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Review

Resveratrol-Mediated Regulation of Molecular and Cellular Signaling Networks in Polycystic Ovary Syndrome

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Abstract

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine–metabolic disorder characterized by dysregulated ovarian signaling, metabolic inflammation, insulin resistance, and aberrant angiogenesis, for which effective disease-modifying therapies remain limited. Resveratrol (RES), a pleiotropic polyphenol, has attracted increasing attention for its ability to modulate multiple molecular and cellular pathways implicated in PCOS pathophysiology. In this review, we synthesize current evidence to clarify how RES regulates key pathological signaling networks in PCOS, including ovarian follicular dysfunction, impaired insulin signaling, hyperandrogenism, oxidative stress, and vascular remodeling. Rather than merely cataloguing isolated mechanisms, we integrate findings from experimental models to highlight major convergent nodes—such as phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mechanistic target of rapamycin (mTOR), sirtuin 1 (SIRT1)/AMP-activated protein kinase (AMPK), nuclear factor kappa-B (NF-κB), and vascular endothelial growth factor (VEGF)-related pathways—through which RES may exert coordinated regulatory effects at the cellular and tissue levels. We further examine the available clinical studies to assess the translational relevance of these mechanistic insights, with particular emphasis on phenotypic heterogeneity, dose dependence, and the treatment window. Although clinical outcomes remain modest and variable, the available evidence suggests that RES may provide context-dependent benefits in selected PCOS subtypes. Collectively, this review offers a network-based framework linking the molecular actions of RES to the complex pathophysiology of PCOS and identifies key knowledge gaps that must be addressed to improve translational precision and therapeutic applicability.

Keywords: polycystic ovary syndrome; resveratrol; signal transduction; insulin resistance; oxidative stress; hyperandrogenism

1. Introduction

Polycystic ovary syndrome (PCOS) is a complex reproductive–metabolic disorder characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology, with substantial heterogeneity in both clinical presentation and underlying pathophysiology [1]. In addition to menstrual irregularities, infertility, hirsutism, acne, and adiposity, PCOS is frequently accompanied by insulin resistance (IR), chronic low-grade inflammation, oxidative stress, dyslipidemia, and increased long-term cardiometabolic risk [2]. Recent epidemiological evidence further indicates that the global prevalence of PCOS varies considerably according to diagnostic criteria and population characteristics, underscoring both its clinical complexity and its public health relevance [3].

Although the precise etiology of PCOS remains incompletely understood, accumulating evidence suggests that its pathogenesis involves dynamic interactions among androgen excess, impaired insulin signaling, mitochondrial dysfunction, redox imbalance, altered granulosa-cell homeostasis, and abnormal ovarian angiogenesis. These abnormalities do not operate independently. Rather, they reinforce one another through interconnected feedback loops. Hyperinsulinemia can amplify ovarian and adrenal androgen production, androgen excess can further exacerbate inflammatory and metabolic dysfunction, and oxidative stress can impair granulosa-cell viability, disturb steroidogenesis, and aggravate insulin resistance [4]. In this context, PCOS is increasingly recognized not as a single ovarian disorder but as a heterogeneous systems-level condition requiring more integrative mechanistic and translational frameworks [1,5].

Resveratrol (RES), a naturally occurring polyphenolic stilbene present in grapes, berries, peanuts, and Polygonum cuspidatum, has attracted increasing attention because of its antioxidant, anti-inflammatory, metabolic, and cytoprotective properties [6]. Experimental studies suggest that RES can influence several molecular pathways highly relevant to PCOS, including phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mechanistic target of rapamycin (mTOR), sirtuin 1 (SIRT1)/AMP-activated protein kinase (AMPK), nuclear factor kappa-B (NF-κB), and vascular endothelial growth factor (VEGF)-related signaling [7], while also modulating mitochondrial homeostasis, autophagic flux, glucose metabolism, steroidogenic activity, and vascular remodeling. Collectively, these pleiotropic actions position RES as a promising adjunctive candidate for PCOS, particularly because it may act on multiple pathogenic compart-

ments simultaneously rather than on a single endocrine abnormality [8].

Several previous reviews have summarized the endocrine, metabolic, and antioxidant effects of RES in PCOS or discussed RES within broader reviews of natural compounds used in PCOS management [9]. However, most have emphasized descriptive aggregation of findings rather than systematic integration of pathway crosstalk, phenotype-specific responsiveness, and translational limitations. In particular, the functional convergence among PI3K/Akt/mTOR, SIRT1/AMPK, NF-κB/ROS, and VEGF-centered signaling has not been sufficiently synthesized in the setting of PCOS heterogeneity. The gap between strong preclinical efficacy and comparatively modest clinical outcomes remains inadequately explained, especially with respect to phenotype stratification, dose dependence, treatment window, and fertility-related safety considerations.

Accordingly, the present review aims to summarize the major molecular and cellular mechanisms through which RES may modulate PCOS pathology, to integrate these mechanisms into a network-based framework centered on shared upstream drivers such as oxidative stress, insulin resistance, mitochondrial dysfunction, and chronic inflammation, and to evaluate the extent to which current clinical evidence supports phenotype-specific therapeutic benefit. In addition, this review highlights the limitations of existing experimental models and clinical studies and aligns future research needs with recent international calls for more phenotype-informed, safety-conscious, and fertility-relevant PCOS research [5].

2. The Role of RES in Polycystic Ovary Syndrome

2.1 Restoration of Ovarian Function

2.1.1 Reversal of Pathologic Ovarian Architecture

The morphological hallmarks of PCOS, including cortical thickening, accumulation of small antral follicles, and stromal hyperplasia, are indicative of arrested follicular maturation. The size of the primordial follicle pool and the rate of its recruitment are pivotal determinants of the cohort of fertilizable oocytes and, by extension, the reproductive outcomes in PCOS [10]. Preclinical studies have demonstrated that RES can effectively reverse these structural anomalies. Kong et al. [11] revealed that RES significantly augments ovarian follicular reserves across various age groups of rats, thereby effectively extending ovarian lifespan. This benefit is attributed to the deceleration of the transition from primordial to primary follicles and the reduction of follicular atresia. Liu et al. [12] further reported that RES increases the number of primordial and primary follicles, enhances telomere length and telomerase activity, and improves oocyte quality. Utilizing a dehydroepiandrosterone-induced PCOS model, Furat Rencber et al. [13] found that RES enlarges the primordial follicle pool and the population of Graafian follicles while mitigating mitochondrial degeneration, autophagosome accumulation, and lipid droplet deposition in thecal cells. These changes were accompanied by the restoration of fractured mitochondrial cristae, indicating near-complete ultrastructural normalization. In letrozole-treated Wistar rats, Yarmolinskaya et al. [14] documented a significant increase in granulosa cell layer thickness and a marked reduction in cystic follicles following RES administration. Hu et al. [15] subsequently demonstrated that RES protects granulosa cells by preserving mitochondrial morphology and function, thereby suppressing mitochondria-driven apoptosis.

These mechanistic observations have also been supported by clinical findings. In a triple-blind, placebo-controlled study, Bahramrezaie et al. [16] showed that 800 mg/day of RES for 60 days significantly increased the rates of top-quality oocytes and high-grade embryos while concurrently lowering serum total testosterone levels. Ajabi Ardehjani et al. [17] randomized patients with PCOS to receive either RES or placebo and observed a significant reduction in follicular-fluid total oxidant status (TOS) and oxidative stress index (OSI), together with enhanced total antioxidant capacity (TAC). These changes were accompanied by improvements in oocyte maturity and embryo quality. Collectively, the available evidence suggests that RES can reverse the characteristic structural abnormalities of PCOS ovaries, expand follicular reserves, improve oocyte competence, and provide antioxidant protection, thereby contributing to the restoration of ovarian morphology and function.

Taken together, these findings indicate that the beneficial effects of RES on ovarian morphology are unlikely to reflect isolated histological improvement alone. Rather, they may represent the tissue-level consequence of broader restoration of granulosa-cell homeostasis, mitochondrial integrity, and follicular developmental competence. This interpretation is particularly relevant because structural recovery in PCOS ovaries is closely linked to the balance among autophagy, apoptosis, oxidative damage, and cellular proliferation within the follicular microenvironment.

2.1.2 Regulation of Granulosa-Cell Fate: Autophagy, Apoptosis, and Proliferative Homeostasis

Granulosa-cell dysfunction is a central event in follicular arrest and ovulatory impairment in PCOS. Although dysregulated autophagy has attracted increasing attention, granulosa-cell fate in PCOS is not determined by autophagy alone. Instead, excessive autophagic activity often coexists with mitochondrial injury, oxidative stress, apoptosis, impaired proliferative renewal, and disrupted bidirectional communication between granulosa cells and oocytes. Therefore, the effects of RES on granulosa-cell biology should be understood within a broader framework of cellular homeostasis rather than as a single-pathway phenomenon [18,19].

Autophagy is a lysosome-dependent degradation process that maintains intracellular quality control by recycling damaged proteins and organelles [20]. In the ovary, appropriate autophagic activity is essential for follicle development and atresia balance, whereas excessive autophagy may contribute to granulosa-cell dysfunction and follicular arrest in PCOS [21,22]. Clinical and experimental studies have shown increased expression of autophagy-related markers, including ATG5, ATG7, BECN1, and LC3-II/I, together with enhanced p62 degradation in ovarian tissue and granulosa cells from PCOS models [23]. Importantly, recent syntheses suggest that dysregulated autophagy in PCOS should not be viewed in isolation, but rather in conjunction with oxidative stress, inflammatory activation, mitochondrial dysfunction, and impaired follicular competence [18].

In PCOS, granulosa cells are exposed to a metabolically stressed microenvironment characterized by oxidative stress, mitochondrial dysfunction, and impaired energy metabolism, all of which can compromise folliculogenesis and oocyte competence [19,24,25]. Dysregulated autophagy is increasingly recognized as part of this pathology, and excessive autophagic activity in granulosa cells has been linked to enhanced apoptosis, follicular arrest, and ovulatory dysfunction [18]. Experimental PCOS models induced by letrozole, testosterone propionate, or high-fat diet exhibit key reproductive and metabolic disturbances, including impaired ovarian function and altered glucose, lipid, and energy metabolism [26]. Against this pathological background and the RES-related evidence discussed above, a key concept is that RES may help restore the autophagy–apoptosis balance in granulosa cells, not merely through direct suppression of autophagy, but by alleviating oxidative stress, improving mitochondrial biogenesis and cellular bioenergetics, and normalizing glycolytic and insulin-signaling pathways. Although direct clinical evidence on autophagy endpoints remains limited, recent translational and clinical studies support the biological plausibility of this mechanism in PCOS.

The PI3K/Akt/mTOR pathway is one of the principal signaling axes through which RES may regulate this balance. mTOR sits at the intersection of cell growth, autophagy control, apoptosis, and metabolic adaptation [27]. In PCOS, both excessive inhibition and excessive activation of PI3K/Akt/mTOR signaling may disturb autophagy homeostasis and impair follicular development [28,29]. RES appears capable of bidirectionally modulating this pathway according to the cellular context. Its effects vary according to cell type, disease state, and concentration. Thus, RES may suppress Akt/mTOR driven survival programs in some pathological settings while preserving or enhancing this axis in ovarian cells under stress [8,30,31]. In granulosa cells, available evidence indicates that RES can enhance p-Akt and p-mTOR levels, reduce Beclin-1 expression and LC3-II/LC3-I ratio, and improve proliferation-related indices, thereby inhibiting excessive autophagy and supporting follicular cell survival [32]. Importantly, this pathway also intersects with insulin signaling and angiogenic regulation, suggesting that the effects of RES on granulosa-cell fate may extend beyond local autophagy control alone. The complete schematic diagram of the process is shown in Fig. 1.

The SIRT1/AMPK pathway represents another major mechanism linking RES to granulosa-cell homeostasis. SIRT1 and AMPK function as key regulators of cellular energy sensing, oxidative-stress adaptation, mitochondrial integrity, and autophagic flux [33]. In PCOS-related settings, RES has been shown to enhance SIRT1 and AMPK signaling, reduce mitochondrial ROS accumulation, attenuate tumor necrosis factor alpha (TNF-α)-associated inflammatory burden, and normalize the expression of autophagy-related markers in granulosa cells [34,35]. Because SIRT1/AMPK signaling is also closely linked to cellular resilience under energetic and oxidative stress, its activation by RES may contribute not only to autophagic correction but also to broader restoration of granulosa-cell integrity and follicular support capacity [13]. The complete schematic diagram of the process is shown in Fig. 2.

In addition to modulating autophagy, RES may influence other aspects of granulosa-cell fate that are highly relevant to follicular development, including apoptosis resistance, mitochondrial-functional recovery, and proliferative homeostasis. Recent literature suggests that mitochondrial impairment in granulosa cells disrupts the balance between proliferation and apoptosis in PCOS, and that regulated cell death pathways beyond classical apoptosis may also contribute to ovarian dysfunction [19,36]. Although direct evidence regarding long-term repair dynamics and turnover remains limited, these processes deserve consideration because they are likely to interact with autophagic and oxidative pathways in determining the overall follicular response to RES.

Overall, current evidence supports the view that RES does not simply inhibit a single pathological process in granulosa cells. Rather, it appears to re-establish a more favorable intracellular equilibrium across autophagy, apoptosis, mitochondrial stability, and proliferative competence. Future studies should further clarify how these processes interact in different PCOS phenotypes and should test the clinical relevance of these mechanistic observations in phenotype-stratified and fertility-relevant study designs [5].

2.2 Regulation of Glucose and Lipid Metabolism

Women with PCOS commonly exhibit features of metabolic syndrome, including dysregulated glucose–lipid homeostasis and obesity [37]. IR with compensatory hyperinsulinemia is highly prevalent (≈60% and up to 65–95% depending on cohort and BMI distribution), indicating that metabolic dysfunction is not restricted to obese pheno-

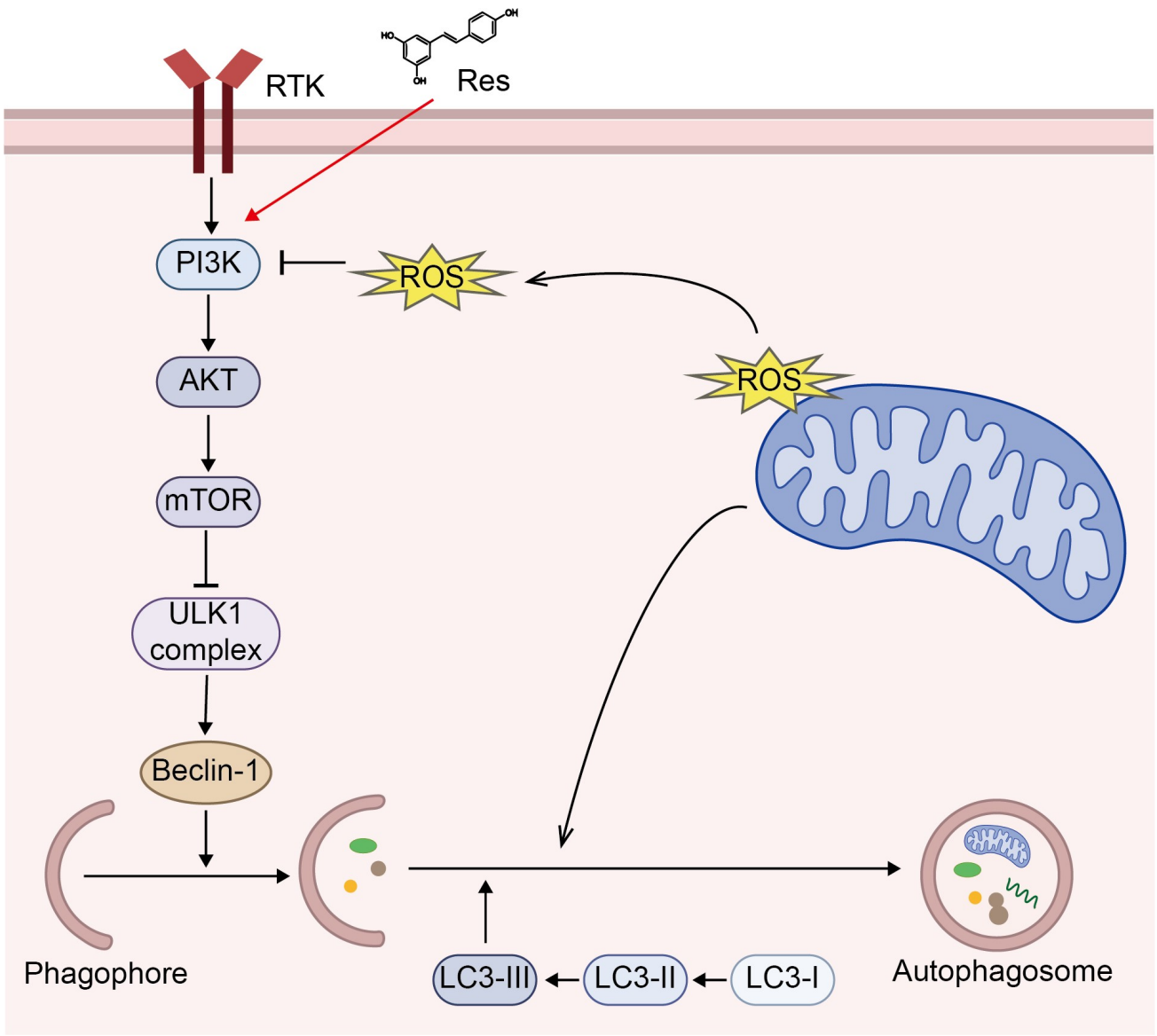

Fig. 1. RES regulates granulosa-cell autophagy through bidirectional modulation of the PI3K/Akt/mTOR pathway in PCOS. This schematic shows how RES may regulate granulosa-cell autophagy in PCOS through the PI3K/Akt/mTOR axis, with downstream effects on ULK1/Beclin-1-associated autophagic flux and mitochondrial ROS-related stress. These changes may help preserve granulosa-cell homeostasis and follicular function. Abbreviations: RES, resveratrol; PCOS, polycystic ovary syndrome; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; mTOR, mechanistic target of rapamycin; ULK1, unc-51-like kinase 1; ROS, reactive oxygen species; LC3, microtubule-associated protein 1 light chain 3.

types [38,39]. Obesity substantially amplifies metabolic–reproductive derangements in PCOS; consistent with bidirectional Mendelian randomization evidence, the causal contribution of obesity to PCOS appears more robust than the reverse, even though women with PCOS tend to exhibit disproportionate central adiposity at a comparable BMI [39,40]. Collectively, these observations support IR/hyperinsulinemia as a central metabolic driver linking adiposity to hyperglycemia and reproductive dysfunction in PCOS [41].

Rather than treating metabolic dysfunction in PCOS as a single process, it is more useful to distinguish three related but non-identical levels at which RES may act. First, RES may attenuate the systemic loop linking insulin resistance, oxidative stress, and chronic inflammation, thereby improving the broader metabolic milieu. Second, it may improve the ovarian microenvironment by restoring granulosa-cell glycolytic competence and follicular energy supply. Third, it may influence adipose and peripheral lipid remodeling, thereby affecting lipid handling beyond the ovary. The following subsections therefore address these three dimensions separately to clarify their mechanistic differences while preserving their pathophysiological connections.

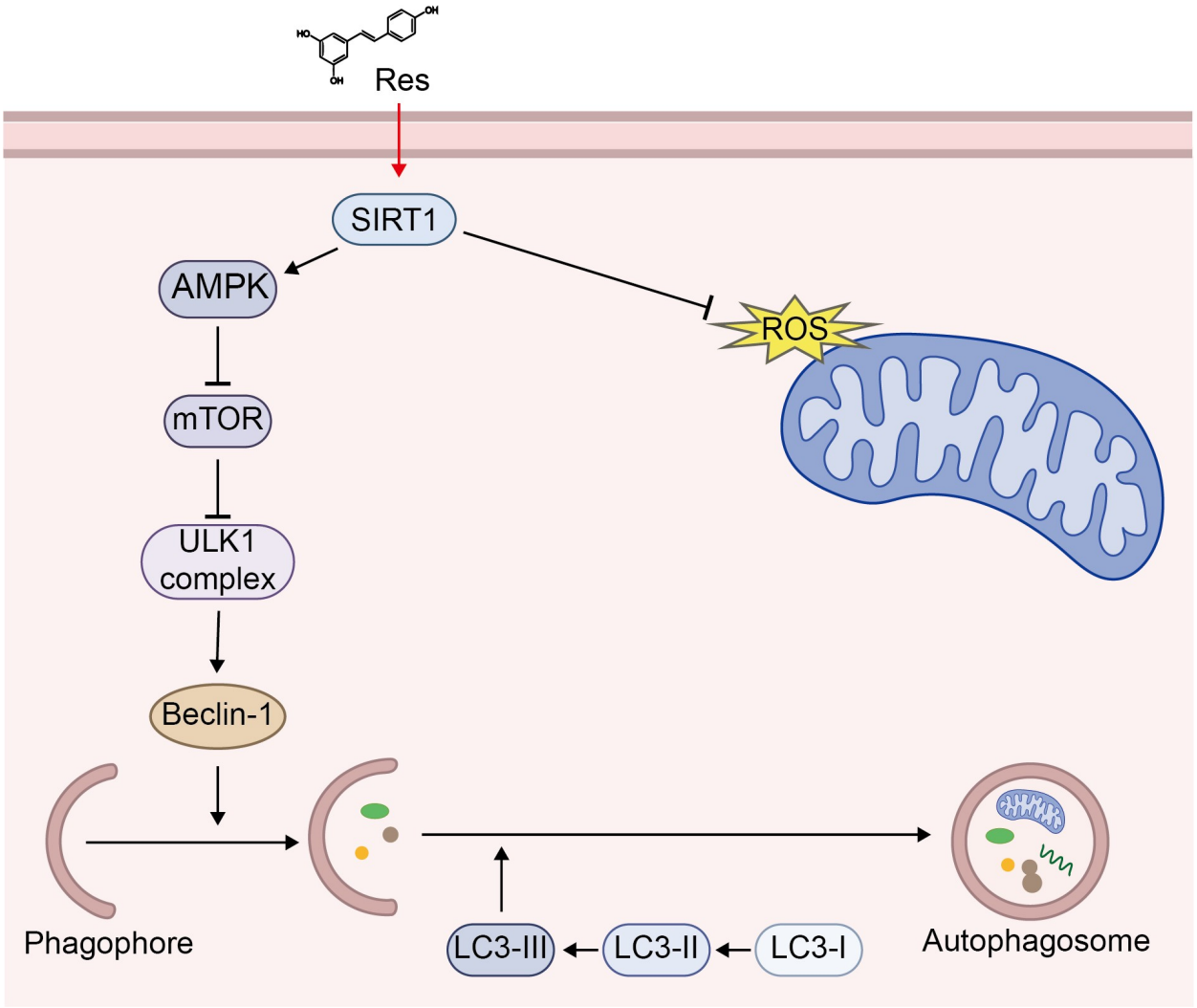

Fig. 2. RES activates the SIRT1/AMPK pathway to correct autophagy imbalance and oxidative injury in PCOS. This figure illustrates the proposed role of RES in activating SIRT1/AMPK signaling, thereby suppressing mTOR activity, regulating autophagy, and reducing mitochondrial oxidative stress in PCOS. These effects may contribute to improved granulosa-cell integrity and ovarian microenvironmental homeostasis. Abbreviations: RES, resveratrol; PCOS, polycystic ovary syndrome; SIRT1, sirtuin 1; AMPK, AMP-activated protein kinase; mTOR, mechanistic target of rapamycin; ULK1, unc-51-like kinase 1; ROS, reactive oxygen species; LC3, microtubule-associated protein 1 light chain 3.

2.2.1 Systemic Insulin Resistance, Oxidative Stress, Inflammation, and Lipid Remodeling

In PCOS, IR and oxidative stress (OS) reinforce one another, forming a self-amplifying pathogenic loop [42]. Excess glucose and free fatty acids (FFA) increase mitochondrial substrate oxidation, elevate NADH and $FADH_2$ generation, and promote reactive oxygen species (ROS) accumulation [43]. ROS then impairs insulin signaling by activating stress kinases such as c-Jun N-terminal kinase (JNK), which favors inhibitory serine phosphorylation of insulin receptor substrate-1 (IRS-1) and reduces glucose transporter type 4 (GLUT4) translocation, thereby aggravating IR [44]. In parallel, IR-driven hyperglycemia further intensifies OS and inflammatory activation through glucose autoxidation, accumulation of advanced glycation end products (AGEs), and flux through the polyol pathway, which collectively activate NF-κB, MAPK, and NLRP3 signaling and increase inflammatory mediators including TNF-α, IL-6, IL-1β, and C-reactive protein (CRP) [45]. These inflammatory cues can further compromise β-cell integrity and suppress IRS/PI3K/Akt signaling, perpetuating metabolic dysfunction [46].

RES and its derivatives appear to interrupt this IR–OS–inflammation loop through multitarget actions that converge on both redox control and restoration of insulin signaling. At the cellular level, 3,3′,4,5′-tetramethoxy-trans-stilbene reduces ROS burden while enhancing IRS/PI3K/Akt activity, suggesting that RES-related compounds can simultaneously attenuate upstream oxidative pressure and repair downstream signaling defects

[47]. In addition, RES can fine-tune this axis through microRNA regulation: upregulation of mmu-miR-363-3p enhances PI3K/Akt signaling and suppresses FoxO1 and glucose-6-phosphatase catalytic subunit (G6PC), thereby reducing gluconeogenic drive [48]. Importantly, clinical evidence supports signaling-level improvements: in patients with type 2 diabetes, short-term RES supplementation reduced HOMA-IR and increased the platelet p-Akt/Akt ratio [49]. Consistently, RES has been reported to increase PI3K and Akt phosphorylation while suppressing FoxO1 and gluconeogenesis-associated genes such as G6PC, thereby alleviating the hyperglycemic burden [50].

Within PCOS-relevant settings, RES also shows systemic anti-inflammatory and antioxidant actions that strengthen the mechanistic plausibility of its metabolic benefits. In animal models, RES improves redox homeostasis and reduces inflammatory activation, while clinical studies in women with PCOS suggest decreases in circulating TNF-α and IL-6 that parallel improvements in insulin-resistance-related indices [51,52]. These effects have been linked to suppression of NF-κB signaling and mitigation of endoplasmic reticulum stress [53]. Because NF-κB not only promotes cytokine transcription but may also amplify ROS generation through induction of NADPH oxidase subunits, inhibition of this pathway provides a plausible mechanism by which RES can weaken the self-reinforcing inflammation–oxidative stress loop that sustains systemic metabolic dysfunction in PCOS [54].

Taken together, the evidence summarized in this subsection supports a primarily systemic role of RES in PCOS metabolic regulation: it may alleviate insulin resistance by dampening the reciprocal amplification among oxidative stress, inflammatory signaling, and impaired insulin-transduction pathways, with recurrent involvement of the PI3K/Akt/FoxO1 axis. The complete schematic diagram of the process is shown in Fig. 3.

2.2.2 Restoration of Granulosa-Cell Glycolytic Competence

Although these systemic abnormalities are important, their reproductive relevance in PCOS ultimately depends on how they reshape the ovarian microenvironment, particularly the metabolic support provided by granulosa cells. Oocytes have a limited capacity to utilize glucose and therefore depend on ovarian granulosa cells (GCs) to convert glucose into lactate, pyruvate, and other small-molecule substrates through glycolysis, thereby sustaining oocyte energy supply and redox balance [55]. Accordingly, the glycolytic capacity of GCs is a key determinant of the follicular energetic milieu and is closely linked to nuclear–cytoplasmic maturation and the subsequent developmental competence of oocytes. In PCOS, however, glycolytic metabolism appears to be broadly suppressed. In animal models, the expression of key glycolytic enzymes is reduced, accompanied by a marked decline in lactate production [56]. Clinically, follicular-fluid lactate is significantly lower in patients with PCOS, supporting impaired glucose utilization in GCs and an energy-deficient follicular niche that may contribute to reduced oocyte competence and ovulatory dysfunction [57]. This defect is further aggravated by dysregulation of the insulin–glucose axis: physiological insulin promotes lactate accumulation in follicular fluid in healthy individuals but shows minimal effect in PCOS, whereas supraphysiological insulin suppresses KGN-cell activity and decreases lactate output [58]. Consistently, hyperinsulinemia has been associated with diminished glycolytic capacity in other experimental contexts, reinforcing the concept of a “high insulin–low glycolysis” state under IR conditions [59]. Moreover, in PCOS rats, HOMA-IR is negatively correlated with ovarian glycolytic rate, suggesting that IR may be mechanistically linked to a local follicular energy crisis.

Recent studies indicate that RES can counteract high-dose insulin–induced growth inhibition in GCs and restore glycolytic function in both *in vivo* and *in vitro* settings. In diet-induced IR models, RES increases glycolytic flux, restores lactate and ATP production, and alleviates pyruvate accumulation, thereby rebalancing lactate–pyruvate homeostasis [60]. Pharmacological inhibition of SIRT2 with AGK2 partially blunts the lactate-restoring effect of RES and leads to renewed pyruvate elevation, implicating SIRT2 as a critical metabolic switch in RES-mediated reprogramming [61]. Mechanistically, SIRT2 is an NAD^+-dependent deacetylase involved in the regulation of glucose metabolism; RES may act on the dysregulated SIRT2-associated glycolytic axis and contribute to the restoration of glycolysis-associated rate-limiting components, thereby accelerating glucose utilization and potentially interrupting the metabolic–reproductive vicious cycle in PCOS [62,63]. Collectively, these data support the view that RES improves follicular energy availability by restoring granulosa-cell glycolysis and lactate–ATP supply, thereby strengthening the metabolic support required for oocyte development.

Beyond reduced glycolytic flux itself, local ovarian energy sensing also appears to be disturbed in PCOS. AMPK activity is frequently downregulated, and this defect may destabilize downstream signaling involving mTOR and Akt, thereby aggravating mitochondrial dysfunction and limiting adaptive responses to energetic stress within granulosa cells [64]. Although reduced ATP availability would ordinarily be expected to activate AMPK, persistent metabolic suppression may render this response inadequate in the PCOS follicular microenvironment [64]. From this perspective, the value of RES in this context may lie not only in restoring lactate–pyruvate balance, but also in improving the local energetic resilience of granulosa cells and, consequently, the metabolic support they provide to the developing oocyte. The complete schematic diagram of the process is shown in Fig. 4.

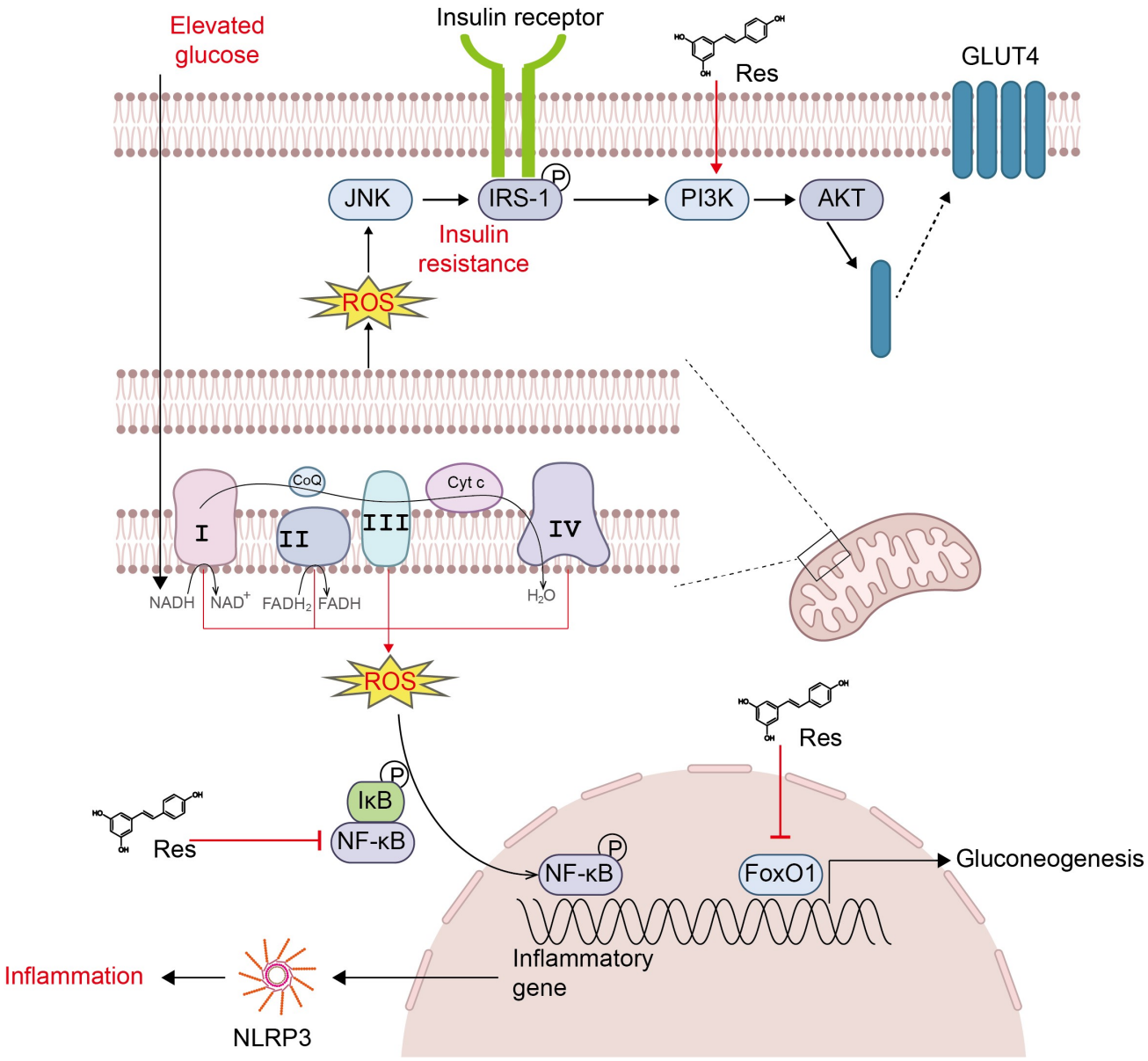

Fig. 3. RES ameliorates glucose metabolic disturbances in PCOS through anti-inflammatory and antioxidative mechanisms. This schematic summarizes how RES may improve glucose metabolic abnormalities in PCOS by enhancing insulin signaling, reducing mitochondrial ROS generation, suppressing NF-κB/NLRP3-associated inflammation, and inhibiting FoxO1-mediated gluconeogenesis. Together, these effects may help alleviate insulin resistance and inflammatory stress. Abbreviations: RES, resveratrol; PCOS, polycystic ovary syndrome; IRS-1, insulin receptor substrate-1; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; GLUT4, glucose transporter type 4; ROS, reactive oxygen species; NF-κB, nuclear factor kappa-B; NLRP3, NOD-like receptor family pyrin domain containing 3; FoxO1, forkhead box O1; JNK, c-Jun N-terminal kinase; IκB, inhibitor of NF-κB.

2.2.3 Regulation of Lipid Remodeling in PCOS

Lipid remodeling represents a distinct metabolic dimension of PCOS and should be considered separately from systemic insulin resistance and granulosa-cell glycolysis. In many patients, adipose dysfunction is characterized by impaired peroxisome proliferator-activated receptor γ (PPARγ)-dependent transcription, reduced adiponectin secretion, and defective thermogenic programming, changes that favor inefficient lipid handling and persistent metabolic burden [65,66,67,68]. RES appears to counteract these abnormalities through coordinated effects on adipose remodeling, adipokine profiles, and peripheral lipid utilization. Experimental evidence indicates that RES enhances brown-adipose thermogenesis and promotes browning of white adipose tissue, in part through upregulation of the PPARγ/PGC-1α/UCP1 axis, while also improving adipokine balance by increasing adiponectin and insulin-like growth factor-1 and reducing TNF-α and leptin resis-

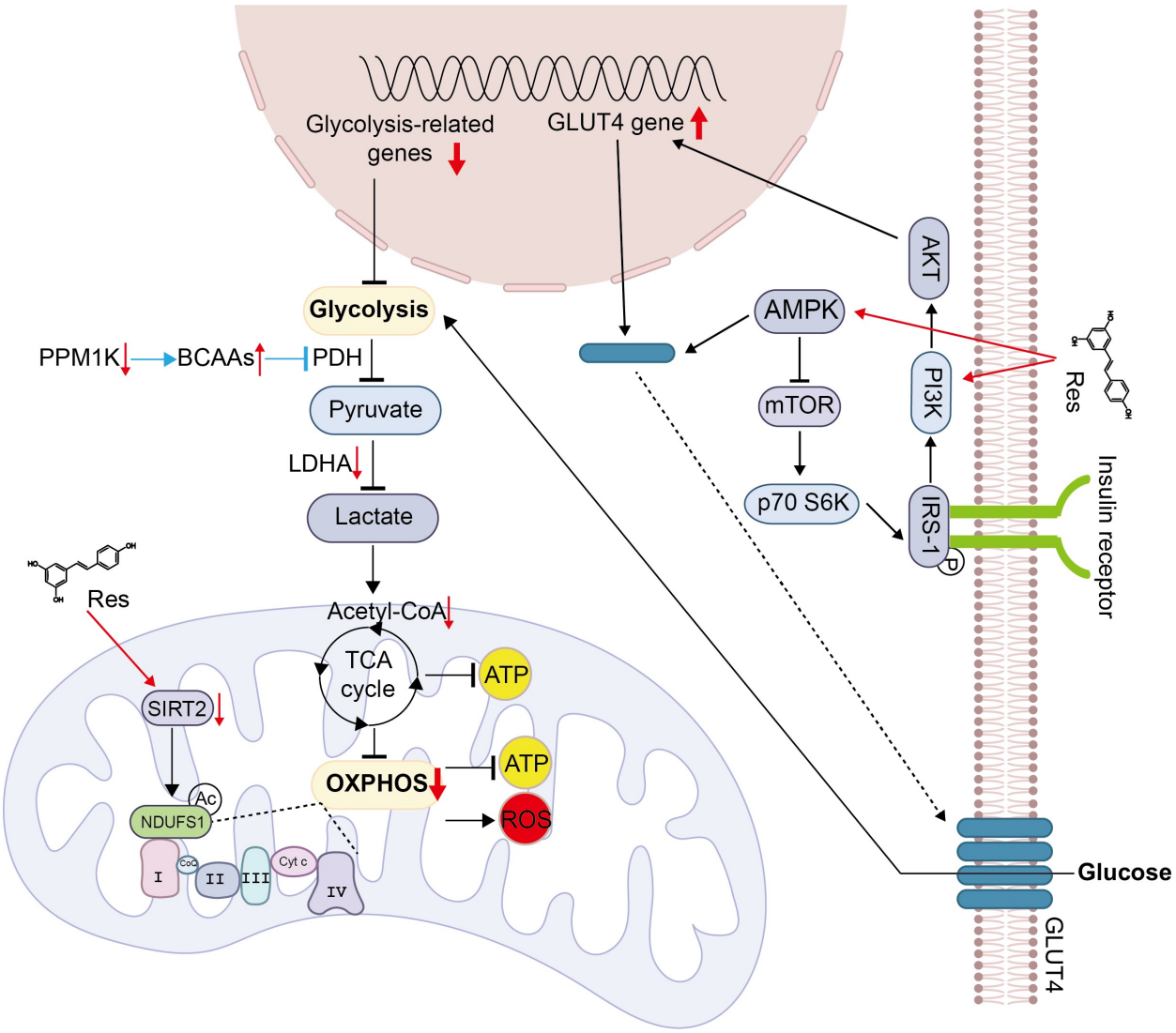

Fig. 4. RES restores glycolytic activity and metabolic competence in granulosa cells in PCOS. This figure depicts the proposed role of RES in counteracting glycolytic impairment and mitochondrial metabolic dysfunction in granulosa cells under PCOS-associated insulin resistance. Red arrows adjacent to molecular labels indicate pathological alterations associated with this condition, whereas arrows originating from RES indicate putative intervention sites. By modulating insulin-related signaling and key metabolic regulators, RES may restore SIRT2-associated glycolysis, improve ATP production, and reduce ROS accumulation. Abbreviations: RES, resveratrol; PCOS, polycystic ovary syndrome; SIRT2, sirtuin 2; AMPK, AMP-activated protein kinase; mTOR, mechanistic target of rapamycin; IRS-1, insulin receptor substrate-1; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; GLUT4, glucose transporter type 4; PDH, pyruvate dehydrogenase; LDHA, lactate dehydrogenase A; TCA, tricarboxylic acid; OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species; ATP, adenosine triphosphate; BCAAs, branched-chain amino acids; PPM1K, protein phosphatase Mg2+/Mn2 dependent 1K; NDUFS1, NADH: ubiquinone oxidoreductase core subunit S1.

tance [69,70,71]. Additional studies suggest that RES may support lipid metabolic flexibility through effects on muscle proteostasis and gut microbiota-derived short-chain fatty-acid metabolism, collectively pointing to a broader role in lipid remodeling in PCOS [72].

2.3 Improvement of Hyperandrogenism

In addition to its effects on glucose handling within the ovarian microenvironment, RES may also influence a broader metabolic dimension of PCOS by modulating adipose and peripheral lipid remodeling. Hyperandrogenemia in PCOS is generally considered to arise from coordinated androgen excess of both adrenal and ovarian origin. Under physiological conditions, adrenocorticotropic hormone (ACTH) stimulates secretion of dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) from the adrenal cortex, whereas luteinizing hormone (LH) promotes androgen biosynthesis in ovarian theca(-

interstitial) cells by upregulating CYP17A1 (P450-17α-hydroxylase/17,20-lyase), thereby facilitating conversion of steroid precursors into androstenedione (AND) and testosterone (T). In PCOS, hyperinsulinemia further amplifies androgen production by dysregulating downstream phosphoinositide 3-kinase (PI3K)/Akt signaling, directly enhancing CYP17A1 expression in theca cells and increasing adrenal responsiveness to ACTH [73]. Androgen excess can then activate the androgen receptor (AR)–NF-κB axis, driving pro-inflammatory cytokine release (e.g., TNF-α and IL-6) and reinforcing a maladaptive "hyperandrogenism–insulin resistance–inflammation" loop that clinically manifests as hirsutism, acne, and alopecia.

RES may interrupt this network through three convergent mechanisms. First, RES directly suppresses ovarian steroidogenesis: in the human theca cell line (theca-SV40), RES (10–50 μM) inhibits CYP17A1 promoter activity, downregulates steroidogenic acute regulatory protein (StAR) and cholesterol side-chain cleavage enzyme (CYP11A1), and reduces T synthesis [74]. Second, RES improves insulin signaling, at least partly by attenuating insulin-induced MAPK/ERK1/2 phosphorylation and restoring insulin receptor substrate-1 (IRS-1) dephosphorylation, thereby indirectly restraining CYP17A1 transcriptional activation [13]. Taken together, RES may alleviate PCOS-related hyperandrogenemia via coordinated inhibition of steroidogenic drivers (notably CYP17A1), improvement of insulin signaling competence, and suppression of the AR–NF-κB inflammatory axis.

Clinical findings further suggest dose-dependent heterogeneity in response. In the first clinical trial, Banaszewska et al. reported reductions of 23.1% in total T and 22.2% in DHEAS after RES treatment, accompanied by a 28% decrease in ovarian CYP17A1 mRNA expression and reduced theca-cell density [75]. In another study, RES combined with inositol improved hirsutism and acne and lowered serum T [76]. By contrast, a trial using 100 mg/day RES found no significant changes in androgen, insulin, or lipid parameters compared with placebo, although menstrual regularity and alopecia showed some improvement [77]. Collectively, these data imply that the clinical efficacy of RES on hyperandrogenemia may depend on dose, treatment duration, and baseline phenotype.

An important unresolved issue is whether the anti-androgenic benefit of RES is phenotype dependent. In patients with metabolically driven PCOS, reduction of hyperinsulinemia and inflammatory signaling may indirectly attenuate ovarian androgen excess, whereas in adrenal-predominant phenotypes, the magnitude and mechanism of response may differ. Likewise, in relatively lean or primarily reproductive phenotypes with lower inflammatory and metabolic burden, the therapeutic effect of RES may be less pronounced or mechanistically distinct. Because most available clinical studies did not stratify participants according to Rotterdam phenotype, BMI, insulin-resistance status, or adrenal contribution, current evidence remains insufficient to define the most RES-responsive subgroup. Future studies should therefore move beyond mean hormonal changes and instead examine whether baseline endocrine–metabolic phenotype predicts the direction and magnitude of response to RES.

2.4 Modulation of Abnormal Angiogenesis in PCOS

A recurrent histopathological feature of PCOS is ovarian stromal hyperplasia accompanied by increased microvascular density and vascular hyperreactivity within the ovary [78]. Vascular endothelial growth factor (VEGF), produced mainly by macrophages and granulosa(-lutein) cells, is widely recognized as a central driver of this pathological angiogenic milieu by increasing vascular permeability and promoting neovascularization, which may further disturb follicular dynamics and steroidogenic balance [79]. Clinically, both circulating and intra-ovarian VEGF levels are elevated in women with PCOS [80,81] and positively correlate with the abundance of active granulosa-lutein cells (GLCs) and VEGF expression in GLCs, suggesting the existence of a local amplification loop [17]. Dysregulated follicular vascular remodeling not only compromises orderly folliculogenesis and ovulation but is also implicated in increased susceptibility to ovarian hyperstimulation syndrome (OHSS) during ovulation induction [82]. Because tightly regulated angiogenesis is essential for cyclic ovulation and luteal function, targeting VEGF-driven vascular dysregulation represents a rational therapeutic node in PCOS [83].

Available experimental evidence supports an anti-angiogenic role of RES in this setting. In animal models, RES reduces VEGF expression in granulosa cells, at least in part through modulation of Akt/protein kinase B (Akt/PKB) signaling, and this effect is accompanied by decreased vascular permeability and partial normalization of follicular cellular composition [83]. Consistent with these findings, limited clinical observations suggest that RES supplementation may downregulate VEGF-related transcriptional programs, including hypoxia-inducible factor-1 (HIF-1), in ovarian cells, together with signals of improved oocyte and embryo quality and attenuation of OHSS-related manifestations; however, the mechanistic and clinical evidence base remains comparatively sparse. Overall, contemporary studies that directly interrogate VEGF-centered angiogenic pathways in PCOS, and delineate how RES reshapes ovarian vascular remodeling, remain limited, highlighting a clear need for updated mechanistic work and well-phenotyped translational cohorts.

Notably, VEGF-driven angiogenic remodeling in PCOS is unlikely to operate independently of other RES-sensitive pathways. Oxidative stress, inflammatory activation, mitochondrial dysfunction, and altered PI3K/Akt signaling may all influence VEGF expression or vascular responsiveness, thereby linking ovarian angiogenesis to

broader metabolic and steroidogenic disturbances. For this reason, the anti-angiogenic effects of RES should be interpreted within the same interconnected signaling network that governs granulosa-cell fate, insulin resistance, and androgen excess.

2.5 Integrative Crosstalk of RES-Regulated Signaling Pathways in PCOS

Although the preceding sections discuss ovarian dysfunction, metabolic disturbance, hyperandrogenism, and angiogenesis separately for clarity, these pathological dimensions are deeply interconnected in PCOS biology and should not be interpreted as isolated processes. A useful integrative framework is to regard oxidative stress, insulin resistance, mitochondrial dysfunction, and chronic low-grade inflammation as shared upstream drivers that initiate and sustain multiple downstream abnormalities. Through these common inputs, different manifestations of PCOS converge at the level of granulosa-cell injury, disordered follicular development, steroidogenic imbalance, metabolic inflexibility, and abnormal ovarian vascular remodeling. This perspective is particularly important when evaluating the potential role of RES, because the biological effects attributed to RES across different experimental systems often reflect modulation of overlapping network nodes rather than correction of a single defect.

Among these nodes, the PI3K/Akt/mTOR axis appears to occupy a central integrative position. In PCOS, dysregulation of this pathway contributes not only to impaired insulin signaling, but also to abnormalities in autophagy, cell survival, ovarian function, and angiogenic responses. Excessive or insufficient mTOR activity may disrupt granulosa-cell homeostasis and alter the balance between survival and stress responses, thereby contributing to follicular arrest. At the same time, PI3K/Akt signaling is closely linked to glucose handling and may influence androgen biosynthesis as well as VEGF-related vascular activity. This broad functional reach helps explain why RES-mediated regulation of PI3K/Akt/mTOR signaling may generate effects across multiple domains, including granulosa-cell protection, improved metabolic signaling, and partial normalization of ovarian microvascular disturbance.

The SIRT1/AMPK pathway represents another major point of convergence linking energy sensing, oxidative-stress adaptation, mitochondrial quality control, and metabolic reprogramming. In the context of PCOS, AMPK suppression and mitochondrial dysfunction may contribute to impaired glucose utilization, persistent energetic stress, and defective cellular adaptation to redox imbalance. SIRT1 and AMPK also interact with autophagy-related machinery and may influence granulosa-cell function, steroidogenic regulation, and local follicular metabolism. Since RES is widely reported to activate SIRT1 and enhance AMPK-related signaling, its effects on PCOS may extend beyond a simple antioxidant mechanism and instead reflect a broader capacity to restore cellular adaptability under conditions of metabolic and oxidative overload. This may be particularly relevant in phenotypes characterized by obesity, insulin resistance, or chronic inflammatory activation.

Inflammatory signaling, especially through the NF-κB axis, provides an additional mechanistic bridge among these processes. NF-κB may be activated by oxidative stress, advanced glycation-related signaling, lipotoxicity, mitochondrial disturbance, and androgen-associated inflammatory amplification. Once activated, it promotes the expression of pro-inflammatory cytokines and may further impair insulin signaling, exacerbate oxidative damage, and alter the ovarian microenvironment. In this sense, NF-κB is not merely a downstream mediator of inflammation but also part of a self-reinforcing pathogenic loop that links systemic metabolic dysfunction to local ovarian injury. The anti-inflammatory actions of RES, including suppression of NF-κB-related signaling, may therefore have consequences that extend beyond cytokine reduction alone, potentially influencing insulin sensitivity, granulosa-cell survival, and steroidogenic balance in parallel.

VEGF-related angiogenic remodeling should also be incorporated into this network model rather than treated as an isolated vascular endpoint. Abnormal ovarian angiogenesis in PCOS is likely shaped by the combined influence of oxidative stress, inflammatory signaling, altered PI3K/Akt activity, and local steroidogenic dysfunction. Elevated VEGF expression may increase vascular permeability, disturb follicular dynamics, and contribute to a microenvironment that is less supportive of orderly ovulation and oocyte development. Because angiogenesis is functionally connected to tissue oxygenation, inflammatory burden, and ovarian structural remodeling, the anti-angiogenic effects of RES may represent one component of a larger systems-level response rather than a discrete mechanism independent of metabolic or endocrine regulation.

Taken together, the available evidence supports a model in which RES acts on several interrelated signaling hubs—most prominently PI3K/Akt/mTOR, SIRT1/AMPK, NF-κB, and VEGF-centered pathways—thereby influencing multiple downstream manifestations of PCOS, including autophagy imbalance, impaired glycolysis, hyperandrogenism, and abnormal angiogenesis. This network perspective has two important implications. First, it helps explain why RES may show pleiotropic benefits in preclinical models, where pathological disturbances are often pronounced and comparatively homogeneous. Second, it also helps explain why clinical findings are more variable, because the relative contribution of oxidative stress, insulin resistance, androgen excess, inflammatory burden, and vascular dysregulation differs substantially across PCOS phenotypes. Therefore, the therapeutic value of RES is likely to depend not only on dose and duration, but also on whether the dom-

Table 1. PCOS experimental models and their human correlations.

Model	Main experimental feature	Closest human PCOS correlate	Main mechanisms captured	Utility for RES research	Major limitations
DHEA-induced model	Exogenous androgen excess with ovarian dysfunction	Hyperandrogenic PCOS, especially androgen-driven or adrenal-androgen-dominant features	Hyperandrogenism, follicular arrest, steroidogenic dysregulation, oxidative stress, mitochondrial injury	Useful for studying anti-androgenic, antioxidative, and follicle-protective effects of RES	May overrepresent androgen excess and incompletely reflect the metabolic heterogeneity of human PCOS
Letrozole-induced model	Aromatase inhibition with ovarian cystic change and ovulatory dysfunction	Ovarian dysfunction-dominant PCOS with disrupted steroid balance	Altered steroidogenesis, anovulation, cystic follicle formation, granulosa-cell dysfunction	Useful for evaluating ovarian structural remodeling and steroidogenic regulation by RES	Does not fully reproduce the systemic inflammatory and metabolic spectrum seen in many patients
High-fat diet (HFD) model	Obesity-associated metabolic stress	Metabolic/obese PCOS phenotype with insulin resistance	Insulin resistance, hyperinsulinemia, ectopic lipid deposition, chronic low-grade inflammation, oxidative stress	Useful for assessing the metabolic, anti-inflammatory, and insulin-sensitizing effects of RES	Reproductive abnormalities may be less pronounced or may arise secondarily rather than as a primary endocrine defect
Combined models (e.g., androgen + HFD)	Reproductive and metabolic insults combined	Mixed PCOS phenotype with both hyperandrogenic and metabolic traits	Crosstalk among hyperandrogenism, IR, inflammation, and oxidative stress	Potentially more suitable for evaluating the pleiotropic, network-level effects of RES	Model complexity increases variability; protocol differences reduce comparability across studies
In vitro granulosa-cell systems	Cell-specific mechanistic perturbation	Local ovarian microenvironment dysfunction rather than a whole-patient phenotype	Autophagy/apoptosis balance, glycolytic dysfunction, ROS stress, mitochondrial quality control, VEGF/HIF signaling	Particularly useful for dissecting direct cellular targets of RES	Cannot recapitulate systemic endocrine-metabolic crosstalk or phenotype heterogeneity at the organism level

No single model fully recapitulates the phenotypic heterogeneity of human PCOS. Therefore, therapeutic conclusions regarding RES should not be generalized across all PCOS phenotypes without considering whether the dominant pathology is hyperandrogenic, ovarian, metabolic, or mixed.

inant pathogenic network in each patient subgroup is sufficiently aligned with the molecular targets that RES is able to modulate.

Because the mechanistic evidence summarized above has been generated from heterogeneous experimental systems, it is important to distinguish which pathological dimensions of human PCOS are best represented by each model and where their translational limitations lie (Table 1).

3. Clinical Therapeutic Potential and Translational Limitations

Accumulating experimental evidence suggests that RES exerts pleiotropic regulatory effects on ovarian, metabolic, and inflammatory signaling networks implicated in PCOS [9,84]. However, when translated to clinical trials, its overall benefit appears modest and heterogeneous. As summarized by Podgrajsek et al., evidence from randomized placebo-controlled studies suggests that RES may improve selected PCOS phenotypes, yet substantial between-study variability persists in study design, endpoints, and effect size [8,16,54,77,78,85,86]. A more recent trial provides additional supportive signals [87], but the overall body of clinical evidence still suggests that RES is better regarded as a context-dependent adjunct rather than a broadly disease-modifying therapy for PCOS.

Despite encouraging mechanistic findings from experimental studies, the clinical effects of RES in women with PCOS remain modest and variable. To facilitate comparison of the available human evidence, Table 2 (Ref. [16,53,75,76,77,86,87]) summarizes the principal clinical studies, with emphasis on study design, patient characteristics, treatment regimen, major efficacy outcomes, and safety-related observations.

Table 2. Clinical studies of RES in women with PCOS.

Study	Design	Population/ phenotype	BMI/IR status	Dose	Duration	Main endpoints	Main findings	Safety/comments
Banaszewska et al., 2016 [75]	Double-blind, randomized, placebo-controlled trial	Women with PCOS	lean/overweight status and baseline IR profile	1500 mg/day	3 months	Total testosterone, DHEAS, fasting insulin, insulin sensitivity, ovarian steroidogenic markers	RES reduced total testosterone and DHEAS, improved fasting insulin and insulin sensitivity, and was associated with downregulation of CYP17A1-related androgenic activity	No major severe adverse signal highlighted in the review; detailed safety outcomes should be checked against the original paper
Bahramrezaie et al., 2019 [16]	Triple-blind, randomized, placebo-controlled clinical trial	PCOS patients undergoing ART/IVF-related treatment	BMI and IR subgroup information	800 mg/day	60 days	Oocyte quality, embryo quality, serum testosterone, granulosa-cell VEGF/HIF-1 expression	RES improved good-quality oocyte and high-grade embryo rates, lowered testosterone, and reduced VEGF/HIF-1 expression in granulosa cells	Important to interpret in the context of peri-conception timing; reproductive safety window should be discussed explicitly
Brenjian et al., 2020 [53]	Clinical interventional study	Women with PCOS	Not clearly stratified in current text	-	-	Inflammatory and ER stress markers	RES was associated with reduced inflammatory mediators and endoplasmic reticulum stress-related markers	Add exact sample size and intervention details from original paper
Mansour et al., 2021 [77]	Randomized placebo-controlled trial	Women with PCOS	obesity / IR phenotype	-	-	Menstrual regularity, hair loss, metabolic and androgenic parameters	Limited or no significant changes in androgen, insulin, or lipid indices were observed, but menstrual cyclicity and hair loss showed improvement	Useful as a "modest/variable efficacy" study and should be discussed as evidence of phenotype- and endpoint-dependent responsiveness
Hassan et al., 2023 [76]	Double-blind randomized clinical trial	Women with PCOS	phenotype and metabolic profile	RES combined with myo-inositol	-	Hirsutism, acne, testosterone, perceived stress	Combination treatment improved hyperandrogenic symptoms and reduced total testosterone and perceived stress	Since this is combination therapy, it should not be interpreted as a pure RES monotherapy signal
Malvasi et al., 2022 [86]	Pilot study	Women with PCOS	body composition profile	RES plus alpha-lipoic acid	-	Weight and body composition	Preliminary evidence suggested possible benefits on body weight/body composition-related outcomes	Combination design and pilot nature limit mechanistic attribution to RES alone
Ardehjani et al., 2024 [87]	Randomized, triple-blind, placebo-controlled trial	PCOS women undergoing IVF/ICSI	phenotype, BMI, and baseline oxidative stress profile	-	-	Follicular fluid oxidative stress indices, TAC, oocyte maturation, embryo quality	RES improved oxidative balance in follicular fluid and was associated with improved oocyte maturation, mitochondrial biogenesis-related parameters, and embryo quality	Particularly valuable for discussing local ovarian oxidative stress modulation; should be distinguished from non-PCOS IVF safety signals

Clinical responsiveness to RES appears to be context dependent. Future trials should stratify participants by Rotterdam phenotype, obesity status, insulin resistance, inflammatory burden, and reproductive setting (general PCOS management vs. ART setting), and should report effect sizes and safety outcomes in a standardized manner. Evidence from combination regimens should be interpreted separately from RES monotherapy.

A parsimonious explanation for the experimental–clinical gap is the marked biological heterogeneity of PCOS, spanning metabolic (obesity with IR), reproductive (lean with relatively higher LH), and adrenal (higher DHEAS) phenotypes. Most available trials did not stratify participants by Rotterdam phenotype, BMI, IR indices (e.g., HOMA-IR), or inflammatory markers, which likely obscures subtype-specific responsiveness [6]. Moreover, null findings in some PCOS cohorts suggest that dose, treatment duration, and baseline disease severity may be important determinants of response [77]. Conversely, in phenotypes with lower baseline inflammation, RES may yield attenuated benefits and, under certain conditions, could theoretically shift toward pro-oxidative effects. These considerations emphasize that future trials should be explicitly phenotype-informed, with prespecified stratification and mechanistically aligned endpoints rather than relying solely on aggregated mean effects.

Safety considerations warrant particularly cautious interpretation in fertility-oriented settings. Importantly, evidence suggestive of reproductive risk does not arise from a single evidence tier. In PCOS-specific randomized studies, including a recent triple-blind, placebo-controlled assisted-reproduction trial, RES did not significantly alter chemical or clinical pregnancy rates and was well tolerated; therefore, currently available PCOS-specific clinical data do not establish a clear increase in miscarriage risk, although pregnancy-loss endpoints remain limited and underpowered [36,87]. By contrast, concern has mainly arisen from IVF-related observations outside strictly defined PCOS populations: a retrospective embryo-transfer cohort reported reduced clinical pregnancy and increased miscarriage odds with continuous RES exposure, whereas a more recent exploratory randomized IVF trial in non-PCOS women did not confirm a detrimental effect on biochemical pregnancy, clinical pregnancy, or live birth, underscoring substantial potential for confounding by indication, exposure timing, and endometrial context [36,84,88,89]. In parallel, experimental and translational data warrant caution but should be carefully qualified rather than directly extrapolated to women with PCOS. Recent reviews of fertility and pregnancy models emphasize that RES shows marked context- and dose-dependence: lower concentrations may support ovarian redox homeostasis, whereas higher exposures have been linked to impaired granulosa-cell viability and steroidogenic function, cleavage arrest or embryo death in preimplantation models, abnormal fetal pancreatic development in pregnancy models, and anti-thyroid/goitrogenic effects *in vivo* [8,90,91].

Therefore, current evidence supports caution, but not overstatement, regarding reproductive toxicity in PCOS. A more balanced interpretation is that the safety and efficacy of RES are likely to depend on dose, exposure window, and reproductive context. If RES is considered in infertility-related management, short-term pre-conception administration with discontinuation before the luteal phase or embryo transfer, together with careful endocrine monitoring—especially thyroid function and early pregnancy-related hormones—appears more appropriate than prolonged exposure extending into implantation or early pregnancy [8,88,89,91]. This interpretation is consistent with a context-dependent, potentially U-shaped dose-response profile, in which antioxidant and metabolic benefits may emerge within a limited therapeutic window, whereas higher or prolonged exposure may shift toward less favorable reproductive or endocrine effects [8,91]. Importantly, reproductive safety should be interpreted with caution and with a clear distinction between different evidence tiers. Signals related to miscarriage or impaired reproductive outcomes should not be generalized from retrospective IVF cohorts not limited to PCOS, nor from animal embryotoxicity studies to all women with PCOS receiving RES. PCOS-specific randomized evidence remains limited and does not yet support a definitive conclusion regarding reproductive harm. Therefore, future clinical studies should explicitly distinguish general metabolic use, ART-related peri-conception use, and post-ovulation or early pregnancy exposure when evaluating the benefit-risk profile of RES.

Another major source of translational uncertainty lies in the experimental models used to study RES in PCOS. DHEA-induced models may preferentially reflect hyperandrogenic biology; letrozole-based models are often more informative for ovarian dysfunction and altered steroidogenic control; and high-fat-diet-based or combined models better capture the metabolic and inflammatory dimensions of PCOS [5,92,93,94,95]. Although each model provides valuable mechanistic insight, none fully reproduces the phenotypic heterogeneity of human PCOS [92,93]. As a result, strong efficacy observed in one model cannot be assumed to generalize across all patient subgroups [93]. Future studies should therefore explicitly align mechanistic questions, preclinical models, and clinical target populations [93,95]. In clinical trials, this means stratifying participants by phenotype, BMI, insulin resistance, inflammatory burden, and reproductive goals [5]. In preclinical research, it means clarifying which dimension of PCOS pathology a given model is intended to represent and avoiding overly broad therapeutic claims based on phenotype-restricted systems. Such alignment may help reduce the current gap between mechanistic plausibility and clinical applicability.

4. Conclusions

In conclusion, current evidence suggests that RES may influence PCOS through a network of interconnected molecular and cellular pathways rather than through a single dominant mechanism. Across preclinical studies, its most consistently implicated actions involve the regulation of oxidative stress, insulin signaling, granulosa-cell homeostasis, steroidogenic activity, local follicular metabolism, and VEGF-associated angiogenic remodeling.

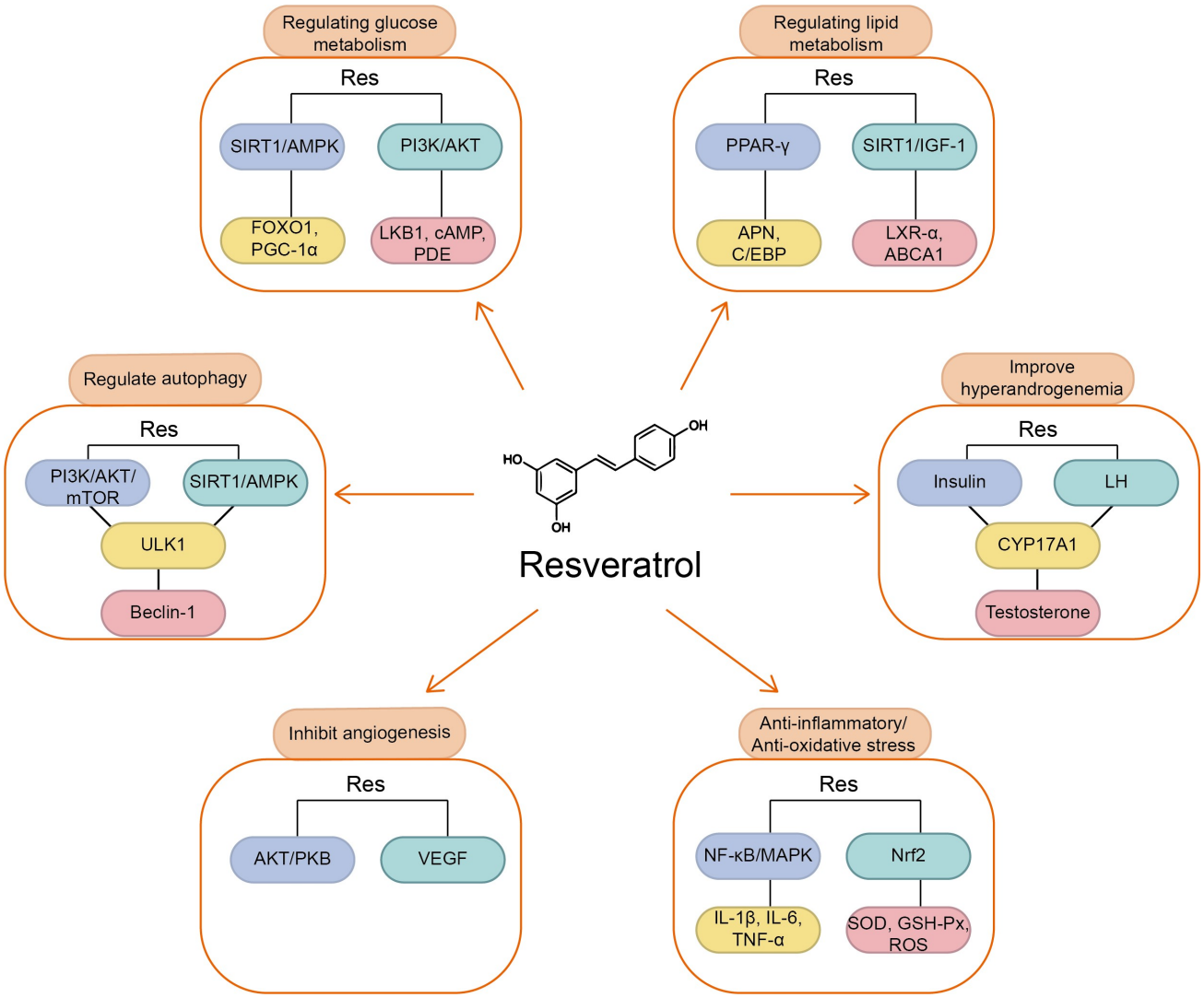

Fig. 5. Integrative schematic summary of the major signaling crosstalk and phenotype-dependent translational implications of RES in PCOS. This integrative overview summarizes the major pathways through which RES may regulate PCOS, including autophagy, glucose and lipid metabolism, hyperandrogenism, angiogenesis, and inflammatory/oxidative stress responses. The figure highlights pathway crosstalk among key nodes such as PI3K/Akt, SIRT1/AMPK, NF-κB/MAPK, Nrf2, VEGF, and CYP17A1, and emphasizes the context-dependent therapeutic implications of RES in different PCOS phenotypes. Abbreviations: RES, resveratrol; PCOS, polycystic ovary syndrome; PI3K, phosphoinositide 3-kinase; Akt/PKB, Ak strain transforming/protein kinase B; mTOR, mechanistic target of rapamycin; SIRT1, sirtuin 1; AMPK, AMP-activated protein kinase; FoxO1, forkhead box O1; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1 alpha; LKB1, liver kinase B1; PDE, phosphodiesterase; PPAR-γ, peroxisome proliferator-activated receptor gamma; IGF-1, insulin-like growth factor 1; APN, adiponectin; C/EBP, CCAAT/enhancer-binding protein; LXR-α, liver X receptor alpha; ABCA1, ATP-binding cassette transporter A1; LH, luteinizing hormone; CYP17A1, cytochrome P450 family 17 subfamily A member 1; NF-κB, nuclear factor kappa-B; MAPK, mitogen-activated protein kinase; Nrf2, nuclear factor erythroid 2-related factor 2; IL, interleukin; TNF-α, tumor necrosis factor alpha; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; VEGF, vascular endothelial growth factor; ULK1, unc-51-like kinase 1.

Within this framework, PI3K/Akt/mTOR, SIRT1/AMPK, NF-κB, and VEGF-related pathways emerge as key convergent nodes through which RES may generate coordinated effects on ovarian structure, metabolic balance, and reproductive function. A schematic summary of these interconnected mechanisms is presented in Fig. 5.

However, the strength of evidence remains uneven across mechanistic domains and clinical settings. Although *in vitro* and animal studies broadly support the biological plausibility of RES in PCOS, the clinical benefit observed to date remains modest, heterogeneous, and strongly influenced by study design, dose, treatment duration, baseline phenotype, and reproductive context. Importantly, the dis-

crepancy between robust preclinical efficacy and variable clinical outcomes likely reflects the marked heterogeneity of PCOS itself, together with the limitations of existing experimental models and the lack of sufficiently stratified human trials.

At present, RES should therefore be regarded as a potentially useful, phenotype-sensitive adjunct rather than a universally effective therapy for PCOS. Future progress will depend on more integrative mechanistic studies, clearer mapping between experimental models and human PCOS subtypes, phenotype-stratified clinical trials with mechanistically aligned endpoints, and more rigorous evaluation of reproductive safety and treatment windows. Such efforts will be essential to determine whether the multi-target actions of RES can be translated into clinically meaningful and precisely targeted benefits for selected PCOS populations.

Author Contributions

Conceptualization, JR, DDM; Methodology, JR, DDM, RRH; Literature Search, RRH, DG; Data Extraction, DG, XYH; Formal Analysis, DG, XYH; writing—original draft preparation, RRH and XYH; writing—review and editing, RRH, DongG and JR; visualization, XYH. RRH and XYH are the co-first authors, while JR and DDM are the co-corresponding authors. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

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