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REVIEW

Resveratrol in Dermatological Therapy: A Critical Review of Mechanisms, Delivery Innovations, and Clinical Frontiers

Quanrui Cui[1], Heping Wang[2]

[1]Department of Dermatology, Heilongjiang University of Chinese Medicine, Harbin, People's Republic of China; [2]Department of Dermatology, The First Affiliated Hospital of Heilongjiang University of Chinese Medicine, Harbin, People's Republic of China

Correspondence: Heping Wang, Department of Dermatology, The First Affiliated Hospital of Heilongjiang University of Chinese Medicine, Harbin, People's Republic of China, Tel +86 15504619899, Email wanghepinghljzyy@163.com

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Abstract: The management of complex dermatological disorders, including chronic inflammatory diseases, non-healing wounds, and skin malignancies, often faces significant challenges. These include limited efficacy against chronic or relapsing conditions, the emergence of drug-resistant pathogens, and significant side effects from long-term therapies. This clinical gap highlights the urgent need for novel therapeutic agents. Resveratrol (RES), a natural polyphenol with pleiotropic bioactivities, has emerged as a compelling candidate substantiated by its diverse modulatory effects on cutaneous pathophysiology. This review aims to critically synthesize the evidence for RES's efficacy, dissect its foundational mechanisms, and explore innovations in drug delivery designed to overcome its clinical limitations. This review critically synthesizes evidence of the efficacy of RES in managing challenging dermatological conditions, including chronic wounds, psoriasis, atopic dermatitis, melanoma, acne, and herpes simplex virus infections, by dissecting its foundational antioxidant, anti-inflammatory, and immunomodulatory mechanisms. Its therapeutic action is mediated through critical molecular pathways, notably the activation of SIRT1/AMPK and suppression of NF-κB, which collectively mitigate oxidative stress, normalize cellular proliferation, and recalibrate immune responses. Although systemic bioavailability limitations have historically hindered RES's clinical translation, innovative delivery systems, including nanoparticles, hydrogels, and advanced transdermal formulations, are now revolutionizing its topical application and markedly enhancing its localized efficacy and stability. This review consolidates robust preclinical evidence from animal models demonstrating RES-driven accelerated wound healing, diminished inflammatory markers, and significant tumor suppression while also appraising nascent yet promising clinical trial data that indicate good tolerability and initial efficacy in human subjects. Ultimately, this synthesis crystallizes RES as a versatile and promising therapeutic agent in dermatology, concurrently underscoring the imperative for continued innovation in delivery methodologies and execution of large-scale stringently designed clinical trials to fully unlock its therapeutic potential.

Keywords: resveratrol, dermatological disorders, therapeutic mechanisms, drug delivery systems, preclinical studies, clinical trials

Introduction to RES

Resveratrol (RES;3,5,4′-trihydroxy-trans-stilbene, Figure 1), a naturally occurring polyphenolic phytoalexin, is widely found in plants such as grapes (*Vitis vinifera*), peanuts (*Arachis hypogaea*), and Japanese knotweed (*Polygonum cuspidatum*).[1] It exhibits diverse biochemical activities, including antioxidant, anti-inflammatory, anti-carcinogenic, and cardioprotective properties, making it a promising candidate for therapeutic applications.[1–3] Despite its low systemic bioavailability owing to rapid sulfate and glucuronide conjugation in humans, RES accumulates in epithelial cells along the aerodigestive tract, suggesting its potential localized efficacy.[4] Its ability to modulate multiple molecular pathways, such as SIRT1 activation, is dependent on the substrate sequence and fluorophore-conjugated peptides, further underscoring its complex but targetable mechanisms.[5,6]

As a phytoalexin, RES is synthesized in plants from the shikimate-derived phenylpropanoid pathway in response to stressors like infection or UV radiation.[3,7] Beyond RES itself, related stilbenoids and derivatives such as its metabolite

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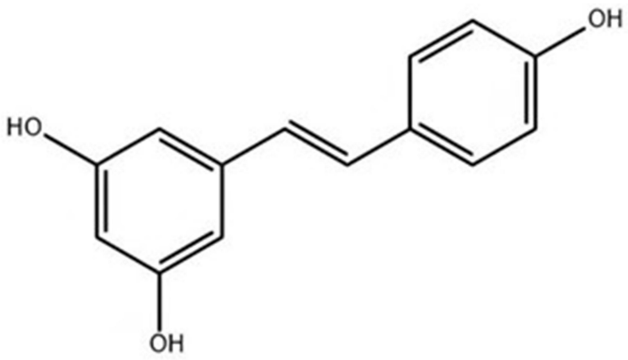

Figure 1 Molecular formula of RES.

piceatannol, its dimer ε-viniferin, and oxyresveratrol have also demonstrated significant bioactivity in skin models, targeting conditions like atopic dermatitis and psoriasis.[8–10] RES's therapeutic potential is rooted in its ability to engage multiple, pivotal signaling pathways. Its primary mechanisms include mitigating oxidative stress via antioxidant pathways (eg, Nrf2),[11] suppressing inflammation by inhibiting key regulators like NF-κB,[3] and modulating cell proliferation and apoptosis through sirtuin activation (eg, SIRT1) and caspase-dependent pathways.[12] Furthermore, its actions extend to critical tissue-remodeling processes, where it modulates collagen homeostasis by preventing degradation and promoting synthesis, while also exerting context-dependent effects on angiogenesis.[13–15] This capacity to target multiple hubs simultaneously allows it to address the complex pathophysiology of the various skin disorders detailed in this review. Figure 2 provides a detailed schematic of these multifaceted molecular interactions.

From a clinical perspective, RES's therapeutic potential is being explored across a wide spectrum of dermatological conditions, reflecting its ability to target diverse pathophysiological processes. These "clinical frontiers" include chronic inflammatory and immune-mediated disorders such as psoriasis and atopic dermatitis; conditions of impaired tissue repair like chronic wounds; and aggressive neoplastic diseases such as melanoma. Furthermore, its utility is under investigation for common concerns including acne, viral skin infections like herpes simplex, and the mitigation of cutaneous aging.[16–22] This review will navigate these frontiers by critically appraising the preclinical and emerging clinical evidence for RES in each of these domains, providing a comprehensive overview of its potential role in future dermatological therapy.

RES in Dermatological Therapeutics: Mechanisms, Delivery Strategies, and Preclinical Evidence

Wound Healing

RES demonstrates multifaceted mechanisms for promoting wound healing, supported by its antioxidant, anti-inflammatory, and proangiogenic properties. RES reduces oxidative stress by scavenging reactive oxygen species (ROS) and upregulating nuclear factor erythroid 2-related factor 2 (Nrf2) and manganese superoxide dismutase (Mn-SOD), thereby protecting fibroblasts and endothelial cells from oxidative damage.[16,23,24] It attenuates inflammation by suppressing pro-inflammatory cytokines and inducible nitric oxide synthase (iNOS) while enhancing anti-inflammatory factors (TGF-β1, Arg-1).[25,26] RES accelerates angiogenesis via activation of the PI3K/AKT, VEGF, and FGF signaling pathways, promoting endothelial cell proliferation, migration, and tube formation.[13] Additionally, RES modulates macrophage polarization toward the M2 phenotype, facilitating tissue repair and reducing chronic inflammation.[27,28] It enhanced fibroblast proliferation, collagen synthesis, and re-epithelialization, supported by improved wound contraction and granulation tissue formation in diabetic models.[14,15] RES also inhibits fibrosis by downregulating the TGF-β3/Smad3, p38 MAPK, and PI3K/AKT pathways, thereby preventing excessive collagen deposition.[25] Furthermore, RES-loaded formulations exhibited antibacterial activity against Staphylococcus aureus and Pseudomonas aeruginosa,

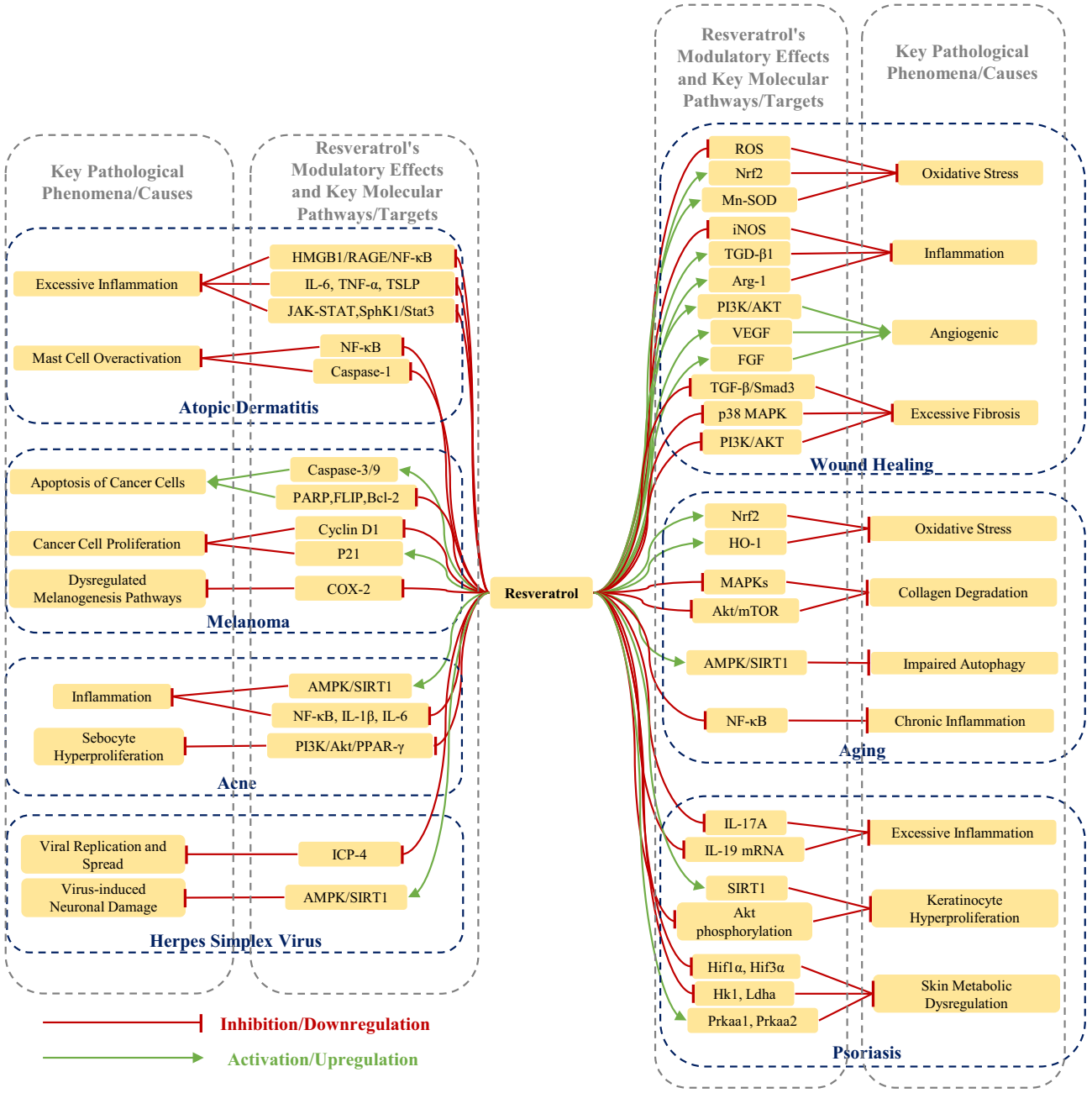

Figure 2 Therapeutic targeting of skin pathologies by RES: Key molecular interaction mechanisms.

reducing biofilm formation and infection risk.[29,30] These mechanisms are synergistically amplified in composite hydrogels or nanoparticle delivery systems, which enables sustained RES release and targeted action.[26,27,31]

Recent advancements in RES delivery systems have significantly enhanced therapeutic efficacy in wound healing. Hydrogel-based formulations, such as supramolecular gelatin hydrogels co-loaded with RES and histatin-1, exhibit injectable and shear-thinning properties, enabling precise adaptation to irregular wounds while simultaneously suppressing inflammation and promoting angiogenesis.[32] Composite hydrogels incorporating RES-loaded mesoporous silica nanoparticles (MSNs) and platelet-derived extracellular vesicles (PDEVs) can achieve sustained drug release, reduce oxidative stress, modulate macrophage polarization, and accelerate diabetic wound closure.[26] Nanostructured lipid carriers (NLCs) co-encapsulating RES with curcumin improve dermal retention and permeability, facilitating prolonged therapeutic action.[33] Additionally, microneedle systems that deliver RES-loaded hemoglobin nanoparticles

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synergistically regulate glucose metabolism and hypoxia in diabetic wounds.[34] The development of innovative delivery platforms such as hydrogels and nanoparticles is pivotal for enhancing RES's localized efficacy. Building upon these advancements, future formulation research should focus on tailoring RES delivery systems to the specific characteristics of different wound types, such as developing highly absorbent hydrogels for exudative wounds versus occlusive films for drier wounds, to optimize the microenvironment. Furthermore, exploring the synergistic potential of RES in systems co-loaded with other bioactive agents, such as growth factors or targeted antimicrobials, to complement its inherent antibacterial activity against pathogens represents a promising avenue for enhancing therapeutic outcomes.

RES has demonstrated significant therapeutic efficacy in preclinical wound healing models. Similarly, in a diabetic rat model, RES-glycerosomal nanovesicles (RES-GLY-NVs) improved wound contraction and collagen deposition, outperforming conventional therapies.[35] In full-thickness burn models, topical 5% RES ointment accelerated reepithelialization, reduced oxidative stress, and mitigated hepatorenal toxicity in rats.[36] Diabetic foot ulcer studies revealed that RES-liposome hydrogels restored glycosaminoglycan levels and reduced blood glucose levels, improving ulcer healing and wound closure on day 9.[37] RES-collagen scaffolds in obese mice induced subcutaneous adipocyte browning, enhanced vascularization, and achieved full wound closure within 10 days.[38] In rats, oral RES (30 mg/kg/day) reduced inflammatory infiltration and preserved tissue transparency by modulating MMP-9 and antioxidant pathways.[39] Clinical trials, although limited, show promise; a randomized study[40] reported 57.82% wound closure in diabetic foot ulcers using RES-impregnated dermal matrices (Dermalix®), doubling healing rates versus standard care. RES-cyclodextrin hydrogels[41] were biocompatible in rabbit skin irritation tests. Synergistic RES-lovastatin combinations[42] inhibited Pseudomonas aeruginosa growth and enhanced mesenchymal stem cell migration in vitro. Pluronic hydrogels containing RES included in hydroxypropyl-beta-cyclodextrin[30] demonstrated rapid bactericidal effects against methicillin-resistant Staphylococcus aureus (MRSA). Although RES demonstrates promising antioxidant and pro-angiogenic effects in diabetic and burn models, research on chronic wounds (eg, venous ulcers) remains limited. Clinical trials are small-scale and lack long-term safety assessment. In addition, successful translation of RES-based therapies into routine clinical practice for chronic wound care will hinge on demonstrating their cost-effectiveness. Future studies should incorporate pharmacoeconomic analyses comparing RES formulations with existing advanced wound care products to establish their value propositions within healthcare systems.

Anti-Aging

RES exerts anti-aging effects through multiple molecular mechanisms, primarily by targeting the oxidative stress, inflammation, and cellular senescence pathways. It activates the Nrf2/HO-1 signaling pathway, enhancing antioxidant defenses by reducing ROS accumulation and lipid peroxidation,[8,43–45] while suppressing UVB-induced matrix metalloproteinase-1 (MMP-1) expression via inhibition of MAPKs and Akt/mTOR pathways to prevent collagen degradation.[17,46] In addition to its effects on collagen, RES addresses photoaging by improving hyperpigmentation. This depigmenting activity is attributed to its ability to downregulate key factors in melanin synthesis, including the enzyme tyrosinase and the master regulator of melanogenesis, MITF. Clinical data support this mechanism, with human studies on topical formulations reporting significant melanin reduction.[47–49] RES modulates sirtuin activity, particularly SIRT1 and SIRT6, which regulate mitochondrial biogenesis, DNA repair, and senescence markers like p16 and p21.[45,50–52] Activation of AMPK/SIRT1 signaling promotes autophagy and restores the mitochondrial membrane potential, counteracting oxidative damage and apoptosis.[43,53,54] Additionally, RES inhibits NF-κB-mediated inflammatory responses by reducing pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β.[55–57] It also attenuates glycation-induced advanced glycation end-products (AGEs) in skin models, preserving collagen expression and epidermal stratification.[17,58] Furthermore, RES enhances circadian clock gene rhythmicity and mitigates age-related declines in antioxidant enzymes such as SOD and catalase.[59,60] These multifaceted actions are supported by formulations improving its bioavailability, such as nanoemulsions and liposomes, which enhance transdermal delivery and sustained release.[61–63]

The clinical translation of RES is challenged by its poor bioavailability, which has prompted innovations in delivery systems. Chitosan-coated nanoemulsions enhanced transdermal absorption, achieving 96.72 +/. ± 2.98% over 36 h of RES release in skin models.[61] Gold nanoparticle-encapsulated RES delayed cataract progression by activating SIRT1/Nrf2 and reducing ROS production and apoptosis in lens epithelial cells.[64] Solid lipid nanoparticles (SLNs) stabilized

RES, enabling sustained release and higher cutaneous retention; the selected formulations prepared at 80 degrees C and 70 degrees C presented encapsulation efficiencies of 70% and 72%, respectively.[58,62] Innovations in delivery, such as nanoemulsions and liposomes designed to enhance transdermal absorption and sustained release, are crucial for overcoming RES's inherent poor bioavailability. Nevertheless, a critical aspect for validating topical anti-aging efficacy is the quantitative assessment of RES penetration into viable epidermal and dermal layers of human skin. Future studies should focus not only on release kinetics but also on determining the concentrations achieved in target cells (keratinocytes, fibroblasts, and melanocytes) and correlating these with tangible biological effects in vivo.

In animal experiments, RES combined with high-intensity interval training (HIIT), it upregulated hippocampal SOD2 and AMPK in aged rats, thereby mitigating oxidative stress.[65] Preconceptional RES supplementation in mice reduces age-related ovarian dysfunction and improves reproductive outcomes, suggesting prophylactic utility.[66] Additionally, RES reversed arsenic-induced hepatocyte senescence by modulating SIRT1 signaling and attenuating liver fibrosis in rodent models.[67] These findings highlight its versatility in addressing multifactorial ageing processes. Emerging clinical data further support RES's safety and efficacy. A Phase I trial of JOTROL™, a bioavailable RES formulation, demonstrated dose-dependent increases in plasma concentrations (Cmax = 455 ng/mL at 500 mg) without adverse effects, paving the way for trials on Alzheimer's and age-related disorders.[68] Human studies on topical RES formulations have revealed significant improvements in skin elasticity, melanin reduction, and wrinkle attenuation, validating their cosmetic anti-aging potential.[48,49] Existing human studies indicate that improvements in skin elasticity, melanin reduction, and wrinkle attenuation with topical RES formulations are promising initial steps. However, to firmly establish RES's role in anti-aging dermatology, rigorous long-term placebo-controlled clinical trials are required to substantiate these findings. Such trials should aim to confirm not only cosmetic enhancements but also genuine histological and molecular anti-aging effects in human skin. Furthermore, the potential utility of RES as a prophylactic agent to slow down or prevent the onset of skin aging signs is an intriguing area that warrants future investigation.

Psoriasis

RES demonstrates multifaceted mechanisms for alleviating psoriasis, primarily through its anti-inflammatory and immunomodulatory properties. It suppresses pro-inflammatory cytokines and modulates immune cell subsets, including T cells and macrophages, to mitigate autoimmune inflammation.[18] Specifically, RES induces apoptosis in hyperproliferative keratinocytes by activating Sirt1, a class III histone deacetylase that inhibits Akt phosphorylation, thereby disrupting keratinocyte survival pathways.[69] In immiquimod-induced psoriasis-like models, RES downregulated IL-17A and IL-19 mRNA levels, attenuated IL-17 signaling, and enhanced retinoic acid-associated gene expression, effectively reducing disease severity.[70] Additionally, RES inhibits the NLRP3 inflammasome pathway by suppressing NLRP3, ASC, TXNIP, and CASP-1 expression, which is elevated in psoriatic lesions, thereby curtailing inflammation and keratinocyte apoptosis.[71] It also ameliorates metabolic dysregulation in psoriatic skin by suppressing hypoxia-inducible factors (Hif1α, Hif3α) and glycolysis-related genes (Hk1, Ldha), while activating AMPK signaling (Prkaa1, Prkaa2), which collectively reduces macrophage infiltration and pro-inflammatory cytokine secretion (IL-23, TNF, and alpha).[72] These mechanisms were corroborated by in vitro and in vivo studies, highlighting RES's potential as a therapeutic agent that targets multiple pathological pathways in psoriasis.

Recent advances in RES delivery systems for psoriasis treatment have focused on overcoming the poor solubility, instability, and limited skin penetration. A supramolecular cyclodextrin deep eutectic solvent (DES)-chitosan eutectogel demonstrated enhanced solubility (via DES) and sustained skin retention of RES through electrostatic and hydrogen bonding interactions, significantly improving psoriasis-like symptoms in mice compared with a commercial calcipotriol ointment.[73] RES-loaded elastic nanocarriers (spanlastics) incorporated into carbopol gel achieved nano-sized particles (particle size: nanoscale range) with sustained drug release (73.76% ± 2.46% over 8 h) and superior in vivo efficacy in reducing erythema and inflammatory cytokines.[74] Polymeric micelles embedded in carbomer gel optimized through QbD showed improved skin deposition and in an vivo anti-psoriatic activity with significant reductions in PASI scores and serum cytokine levels in imiquimod-induced mice.[75] A triple bioactive nanoemulsion gel (curcumin-thymoquinone-RES) exhibited synergistic effects, achieving 76.20 ± 1.67 nm droplet size and significant anti-angiogenic activity in HET-CAM assays.[76] Lastly, QbD-driven nanoemulgel formulations significantly increased skin deposition (668.65 ± 11.98

μg·cm^{-2}) compared to conventional gels.[77] These innovations collectively address formulation challenges while enhancing the therapeutic outcomes in preclinical models.

RES has demonstrated therapeutic efficacy in preclinical and clinical models of psoriasis. In mice with Imiquimod-induced psoriasis, RES significantly attenuated erythema, scaling, and skin thickening.[70] RES-treated imiquimod-induced mice exhibited reduced keratinocyte proliferation, hypoxia-related gene expression, and glycolysis markers, along with decreased macrophage infiltration and pro-inflammatory cytokine secretion.[72] In a murine psoriasis model, EFLA 945 (containing RES) suppressed AIM2 inflammasome activation, reduced caspase-1-dependent IL-1β maturation and IL-17 production, and improved the clinical severity scores.[78] Topical ε-viniferin (an RES dimer) demonstrated higher skin accumulation (0.067 nmol/mg vs RES 0.029 nmol/mg) in psoriasis-like skin with impaired barrier function, correlating with enhanced IL-23 suppression.[9] However, given that psoriasis is a chronic, relapsing condition, its effective management requires therapies that can induce and maintain remission. Therefore, future clinical trials should be designed to assess the long-term efficacy and safety of RES, specifically investigating its potential to sustain improvement and prevent flare-ups, which is a critical aspect for patient quality of life. Beyond its potential as a monotherapy, exploring RES in combination with established psoriasis treatments could offer significant advantages. Given its distinct mechanisms, such as Sirt1 activation and NLRP3 inflammasome inhibition, future research should investigate the synergistic effects of RES co-administered with topical corticosteroids, vitamin D analogs, or in conjunction with phototherapy. Such combination approaches might allow for reduced dosages of conventional drugs, thereby minimizing side effects while enhancing overall therapeutic efficacy.

Atopic Dermatitis

RES demonstrates multifaceted mechanisms for alleviating atopic dermatitis (AD) through anti-inflammatory, immunomodulatory, and epithelial barrier restoration. It suppresses pro-inflammatory cytokines and signaling pathways, as evidenced by reduced serum IgE and IL-31 levels;[19] inhibition of the HMGB1/RAGE/NF-κB axis;[79,80] and downregulation of IL-6, TNF-α, and TSLP in keratinocytes.[80–82] Furthermore, RES targets mast cell activity by decreasing TSLP production via NF-κB and caspase-1 inhibition[83] and reduces Fc epsilon RI receptor expression, thereby attenuating degranulation and inflammatory mediator release.[84] The modulation of the AHR-NRF2 axis upregulates SEMA3A, a nerve-repellent factor that limits epidermal innervation linked to pruritus.[85] Topical formulations enhance therapeutic efficacy by improving skin retention[80,86] and suppressing oxidative stress.[87,88] Additional mechanisms include inhibition of the JAK-STAT[10] and SphK1/Stat3/NF-κB p65 pathways[89] as well as restoration of keratinocyte differentiation markers (filaggrin and loricrin).[81,90] These actions collectively ameliorate epidermal hyperplasia, immune cell infiltration, and skin barrier dysfunction in AD models.[19,79,80,82]

Recent advancements in RES delivery strategies for atopic dermatitis (AD) have focused on enhancing the topical bioavailability and therapeutic efficacy using innovative formulations. A solvent-free nanoformulation utilizing ethoxylated hydrogenated castor oil produced stable lipid nanoparticles (140–180 nm) with high RES encapsulation (up to 30 mg/mL) and prolonged stability (>6 months), demonstrating improved antioxidant activity and cellular uptake in preclinical AD models.[87] RES-loaded nanoemulgel (0.5–1% w/w) optimized via spontaneous nano-emulsification exhibited enhanced skin retention compared to free RES, which was attributed to monodispersed globule sizes (180–230 nm) and a SEPINEO™ P 600 gel base, resulting in significantly higher skin retention of RES from RES-loaded nanoemulgel compared to free RES-loaded gel.[80] Hyaluronic acid hydrogels embedded with RES-loaded chitosan nanoparticles (120–500 nm, 80% encapsulation) demonstrated sustained release kinetics, reducing oxidative stress and pro-inflammatory cytokines in TNF-α/IFN-γ-treated keratinocytes, while delaying nanoparticle degradation.[86] Furthermore, polyvinylpyrrolidone (PVP) films incorporating RES solid dispersions provided prolonged drug release (82–93% over 24 h) and significant cutaneous retention (42–53%), effectively reducing inflammation in barrier-defective skin models.[91] These formulation strategies collectively address RES's solubility and stability limitations, thereby enabling targeted and sustained delivery for AD management.

RES has demonstrated therapeutic efficacy in preclinical models of atopic dermatitis (AD) through diverse mechanisms. In DNCB-induced NC/Nga mice, topical application of RES-enriched rice (RR) significantly reduced scratching frequency, dermatitis severity, and serum IgE/IL-31 levels while improving skin hydration.[19] Similarly,

oral RES (20 mg/kg) attenuated HMGB1 signaling and downregulated pro-inflammatory cytokines (IL-1β, TNF-α, and IL-2R α) in house dust mite-induced NC/Nga mice.[79] Systemic RES administration (30 mg/kg/day) to BALB/c mice ameliorated 2,4-dinitrofluorobenzene-induced epidermal hyperplasia, suppressed epithelial apoptosis, and reduced IL-25, IL-33, and TSLP expression.[82] In another DNCB-challenged BALB/c model, RES (5–25 mg/kg) restored skin barrier proteins (filaggrin and envoplakin) and suppressed kallikrein 7 expression, correlating with reduced Th2 cytokines (IL-4 and IL-5).[90] Piceatannol, an RES metabolite, attenuates Dermatophagoides farinae-induced AD-like lesions in NC/Nga mice by inhibiting JAKSTAT signaling and reducing TARC/MDC levels.[10] While clinical data remain limited, in vitro studies using PBMCs from atopic dogs have shown that RES (9 μg/mL) reduces MCP-1 and IL-6 secretion without cytotoxicity.[92] Considering the chronic nature of AD and the potential side effects associated with long-term topical corticosteroid use, a clinically significant area for future investigation is the steroid-sparing potential of RES. Studies designed to evaluate whether topical RES, when used as an adjunct or maintenance therapy, can reduce reliance on corticosteroids, decrease their cumulative dose, or prolong flare-free intervals, would provide valuable insights for the long-term management of AD. While preclinical evidence for RES in AD models is encouraging and initial formulation advancements show promise for topical delivery, it is imperative to consider the specific needs of the pediatric population, in whom AD often first manifests. Future clinical research must include dedicated studies to establish the efficacy and safety of topical RES in children, taking into account potential differences in their skin barrier properties, surface area-to-volume ratio, and drug absorption profiles compared with adults.

Melanoma

RES demonstrates multifaceted mechanisms in melanoma treatment, primarily through apoptosis induction, cell cycle arrest, and modulation of key signaling pathways. It inhibits proliferation by inducing G0/G1 phase arrest via down-regulation of Cyclin D1, coupled with upregulation of p21, as observed in human and murine melanoma models.[20,93–95] Apoptosis is triggered through mitochondrial pathways, evidenced by increased Bax/Bcl-2 ratio, caspase-3/9 activation, and PARP cleavage.[20,94,96–98] RES suppresses pro-survival molecules such as FLIP and Bcl-2, while enhancing radiation sensitivity.[97,99] Mechanistically, it inhibits SIRT1/SIRT3, disrupting mitochondrial metabolism (reduced NAD+/NADH ratio and lactate production).[20,99] Additionally, RES modulated ERK1/2 signaling via SHCBP1 inhibition and PI3K/Akt pathways, impairing melanogenesis through COX-2 downregulation and the subsequent reduction of MITF and tyrosinase.[47,93,100] It also targets the miR-492–CD147 axis, further promoting apoptosis.[98] These effects are synergistically enhanced when combined with radiotherapy or chemotherapeutic agents, underscoring its potential as adjuvant therapy.[97,101]

Recent advancements in nanotechnology and transdermal delivery systems have significantly enhanced the therapeutic efficacy of RES in melanoma. A biodegradable non-silicon microneedle system loaded with RES nanocrystals demonstrated improved solubility (84.14% dissolution within 120 min) and mechanical strength (1.26 N/needle), enabling efficient transdermal delivery with rapid drug release post-skin penetration.[102] Encapsulation of RES in mesoporous silica nanoparticles (MSNs) achieved high loading efficiency (>93%) and pH-responsive release, with accelerated drug release at acidic pH[97] mimicking tumor microenvironments.[103] Solid lipid nanoparticles (SLNs) co-loaded with curcumin and RES exhibited synergistic cytotoxicity against melanoma cells and localized skin binding (>70%), highlighting their potential for topical therapy.[101] A co-delivery dissolvable microneedle patch incorporating RES nanocrystals and fluorouracil@HP-β-CD achieved a sustained release, demonstrating enhanced permeation and biosafety.[104] Furthermore, RES-loaded PLGA nanoparticles integrated into hydrogels significantly lowered the IC50 values (1.26-fold reduction) and inhibited metastatic melanoma cell proliferation via G2/M phase arrest.[105] These innovations collectively address RES's bioavailability limitations, while enabling targeted, sustained, and combinatorial therapeutic approaches for melanoma. Although innovations such as microneedle systems are promising for transdermal delivery to cutaneous melanoma, metastatic disease remains a major challenge. The development of systemic delivery strategies, such as conjugated RES nanoparticles that exhibit enhanced tumor suppression and improved plasma stability, is critical. However, rigorous evaluation of the efficacy and long-term

safety profiles of these systemic RES nanoformulations, specifically in the context of metastatic melanoma, are essential before clinical translation can be considered.

In vivo studies using murine melanoma models have validated RES's therapeutic potential. In Braf (V600E)/Pten(NULL) mice, intraperitoneal administration of the dual SIRT1/SIRT3 inhibitor 4′-bromo-RES (4′-BR, 30 mg/kg) significantly reduced primary tumor volume and lung metastasis without adverse effects, accompanied by downregulation of metastasis-promoting and immune-modulating genes.[99] In a subcutaneous B16-F10 melanoma model, conjugated RES nanoparticles (NPs) showed enhanced tumor suppression compared to free RES, which was attributed to improved plasma stability and reduced hepatic metabolism.[106] Additionally, RES nanocapsules inhibited tumor growth in melanoma-bearing mice by increasing necrotic areas and inflammatory infiltrates while preventing pulmonary metastasis.[107] A co-delivery dissolvable microneedle patch loaded with RES nanocrystals and fluorouracil@HP-β-CD achieved a sustained in vivo drug release (81.24% and 72.48% for RES and fluorouracil, respectively), highlighting its translational potential.[104] Considering the transformative impact of immune checkpoint inhibitors on melanoma treatment, a highly relevant and promising future direction is the investigation of RES's potential to synergize with these immunotherapies.

Acne

RES demonstrates multifaceted mechanisms of action in acne treatment, primarily through its antimicrobial and anti-inflammatory actions. It exhibits potent antibacterial activity against Cutibacterium acne (C. acne) by disrupting bacterial membrane integrity and extracellular structures.[21,108] Subinhibitory concentrations also inhibited the biofilm formation.[109] Anti-inflammatory effects are mediated through AMPK/SIRT1 pathway activation, reducing NF-κB signaling and pro-inflammatory cytokines (IL-1β and IL-6)[110] while suppressing PM-induced oxidative stress and inflammatory markers in sebocytes.[111] Additionally, RES inhibits sebocyte lipogenesis via AMPK-mediated downregulation of lipid synthesis pathways[110] and reduces sebocyte proliferation by modulating PI3K/Akt/PPAR-γ signaling.[112]

Innovations in RES delivery for acne include nanoemulsion-based formulations that enhance bioavailability and reduce toxicity. One study developed isotretinoin-loaded self-nanoemulsifying drug delivery systems (SNEDDS) combined with RES, achieving a globule size below 300 nm and significantly improving ex vivo permeation (40.77% for isotretinoin; 29.94% for RES), demonstrating synergistic efficacy and hepatoprotection.[113] Topical RES gel (carboxymethylcellulose-based) applied once daily reduced the microcomedone area by 66.7% and Global Acne Grading System scores by 53.75% in a clinical trial, with no reported adverse effects.[114] Another approach utilized phenolic compound-containing formulations for topical application, showing a 40% reduction in edema and lowered oxidative stress markers (TBARS, IL-1β) in C. acne-induced inflammation models.[115]

RES exhibits anti-inflammatory effects in human SZ95 sebocytes by suppressing NF-κB signaling via AMPK/SIRT1 activation and by reducing IL-1β and IL-6 secretion under peptidoglycan stimulation.[110] In C. acne-pretreated mice, topical RES (1 μM) significantly attenuated PM10-induced inflammatory cytokine (IL-1β, TNF-α) and matrix metalloproteinase expression while reducing sebum production.[111] The findings from this single-blind, vehicle-controlled pilot study, in which topical RES gel significantly reduced the microcomedone area and Global Acne Grading System scores, provide encouraging preliminary evidence of its efficacy. However, to firmly establish RES's therapeutic value and its specific location in the acne treatment armamentarium, these results need to be validated in larger, multicenter, randomized controlled trials that directly compare RES with standard-of-care treatments such as benzoyl peroxide, topical retinoids, or antibiotics.

Herpes Simplex Virus

RES inhibits herpes simplex virus (HSV) replication by targeting early viral entry and immediate early protein synthesis, including inhibition of ICP-4 expression and cell cycle arrest at the S-G2/M phase.[116] It activates the AMPK/Sirt1 axis, reducing viral titers and neurodegeneration by inhibiting caspase-3 and hyperphosphorylating tau.[117] Additionally, RES regulates neuroinflammation through STING/NF-κB signaling and interacts with HSP90β to limit HSV-1 replication in microglia.[22]

Topical 12.5–25% RES cream five times daily within 1 and 6 h post-infection significantly inhibited HSV-1-induced cutaneous lesions in SKH1 mice, demonstrating efficacy comparable to 5% acyclovir ointment, including that against acyclovir-resistant strains.[118] Oral administration of oxyresveratrol (500 mg/kg/dose) initiated 8 h pre-infection and delayed skin lesion progression three times daily in murine HSV-1 models.[119] In HSV-1-infected neurons, RES pretreatment reduced viral titers, caspase-3 activation, and hyperphosphorylated tau levels, suggesting neuroprotective effects in herpes encephalitis models.[117] These findings underscore the therapeutic potential across delivery routes and stages of infection. Preclinical data demonstrating that topical 12.5–25% RES cream significantly inhibits HSV-1-induced cutaneous lesions in SKH1 mice, with efficacy comparable to 5% acyclovir ointment, and even against acyclovir-resistant strains, are highly promising. However, these compelling animal model results urgently require translation into human clinical settings. Well-designed, randomized, placebo-controlled, and active comparator (eg, acyclovir) clinical trials are essential to evaluate the efficacy and safety of topical RES for common manifestations, such as herpes labialis and herpes genitalis, in humans.

Conclusion

RES has emerged as a highly versatile therapeutic candidate for a wide spectrum of dermatological pathologies. As summarized in Figure 2, its principal benefit lies in its pleiotropic capacity to modulate a vast array of pathological pathways simultaneously. This allows it to address the multifaceted nature of complex skin disorders like psoriasis and atopic dermatitis by concurrently targeting inflammation, oxidative stress, and cellular hyperproliferation. However, this same multi-targeting capability presents a challenge, as the context-dependent nature of its effects (eg, pro- vs anti-angiogenic) requires careful optimization to maximize therapeutic benefit while minimizing potential off-target effects.

The primary hurdle impeding the clinical translation of these promising mechanisms is RES's inherent physicochemical drawbacks. As illustrated in Figure 3, advanced drug delivery systems—such as nanoparticles, hydrogels, and polymeric micelles—have become the cornerstone strategy to overcome these limitations. The benefits of these formulations are clear: they enhance bioavailability, protect RES from degradation, and facilitate targeted local delivery. Nevertheless, the clinical translation of these sophisticated delivery systems faces its own set of challenges, including issues of manufacturing scalability, long-term stability, regulatory approval hurdles, and demonstrating cost-effectiveness.

To crystallize the transition from preclinical success to clinical reality, we have summarized the current evidence, potential applications, and future research directions for each condition in Table 1. As this summary highlights, while the mechanistic basis for RES is strong, the key future direction across all domains is the execution of large-scale, methodologically rigorous clinical trials to firmly establish its therapeutic value in dermatological practice.

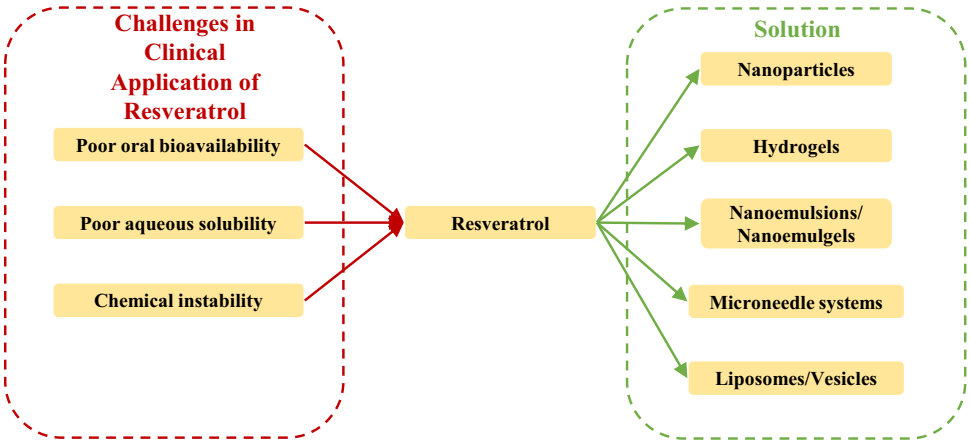

Figure 3 RES Delivery Systems: Strategies to Overcome Bioavailability Challenges.

https://doi.org/10.2147/CCID.S543849

Table 1 Clinical Frontiers of RES in Dermatology: A Summary of Current Evidence and Future Directions

Dermatology	Summary of Evidence	Current Status/Potential Immediate Application	Challenges & Future Directions
Wound Healing	Accelerates healing, promotes angiogenesis, and reduces inflammation in diabetic and burn models.[16,25]	A dermal matrix impregnated with RES has shown superior efficacy over standard care in a clinical trial for diabetic foot ulcers. This suggests a potential for immediate application in advanced wound care.[41]	Long-term safety and cost-effectiveness are yet to be established. Further large-scale trials are needed, especially for other chronic wounds like venous ulcers.
Anti-aging	Prevents collagen degradation, reduces oxidative stress, and improves skin elasticity and hyperpigmentation.[8,17,48]	Already present in some topical cosmetic formulations. Human studies have validated its cosmetic potential for improving skin elasticity and reducing melanin.[49,61]	Rigorous, long-term, placebo-controlled clinical trials are required to confirm genuine histological and molecular anti-aging effects in human skin.
Psoriasis	Attenuates erythema, scaling, and inflammation in animal models by inhibiting pathways like IL-17 and the NLRP3 inflammasome.[69]	Preclinical evidence is strong. In mouse models of psoriasis, RES significantly reduced erythema, scaling, and skin thickening. It works by inhibiting keratinocyte proliferation and reducing inflammatory cell infiltration.[70,72]	Long-term clinical trials are needed to assess its ability to maintain remission and prevent flare-ups. Investigating synergy with conventional therapies (eg, corticosteroids, phototherapy) is a key future direction.
Atopic Dermatitis	Reduces dermatitis severity, pruritus, and inflammation in mouse models; helps restore skin barrier proteins.[10,89,90]	In various mouse models of AD, RES has been shown to reduce dermatitis severity and scratching frequency, lower serum IgE levels, and restore crucial skin barrier proteins like filaggrin.[19,72,90]	The "steroid-sparing potential" of RES is a critical area for future clinical investigation. Efficacy and safety in the pediatric population must be established in dedicated trials.
Melanoma	Induces cancer cell apoptosis and reduces tumor volume and metastasis in preclinical murine models.[93,94]	In murine models, RES and its derivatives have been shown to reduce primary tumor volume, inhibit lung metastasis, and induce cancer cell apoptosis. It also shows potential as an adjuvant therapy to enhance the effects of radiotherapy.[97,99,107]	Systemic delivery systems for metastatic disease are a major challenge requiring further development. Synergy with immune checkpoint inhibitors is a highly promising future direction.
Acne	Exhibits antimicrobial activity against acne and reduces inflammation and sebum production.[110,112]	A pilot clinical study showed a topical RES gel was effective and well-tolerated, reducing microcomedone area by 66.7%. This indicates a potential near-term application.[114]	Needs validation in larger, multicenter, randomized controlled trials that compare it against standard-of-care treatments like benzoyl peroxide or retinoids.
Herpes Simplex Virus	Inhibits HSV replication in preclinical models, including against acyclovir-resistant strains.[116]	In mouse models, topical RES cream demonstrated efficacy comparable to 5% acyclovir ointment in inhibiting cutaneous HSV-1 lesions. Notably, it was also effective against acyclovir-resistant strains.[118]	Urgently requires translation into human clinical trials to evaluate its efficacy for herpes labialis and genitalis against both placebo and active comparators like acyclovir.

Disclosure

The authors report no conflicts of interest in this work.

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