



# Implications of grape extract and its nanoformulated bioactive agent resveratrol against skin disorders

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## Abstract

The grape seed extract (GSE) and its main active polyphenol, resveratrol (RES), have shown considerable antioxidant activities, besides possessed protective and therapeutic effects against various skin complications. This paper discusses the favorable effects of RES, GSE and their nanoformulations for dermatological approaches, with specific emphasis on clinical interventions. In this manner, electronic databases including PubMed, Science Direct and Google Scholar were searched. Data were collected from 1980 up to February 2019. The search terms included “*Vitis vinifera*”, “grape”, “resveratrol”, “skin”, “dermatology”, and “nanoformulation”. To increase the skin permeability of GSE and RES, several innovative nanoformulation such as liposomes, niosomes, solid–lipid nanoparticles, nanostructured lipid carriers, and lipid-core nanocapsule has been evaluated. According to our extensive searches, both RES and GSE have beneficial impacts on skin disorders such as chloasma, acne vulgaris, skin aging, as well as wound and facial redness. More clinical studies with nanoformulation approaches are recommended to achieve conclusive outcomes regarding the efficacy of RES and GSE in the management of skin diseases.

**Keywords** Skin diseases · Nanoformulations · Stilbenes · Grape extract · Resveratrol

## Abbreviations

CVI	Chronic venous insufficiency
DPPH	2,2-Diphenyl-1-picrylhydrazyl
EGCG	Epigallocatechin gallate
EIM	Ethanol injection-modified method
GS–MS	Gas chromatography–mass spectrometry
GSE	Grape seed extract
HPLC	High-performance liquid chromatography

ICD	Irritant contact dermatitis
LNC	Lipid-core nanocapsule
MPO	Myeloperoxidase
NLC	Nanostructured lipid carriers
PAMAM	Polyamidoamine
PG	Propylene glycol
PUVA	Psoralen with ultraviolet-A
PSR	Psoralen

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RES	Resveratrol
QUE	Quercetin
ROS	Reactive oxygen species
SDC	Deoxycholate
SNL	Solid–lipid nanoparticles
TPA	12- <i>O</i> -Tetradecanoylphorbol 13-acetate
UDL	Ultra-deformable liposomes
UV	Ultraviolet
VE	Vitamin E

## Introduction

Skin is the outermost covering and the largest organ of the human body, consisting of epidermis, dermis, and hypodermis layers [50, 70]. Each layer owns specific cells and a unique structure, making the first line of defense for living body and, hence, acts as an effective barrier [78]. Skin protects underlying tissues and organs from radiation, pathogens and excessive water loss, and also this organ has insulator, temperature regulator and sensory functions against external stimuli [78]. Skin is damaged by factors such as ultraviolet (UV) radiation, bacterial/viral/fungal/parasitic infections, leading to rashes, pigmentation disorders, wrinkles, acne rosacea, acne vulgaris and different types of skin cancer [43]. Such adverse conditions can disrupt skin performances, likewise can affect on community relations, daily routines, mental health and other aspects of person's life' [9].

Treatment of skin disorders includes medications that can be applied both externally and internally, mainly consisted of antibiotics, anti-inflammatory, analgesic, UV protecting, antioxidants, and moisturizing agents.

Concerning herbal remedies, polyphenols showed many beneficial health promoting properties that can be used for nutraceutical and medicinal applications [6, 45]. Polyphenols are generally classified into flavonoid and non-flavonoid (stilbenes) compounds [40]. Grapes (genus *Vitis*) are consumed either in the form of raw fruits or as processed food items such as juice, wine, and jams. The seeds and skin of grape are one of the main sources of phenolic compounds alike terpenes, proanthocyanidins, alkaloids, steroids, cardiac glycosides and saponin [40, 57], with potent antioxidant, antibacterial, antifungal and anti-inflammatory activities, and thus are considered as protective compounds for skin health [45]. Grapes include vitamin C that is essential for the formation of collagen, a fiber-like protein that supports retaining skin elasticity and reverses aging. Also, the antioxidants existing in the grapes keep the skin from the destructive effects of the free radicals and reverse the appearance of dark spots and wrinkles [40, 44].

Resveratrol (3,5,4'-trihydroxy-*trans*-stilbene) (RES) is a natural phenolic compound, abundant in different dietary sources such as grape skin, peanuts, cranberries,

pomegranates, mulberries and bilberries [2]. RES is composed of two main isomers, t-RSV and c-RSV, and the functional difference between these isomers has not completely been recognized. Several studies have demonstrated the concentration-dependent biphasic effects of RES on cells [2, 22]. RES exerts health-promoting activity against cardiovascular, cancer, and neurodegenerative diseases and also it has anti-aging, anti-inflammatory and antioxidant features, which all are beneficial for skin [68]. Moreover, RES inhibits ROS production by down-regulating the expression and activity of the oxidase and decreases mitochondrial superoxide generation by stimulating mitochondria biogenesis and increases the expression of various antioxidant enzymes, so it is known as an antioxidant and pro-oxidant agent [68].

Considering multiple advantages of GSE and RES against skin disease, this review highlights their beneficial effects and RES nanoformulations for dermatological purposes, with special emphasis on clinical studies regarding their safety and efficacy. Electronic databases including PubMed, Google Scholar, and Science Direct were searched for terms including “*Vitis vinifera*”, “grape”, “resveratrol”, “skin”, “dermatology”, and “nanoformulation”. Data were collected from 1980 up to February 2019 (Fig. 1).



Fig. 1 Study selection diagram

## Chemistry and bioavailability

Grape is one of the world's largest fruit crop and its broad biological activities have mostly been attributed to its rich polyphenolic content, resulting in strong antioxidant properties [77]. The fruits of grape contain several nutrient elements such as minerals, carbohydrates, vitamins, edible fibers and other phytochemicals [64]. As the main phytochemicals in grape, polyphenol compounds enclose stilbenes (RES), anthocyanins, proanthocyanidins, flavonols, flavanols and phenolic acid (Fig. 2) [67]. Flavonoids are commonly dispersed in grape plant parts, particularly in stems, and seeds, predominantly including epicatechin, catechins and procyanidin polymers. Anthocyanins are remarkably presented in red grape skins as dominant pigments, whereas flavanols are more abundant in white varieties [15]. Several studies demonstrated a quick absorption rate of polyphenols (i.e., flavanols, quercetin (QUE), procyanidins) into the plasma, although the increase in the plasma level of these compounds occurs at two or three hours after the ingestion [5].

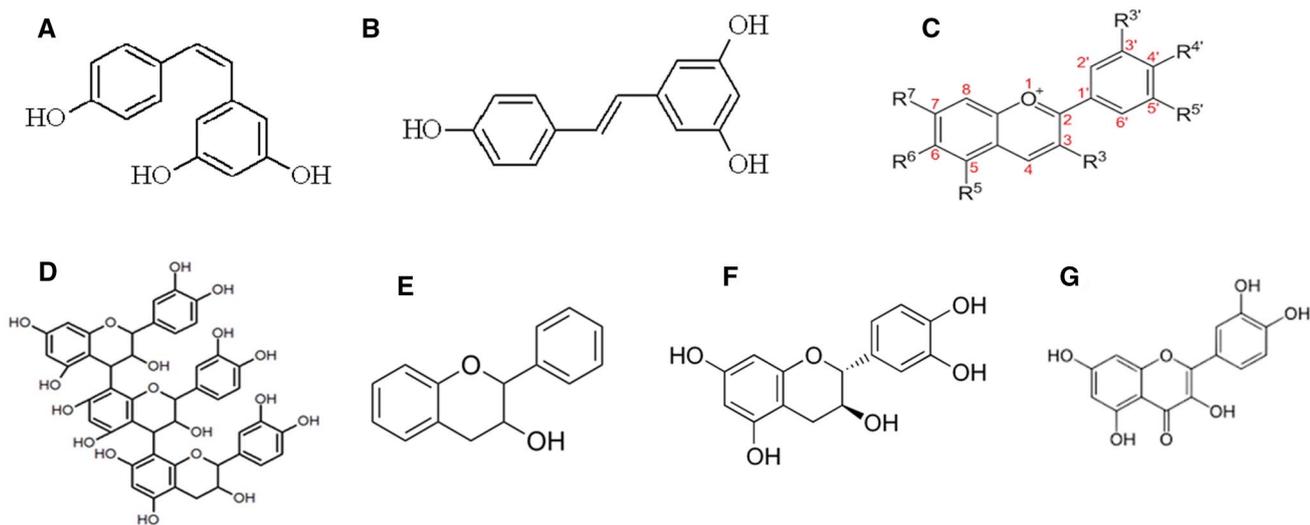
RES is a natural polyphenolic phytoalexin and possesses a number of pharmacological and biological functions. *Trans* form of RES is more thermo- and photo-stable, while the *cis* form is very unstable and simply isomerizes to the *trans* form [27]. *Trans* RES is affected by various factors such as wavelength, irradiation time, physical state of the molecule (i.e., solution or solid), pH and temperature [72]. The oral bioavailability of RES is very poor (less than 1%) with a short initial half-life (8–14 min) [40]. Its rapid and extensive metabolism and

elimination in the liver and intestine lead to the production of some metabolites, sulfates and glucuronides [75]. Topical formulation of RES has demonstrated strong chemopreventive and anti-proliferative properties against skin carcinogenesis and a considerable protection against skin destruction from UVB exposure [4]. RES, as one of the main bioactive constituents of grape, is highly photosensitive molecule and in light and easily converts from the active *trans* isomer to the inactive *cis* form, which coupled with poor water solubility (50 mg/ml) [61]. To address these limitations, nanoformulation of GSE and RES was developed to improve its bioavailability and bio-stability [42].

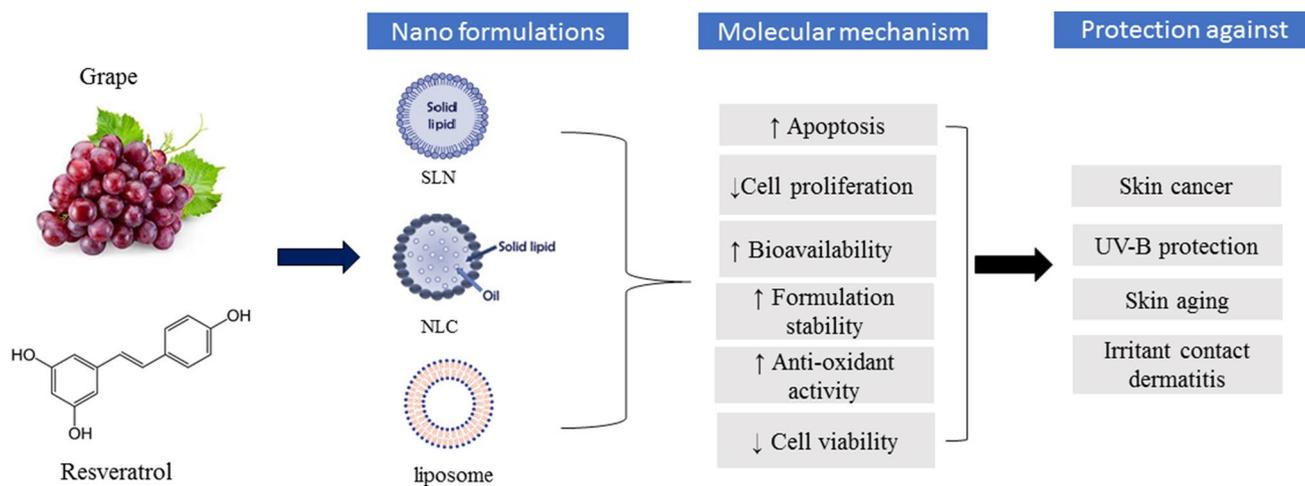
## GSE and RES nanoformulations for dermatological purposes

Due to insufficient solubility and instability (light, temperature, and pH) of RES, nano-particulate delivery systems have been confirmed to be effective in controlling its release, protection, and actions [3, 13]. The main molecular mechanisms of nanoformulated RES and GSE are depicted in Fig. 3.

In a study by Caddeo et al. [11], a co-incorporated liposomal formulation of QUE and RES was assessed in animal model of cancer-mediated skin tissue damage. The formulation showed a high in vitro antioxidant capacity against 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay, associated with the antioxidant potential of both empty vesicles and the polyphenols. The polyphenol-loaded liposomes could improve the viability of normal human



**Fig. 2** Structure of the resveratrol and other grape's bioactive compounds. (A) *Cis*-resveratrol, (B) *Trans*-resveratrol, (C) Anthocyanin, (D) Procyanidin (E), Flavanol, (F) Catechin, (G) Quercetin



**Fig. 3** Grape and resveratrol nanoformulations and their molecular mechanisms in skin disorders

dermal fibroblast cells, possibly related to the reduction of intracellular ROS formation. In the mouse model of 12-*O*-tetradecanoylphorbol 13-acetate (TPA)-induced skin damage, edema and wound size was significantly decreased in comparison with negative control. The RES–QUE liposomal formulation could reduce myeloperoxidase (MPO) level of damaged tissue [11].

The influence of RES formulated in liposomes on UV-B protection was evaluated in an in vitro model of human embryonic kidney cells (HEK) by Caddeo et al. [12]. Formulated liposomes increased cell proliferation and reached the most efficient photoprotection at RES concentration of 10  $\mu\text{M}$  and reduced the cell viability at 100  $\mu\text{M}$ . Liposomes enhanced the RES's capability to survive under stress conditions resulted by UV-B and their ability to stimulate the proliferation of the cells. In addition, the cytotoxicity of RES at high concentrations up to 100  $\mu\text{M}$  was inhibited by liposomes. Together, liposomal incorporation could increase the efficacy of RES for treatment and prevention of human skin diseases, caused by an extreme exposure to UV radiation [12].

In case of adipocytes (dissolving the subcutaneous fat), co-encapsulation of RES and QUE in sodium deoxycholate (SDC) liposomal formulation was investigated by Cadena et al. [13]. Both RES and QUE were able to enhance apoptosis in adipocytes and potentially caused a synergic inhibition of the adipogenesis. Due to the fact that the size of liposomes directly affects the absorption of subcutaneous injected therapeutic agents, the size of RES- and QUE-entrapped liposomes was found proper (more than 100 nm) for subcutaneous injection. Detergent activity of SDS in lipid compositions with high levels of phospholipid caused several side effects; however, the formulated liposomes decreased the usage of cholesterol and phosphatidylcholine by 68.4% and 17.7%, respectively. QUE/RES-loaded elastic

liposomes were suitable and stable for subcutaneous injection with high efficiency, approximately 97% [13].

A formulation consists of propylene glycol (PG)-liposomes and liposomes, stabilized by grape–silver nanoparticles were developed in vitro by Castangia [14]. The colloidal silver was expected to act as an antimicrobial factor, while the grape extract was considered as an antioxidant. The combination was found useful in eliminating several pathogenic microorganisms and dangerous free radicals and supplied an excellent protection of fibroblasts and keratinocytes against oxidative stress, thus suggesting a proper formulation for topical cure of skin injuries [14].

Dermal and transdermal drug delivery of vitamin E (VE), epigallocatechin gallate (EGCG) and RES lipid nanoparticles with potential carriers including NLCs and SLN were evaluated for skin care applications. Both VE and RES lipid nanoparticle formulations demonstrated effective protection against UV-induced degradation, while EGCG was not active. These findings indicated that lipid nanoparticles are viable carriers for the delivery of VE and RES to supply long-lasting antioxidant, i.e., over 70% release after 24 h for RES to the skin [16].

Ultradeformable liposome formulations of RES and 5-fluorouracil were investigated in in vitro model of human skin cancer cells for the potential treatment of squamous cell carcinoma by Cosco [18]. These multi-drug ultra-deformable liposomes enhanced the action of RES and adjusted the activity of 5-fluorouracil and, consequently, suppressed cell proliferation. These formulations significantly increased the percutaneous permeation and produced a cutaneous depot from 5-fluorouracil and RES in deeper skin layers, which were gradually released. The authors concluded that the co-encapsulated ultra-deformable liposomes could be used for the treatment of squamous cell carcinoma, i.e., Bowen's disease, actinic keratosis, and keratoacanthoma [18].

Ultra-deformable liposomes (UDL) co-loaded with RES and psoralen (PSR) were assessed *in vitro* for vitiligo treatment. RES and PSR co-loaded UDL with particle size less than 150 nm illustrated high entrapment efficiency that decreased the drug dose and prevented frequent drug administration due to sustained release. RES played a significant role in stimulation of tyrosinase activity and melanin content by providing antioxidative protection. The proposed formulation was found potent for vitiligo management [20].

Anti-aging applications of nanoparticles loaded with antioxidants including linseed oil, grape seed oil, coenzyme Q10, tocopheryl acetate and retinylpalmitate were evaluated by Felippi et al. [23]. *In vitro* safety assay (Hen's Egg Test Chorioallantoic Membrane) showed that nanoparticles did not induce cytotoxicity, skin irritant effects or oxidative stress, and did not cause phototoxicity after UVA exposure. The efficacy was monitored in healthy volunteers for 21 days, so the administration of nanoparticles (5% w/v) caused a significant reduction in wrinkles intensity compared to the control [23].

Gas chromatography–mass spectrometry (GC–MS), spectrophotometric and high-performance liquid chromatography (HPLC) analysis illustrated that the concomitant use of beta-carotene and *trans*-RES in sunscreens resulted in more photostable formulations with improved safety and efficacy [28]. In another study by the same group, cutaneous penetration of beta-carotene and *trans*-RES combined with the most marketed UV filters in sunscreens was evaluated. *In vitro* skin penetration assays (on vertical Franz type diffusion cells and ear porcine skin) exhibited that this combination positively promoted the skin penetration amount of about 90% in the stratum corneum. Moreover, RES in combination with beta-carotene developed sunscreen safety by decreasing delivery of four UV filters into the viable epidermis and stratum corneum [29].

Simultaneous delivery and the skin penetration level of RES and curcumin in lipid-core nanocapsule (LNC) formulation were examined in an *in vitro* release study, indicating that the encapsulation of polyphenols into LNC enhanced their photostability. Further, interaction of curcumin with stratum corneum simplified the skin absorption of RES; thus, concurrent delivery of curcumin and RES by LNC provided an ingenious way for sustained and immediate polyphenol delivery for skin disorder treatment [30].

Dermal application of RES-loaded NLCs and SLNs formulations empowered the antioxidant capacity of RES at 50  $\mu$ M. *Ex vivo* skin studies showed that NLCs are more effective in deeper penetration of RES to the epidermis [32].

High deposition and permeation of a topical formulation of RES niosome-based hydrogel were confirmed via *ex vivo* permeation studies. Dermatokinetic studies illustrated that niosomal gel increased the biological half-life and decreased

$T_{\max}$  of the drug. Accordingly, the anti-inflammatory activity of RES hydrogel was proven [52].

*Ex vivo* cutaneous absorption of RES in niosomes and liposomes was evaluated by Pando et al. [53]. Liposomes were formulated using soy phosphatidylcholine and niosomes formulated with Peceol or Plurololeique; oleins were used in their formulations as penetration enhancers. They observed that niosomes were able to encompass a great amount of RES (~82%), and also iosomes made from Peceol or Plurololeique increased cutaneous delivery of RES in contrast to conventional liposomes [53].

In a pre-clinical study, topical delivery of RES-entrapped niosomes formulations was provided, either with ethanol injection-modified method (EIM) with the size of 299–402 nm, or by thin film hydration method with sonication (TFH-S) method with the size of 293–496 nm. *Ex vivo* transdermal experiments on newborn pigskin displayed that the smaller niosomes enhanced the stability and this method was more effective for RES penetration in dermis and epidermis [54].

The anti-melanogenic effects of a novel hybrid derivative of RES and glycolic acid, resveratryl triglycolate (RTG), on human epidermal melanocytes (HEMs) and murine melanoma (B16/F10) cells were analyzed in comparison with glycolic acid, RES, arbutin and resveratryl triacetate (RTA). The study anticipated that RTG, such as RTA and RES, could decrease cellular melanin synthesis efficiently through inhibiting the catalytic activity of human tyrosinase with similar cytotoxicity of RES and RTA and, thus, RTG has skin whitening potential, as a cosmeceutical ingredient [55].

A topical anti-aging cream and solutions from polyamidoamine (PAMAM) dendrimer improved the solubility of RES loading and its skin penetration via increased stability in solution and semisolid dosage forms [56].

A comparative study between different nano-carriers including ethanol-containing vesicles and transfersomes for topical application of RES was conducted by Scognamiglio [62]. The nano-carriers with a mean diameter of 83 and 116 nm had a high RES encapsulation efficiency ( $\geq 70\%$ ). This study illustrated that ethanol-containing vesicles based on soy phosphatidylcholine (SPC) as surfactant were capable of developing RES passage through the skin [62].

Skin targeting of RES–SLNs incorporated into carbopol gel showed that RES–SLNs with a mean size below 100 nm have 68–89% entrapment efficiency. The RES–SLN gel displayed controlled drug release up to 24 h without any skin irritation. In addition, the gel suppressed ear swelling and decreased skin water content in the BALB/c mouse model of irritant contact dermatitis [65].

It was found that the nano-suspensions with a mean diameter of 0.2–0.3  $\mu$ m, made by the wet media milling technique, utilizing Tween 80 or Poloxamer 188 as stabilizers

increased RES penetration to the deeper layers of pig ear skin compared to coarse suspensions [66].

It was evidenced that RES stability, solubility and intracellular delivery were enhanced by loading into SLN with a size below 180 nm without inducing cytotoxicity. Correspondingly, RES loaded in SLN reduced cell proliferation and efficiently, thereby showing potential for the prevention of skin cancer [71].

Transdermal bioavailability of RES-loaded nano-emulsion was assessed in vivo and in vitro. This nano-structured emulsion formulation including isopropyl myristate (IPM) and low amounts of Tween80/Span 20 (as surfactant) with low viscosity ranging from 2.15 to 17.53 cps, and the nano-sized of 23.4–422.2 nm exhibited an utmost permeation ability. Following the topical application of this emulsion, the level of RES was increased in the plasma. The histological consideration in the same study illustrated noticeably less irritation than the standard irritation group [73].

Vitonyte et al. [74] determined the antioxidant and antimicrobial activities of liposomes of gallic acid and RES, co-loaded in phospholipid nanovesicles for skin protection. Glycerosomes and penetration enhancer-containing vesicles (PEVs) were prepared by liposomes using phenols and phospholipids dispersed in water/glycerol or water/propylene glycol, respectively. To enhance the viscosity and stability of the vesicle systems, glycerol or propylene glycol was used. The presence of phenols, especially gallic acid, illustrated that it has a great capacity to preserve fibroblasts and keratinocytes from oxidative damage and development of the antimicrobial activity [74].

## Clinical studies

Table 1 represents clinical trials on the effectiveness of GSE and RES formulations for skin disorders.

### Skin aging

Skin aging is a mixed biological procedure affected by the combination of intrinsic or endogenous (i.e., cellular metabolism, genetics, metabolic processes and hormones) and extrinsic or exogenous (i.e., pollution, chronic light exposure, toxins, chemicals, ionizing radiation) factors [31]. Reactive oxygen species (ROS) are tightly involved in age-related skin disorders. It has been suggested when the richest source of antioxidants, means polyphenols, is supplied by nutrition, it helps to delay skin aging and to improve skin conditions [44]. In vitro studies have proven that RES preserves normal human fibroblasts from the destructive influences of hydrogen peroxide through binding to the particular receptors in the epidermis [7].

Buonocore et al. [53] reported the first clinical proof of 60 days' chronic treatment with a nutraceutical supplement including RES, ellagic acid and procyanidin from grape dried fruits extract and found that all parameters related to oxidative stress and skin roughness in healthy individuals improved significantly, mainly by developing the plasma antioxidant contents and decreasing systemic peroxidized metabolites [53].

In a randomized double-blind controlled trial, treatment with RES for 3 months caused a significant reduction in skin folding grade [19]. Similarly, clinical and bio-instrumental studies showed the skin firmness significantly developed and skin wrinkles were decreased, following 2-month application of a skincare product including oligoside (4%) and RES (0.25%) [19].

Eight weeks of treatment with stable emulsion cream containing 2% black GSE in 110 healthy individuals enhanced skin elasticity (as potential anti-ageing), reduced melanin content (natural skin whitening) and showed moisturizing effect. Furthermore, this formulation reduced skin sebum content and erythema effects, which was effective against acne vulgaris [63].

Wu et al. [76] evaluated the protecting effects of resveratrate (stable derivative of RES) against skin damage induced by repetitious solar simulator UV pre-procedure and post-procedure. It was shown that resveratrate markedly increased erythema and inhibited sunburn cell formation through scavenging ROS [76].

In a randomized, single-blind trial, a mixture of the shoot extract of *V. vinifera* and Ronacare Hydroine (biotechnological extract) decreased ROS level as compared with untreated controls [17].

A single-blinded study was carried out to investigate the protective activity of formulations containing RES,  $\beta$ -cyclodextrin and both on 8 women (ages 45–70 years) diagnosed with aging on both hemi-faces. It was found that the usage of RES in combination with  $\beta$ -cyclodextrin was more efficient than RES alone [47].

### Wound healing

Wound healing is a natural biological dynamic process and a response to tissue injury with several highly programmed phases [34]. Several systemic and local factors such as age, nutrition and certain medications may also affect the healing process [35, 48], via decreasing the healing time and scarring [25]. It is well known that the topical application of GSE can accelerate the release of endothelial growth factors that also causes in closure and contraction of the skin wound [49].

A randomized double-blind clinical study reported that topical application of GSE 2% cream formulation on surgery

**Table 1** Clinical trials on the effectiveness of GRE and RES formulations for skin disorders

Type of skin disease	Formulation	Doses	Route of administration	Type of study	Duration of treatment	Subjects	Outcomes	References
Aging (wrinkles, dull complexion, brown spots)	Capsule	133 mg grape ( <i>V. vinifera</i> ) dried fruit extract, once daily	Oral	Placebo-controlled, double-blind study	60 days	50 healthy males and females, aged 35–65 years, (25 treated with supplement and 25 with placebo)	↓Systemic oxidative stress, ↑plasmatic antioxidant capacity, ↑skin antioxidant power, ↑skin moisture, ↑skin elasticity, ↓skin roughness, ↓depth of wrinkles, ↓intensity of age spots	[53]
Surgery wound healing	Cream	Grape seed extract cream 2%, b.i.d.	Topical	Randomized, double-blind clinical trial	3 weeks	40 patients, age between 14 and 50 years	↑Wound contraction and closure, ↓wound size, ↑wound healing	[63]
Aging	–	Resveratrol 0.25%, b.i.d.	Topical	Double-blind, randomized, controlled study	3 months	40 volunteers, age between 45 and 65 years	↓Skin folding grade	[54]
Aging	–	Resveratrol 0.25% and the oligoside 4%	Topical	Bioinstrumental and clinical studies	2 months	40 volunteers, age between 45 and 65 years	↑Skin firmness	[54]
Aging	–	Resveratrol 0.25% and the oligoside 4%	Topical	Bioinstrumental and clinical studies	2 months	60 volunteers, age between 45 and 65 years	↓Skin wrinkles	[54]
Aging	–	<i>V. vinifera</i> shoot extract + Ronacare-Hydroine, q.i.d.	Topical	Comparative, randomized, single-blind trial	1 day	27 subjects	↓Fluorescence, ↓level of ROS, product had a scavenging effect	[57]
Aging (photoaging skin)	Serum or serum plus cream	<i>V. vinifera</i> shoot extract in hydroglycolic solution, or Sarmentine, and Ronacare Hydroine, b.i.d.	Topical	–	28 days	60 female subjects	↑Firmness, ↑radiant glow, ↑evenness, ↑smoothness, ↑hydration, ↑texture, ↑softness, ↓wrinkles, ↓fine lines	[57]
Photoaging	Cream water-in-oil (W/O)	0.1% w/v <i>trans</i> -resveratrol, b.i.d. binary system (0.1% w/v <i>trans</i> -resveratrol+ β-CD) b.i.d.	Topical	Single-blind study	30 days	8 women, age between 45 and 70 with photoaging	↑Skin hydration, ↑skin luminosity, ↑skin elasticity, no side effects, binary system was more effective than RES alone	[58]

Table 1 (continued)

Type of skin disease	Formulation	Doses	Route of administration	Type of study	Duration of treatment	Subjects	Outcomes	References
Rejuvenation	Cream (water-in-oil (W/O) emulsion)	2% blue-black grape seed extract, b.i.d.	Topical	Single-blinded, randomized study	8 weeks	110 healthy adult male volunteers, (age between 20 and 29 years)	↓Skin melanin content, ↑skin elasticity, ↓skin sebum content, (suppressing $\alpha$ -5 reductase), ↓erythema, ↑skin moisture, no skin hypersensitivity	[55]
Chloasma (melasma)	Grape seed extract	67 mg of grape seed extract (54 mg of proanthocyanidins) t.i.d.	Oral	Open design study	12 months	12 nonpregnant women, age between 34 to 58 years	↑L value (lightening), ↓skin melanin-index, ↓size of chloasma, ↓hyperpigmentation, no side effects	[67]
Acne vulgaris	Gel	Resveratrol 0.01% weight in volume, once daily	Topical	Single-blind, pilot Study	60 days	20 patients (12 men and 8 women) with facial acne vulgaris, age between 18 and 23 years	↓GAGS score, ↓clinical lesions, ↓degree of acne severity, ↓average area of microcomedones, no side effects	[79]
Melasma	Gel-cream	Hydroquinone 4% twice a day + SWC 5%	Topical	Double-blind comparative study	90 days	13 women	↓Size of chloasma, ↓skin melanin content	[68]
Chronic venous insufficiency	Film coated tablet	360 mg red-vine-leaf extract b.i.d.	Oral	Multicentre, randomized, double-blind, placebo-controlled study	12 weeks	248 patients, age between 21 and 87 years	↓Lower limb volume, ↓leg edema, ↓tired heavy legs, ↓pain in the legs, ↓sensation of tension in the legs	[73]
Chronic venous insufficiency	Tablet	360 mg of dry extract of red vine leaves once daily	Oral	Randomized, double-blind, placebo-controlled, crossover trial	6 weeks	71 men and women, aged $\geq$ 18 years	↑Microvascular blood flow values, ↑tcpO <sub>2</sub> , ↓leg circumference	[74]
Chronic venous insufficiency	Capsule	360 mg or 720 mg once daily	Oral	Randomized, double-blind, placebo-controlled, parallel-group, multicenter study	12 weeks	260 patients' males and females, age between 25 and 75 years	↓Lower leg volume, ↓calf circumference, ↓ankle circumference	[75]

**Table 1** (continued)

Type of skin disease	Formulation	Doses	Route of administration	Type of study	Duration of treatment	Subjects	Outcomes	References
Photoprotection against ssUVR induced skin damage	–	1% resveratrol (resveratrol triphosphate) and 1% resveratrol+antioxidant	Topical	Before and after treatment	2 weeks	15 healthy female volunteers, age between 45 and 58 years	↓Erythema, ↓sunburn cell formation, ↓Fontana-Masson staining, ↓Melanin synthesis	[56]
Facial redness	–	Resveratrol-enriched product (including resveratrol, green tea polyphenols, and caffeine) b.i.d.	Topical	–	6 weeks	16 patients with facial redness	↓Facial redness, no adverse effects	[80]
Cutaneous damages induced by radiotherapy	Cream	<i>V. vinifera</i> A.s.-I.-M.t. O.dij 2–3 times/day	Topical	Retrospective study	First day of radiotherapy and lasted until 3 months' after the end of radiation treatment	20 women affected by breast cancer, with an average age of 47 years	Protect skin from the cutaneous damage	[81]

b.i.d. twice a day, GAGS global acne grading system, GRE grape seed extract, q.i.d. four times a day, RES resveratrol, ROS reactive oxygen species, t.i.d. three times a day

wounds resulted in decreased wound size, and improvement of wound contraction and closure [36].

### Chloasma (melasma)

Chloasma is a common facial hyper melanosis that is characterized by irregular light to dark brown patches. Several agents such as phototoxic drugs, cosmetics, hormonal therapies and pregnancy are found to be responsible for chloasma [37]. UV exposure is known to be the principal factor, which enhances the melanization and induces ROS production in the skin [58]. It has been evidenced that antioxidants and ROS scavenger products such as proanthocyanidin-rich GSE formulation are able to decrease melanin biosynthesis and UV-induced hyperpigmentation in animal models [79].

Improvement of facial hyperpigmentation of women with chloasma was recorded following oral administration of proanthocyanidin rich GSE for 12 months without any adverse effect [80].

Similarly, topical formulation of hydroquinone and grape extract for 3 months caused a noticeable reduction in skin melanin content and the size of chloasma [46].

### Chronic venous insufficiency (CVI)

CVI is a common disorder in adult population.

CVI occurs when the venous wall or valves do not function efficiently in the lower limbs and make it difficult to allow the blood return from the limbs [8]. Typical clinical manifestations such as pain, venous eczema, skin hyperpigmentation, edema, venous ulcers, and white atrophy [1] are CVI symptoms and signs that have a significant negative effect on the quality of life. Besides traditional anti-edema medications, studies have shown that flavonoids are the major therapeutic targets in the pathogenesis of CVI that are able to repair the endothelial cells lesions and prevent these cells from damages [26, 51].

In 12-week randomized, double-blind controlled trial on patients with moderate-to-severe CVI, administration of tab AS195 with 360 mg red-vine-leaf extract (folia *V. vinifera*) reduced the lower limb volume, leg edema and other symptoms of disease [60]. The same formulation showed beneficial effects on CVI symptoms: reduced ankle and calf circumference, increased microvascular blood flow values, and decreased lower leg volume [39, 42].

### Acne vulgaris

Acne vulgaris is a common chronic disease of the skin pilosebaceous units [33], affecting the quality of life which along with the risk of depression and suicide needs proper care and treatment [69]. The main pathogenic factors playing key roles in the development of acne include the

proliferation of *Propionibacterium acnes*, follicular hyperkeratinization, inflammatory and excessive sebum production [81]. Isotretinoin or antibacterials, both topical and oral forms, are used to treat inflammatory acne. In a single-blind study on subjects with facial acne vulgaris, RES-containing hydrogel significantly declined the average area of microcomedones, clinical lesions, and the Global Acne Grading System (GAGS) scores [21].

### Facial redness and cutaneous damages induced by radiotherapy

Facial redness can be a result of a number of conditions including seborrhea, broken blood vessels from sun damage, rosacea and acne. In a study by Ferzli et al. [24], the positive effect of topical RES-enriched product was recorded in reducing facial redness in 16 patients for 6 weeks intake [24]. A topical cream formulation containing *V. vinifera* exhibited an effectuals protection against destructive effects of radiotherapy on skin in patients with breast cancer [60].

### Conclusion

Skin is the largest organ of human body, thus any disparity in this organ can affect on different aspects of a person's life. Sun light, in particular UV, is an essential factor in the pathogenesis of many skin disorders such as aging. UV light can cause DNA damage and also trigger a cascade of oxidative stress and associated signaling, leading to irrecoverable damages to the cells and mutation initiation. Accordingly, it is important to develop novel approaches to manage cutaneous disorders, which progress every day. Grape fruits and RES have shown protective effects against cutaneous injuries, and UV-induced oxidative stress, and also exhibited satisfying therapeutic benefits towards various skin complications. In this review, we have summarized the therapeutic/cosmeceutical applications of GSE, RES and their nanoformulations meant for dermatological purposes, with special emphasis on clinical studies. Due to poor water solubility and instability of RES against temperature, pH and light, nanoformulations of RES seem proper solutions to achieve higher efficacy. According to clinical interventions, RES and GSE are notably effective on various skin disorders such as aging, wounds, chloasma, acne vulgaris, facial redness and etc., hence, well-designed clinical trials specifically with nanoformulations seems promising and are obligatory.

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