen synthesis through the upregulation of steroidogenic enzymes, including Cytochrome P450 17A1 (CYP17A1), thereby exacerbating reproductive abnormalities in PCOS (Mansour *et al.*, 2021).

Emerging evidence suggests that RV effectively suppresses ovarian androgen biosynthesis through multiple mechanisms. Experimental studies have demonstrated that RV downregulates the expression of CYP17A1 and other steroidogenic enzymes involved in androgen production while simultaneously improving insulin sensitivity, thereby indirectly reducing hyperinsulinemia-induced androgen synthesis. Furthermore, RV has been shown to inhibit ovarian theca cell proliferation and modulate signaling pathways implicated in steroidogenesis. Clinical investigations have also reported reductions in circulating testosterone concentrations following RV supplementation in women with PCOS. Collectively, these findings indicate that RV exerts anti-hyperandrogenic effects that may contribute substantially to restoring normal ovarian physiology (Arentz *et al.*, 2014).

Improvement of Insulin Resistance and Metabolic Dysfunction

Insulin resistance affects a significant proportion of women with PCOS and plays a central role in the development of hyperandrogenism, obesity, and impaired glucose metabolism. Hyperinsulinemia promotes ovarian androgen synthesis while simultaneously disrupting follicular maturation and ovulatory function. Consequently, therapeutic interventions targeting insulin signaling pathways have emerged as important strategies in PCOS management (Dutta *et al.*, 2025).

RV exhibits potent insulin-sensitizing properties through the activation of SIRT1 and AMP-Activated Protein Kinase (AMPK), two critical regulators of cellular metabolism and energy homeostasis. Activation of the SIRT1/AMPK axis enhances glucose uptake, improves insulin signaling, and suppresses hepatic gluconeogenesis, thereby contributing to improved metabolic outcomes. Additionally, RV modulates the PI3K/Akt signaling pathway, which plays a pivotal role in insulin-mediated glucose metabolism. Experimental studies have demonstrated improvements in fasting glucose levels, insulin sensitivity, and lipid metabolism following RV administration, highlighting its therapeutic potential in addressing metabolic abnormalities associated with PCOS (Chen and Zheng, 2021; Kaźmierczak *et al.*, 2025).

Modulation of Oxidative Stress

Increasing evidence implicates oxidative stress as a major contributor to ovarian dysfunction in PCOS. Excessive production of Reactive Oxygen Species (ROS) disrupts mitochondrial function, promotes granulosa cell apoptosis, and impairs follicular development. Oxidative stress additionally exacerbates insulin resistance and inflammatory responses,

creating a pathological cycle that perpetuates disease progression (Karunakar *et al.*, 2024; Li *et al.*, 2020).

RV possesses potent antioxidant properties attributable to its polyphenolic structure and its ability to regulate endogenous antioxidant defence systems. It enhances the expression and activity of antioxidant enzymes, including superoxide dismutase, catalase, and glutathione peroxidase, while simultaneously reducing lipid peroxidation and ROS accumulation. Furthermore, activation of the Nrf2 pathway by RV promotes cellular resistance against oxidative injury and preserves mitochondrial integrity. By mitigating oxidative stress-induced cellular damage, RV contributes significantly to the maintenance of normal ovarian function and improved reproductive outcomes in PCOS (Bezdoode *et al.*, 2025; Nandhini *et al.*, 2024a; Pang *et al.*, 2017; Venugopal *et al.*, 2023).

Anti-inflammatory Mechanisms

Chronic low-grade inflammation is increasingly recognized as a fundamental pathological component of PCOS. Elevated circulating concentrations of pro-inflammatory cytokines, including Tumor Necrosis Factor-alpha (TNF-α), Interleukin-6 (IL-6), and interleukin-1β (IL-1β), contribute to insulin resistance, ovarian dysfunction, and impaired folliculogenesis. Activation of NF-κB signaling further amplifies inflammatory responses and promotes oxidative stress-mediated cellular injury (Ma *et al.*, 2015).

RV exerts pronounced anti-inflammatory effects through the inhibition of NF-κB activation and subsequent suppression of inflammatory cytokine production. Additionally, it attenuates inflammatory signaling by modulating SIRT1-dependent pathways and reducing oxidative stress-mediated inflammatory responses. Experimental studies have demonstrated that RV suppresses inflammatory mediators and improves cellular homeostasis within ovarian tissues. The simultaneous regulation of inflammation and oxidative stress highlights the multifaceted therapeutic potential of RV in PCOS management (Hoeger *et al.*, 2021).

Regulation of Folliculogenesis and Ovulatory Function

Abnormal follicular development and chronic anovulation are characteristic reproductive manifestations of PCOS. Elevated androgen concentrations, insulin resistance, oxidative stress, and inflammatory signaling collectively disrupt granulosa cell function and impair follicular maturation, resulting in the accumulation of immature follicles within the ovaries.

RV has demonstrated beneficial effects on ovarian physiology through the modulation of apoptosis, mitochondrial function, and cellular metabolism. Experimental investigations suggest that RV promotes granulosa cell survival and improves follicular development by regulating oxidative stress-related pathways and restoring metabolic homeostasis. Furthermore, improvements in insulin sensitivity and reductions in androgen production indirectly contribute to the normalization of ovulatory function. These observations suggest that RV may simultaneously target multiple reproductive abnormalities characteristic of PCOS (Chen *et al.*, 2010; Tas, 2024).

Effects on Angiogenesis and Ovarian Microenvironment

Abnormal ovarian angiogenesis has been implicated in the pathogenesis of PCOS and is associated with elevated expression of Vascular Endothelial Growth Factor (VEGF) and Hypoxia-Inducible Factor-1 alpha (HIF-1α). Dysregulated angiogenic signaling contributes to altered follicular development, ovarian remodeling, and inflammatory responses within the ovarian microenvironment (Hu *et al.*, 2019).

RV has been reported to modulate angiogenic pathways through the regulation of VEGF expression and hypoxia-related signaling mechanisms. Its antioxidant and anti-inflammatory activities further contribute to maintaining cellular homeostasis within ovarian tissues. By improving the ovarian microenvironment and attenuating pathological angiogenesis, RV may facilitate normal follicular development and reproductive function (Joshi *et al.*, 2021). Figure 3 explains the molecular mechanisms of RV in PCOS.

Pharmacological Effects of RV in Accordance with PCOS

Adding the pharmacological effects of RV to PCOS management is vital because it addresses key aspects of the syndrome's complexity. RV's anti-inflammatory, antioxidant, anti-obesity, and cardiovascular protective properties directly counteract PCOS-related issues such as inflammation, oxidative stress, obesity, insulin resistance, and cardiovascular complications. Figure 4 illustrates the effects of RV on PCOS pathogenesis.

Antioxidant effects

As an antioxidant, RV can do two things: it can make antioxidant enzymes work better and it can get rid of free radicals (Izzo *et al.*, 2021). Researchers discovered that daily dosing with 500 mg of RV significantly increased overall antioxidant capacity and blood SOD levels while decreasing serum MDA levels. Research has demonstrated that RV can maintain antioxidant levels sufficient for biological activities. Some research suggests that RV may increase activity of antioxidant enzymes such glutathione reductase, glutathione S-transferase, and GPx. It was discovered that SOD levels went up, GPx levels stayed the same, and catalase levels went down. So, keeping the right amount of antioxidative chemical activity is very important if you want to stop cancer from happening (García-Martínez *et al.*, 2021; Samsamikor *et al.*, 2016). One crucial feature is that RV can neutralise radicals such as hydroxyls and superoxides. Cell wall

lipid peroxidation and DNA damage are halted by this. Increasing the concentration of this molecule improved RV's antioxidant activity in a laboratory setting, indicating it was more effective at eliminating radicals. Theoretically, RV inhibits atherosclerosis in C2C12 cells by reducing low-density lipoprotein oxidation (Ho *et al.*, 2001). Based on Palmitate's hypothesis, NOS decreases RV expression and increasing GSH and SOD activity elevates it, while leaving unchanged PI3K/Akt components like PTEN, p-Akt, p/p-GSK3b, or redox DJ form levels-1 (Abdel-Aleem *et al.*, 2016). Previous research by Aydin and colleagues demonstrated that renal-hepatic sepsis induced oxidative DNA damage in rats when administered RV (100 mg/kg) through IP. GPx and MDA levels are lowered, GSH and SOD levels are raised, and TNF-prominent cytokine levels are lowered. Adding RV is helpful because it cleans, protects against free radicals, and reduces inflammation through a number of intracellular signaling pathways, such as better control of MAP/HO-1 ROS and ROS (Aydın *et al.*, 2016).

Based on the findings of Price *et al.*, it is thought that skeletal muscles, brown fat, and SIRT1 are involved in amplifying mitochondrial biogenesis and oxidative phosphorylation (Price *et al.*, 2012). PGC1a, an activating γ-coactivator 1-α growth factor, may be a downstream target of SIRT1. Some research suggests that RV can lower blood sugar levels by influencing how well GLP-1 and glucagon work (Acquaviva *et al.*, 2002; Dao *et al.*, 2011; Goswami and Das, 2009; Liu *et al.*, 2015; Losa, 2003).

Anti-inflammatory effects

Protein kinase B, COX, and 5-LOX are among RV's targets. This occurs because it has the ability to inhibit the activities of COX-1 and COX-2, in addition to transcription factors that play

Table 1: Outlines the therapeutic benefits of RV in treating PCOS. This table showcases the potential of RV in addressing many symptoms and underlying mechanisms of PCOS, emphasizing its significance as a prospective treatment agent.

Sl. No.	Dose	Detail	Cell line / Models	Reference
		***In vitro* Studies**		
1.	10-50 µM	Reduction of VEGF in granulosa cells	Granulosa cells	(Ortega, Wong, *et al.*, 2012)
2.	100 mg/kg	The p66Shc was subjected to mediated deacetylation, resulting in a decrease in the generation of ROS and fibrotic components.	DHEA-induced PCOS Rats model	(Wang *et al.*, 2020)
3.	5-50 µM (DMSO)	Blockage of the Akt/PKB signalling cascade	NCI-H295R cells	(Marti *et al.*, 2017)
4.	3-10 µM	Obliterated the activity of the mevalonate pathway and the phosphorylation of Akt/PKB.	The interstitial cells of the ovary	(Ortega, Villanueva, *et al.*, 2012)
5.	1-10 µM	Inhibited Cyp17a1 mRNA expression by blocking the activity of the Akt/PKB signalling pathway.	The interstitial cells of the ovary	(Ortega, Villanueva, *et al.*, 2012)
		***In vivo* Studies**		
6.	20 mg/kg	The resumption of the inward flow of calcium ions triggered the activation of CaMKIIβ, leading to the production of TZPs.	TBT-induced PCOS rats model	(M. Chen *et al.*, 2022)
7.	20 mg/kg	Stimulated the AMPK-SIRT-1 pathway and decreased the concentrations of AMH, testosterone, LH, and LH/FSH.	DHEA-induced PCOS rats model	(Rencber *et al.*, 2018)
		Clinical study		
8.	1500 mg	Diminished concentrations of testosterone and DHEA	PCOS Patients	(Banaszewska *et al.*, 2016)
9.	800 mg	Modified the expression of genes associated with the Unfolded Protein Response (UPR) pathway.	PCOS Patients	(Brenjian *et al.*, 2020)
10.	800 mg	Suppressed the expression of VEGF and HIF1 genes.	PCOS Patients	(Bahramrezaie *et al.*, 2019)

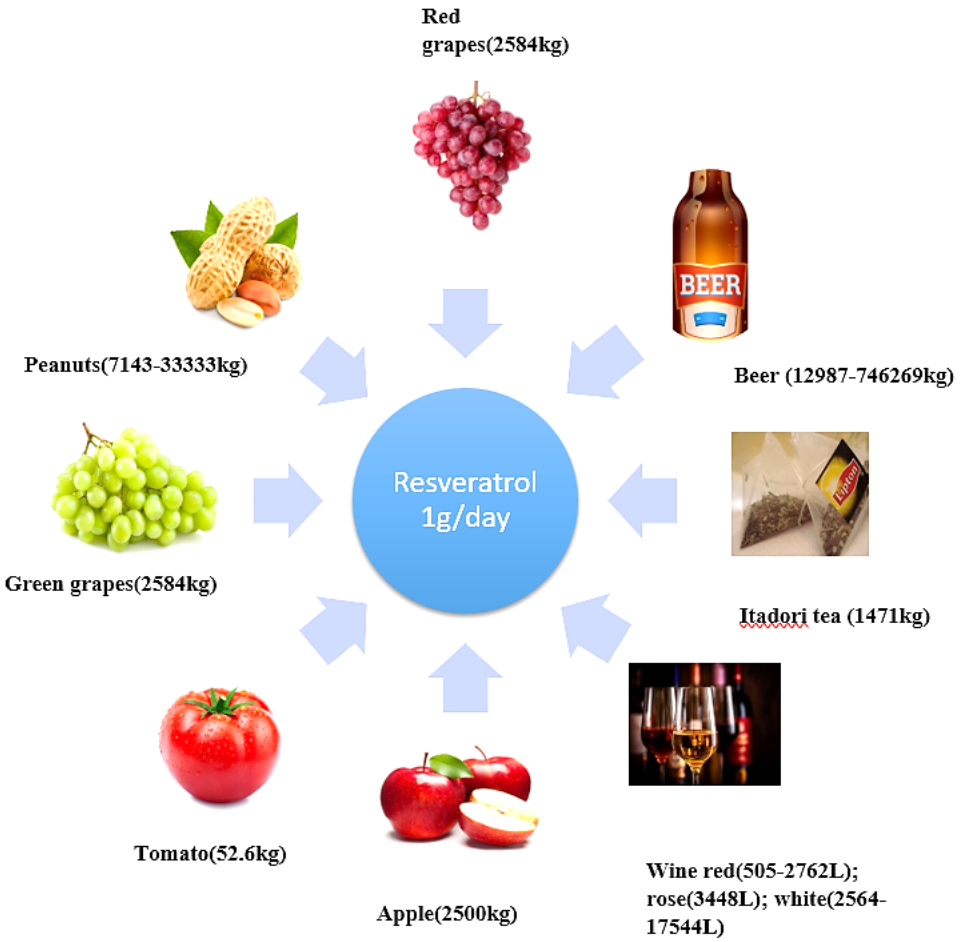


Figure 1: The amount of food and drink needed to reach a therapeutic dose may differ. Therapeutic intervention with RV is recommended at doses ranging from several grams to hundreds of milligrams per day, based on animal research. A person's daily food and drink consumption should be represented if they desire to consume 1 g of RV.

a direct role in controlling the activity of COX (Dvorakova and Landa, 2017; Kong *et al.*, 2017). According to research, RV can lower inflammatory factor secretion and expression. By reducing levels of NF-κB, TNF-α, IL-6, macrophage inflammatory protein-2, COX-2 activity, caspase-3, and ROS production, RV's anti-inflammatory effects mitigate inflammation caused by acute pharyngitis in rabbit models (Nandhini *et al.*, 2024b; Zhou *et al.*, 2018). Analgesic and anti-inflammatory properties of RV are supported by its effects on mouse ear edema, white blood cell counts, and pleurisy exudates; acetic acid-induced pleurisy test results show decreased NO production and increased SOD serum activity; carrageenan-induced synovitis test results show reduced MDA content and increased T-SOD serum activity; and RSV inhibits TP, PGE2, NO, and MDA expressions in the carrageenan-induced synovitis test, demonstrating its analgesic and anti-inflammatory effects (Wang *et al.*, 2017). RV inhibits neuroinflammation signaling pathways, microglia activation, and the release of pro-inflammatory proteins and ROS *in vitro*. At dosages ranging from moderate to high, RV down-regulates NF-κB activation and prevents mitochondrial dysfunction, hence modulating the inflammatory response in intestinal cells. This finding was validated *in vivo*, where RV suppresses intestinal carcinogenesis through modulating anti-inflammatory miRNA, inhibits TNF-α e generation and NF-κB activation, and lowers neutrophil infiltration in the intestinal mucosa (Nunes *et al.*, 2018; Patel *et al.*, 2010; Zhang *et al.*, 2010). Research by Chen *et al.* (2018) suggests that RV may be effective in the treatment of arteriosclerosis by suppressing the TLR-4/MyD88/NF-κB signaling pathway in lysophosphatidylcholine-induced inflammation and damage. Research suggests that RV may have several health benefits, including lowering the risk of cancer and oxidative stress, improving patients' quality of life, and acting as an anti-inflammatory agent (Chen *et al.*, 2018).

Anti-obesity effects

Obesity prevention has recently attracted a lot of attention from RV. There have been new reports that it can help animals avoid becoming overweight, improve their blood sugar regulation,

and even prevent insulin resistance and diabetes. 3T3-L1 preadipocytes were also treated by the researchers, however this time it was 24 hr. The researchers found that this polyphenol prevented adipogenesis when cultivated RV cells were exposed to doses of 25 and 50 µM. Decreased levels of C/EBP and PPAR-γ proteins were noted in a different discovery. These results are in agreement with those of other 2011 studies, which found that after only one day of incubation, RV had already demonstrated its anti-adipogenic effects (Kwon *et al*., 2012). The 2008 study by Srujana *et al*. found that after six days of incubation, 3T3-lipids significantly reduced the formation of RV at concentrations of 25 and 50 µM in L1 preadipocytes (Rayalam *et al*., 2008). According to another study, the reason RV reduces lipid accumulation is because it leads to less cell viability and less fat development (Le Duc *et al*., 2021). Although Hu *et al*. (2019) demonstrated adipogenic activity Kang *et al*. (2012) found anti-adipogenic effects. All of the studies that used RV as an anti-adipogenic chemical did so at concentrations greater than 10 µM. Thermogenic activity and brown adipocyte production are enhanced in mice when a study by Zou and colleagues discovered that RV activates AMPKα1, which in turn enhances the expression of brown fat-forming markers (Jayaprakash *et al*., 2025; Zou *et al*., 2017). There is a direct correlation between Lipopolysaccharide (LPS) and protein down-regulation, which in turn causes inflammation and electron transport chain pathways. After two weeks of oral administration of 100 mg/kg/day of RV, insulin resistance, blood glucose levels, and the regeneration of damaged adipose tissue produced by inflammatory stimuli were all markedly improved. Both total body weight and fat percentage are further decreased. Lung tissue SOD concentrations were shown to be higher in obese mice after RV considerably enhanced pAMPK, which in turn reduced p47 phox generation and ROS (André *et al*., 2016). Researchers found that high-fat diet C57BL/6J mice were protected from osteoarthritis when given RV orally. The drug reduced body weight rejuvenated the mice, and degraded type II collagen. Chondrocyte apoptosis suppression and cartilage type II collagen and C-terminal peptide-type II (CTX-II) expression retention (Gu *et al*., 2016).

Cardiovascular activity

Researchers found that diabetic rats given RV for protection had better cardiovascular function. Contributions included a decrease in cardiac environmental inflammation, a significant recovery of ventricular function, and the preservation of functional capacity of mature cardiac cells and the compartments containing cardiac stem/progenitor cells (Yan *et al*., 2018). Heart failure was ameliorated by RV through improvements in left ventricular function, reductions in cardiac hypertrophy, contractile dysfunction and remodeling, interstitial fibrosis, and plasma BNP levels. RV has several molecular functions, including suppressing prohypertrophic signaling molecules, improving myocardial Ca2+ handling, decreasing inflammation and oxidative stress, and phosphorylating pathways involved in stress signalling (MKP-1) and prosurvival (Akt-1, GSK-3b) (Delucchi *et al*., 2012). Research conducted by Yan *et al*. (2018) suggests that RV could potentially prevent diabetic rats from myocardial

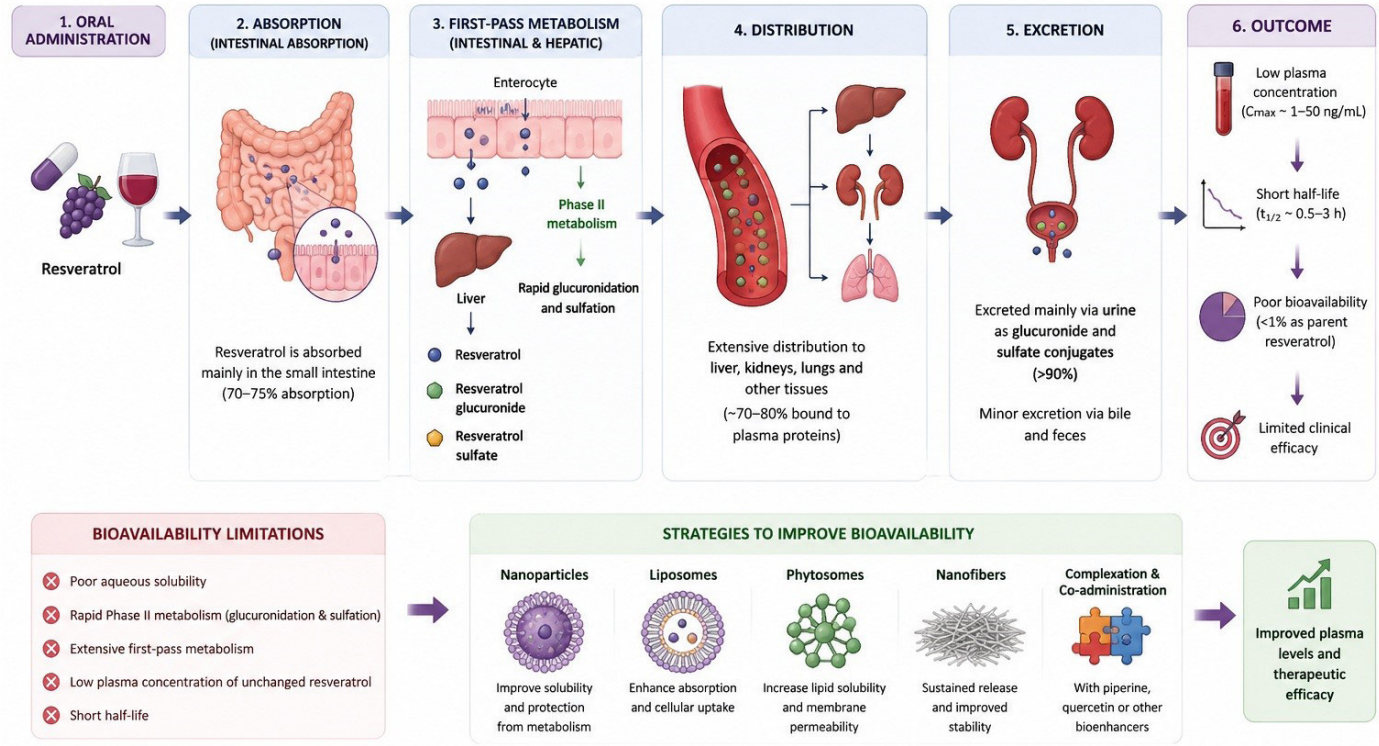


Figure 2: Pharmacokinetic profile of RV.

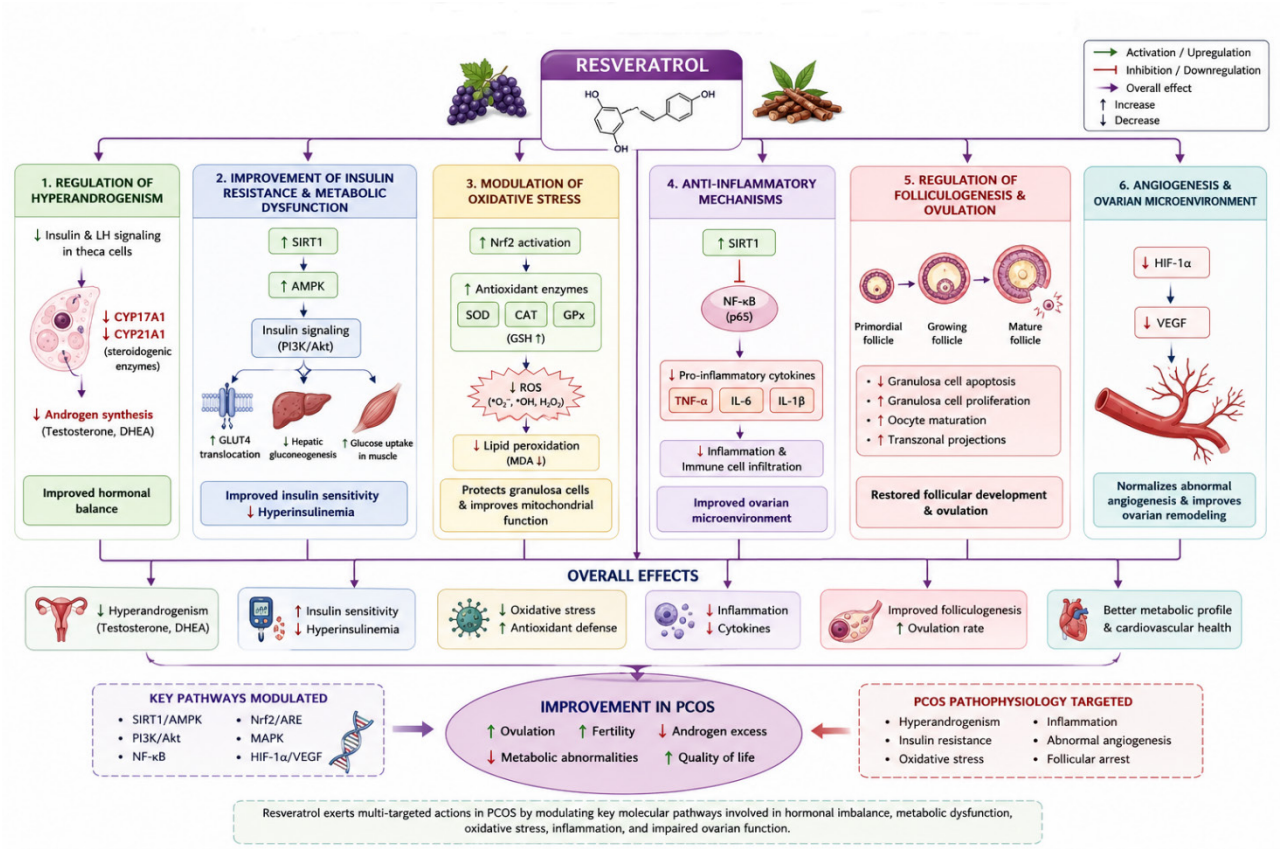


Figure 3: Molecular mechanisms of RV in PCOS.

infarction by reducing levels of p38 phosphorylation, endothelial nitric oxide synthase, and VEGF expressions. In diabetic rats that had a myocardial infarction, RV treatment led to a dramatic rise in total plasma insulin levels while simultaneously lowering blood glucose, plasma triglyceride levels, weight, heart rate, and the ratio of AST to ALT (Riba *et al.*, 2017). RV also markedly decreased levels of inflammatory markers and the oxidative stress marker malondialdehyde. These findings demonstrated that RV therapy mitigates myocardial ischemia-reperfusion injury, atherosclerosis, and vasodilation, and improves cardiovascular function (Bishayee *et al.*, 2010; Devaraji *et al.*, 2024; Öztürk *et al.*, 2017). On the other hand, RV inflates blood vessels and reduces the risk of hypertension and cardiovascular disease when taken in physiological doses (Das *et al.*, 2007; Hung *et al.*, 2000). Additionally, these findings provide credence to the traditional Chinese medicine's usage of *Polygonum cuspidatum* as a RV source for the treatment and prevention of hyperlipidemia and arteriosclerosis. Several molecular targets have been associated with RV's cardioprotective effects; these findings may inform the creation of new treatments for conditions such as metabolic syndrome, atherosclerosis, heart failure, and ischemia/reperfusion (Kurita *et al.*, 2014; Zahedi *et al.*, 2013; Zhang *et al.*, 2013).

Anti-diabetic effects

Diabetes is a prevalent metabolic illness that is rapidly increasing worldwide. It is characterized by high levels of glucose in the blood, which is caused by excessive production of glucose by the liver and increased absorption of glucose by the liver. While antihyperglycemic medications and insulin sensitizers are important in managing hyperglycemia, herbs can also serve as a helpful therapy alternative, especially considering the potential adverse effects associated with other treatments (Anwar *et al.*, 2021). The effects of RV20 on apelin gene expression in rats with type 2 diabetes mellitus were investigated in a study by Zarei and colleagues. The researchers also looked at metabolic markers and tolerance in adipose tissue. Results showed that RV reduced glucose levels in the blood, increased insulin production, and inhibited drug-resistant gene expression in rats treated with streptozotocin and nicotinamide. This led to an improvement in insulin sensitivity. Moreover, RV affected the heme oxygenase-1 (HO-1) gene and the Nrf2 gene, both of which are involved in the retina (Zarei *et al.*, 2016). The effect of vascular endothelium response was studied in diabetic rats by Wang and colleagues. Scientists discovered that RV significantly improves capillary growth and density in addition to lowering blood glucose and TG levels. In addition, there was a slow reversal in the normalization of the Nrf2 and HO-1 genes' transcript levels. This study's findings provide more evidence that RV may modulate the Nrf2/HO-1 pathway, protect vascular endothelial cells from diabetic damage, and lower blood glucose and cholesterol levels (Bai *et al.*, 2017). In a study involving people with type 2 diabetes mellitus, Asadi and colleagues examined the right ventricle's reaction to

various oxidative markers, including blood glucose, serum zinc, copper, and SOD (Asadi *et al.*, 2017). The administration of RV resulted in a reduction in glucose and copper levels in both blood and serum, whereas zinc levels were seen to increase in the experimental laboratory animals. An elevation in the activity of SOD resulted in an enhancement in oxidative state. The data showed that RV plays a function in reducing blood sugar levels, while also helping to retain trace elements and increasing the level of SOD (Baur *et al.*, 2006). Also, in STZ-induced diabetes, interstitial fibrosis, levels of oxidation, and mild expression of associated proteins were observed when RV was administered at doses of 5 or 25 mg/kg/day (Bagatini *et al.*, 2017). Furthermore, RV has enhanced the distinction of myofibroblast cells by suppressing ROS/ERK/TGF-P/periostin pathways in laboratory animals used in experiments. The data revealed that there was an increased likelihood of freezing behavior in the experimental mice when they were administered a dosage of RV at either 10 or 20 mg/kg. Furthermore, it has been noted that consumption of RV at a dosage of 480 mg/day leads to a decrease in glucose, LDL, and TG levels, as well as an increase in sensitivity to GDL and insulin in individuals with type 2 diabetes mellitus. This suggests that RV supplementation could be a beneficial additional treatment for diabetes patients who are resistant to insulin (Muralidas *et al.*, 2023; Sundaram *et al.*, 2024; Wu *et al.*, 2022; Zare Javid *et al.*, 2017). Modern research has shown that traditional herbs can help lower blood sugar levels, which has led to a surge in their popularity. Additionally, these herbs have minimal adverse effects on the individuals who use them, which further contributes to their appeal. RV, a natural polyphenol, has been found to effectively reduce glucose levels in food and inhibit the activity of carbohydrate enzymes (Alamgeer *et al.*, 2016; Shen *et al.*, 2017). Overall, Figure 5 depicts the potential impacts of RV on many organs, emphasizing its extensive array of advantages. These findings indicate that RV is a highly adaptable and beneficial bioactive molecule. Its wide range of uses in enhancing health and preventing illness make it a valuable prospect for additional investigation and utilization in various therapeutic and preventative approaches.

FUTURE DIRECTIONS AND RESEARCH GAPS

Although substantial evidence supports the therapeutic potential of RV in PCOS, several challenges remain to be addressed before its successful clinical translation. Future research should focus on the development of novel delivery systems and nano-enabled formulations to improve the poor aqueous solubility, bioavailability, and targeted delivery of RV. Recent advances in nanotechnology and sustainable bio-nanocomposite systems have demonstrated considerable promise in enhancing the therapeutic performance of bioactive compounds, highlighting their potential application in RV-based formulations for PCOS management (Nandhini *et al.*, 2024a). Moreover, multifunctional nanomaterials may provide additional antioxidant and anti-inflammatory benefits that are particularly relevant to the complex pathophysiology of PCOS. Further investigations are also warranted to explore the role of phytochemical-based formulations and nano-carriers in improving metabolic and reproductive outcomes associated with

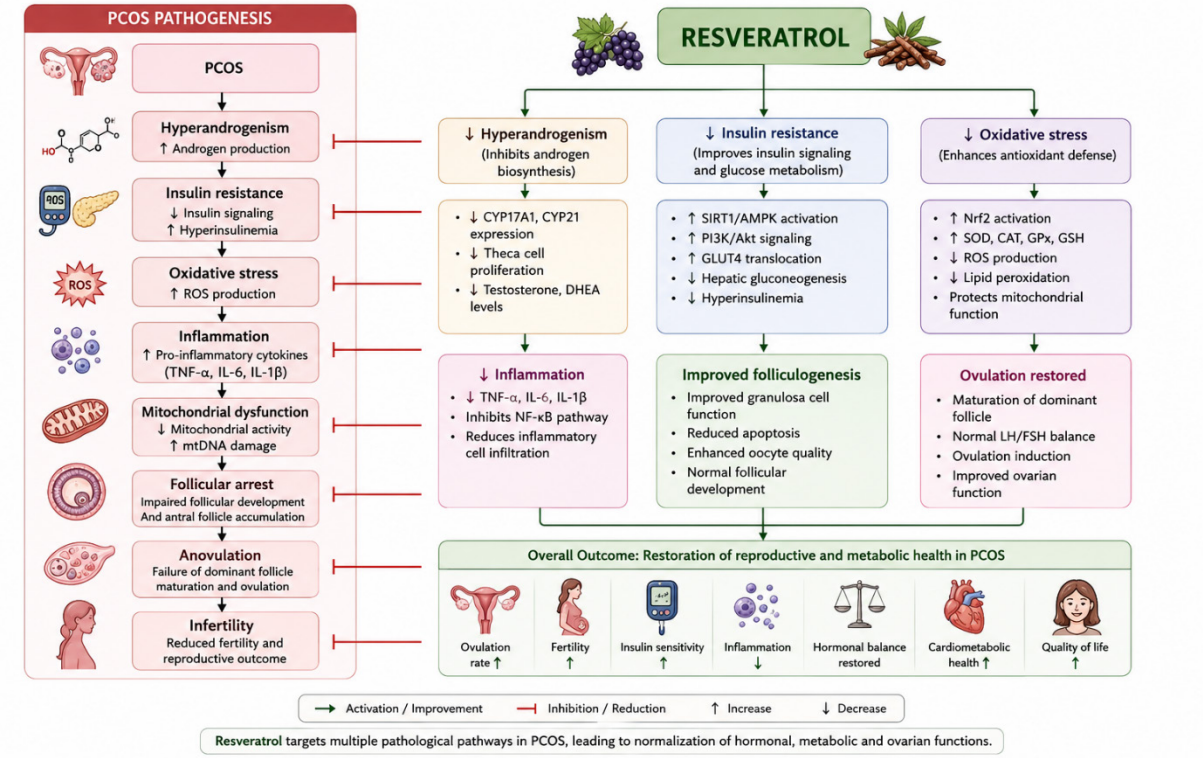


Figure 4: Effects of RV on PCOS Pathogenesis.

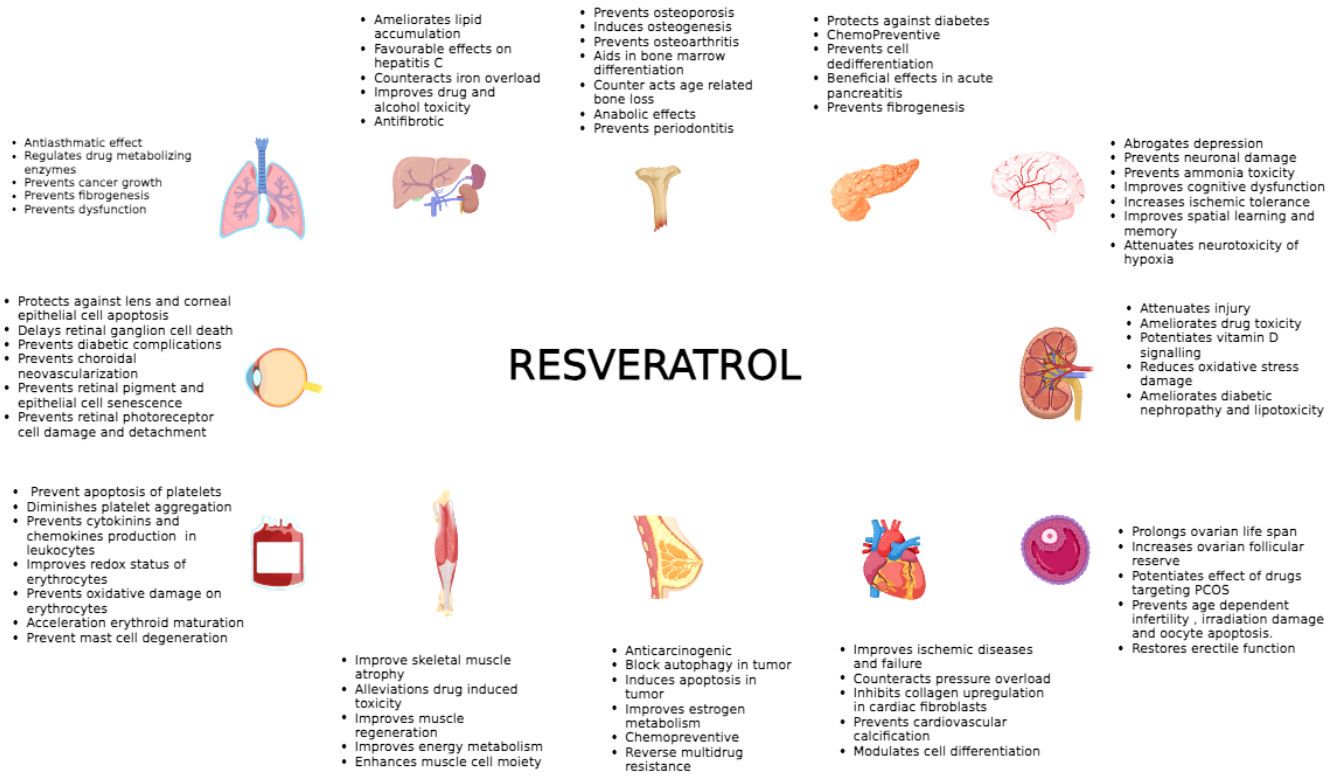


Figure 5: The potential positive impacts of RV on multiple organs.

the disease. Future studies should emphasize standardized dosing regimens, long-term safety assessments, and well-designed clinical trials to facilitate the translation of RV into evidence-based therapeutic interventions for women with PCOS. In addition, the integration of advanced drug delivery strategies and bioactive phytopharmaceutical formulations may open new avenues for developing personalized and more effective therapeutic approaches for PCOS (Nandhini *et al.*, 2024b).

CONCLUSION

RV has emerged as a promising multi-target phytochemical for the management of polycystic ovary syndrome by modulating several interconnected pathological mechanisms underlying the disease. Its antioxidant, anti-inflammatory, insulin-sensitizing, anti-hyperandrogenic, and cardiometabolic protective properties enable it to simultaneously target reproductive and metabolic abnormalities associated with PCOS. Experimental and clinical evidence indicates that RV can improve insulin resistance, reduce androgen synthesis, attenuate oxidative stress and inflammatory signaling, and support normal follicular development and ovarian function through the regulation of key molecular pathways, including SIRT1/AMPK, PI3K/Akt, NF-κB, and Nrf2. Despite its considerable therapeutic potential, the clinical translation of RV remains limited by poor aqueous solubility, rapid metabolism, and low oral bioavailability. Furthermore, the lack of standardized dosing regimens and long-term clinical studies in women with PCOS highlights the need for additional research. Advances in drug delivery strategies, including nanoformulations and sustained-release systems, may overcome these limitations and improve its therapeutic efficacy. Overall, RV represents a promising natural therapeutic candidate for PCOS owing to its pleiotropic pharmacological activities and ability to target multiple disease pathways simultaneously. Future well-designed preclinical and clinical investigations are warranted to establish its optimal dosage, long-term safety, and clinical effectiveness, thereby facilitating its successful translation into evidence-based therapeutic strategies for the management of PCOS.

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ABBREVIATIONS

PCOS: Polycystic Ovary Syndrome; **RV:** Resveratrol; **SIRT1/AMPK:** Sirtuin 1/AMP-Activated Protein Kinase Signaling Pathway; **PI3K/Akt:** Phosphoinositide 3-Kinase/Protein Kinase B Signaling Pathway; **NF-κB:** Nuclear Factor Kappa B; **Nrf2:** Nuclear Factor Erythroid 2-Related Factor 2; **CYP17A1:** Cytochrome P450 Family 17 Subfamily A Member 1; **ROS:** Reactive Oxygen Species; **TNF-α:** Tumor Necrosis Factor-Alpha; **IL-6:** Interleukin-6; **IL-1β:** Interleukin-1 Beta; **VEGF:** Vascular Endothelial Growth Factor; **HIF-1α:** Hypoxia-Inducible Factor-1 Alpha; **UGTs:** Uridine 5′-Diphospho-Glucuronosyltransferases; **SULTs:** Sulfotransferases; **SOD:** Superoxide Dismutase; **HIF-2:**

Hypoxia-Inducible Factor-2; **GDL:** Glucose Disposal Rate; **LH:** Luteinizing Hormone; **FSH:** Follicle-Stimulating Hormone; **BNP:** B-Type Natriuretic Peptide; **AMPK:** AMP-Activated Protein Kinase; **COX:** Cyclooxygenase; **5-LOX:** 5-Lipoxygenase; **GPx:** Glutathione Peroxidase; **MDA:** Malondialdehyde; **TBT:** Tributyltin; **AMH:** Anti-Müllerian Hormone; **CaMKIIβ:** Calcium/Calmodulin-Dependent Protein Kinase II Beta; **TZPs:** Transzonal Projections; **UPR:** Unfolded Protein Response; **DHEA:** Dehydroepiandrosterone; **STZ:** Streptozotocin; **LDL:** Low-Density Lipoprotein; **AST:** Aspartate Aminotransferase; **ALT:** Alanine Aminotransferase.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

VV: Conceived and drafted the manuscript. **TR:** Critically reviewed and revised the manuscript for intellectual content. **SS, MM, TB, and AS:** Contributed to the conceptualization of the review. All authors critically reviewed and approved the final version of the manuscript and take responsibility for its content and originality.

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