

INVITED REVIEW

The impact of resveratrol on skin wound healing, scarring, and aging

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Abstract

Resveratrol is a well-known antioxidant that harbours many health beneficial properties. Multiple studies associated the antioxidant, anti-inflammatory, and cell protective effects of resveratrol. These diverse effects of resveratrol are also potentially involved in cutaneous wound healing, scarring, and (photo-)aging of the skin. Hence, this review highlighted the most relevant studies involving resveratrol in wound healing, scarring, and photo-aging of the skin. A systematic review was performed and the database PubMed was searched for suitable publications. Only original articles in English that investigated the effects of resveratrol in wound healing, scarring, and (photo-)aging of the skin were analysed. The literature search yielded a total of 826 studies, but only 41 studies met the inclusion criteria. The included studies showed promising results that resveratrol might be a feasible treatment approach to support wound healing, counteract excessive scarring, and even prevent photo-aging of the skin. Resveratrol represents an interesting and promising novel therapy regime but to confirm resveratrol-associated effects, more evidence based in vitro and in vivo studies are needed.

KEYWORDS

chronic wound, resveratrol, scarring, skin aging, wound healing

1 | INTRODUCTION

Resveratrol (3,5,4'-trihydroxy-*trans*-stilbene) belongs to the stilbenoid group of polyphenols. It consists of two phenol rings linked by an ethylene bridge, which gives rise to two geometric isomers: the active *trans*-isomer and an inactive *cis*-isomer.¹ Resveratrol has been found in more than 70 different plant species and important dietary sources are grapes (skin and seeds), red wine,

peanuts, and soy.² The so-called “French Paradox” that describes the potential health benefits associated with regular and moderate wine consumption was first correlated to wine polyphenols, especially resveratrol, by Renaud and De Logeril in 1992.³ Since then, resveratrol has received increasing scientific attention regarding its diverse biological activities, including antioxidant, anti-inflammatory, antiobesity, and anticancer properties.

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Among these diverse biological effects of resveratrol, the antioxidant properties are most prominent. Resveratrol has been shown to protect cells against hydrogen peroxide-induced oxidative stress, as well as UV-irradiation-mediated cell death. These results were partially attributed to direct effects of resveratrol as a radical scavenger but indirect effects were also observed, where resveratrol was able to modulate cellular antioxidant pathways.⁴⁻⁷

Resveratrol has also been known to interfere with inflammatory responses and to reveal anti-inflammatory properties, as it targets nuclear factor- κ B (NF κ B), expression of pro-inflammatory cytokines (e.g. interleukin 6, IL6), and also genes involved in eicosanoid production.^{1,8} Resveratrol also targets toll-like receptor (TLR) signalling, such as TLR2, TLR3, and TLR4 signalling.⁹⁻¹³ In skin, resveratrol reduces imiquimod-induced, TLR7, TLR8, TLR9-mediated, psoriatic inflammation in animal models, most likely via interfering with NF- κ B activation.^{14,15} This anti-inflammatory activity of resveratrol can be associated with health benefits for several autoimmune and chronic inflammatory conditions.⁸

Numerous *in vitro* and *in vivo* studies confirmed the inhibitory effects of resveratrol on carcinogenesis in all stages, such as initiation, promotion, and progression.^{16,17}

Resveratrol serves as a chemopreventive agent^{18,19} and displays chemotherapeutic properties that are attributed to its antioxidant, anti-inflammatory, proapoptotic, and antiproliferative features.^{17,20} Resveratrol is supposed to target intracellular signalling pathway components including regulators of cell survival and apoptosis, pro-inflammatory mediators, and key components of tumour angiogenesis and metastasis by interfering with a distinct set of transcription factors, upstream kinases, and their regulators.²¹⁻²³

In vivo studies demonstrated that resveratrol additionally exerted beneficial effects on metabolic syndrome-related alterations, for example, glucose and lipid homeostasis improvement and a reduction in fat mass, blood pressure, low-grade inflammation, and oxidative stress.²⁴⁻²⁸ Further studies verified that resveratrol mimics caloric restriction via the activation of sirtuin 1 (SIRT 1)^{26,29} resulting in improved exercise performance and insulin sensitivity, as well as showing body fat-lowering effects by inhibiting adipogenesis, and increasing lipid mobilisation in adipose tissue.^{30,31}

These diverse effects of resveratrol are also potentially involved in cutaneous wound healing, scarring, and (photo-) aging of the skin, which is reflected by an increasing number of publications in this field over the past decade. This review will therefore summarise the most relevant studies involving resveratrol in wound healing, scarring, and photo-aging of the skin.

Key messages

- Resveratrol accelerates wound healing due to anti-inflammatory properties
- Resveratrol could serve as potential treatment in wound healing
- Resveratrol showed antifibrotic properties in a non-clinical setting
- Resveratrol might be a promising agent to reduce (photo-)aging of the skin

2 | METHODS

The online database PubMed was used to review the medical literature covering resveratrol application in wounds, skin aging, and scars. The day the database was accessed was on 28 November 2020, and the last 10 years have been analysed. The following MeSH terms have been used [“Resveratrol”[Mesh] AND (“Wounds and Injuries”[Mesh] OR “Wound Healing”[Mesh] OR “Re-Epithelialization”[Mesh] OR “Skin Aging”[Mesh] OR “Aging”[Mesh] OR “Cicatix”[Mesh])]. To minimise the risk of missing relevant data, the search term [resveratrol AND (“Wound*” OR “Anti-Aging” OR “Cicatix” OR “Scar”)] has been used additionally.

All search results were listed in an excel sheet (Microsoft Excel 2016 MSO [16.44] 32-bit) and duplicates have been removed. Titles, abstracts, and if available, full-text articles have been analysed, which concern the exact study purpose. Non-English articles, reviews, commentaries, and studies that aimed at wrong topics were excluded. The remaining studies were included and analysed for their specific content. In order to minimise the bias of wrongful exclusion, each study was evaluated by at least two reviewers (AH and MS), and exclusion decisions were based on the consensus of the reviewing authors. If a discrepancy between the reviewers occurred, the literature was evaluated by a third reviewer (EH).

The initial literature search yielded a total of 942 studies with 539 results in PubMed with MeSH-terms and 403 results in PubMed without MeSH terms. After duplicate exclusion (116 duplicates), 784 studies of the remaining 826 studies were excluded according to the prior mentioned exclusion criteria.

Thirty studies were excluded due to non-English, 217 studies because they were reviews or commentaries, and 538 studies because of wrong topic. In total, 41 studies about the effects of resveratrol have been included. A flowchart, summarising the systematic algorithm, as well as the quantitative results can be found in Figure 1. A

summary of *in vitro*, *in vivo*, and clinical studies investigating the effects of resveratrol in the context of wound healing, scarring and photo-aging, are presented in Tables 1-3. The included studies can be divided into these major effects: wound healing, antiscarring, and antiaging properties of resveratrol, which will be presented in the following.

3 | RESVERATROL IN SKIN WOUND HEALING

Wound healing is a complex, highly regulated process crucial for maintaining the skin's barrier function.⁷¹ Numerous disease processes are associated with an impairment of pathways involved in wound healing, resulting in chronic, non-healing wounds that expose the patient to significant discomfort.⁷¹ Insufficient vascularisation, infections, and prolonged inflammatory responses cause poor and delayed wound healing. Resveratrol has become a subject of interest to improve wound healing by promoting anti-inflammatory, antioxidant, and angiogenic effects.¹

Resveratrol has an impact on the regulation of inflammation and therefore, repair-related processes in

the skin.⁵⁰ According to Pastore et al, anti-inflammatory and wound healing effects of resveratrol depend rather on their interaction with epidermal growth factor receptor (EGFR)-controlled cytoplasmic and nuclear pathways than on their direct antioxidant and free radical scavenging activity.³⁵ An *in vivo* study in rats showed that resveratrol can limit the infiltration of mast cells toward the wounded area, while the infiltration of lymphocytes and macrophages is stimulated.⁶⁰ It is assumed that resveratrol is able to suppress an acute antigen-dependent reaction (Th1-type response) in favour of a Th2 response. The infiltration of neutrophils differs depending on the type of pathogen.⁶⁰

In vitro studies demonstrated protective effects on fibroblasts by decreasing oxidative stress levels. Due to its antioxidative properties, resveratrol can stabilise cell proliferation, and improve migration quality and ultrastructural preservation.^{36,41} Also, *in vivo* results demonstrated significantly improved wound healing following resveratrol application based on antioxidant activity.⁵²

Angiogenesis also plays a central role in wound healing, and resveratrol is discussed to influence neovascularisation.⁶² Among the known growth factors, vascular endothelial growth factor (VEGF) is believed to be one of the most prevalent, effective, and long-term signal-

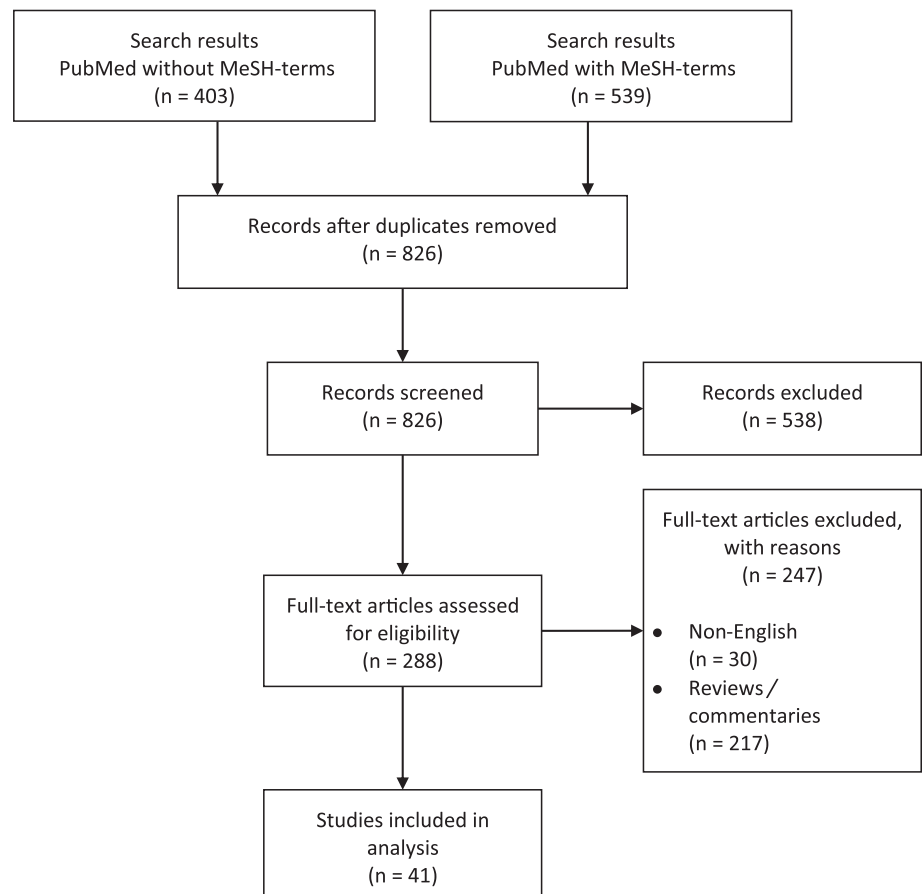


FIGURE 1 Review process depicted in a flowchart

TABLE 1 Summary of in vitro studies investigating the effects of resveratrol on wound healing, scarring, and photo-aging

Study topic	Author, year	Cohort	Test substance	Setting	Effects
Wound healing	Brakenhielm et al (2001) ³²	Bovine capillary endothelial cells, chick chorioallantoic membrane	1–100 µg RES discs	Effect of RES on fibroblast growth factor 2 (FGF-2)-induced activation of mitogen-activated protein kinases in bovine capillary endothelial cells; effect of RES in porcine aortic endothelial cell lines; antiangiogenic activity of RES in chick chorioallantoic membrane (1–100 µg per disc.) Parameters evaluated: FGF-2 and vascular endothelial growth factor (VEGF) receptor-mediated endothelial cell growth and chemotaxis	RES inhibits FGF-2 and VEGF receptor-mediated endothelial cell growth and chemotaxis. Dose-dependent inhibitory effect on angiogenesis of RES.
	Khanna et al (2001) ³³	Human keratinocytes (line HaCaT)	GSPE (grape seed proanthocyanidin extract) containing 5000 ppm <i>trans</i> -RES	Keratinocytes treated with GSPE; washed with GSPE-free medium before, then challenged with H ₂ O ₂ (hydrogen peroxide) or TNF-α Parameters evaluated: VEGF	Treatment with GSPE upregulated H ₂ O ₂ and TNF-α induced VEGF expression and release
	Chan et al (2002) ³⁴	Bacteria and dermatophytes	3.12, 6.25, 12.5, 25, 20, 100 µg/mL RES	Susceptibility testing of bacteria (<i>Staphylococcus aureus</i> , <i>Enterococcus faecalis</i> , <i>Pseudomonas aeruginosa</i>) and dermatophytes (<i>Trichophyton mentagrophytes</i> , <i>Trichophyton tonsurans</i> , <i>Trichophyton rubrum</i> , <i>Epidermophyton floccosum</i> , <i>Microsporum gypseum</i>) in control medium, dimethyl sulphoxide solvent, and RES.	RES inhibited the growth of bacteria and dermatophytes in a dose-dependent manner. Higher RES concentration resulted in better growth inhibition of bacteria and dermatophytes.
	Pastore et al. (2013) ³⁵	Human epidermal keratinocytes (HEK)	50 µM RES	HEK from 4 healthy donors: verbasoside (control), RES 50 µM Parameters evaluated: IL-8 expression, extracellular-signal regulated kinase (ERK), p65, c-Fos, epidermal growth factor receptor (EGFR), NHEK proliferation	IL-8 overexpression, ERK phosphorylation was transiently inhibited, enhanced p65 and EGFR phosphorylation, c-Fos upregulation, NHEK proliferation inhibited
	Eroğlu et al (2014) ³⁶	Normal skin-derived fibroblasts (NSFBs);	RES loaded into microparticles consisting of dipalmitoylphosphatidylcholine and hyaluronic acid	Cell culture of NSFBs: RES-loaded microparticles Parameters evaluated: cellular proliferation (CP), total glutathione (GSH), oxidised glutathione (GSSG), glutathione peroxidase (GPx), malondialdehyde (MDA), superoxide dismutase (SOD)	RES-loaded microparticles increased CP, decreased oxidation in cells by GSH/GSSG ratio reduction. No effect of RES in GPx, MDA, and SOD.
	Abbas et al (2019) ³⁷	Human fibroblasts	Flavonoids (chrysin, naringenin, RES) with β-sitosterol	Scratch-wound migration assay: Parameters evaluated: closure rate, cytotoxicity, fibroblasts migration	β-sitosterol combined with RES and β-sitosterol combined with naringenin achieved the best closure rates. No toxic effect on fibroblasts was detected.
	Comotto et al (2019) ³⁸	Human keratinocytes	Alginate dressings with natural antioxidants (curcumin; RES)	Determination of the optimal concentration of the active compounds Parameters evaluated: release rate, cellular growth, bacterial growth	Release rate: burst release followed by a gradual release; 300 µg/mL of RES did not induce any toxicity; curcumin and RES showed an improved cell viability; curcumin was superior regarding anti-microbial properties

TABLE 1 (Continued)

Study topic	Author, year	Cohort	Test substance	Setting	Effects
	Meng et al (2019) ³⁹	Human adipose stem cells	Bacterial cellulose conjugated with RES, collagen conjugated with RES	In vitro biocompatibility: adipose stem cells were cultured in keratinocyte serum-free medium with foetal bovine serum. Examination of the samples by immunocytochemical staining.	RES-conjugated bacterial cellulose created a biocompatible environment for stem cell attachment and cell growth.
	Huang et al (2019) ⁴⁰	Human umbilical vein endothelial cells (HUVECs)	10 μ M RES	HUVECs in high glucose medium (HGM), HGM + 10 μ M RES, normal glucose medium (NGM), NGM + 10 μ M RES Parameters evaluated: CP, cell migration, apoptosis	RES treatment increased hyperglycemia-impaired endothelial CP. HGM induced cell migration and apoptosis alleviated by RES
	Kaleci et al (2020) ⁴¹	3 T3 Swiss Albino fibroblasts	1, 5, and 10 μ M RES in combination with 500 μ M H ₂ O ₂	Fibroblasts, 4 groups: control group, 500 μ M H ₂ O ₂ , RES, 500 μ M, H ₂ O ₂ + RES group Parameters evaluated: CP, OS (oxidative stress) level, collagen-I-expression, cell migration	RES application showed better CP rates compared to the other groups. Best CP results with 1 μ M RES. RES decreased H ₂ O ₂ -induced high OS. No impact of RES in collagen-I-expression or cell migration compared to control group.
Scarring	Zeng et al (2013) ⁴²	Hypertrophic scar-derived fibroblasts (HSFBs)	RES 25, 75, 150, 300 and 400 μ M	Cell culture of HSFBs and NSFBS from two young female donors: control, RES 25 μ M, RES 75 μ M, RES 150 μ M, RES 300 μ M, and RES 400 μ M over the time (24 h, 48 h and 72 h) Parameters evaluated: cell proliferation (CP), cell cycle progression, apoptosis, hydroxyproline, collagen	RES suppressed cell growth, arrested cell cycle progression, triggered apoptosis in a dose- and time-dependent manner (increased effect with longer duration and higher concentration). RES downregulated mRNA expression of type I and III procollagen in fibroblasts, resulting in significant decreases in hydroxyproline and collagen
	Zhai et al (2015) ⁴³	Human pathologic scar-derived fibroblasts (PSFBs)	RES 10, 50, and 100 μ mol/L	Cell culture with fibroblast from 20 patients. 4 groups: control, RES 10, RES 50, 100 μ mol Parameters evaluated: morphological changes in target cells, CP, TGF- β 1, Smad-2,3,4,7	Apoptotic morphological alterations and reduced CP in RES-treated pathological scar fibroblasts. Inhibitory effect in CP enhanced with increasing RES concentration. TGF- β 1, Smad-2,3,4 negatively and Smad-7 positively correlated with RES concentration.
	Bai et al (2016) ⁴⁴	HSFBs and NSFBS	RES 2.5, 5, 10, 20, and 40 mM	Cell culture of HSFBs and NSFBS from 9 patients. SIRT1 upregulation by RES. Parameters evaluated: SIRT1, collagen 1, collagen 3, α -smooth muscle Actin (α -SMA), TGF- β 1	SIRT1 intensity lower in HSFBs compared to NSFBS. RES down-regulated mRNA levels of collagen 1, collagen 3, α -SMA due to upregulation of SIRT1 in a dose-dependent manner. RES inhibited TGF- β 1-induced mRNA/protein level increase of collagen 1, collagen 3, and α -SMA.
	Tang et al (2017) ⁴⁵	PSFBs and NSFBS	RES 10, 50, and 100 μ mol/L	Cell culture of PSFBs and NSFBS from patients: control, RES 10 μ mol/L, RES 50 μ mol/L, 100 μ mol/L Parameters evaluated: mammalian target of rapamycin (mTOR), ribosomal protein S6 kinase (70S6K)	Strengthened mTOR and 70S6K expression in PSFBs compared to NSFBS. Decreased expression of mTOR and 70S6K in dose-dependent manner.

(Continues)

TABLE 1 (Continued)

Study topic	Author, year	Cohort	Test substance	Setting	Effects
	Pang et al (2020) ⁴⁶	HSFBs and NSFBS	RES 0, 1, 10, 100 $\mu\text{mol/L}$	Cell culture of HSFBs and NSFBS: control, RES 1 $\mu\text{mol/L}$, RES 10 $\mu\text{mol/L}$, 100 $\mu\text{mol/L}$ over the time (24, 48, 72 h) Parameters evaluated: cell viability (CV), microRNA-4654, Rheb, 1A/1B-light chain (LC3), Beclin 1	RES decreased CV in dose-dependent manner (increased effect with higher concentration). RES upregulated microRNA-4654 expression level in dose-dependent manner, thus downregulated Rheb expression level and upregulated autophagy markers LC3 and Beclin 1
Photo-aging	Subedi et al (2017) ⁴⁷	NSFBs	RES and RES1-enriched rice (RR)	Cell culture with NSFBS from a healthy young male donor UV-B irradiation and treatment with normal rice, RR and RES afterwards Parameters evaluated: ROS (reactive oxygen species), MMP-1 (matrix metalloproteinase 1), collagen I	RR demonstrated the most effective reduction of ROS production compared to normal rice or RES alone. RR induced a downregulation of MMP-1 (matrix metalloproteinase 1), inhibition of inflammatory cascades, and upregulation of collagen type I.
	Zhou et al (2018) ⁴⁸	Human keratinocytes (HaCaT cell line)	RES (<99%): 2.5, 5, 7.5, and 10 mm	Cell culture with keratinocytes s, UV-B irradiation for 5 min at 10 cm below the lamp (irradiation intensity: 0.1 mW/cm ²) Parameters evaluated: CV, apoptotic rate	Dose-dependent increase of CV of RES pretreated cells and decrease of apoptotic rate. Increase of HSP27 expression resulting in antiapoptotic effects through inhibiting NF-KB and caspase-3 activation.

Abbreviations: α -SMA, α -smooth muscle actin; CP, cellular proliferation; EGFR, epidermal growth factor receptor; ERK, extracellular-signal regulated kinase; FGF-2, fibroblast growth factor 2; GPx, glutathione peroxidase; GSH, total glutathione; GSPE, grape seed proanthocyanidin extract; GSSG, oxidised glutathione; H₂O₂, hydrogen peroxide; HGM, high glucose medium; HSFBS, hypertrophic scar-derived fibroblasts; HUVECs, human umbilical vein endothelial cells; LC3, 1A/1B-light chain; MDA, malondialdehyde; MMP-1, matrix metalloproteinase 1; NGM, normal glucose medium; NSFBS, normal skin-derived fibroblasts; OS, oxidative stress; PSFBs, pathologic scar-derived fibroblasts; RES: resveratrol; ROS, reactive oxygen species (ROS); RR, resveratrol-enriched rice; SOD, superoxide dismutase; TNF- α , tumour necrosis factor alpha; VEGF, vascular endothelial growth factor.

TABLE 2 Summary of in vivo studies investigating the effects of resveratrol wound healing, scarring, and photo-aging

Study type	Author, year	Cohort	Test substance	Setting	Effects	Adverse events
Wound healing	Bräkenhielm et al (2001) ³²	Mice (neovascularisation group) Murine T241 fibrosarcoma (fibrosarcoma model) C57Bl6/J mice (wound model)	5.7 mg/mL RES	Neovascularisation group: corneas of mice implanted with VEGF and FGF-2. Oral application of RES. Drinking solutions for mice with RES (equivalent of 3 glasses of red wine) compared to control group (drinking water). Fibrosarcoma group: oral administration of RES (1 mg/kg per day) for mice with fibrosarcoma Full-thickness skin wound group: oral administration of RES (1 mg/kg per day) for C57Bl6/J mice	Inhibition of VEGF and FGF-2 in RES group and vessel density reduction compared to control group. RES treatment inhibited fibrosarcoma growth and delayed wound healing.	No minor or major adverse events
	Khanna et al (2002) ⁴⁹	9 BalbC mice	GSPE containing 5000 ppm trans-RES	Parameters evaluated: VEGF, FGF-2 vessel density, fibrosarcoma growth, wound healing	Two full-thickness excisional wound in each mice. One of the two wounds treated with 25 mL of 100 mg/mL GSPE for 5 d. Second wound served as control. Parameters evaluated: wound healing, histology, glutathione/glutathione disulphide ratio	No minor or major adverse events
	Lin et al (2016) ⁵⁰	30 male Balb/C mice	RES ointment (1, 100, 500 ng/mL)	7 groups, full-thickness excision of burn skin wound: vaseline (control), aloe emodin (1, 100, and 500 ng/mL), RES (1, 100, and 500 ng/mL). Parameters evaluated: wound healing, histology, IL-1 β , MCP-1, VEGF	RES treatment increased wound healing and glutathione/glutathione disulphide ratio RES application presented more well-defined hyperproliferative epithelial region, higher cell density, enhanced deposition of connective tissue, improved histological architecture. Decreased healing time in RES-treated group compared to control group. Histology: increased cellular infiltration IL-1 β , MCP-1, and VEGF increased in RES group compared to control group	No minor or major adverse events
	Poornima et al (2017) ⁵¹	9 female albino Wistar rats	RES and ferulic acid	3 groups of 3 rats, full-thickness excision wounds: controls, chitosan polycaprolactone nanofibres, RES-ferulic-acid-loaded nanofibres. Parameters evaluated: wound closure rate, wound vicinity, tensile strength, histology	Accelerated healing time in RES-treated group compared to control (15 d vs 20 d). Smaller wound vicinity in the RES-treated group. histology showed a higher collagen synthesis and more collagen deposition with tight packing in the RES-treated group	No minor or major adverse events

(Continues)

TABLE 2 (Continued)

Study type	Author, year	Cohort	Test substance	Setting	Effects	Adverse events
	Gokce et al (2017) ⁵²	42 male Wistar albino rats	RES-loaded hyaluronic acid and dipalmitoylphosphatidylcholine (DPPC) microparticles in dermal matrix	7 groups of 6 rats, full-thickness wound. Two control groups: non-diabetic control, diabetic control (streptozotocin induced). Five intervention groups (diabetic wounds, streptozotocin induced): control, RES solution, RES-loaded microparticles, dermal matrix, RES-loaded microparticle impregnated dermal matrix (DM-MP-RES). Parameters evaluated: histology, wound healing, glutathione (GSH), oxidised glutathione (GSSG), glutathione peroxidase (GPx), malondialdehyde (MDA), superoxide dismutase (SOD)	Highest amount of collagen fibres and efficient re-epithelialisation in DM-MP-RES group. DM-MP-RES application enhanced wound healing process in diabetic conditions, decreased SOD compared to diabetic wound control group and decreased GPx compared to diabetic control group.	No minor or major adverse events
	Zhao et al (2017) ⁵³	female C57BL/6 mice 24 Sprague-Dawley rats (12 wk old) 24 Sprague-Dawley rats (18 mo old) female New Zealand White rabbits	RES 50 µM	Full-thickness wound 4 groups: control (ethanol), 2 µM metformin, 200 nM rapamycin, 50 µM RES. Agents locally applied to wound beds (100 µL per time in mice / rabbits and 225 µL per time in rats). Chronic application: one time every day and intermittent application: three times every other day in week 1 followed by a treatment-free week. Treatment for 2 wk. Parameters evaluated: wound healing, vascularisation	RES treatment improved wound healing in young rodents compared to control group. RES group in young rodents presented smaller wound size, thicker epidermis, more collagen deposition, higher number of hair follicles compared to control group. RES treatment improved vascularisation/number of capillary vessels in young and old rodents compared to control group.	No minor or major adverse events
	Berce et al (2017) ⁵⁴	20 male Crl:CD1 (ICR) mice	Chitosan-sodium hyaluronate-RES polymer sponge (RES: 20 mg)	2 groups of 10 mice, full-thickness wounds: control, chitosan-sodium hyaluronate-RES polymer sponge for 14 d. Parameters evaluated: wound healing, histology	chitosan-sodium hyaluronate-RES polymer stimulated wound healing, showed bacteriostatic properties and inhibited inflammation.	No minor or major adverse events
	Lakshmanan et al (2019) ⁵⁵	C57BL/6 mice	Electrospun scaffold loaded with RES	Full-thickness ischaemic wound, 4 groups: no treatment, collagen patch, blank scaffolds without RES, scaffolds with RES. Parameters evaluated: wound healing, histology, thioredoxin-1, hemoxygenase-1, vascular endothelial growth factor (VEGF), Bcl-2 protein	Treatment with RES-loaded scaffold improved wound healing compared to control group. Activation of thioredoxin-1, hemoxygenase-1, VEGF, and Bcl-2 protein in RES-loaded scaffold group.	No minor or major adverse events

TABLE 2 (Continued)

Study type	Author, year	Cohort	Test substance	Setting	Effects	Adverse events
	Christovam et al (2019) ⁵⁶	32 male Wistar rats	2% RES	4 groups of 8 rats, full-thickness wound after 18 d of caloric restriction (CR) / ad libitum diet: control, 2% RES, 30% CR + control solution, 30% CR + 2% RES. Parameters evaluated: collagen I + III, thiobarbituric acid-reactive substances (TBARS), total sulphydryl content (TSC), VEGF, SIRT1	Increased expression of collagen I and collagen III in RES groups compared to control. RES treatment decreased TBARS concentration and inhibited an increase of TSC. VEGF protein expression in 30% CR + 2% RES group was higher compared to control / 2% RES group. SIRT1 was higher in 2% RES group compared to control.	No minor or major adverse events
	Meng et al. (2019) ³⁹	18 male Sprague-Dawley rats	Bacterial cellulose-conjugated scaffold with 50 µM RES, collagen-conjugated scaffold with 50 µM RES	5 groups, excisional wounds: control, bacterial cellulose (BC), BC + RES, collagen, collagen + RES. Parameters evaluated: wound area, histology	BC + RES conjugated scaffold induced re-epithelialisation and preserved normal collagen pattern.	No minor or major adverse events
	Li et al (2019) ⁵⁷	12 Male db/db mice	5 mmol/L trans-RES + 5 mmol/L hesperetin	2 groups of 6 mice, full-thickness excision: control, 5 mmol/L tRES + 5 mmol/L hesperetin to induce glyoxalase 1 expression. Parameters evaluated: wound healing	tRES- hesperetin treatment induced faster wound closure with more capillary formation compared to control.	No minor or major adverse events
	Ávila-Salas et al. (2019) ⁵⁸	25 Sprague-Dawley rats	Hydrogels loaded with bioactive compounds (RES, allantoin, dexpanthenol, caffeic acid)	Full-thickness excisional wounds: Madecassol (control), film dressing without bioactive compounds, hydrogels loaded with bioactive compounds (RES, allantoin, dexpanthenol, caffeic acid). Parameters: wound closure rate, wound size, histology	All four bioactive compounds showed a better and faster re-epithelialisation and a better organisation of the granulation tissue compared to controls. All formulations were associated with a faster wound closure rate than controls.	No minor or major adverse events
	Huang et al (2019) ⁴⁰	6 db/db mice	RES 50 mg/kg/d	Two full-thickness excision wounds in each db/db mice: control wound, 10 µM RES. RES application 50 mg/kg/d for 4 wk Parameters evaluated: Ki67, apoptosis, c-Caspase-3, wound healing	Ki67 increased due to RES treatment. Endothelial cells apoptosis alleviated by RES treatment. RES decreased c-Caspase-3 intensity. RES treatment accelerated wound healing.	No minor or major adverse events
	Orłowski et al (2020) ⁵⁹	C57BL6 female mice	Bimetallic Au@AgNPs modified with different polyphenols (with 200 µM RES)	Wound model in vivo: 5 mice per group, splint mouse model, Au@AgNPs with different polyphenols. Parameters:	RES-Au@AgNPs improved wound healing and induced TGF-β expression during the inflammatory phase as well as the expression of VEGF in the remodelling phase of wound healing.	No minor or major adverse events

(Continues)

TABLE 2 (Continued)

Study type	Author, year	Cohort	Test substance	Setting	Effects	Adverse events
				<p>Wound healing, transforming growth factor β (TGF-β), VEGF, matrix metalloproteinase 9 (MMP-9), tumour necrosis factor α (TNF-α)</p> <p>Local lymph node assay: 3 mice per group, splint mouse model: negative control, positive control and a 25% w/v of polyphenol-modified Au@AgNPs in vehicle or corresponding tannin solution were applied</p> <p>Parameters: lymphocyte proliferation</p>	<p>RES-Au@AgNPs inhibited MMP-9 and TNF-α expression.</p> <p>RES-Au@AgNPs induced down-regulation of lymphocyte proliferation.</p>	
	Shevelev et al (2020) ⁶⁰	200 male Wistar rats	RES	<p>4 groups of 50 rats, full-thickness excision including (1) no infection, (2) <i>S aureus</i>, (3) <i>P aeruginosa</i>, and (4) <i>C albicans</i>. Each group divided into five treatment subgroups: placebo, positive control, RES, dihydroquercetin, dihydromyricetin. 14 d wound evaluation.</p> <p>Parameters evaluated: wound healing, histology</p>	<p>Decreased healing time in RES-treated group compared to placebo group in a pathogen type-dependent manner. In <i>P aeruginosa</i> RES-treatment subgroup, no wound square reduction compared to placebo group over 14 d. Increased healing rate in RES treatment group on days 10–14.</p> <p>Decreased infiltration of mast cells and increased infiltration of lymphocytes and macrophages in histological wound area.</p>	No minor or major adverse events
	Zheng et al (2020) ⁶¹	18 male Sprague-Dawley rats	Host-guest gelatin hydrogel (HGM) loaded with RES and histatin-1	<p>Four full-thickness burn wounds in each rat. Treatment with 4 hydrogels / dressings in each rat: control, HGM, HGM + RES, HGM + Histatin-1, HGM + RES + histatin-1 for 2 wk.</p> <p>Parameters evaluated: wound healing, interleukin-6 (IL-6), interleukin-1β (IL-1β), TNF-α, transforming growth factor β1 (TGF-β1)</p>	<p>HGM + RES + histatin-1 hydrogel treatment decreased wound area compared to other groups.</p> <p>HGM + RES + histatin-1 hydrogel treatment inhibited IL-6, IL-1β, and TNF-α and increased TGF-β1.</p>	No minor or major adverse events
	Bigic et al (2020) ⁶²	18 adult female Sprague-Dawley rats	RES (0.5 mg/kg)	<p>3 groups of 6 rats, full-thickness wounds: control, RES intraperitoneal (systemic), subcutaneous RES (local) daily for 14 d.</p> <p>Parameters evaluated: wound healing, histology</p>	<p>RES treatment (local and systemic) improved wound healing, collagen deposition, and tensile strength compared to control group.</p>	No minor or major adverse events

TABLE 2 (Continued)

Study type	Author, year	Cohort	Test substance	Setting	Effects	Adverse events
Scarring	Bai et al (2016) ⁴⁴	24 Balb/C mice	RES (4.4 mM, 0.5 mL/100 g bodyweight)	Cutaneous excision wound models, intradermal injection of RES or SIRT1 shRNA (SIRT1 knock out). After 4 wk wound tissue evaluation. Parameters evaluated: histology, SIRT1, α -smooth muscle Actin (α -SMA)	More neatly arranged and thinner collagen fibres compared to SIRT1 shRNA group. Increased SIRT1-expression and decreased α -SMA expression.	No minor or major adverse events
	Zhao et al (2020) ⁶³	24 adult male Sprague-Dawley rats	RES 8 and 32 μ g/mL loaded into peptide hydrogel to form wound dressing	4 groups of 6 rats, full-thickness skin wound: no treatment, 200 μ L peptide hydrogel, 200 μ L peptide hydrogel + 8 μ g/mL RES and 200 μ L peptide hydrogel + RES 32 μ g/mL. Treatment for 2 wk. Parameters evaluated: Histology	Treatment with RES-loaded peptide hydrogel showed more regular and thinner collagen deposition compared to both treatments without RES.	No minor or major adverse events
Photo-aging	Abbas et al (2018) ⁶⁴	40 adult male Wistar rats (6–8 wk)	Compritrol ATO-based RES colloidal carriers (CCCs)	4 groups of 10 rats, 10 consecutive days: daily UVB irradiation/UVB irradiation + CCC6/UVB irradiation + resveratrol suspension /no irradiation. Parameters evaluated: catalase, GSH, superoxide dismutase, IL-6, IL-8, NF- κ B, matrix metalloproteinase 1 (MMP-1), GM-CSF	RES showed a protective effect when applied prior UVB irradiation compared to the positive control group. A superior dermal photoprotection was detected in the binary mixture of surfactants (P0407/P188).	No minor or major adverse events
	Kim et al (2019) ⁶⁵	56 mice 25–30 g of bodyweight	RES (2/10/50 mg/kg) dissolved in a vehicle containing 10% ethanol and 10% Tween-80 in drinking water (oral administration)	3 RES groups (out of 7): Oral administration of RES 3 \times /wk for 6 wk. UVB irradiation from week 2 to week 6. Parameters evaluated: nuclear factor erythroid 2-related factor 2 (Nrf2) level, MMP-1; MMP-9 Histopathological assessment, wrinkle formation	Groups orally administered with RES tended to attenuate UVB-caused wrinkle formation to the extent to the control group. RES administration enhanced Nrf2 level in liver and skin, suppressed UVB-induced MMP-1 and MMP-9 expression.	No minor or major adverse events

Abbreviations: α -SMA, α -smooth muscle actin; BC, bacterial cellulose; CR, caloric restriction; CCCs, colloidal carriers; DPPC, dipalmitoylphosphatidylcholine; GSH, total glutathione; GSSG, oxidised glutathione; GPx, glutathione peroxidase; HGM, host-guest gelatin hydrogel; IL-6, interleukin-6; IL-8, interleukin-8; IL-1 β , interleukin-1 β ; MDA, malondialdehyde; MMP-1, matrix metalloproteinase 1; MMP-9, matrix metalloproteinase 9; MCP-1, monocyte chemoattractant protein-1; Nrf2, nuclear factor erythroid 2-related factor 2; RES, resveratrol; DM-MP-RES, RES-loaded microparticle-impregnated dermal matrix; SOD, superoxide dismutase; TSC, total sulfhydryl content; TGF- β 1, transforming growth factor β 1; TNF- α , tumour necrosis factor α ; VEGF, vascular endothelial growth factor.

TABLE 3 Summary of clinical studies investigating the effects of resveratrol on wound healing and photo-aging

Study topic	Author, year	Cohort	Test substance	Setting	Effects	Dropout	Follow-up	Adverse events
Wound healing	Bashmakov et al (2014) ⁶⁶	15 male and 9 female participants; average age of 56.4 y (± 9.1) with diabetic foot ulcers type 2 diabetes	50 mg <i>trans</i> -RES	Double blind, parallel-group, randomised, controlled clinical trial. 2 groups: 14 patients with 50 mg <i>trans</i> -RES, 10 patients with placebo; application twice a day over a 60-d time period. Parameters evaluated: diabetic ulcer size, plasma fibrinogen level, C-reactive protein level	RES treatment induced a reduction of foot ulcer size and reduced plasma fibrinogen level compared to control group.	No dropout	every 2 wk	No minor or major adverse events
	Çetinkalp et al (2020) ⁶⁷	48 male and female participants; age 18–80, with diabetic foot syndrome and type 1 or type 2 diabetes	RES and hyaluronic acid (Dermalix; 3D dermal matrix impregnated with RES and HA)	Open, prospective, comparative parallel-armed, randomised medical device clinical study of Dermalix. Parameters evaluated: wound closure, cytokine tissue concentration (TNF- α , complement component 3)	Dermalix treatment significantly enhanced wound closure compared to standard wound treatment. Dermalix significantly decreased TNF- α tissue concentration and reduced/oxidised glutathione levels.	3 drop outs	2 mo follow-up	No adverse events related to Dermalix
Photo-aging	Moyano-Mendez et al (2013) ⁶⁸	8 women aged between 45 and 70 y	RES, RES + β CD (β -cyclodextrin) binary system	In vitro: cell culture of human keratinocytes (HaCaT cell line). Investigation of cytotoxicity and reactive oxygen species (ROS) inhibition. Clinical: daily application of RES, RES + β CD for 30 consecutive days. Parameters evaluated: skin hydration, luminosity, and elasticity	Application of RES reduced ROS generation by 32.26% (0.34%). The binary system showed a ROS reduction of 61.82 (0.22%). For the hemiface treated with the binary system, the skin parameters measured increased to a higher extent compared to RES alone.	No dropout	No follow-up	No minor or major adverse events
	Fariss et al (2014) ⁶⁹	Dermatomed human skin (3 donors)	Topical antioxidant (RES, Baicalin, vitamin E)	In vitro: application of 2 mg/cm ² for 24 h at 32°C.	Induction of the nuclear factor erythroid 2-related	No dropout	No follow up	No minor or major adverse events

TABLE 3 (Continued)

Study topic	Author, year	Cohort	Test substance	Setting	Effects	Dropout	Follow-up	Adverse events
		55 healthy female subjects aged between 40 y and 60 y		Clinical: daily application to face and neck areas at bedtime for 12 wk. Parameters evaluated: firmness, elasticity, laxity, radiance, skin tone evenness, roughness, hyperpigmentation, tactile density, overall appearance, gene expression changes (via biopsy analysis)	factor 2 (Nrf2) pathway, decrease of ROS prevalence. Increase in collagen type-II alpha-1 gene. Improvement in fine lines, wrinkles, elasticity, laxity, skin tone, hyperpigmentation, radiance and tactile roughness was noted after week 4.			
	Igielska-Kalwat et al (2019) ⁷⁰	20 healthy volunteers	RES Cream	6 consecutive weeks: daily application of RES cream or placebo cream twice a day. Parameters evaluated: skin hydration measured every 2 wk	Hydration level in the epidermis increased during a regular use of the formulation containing RES from week 0 to week 6. Due to an increased hydration level in the <i>stratum corneum</i> , transepidermal water loss (TEWL) can be inhibited.	No Dropout	No Follow Up	No minor or major adverse events

Abbreviations: β CD, β -cyclodextrin; Nrf2, nuclear factor erythroid 2-related factor 2; RES, resveratrol; ROS, reactive oxygen species; TEWL, transepidermal water loss; TNF- α , tumour necrosis factor alpha.

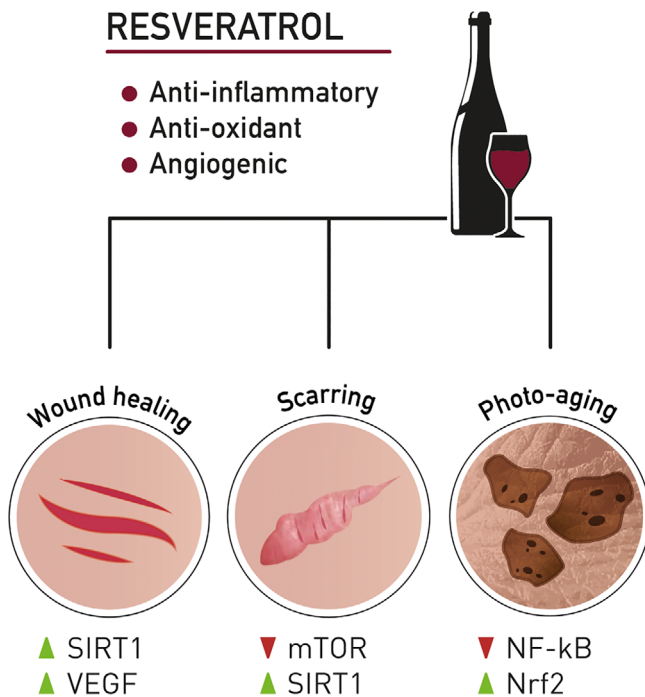


FIGURE 2 Resveratrol and its potential targets in wound healing, skin scarring, and photo-aging

stimulating angiogenesis in wounds.⁴⁹ Several studies showed that resveratrol induces VEGF expression and subsequently regulates angiogenesis.^{49,55,67} Christovam et al ascribed the proangiogenic properties of resveratrol to its activation of SIRT1. SIRT1 is associated with the induction of angiogenesis, fibroplasia, and collagen organisation. Therefore, resveratrol, as an activator of SIRT1, shows several beneficial effects for wound healing.⁵⁶

Khanna et al showed that the wound site is rich in oxidants, which promote VEGF expression and thereby support wound healing. According to their study, resveratrol treatment enhanced the oxidising environment at the wound site and was also associated with increased VEGF and tenascin expression in the wound edge.⁴⁹ Another in vitro study supports these findings and showed that resveratrol induced oxidant-induced VEGF expression in keratinocytes.³³ Data from another in vivo study also found angiogenic properties of resveratrol following chronic topical administration. Improved vascularisation of the wound bed was attributed to the stimulation of the AMPK pathway, a key mediator of wound healing.⁵³

However, Bråkenhielm et al proposed that resveratrol might block both VEGF- and FGF-receptor-mediated angiogenic responses, inhibiting capillary endothelial cell growth, and therefore the antiangiogenic effect would cause a delay in wound healing.³² To clarify the exact mechanism on how resveratrol treatment affects angiogenesis, more studies using suitable in vitro and in vivo models are needed.

Resveratrol is associated with antibacterial and antifungal properties and showed immune-stimulating effects in the wound site.^{34,60} Shevelev et al showed that topical resveratrol treatment exhibited a significant antimicrobial efficacy against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Candida albicans*, which are discussed as significant pathogens in the context of non-healing wounds.⁶⁰ Resveratrols' antimicrobial effects seemed to be even superior than some commercial antimicrobial (Levomecol) and antifungal (Clotrimazole) ointments.⁶⁰ Further in vitro studies showed that resveratrol directly inhibited microbial growth in dose dependently and therefore resveratrol might be a promising agent in fighting skin infections.³⁴

3.1 | Non-healing wounds

Resveratrol also showed promising potential for the treatment of diabetic ulcers.⁶⁶ Resveratrol prevented hyperglycemia-induced endothelial dysfunction and angiogenic impairment by activating endothelial SIRT1 and promoting forkhead box O1 (FOXO1) degradation, following a de-repression of c-Myc expression.⁴⁰ Furthermore, resveratrol is involved in improved angiogenesis induced by glyoxalase 1 (GLO1) overexpression in the context of diabetic non-healing wounds. GLO1 might support wound healing through multiple pathways, in addition to supporting inositol-requiring enzyme 1 α (IRE1 α) action.⁵⁷

4 | ANTISCARRING PROPERTIES OF RESVERATROL

Pathological scar formation is a type of tissue fibrosis caused by excessive deposition of extracellular matrix (ECM) components such as collagen and an unbalance in fibroblasts proliferation and apoptosis.⁴² These pathological processes are mediated by transforming growth factor beta 1 (TGF- β 1). Through its profibrotic properties, TGF- β 1 is one of the key players in pathological scar formation.^{43,46} Currently, there are several treatment options available, but due to the lack of permanent improvement or absence of therapy-related side effects, pathological scars remain a major health problem, but there is increasing evidence that resveratrol exhibits antifibrotic properties.^{42,43}

On a cellular level, Zeng et al were able to show that resveratrol treatment in human hypertrophic scar-derived fibroblasts (HSFBs) suppressed cell proliferation, which lead to cell cycle arrest and induced apoptosis in a dose- and time-dependent manner.⁴² Treatment with

resveratrol for 24 hours achieved an antiproliferative effect through an induction of apoptosis. The effect was enhanced with longer resveratrol treatment duration and higher resveratrol concentration. In addition, resveratrol downregulated Type I and III procollagen mRNA expression in HSFs, which resulted in a decreased collagen deposition.⁴² Similar results were reported by Zhai et al and by Pang et al regarding the apoptosis induction by resveratrol in HSFs.^{43,46}

A small number of studies investigated the genes and signalling pathways involved in the proliferation of pathological scar fibroblasts. In this context, Zhai et al showed that a resveratrol-associated suppression of cell proliferation and induction of apoptosis in HSFs is caused by altering TGF- β 1/Smad signalling.⁴³ Here, a resveratrol treatment suppressed TGF- β 1 and Smad-2,3,4 protein expression in HSFs and thereby induced antifibrotic effects.⁴³ Pang et al demonstrated that microRNA-4654 expression, which is involved in cell proliferation, cell differentiation, apoptosis, and autophagy regulation, was significantly downregulated in HSFs compared to normal skin-derived fibroblasts (NSFs). Resveratrol treatment of HSFs induced autophagy via downregulation of Ras homologue enriched in brain (RHEB) expression, a GTP-binding protein and target gene of microRNA-4654, through the upregulation of microRNA-4654.⁴⁶ Besides RHEB, the mammalian target of rapamycin (mTOR) signalling pathway also seems to have an influence on the specific proliferation mechanism in pathological scar formation.⁴⁵ An enhanced expression of mTOR and its corresponding downstream target protein ribosomal protein S6 kinase (70S6K) was found by Tang et al in HSFs in 2017 while no explicit expression was found in NSFs. Resveratrol treatment of HSFs decreased the expression of mTOR and 70S6K mRNA.⁴⁵ Similar results regarding the relationship between mTOR signalling pathway and resveratrol treatment were confirmed by Tang et al in 2020. In addition, further key factors of the mTOR signalling pathway such as PI3K and AKT were identified to be elevated in HSFs. The expression of AKT in HSFs was reduced by a resveratrol intervention.⁷² The molecular mechanisms underlying microRNA-4654, TGF- β 1/Smad and mTOR signalling pathway and the influence of resveratrol on their regulation, may be a new approach for novel potential therapeutic strategies in pathological scar formation.

In addition to the before mentioned potential molecular targets for prevention or therapy of pathological scar formations, the deacetylase SIRT 1 seems to play an important role as a drug target in fibrotic diseases.⁴⁴ Compared with NSFs, a decreased expression of SIRT 1 in HSFs was observed by Bai et al. As an agonist to SIRT 1, resveratrol downregulated mRNA levels of

collagen I, collagen III, and α -smooth muscle actin (α -SMA) due to upregulation of SIRT1 in a dose-dependent manner. Furthermore, resveratrol inhibited TGF- β 1-associated trans-differentiation of fibroblasts into myofibroblasts due to SIRT 1 upregulation, resulting in a decreased expression of fibrotic markers such as collagen I, collagen III, and α -SMA.⁴⁴ The same authors confirmed the *in vitro* results in a mouse wound model with full-thickness wounds. By using intradermal injection of a recombinant lentiviral vector for silencing SIRT 1 (SIRT1 shRNA), the authors blocked SIRT 1 expression in the mouse wound. Compared to the SIRT1 shRNA-treated mice, resveratrol treatment led to a more organised and thinner collagen fibres.⁴⁴ The results revealed that SIRT1 upregulation with resveratrol has the potential to prevent *in vivo* pathological scar formation. A novel resveratrol-loaded peptide-hydrogel wound dressing showed similar results with regard to collagen deposition in an *in vivo* full-thickness rat wound model.⁶³

Although resveratrol improved antifibrotic properties within different targets in a small number of *in vitro* and *in vivo* studies, these resveratrol-associated effects still need to be confirmed in more animal models and, especially, in more clinical studies. Yet, no clinical studies could be found which investigated the antifibrotic effect of resveratrol.

5 | PHOTOPROTECTIVE AND ANTI-AGING PROPERTIES OF RESVERATROL

Numerous studies have repeatedly revealed the damaging effects of UV irradiation as a major cause of skin aging: Chronic UV exposure induces reactive oxygen species (ROS) production, activating three major skin aging cascades. These are the matrix metalloproteinase 1 (MMP-1)-mediated aging, inflammation-induced aging (“inflammaging”) via interleukin 6 (IL6) and interleukin 8 (IL8), and/or apoptosis-induced aging via, for example, nuclear factor-kappa B (NF-kB) or caspase 3.^{47,48} Resveratrol has been widely used to prevent photo-aging through anti-inflammatory, antioxidant, and antitumour pathways. However, the specific mechanism underlying the protective effect on UV-induced damage on a cellular level has not fully been elucidated yet.^{47,48} Recently, Subedi et al were able to show a promising downregulation of the abovementioned pathways by resveratrol in *in vitro* irradiated cells. Resveratrol and resveratrol enriched rice (RR) downregulated UVB-induced ROS production in normal human dermal fibroblast cells (NHDFs). As a result, MMP-1 expression and

transcription of inflammatory cytokines responsible for “inflammaging” were reduced while the expression of type I collagen was increased.⁴⁷

Similar results were reported by Zhou et al where a photoprotective effect of resveratrol was achieved via the upregulation of heat shock protein 27 (HSP27) expression. Further, resveratrol treatment showed antiapoptotic effects through inhibition of NF- κ B and caspase-3 activation. Consequently, the viability of cultured human keratinocytes (HaCaT cell line) pretreated with different doses of resveratrol significantly increased up to 94%.⁴⁸

Results of prior *in vitro* studies were also transferable to following *in vivo* investigations. A recent *in vivo* study using mice revealed that oral or topical administration of resveratrol resulted in a suppression of UVB-induced epidermal thickening.⁶⁵ On a cellular level, the expression of MMP-1 and MMP-9 was decreased through resveratrol treatment.⁶⁵ Activation of the intracellular Nrf2-mediated antioxidant signalling pathway provides protection from UV-induced cellular damage.⁶⁵

A further *in vivo* study in adult male Wistar rats by Abbas et al also indicated a photoprotective effect of topically applied resveratrol. To enhance the penetration through the epidermis, the authors used lipid nanoparticles as a drug carrier. The compritol ATO-based resveratrol colloidal carrier CCC6 containing P407/P188 as bisurfactant attained the highest drug loading and release efficiency during a span of 24 hours. This binary mixture of surfactants even showed superior dermal photoprotection compared to the resveratrol suspension alone.⁶⁴

The potential of resveratrol containing binary systems was also investigated by Moyano-Mendez et al, who showed a significant inhibition of ROS *in vitro*, similar to Subedi et al.^{47,68} Resveratrol and a combination with β -cyclodextrin (β CD) as a solubilising excipient were subsequently tested in eight women aged between 45 and 70 years, showing clear clinical signs of photo-aging considered as loss of luminosity, hydration, and elasticity. After 30 days of daily application, a visible improvement of the skin condition with a remarkable decrease of aging signs in the hemi face treated with the β CD-containing formula could be detected in all patients.⁶⁸

Yet, only a small number of further clinical studies investigated the effect of resveratrol in photo-aged skin or its protection. A recent study by Farris et al reported significant improvement in several skin parameters after a daily usage of a night-time topical antioxidant containing resveratrol, baicalin, and vitamin E for 12 weeks. Besides an induction of the Nrf2 pathway and a decrease of ROS, the authors were able to detect a significant increase in collagen type II alpha 1 gene expression. This finding was

supported with a clinical improvement in elasticity and skin thickness as measured by ultrasound.⁶⁹

In 2019, Igielska-Kalwat et al were not only able to verify tightening but also skin-moisturising properties of resveratrol, in an observation of 20 volunteers during a period of 6 weeks. During the regular use, a 20% increase in skin hydration was detected after 2 weeks of treatment. The authors showed that resveratrol is able to replenish and modify the natural water-lipid layer and intercellular cement in skin deeper layers, leading to an inhibition of transepidermal water loss (TEWL).⁷⁰

6 | CLINICAL VALUE

Even though several studies elucidate the potential for therapeutic application of resveratrol, the fast metabolism and excretion, is the main issue for its clinical use. Therefore, improving the bioavailability of resveratrol is the subject of extensive biotechnology research. Studies aim to develop innovative drug delivery systems for local and topical resveratrol application or improve its bioavailability during systemic intake. Regarding wound healing, a controlled and prolonged release directly at the target site would ensure the beneficial effects of resveratrol.⁵¹ The combination of specific wound dressing properties and resveratrol even lead to synergistic beneficial effects.^{39,54,59,67,73} Especially hydrogels with encapsulated resveratrol seem to provide a gradual release of resveratrol, show excellent biocompatibility, and appear promising as dressing materials to support wound healing.^{38,58,63} A small number of studies examined the effects of resveratrol in combination with other agents for wound healing such as histatin, ferulic acid, or β -sitosterol, and report promising results. However, beneficial effects cannot only be ascribed to resveratrol itself.^{37,51,58,61}

Nevertheless, the studies that were included in this review show promising results that resveratrol might be a feasible approach to support dermal wound healing, counteract excessive scarring, and even prevent photo-aging of the skin.

7 | CONCLUSION

Despite numerous beneficial effects and mechanisms of action of resveratrol that have been studied intensively, there is still room for improvement in the context of skin wound healing and photo-aging. Our literature research yielded only 41 relevant original research articles that studied the effects, outcomes, or applicability of resveratrol in the treatment of acute or chronic wounds,

hypertrophic scars, and skin aging. Interestingly, the experimental *in vitro* and *in vivo* studies that were discussed here highlighted that similar pathways are targeted by resveratrol treatment in wound healing, scarring, or the prevention of photo-aging and are further summarised in Figure 2. Although there is little clinical evidence for the efficacy and applicability of resveratrol treatment, the studies summarised in Table 3 show promising results and underline the importance of more systematical clinical investigation. Nevertheless, resveratrol represents an interesting and promising novel therapy regime or could also be used as a supplementary treatment for classical treatment regimes. Therefore, more studies that investigate and improve the resveratrol skin pharmacokinetics and their clinical relevance are urgently needed.

8 | LIMITATIONS

In this review, some limitations occur that should be mentioned. Firstly, only studies that are published in the English language were investigated. Secondly, PubMed was the only database that was searched. These limitations leave the risk of studies being missed in this analysis. Five out of the 41 included studies investigated resveratrol within a clinical setting. These studies presented partially small cohorts, missing control groups that were judged as standard of care, and short or no follow-up. The remaining 36 studies examined the effects of resveratrol *in vivo* and mostly *in vitro* studies. Hence, the results presented in this review offer limited insight in the context of clinical application.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualisation: AH, PK, EH, LPK; *Methodology:* AH, SPN; *Investigation:* AH, MS, EH, HL; *Visualisation:* HL; *Formal Analysis:* SPN, PK, LPK; *Writing – Draft Preparation:* AH, MS, HL, EH; *Writing – Review & Editing:* EH, PK, LPK; *Supervision:* PK, LPK. All authors have read and agreed to the published version of the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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