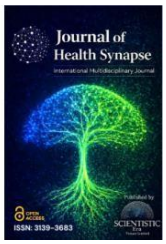
Research Article **ISSN: 3139-3683**

JOURNAL OF HEALTH SYNAPSE (JHS)
Peer Reviewed Refereed Open Access International Multidisciplinary Journal
Publisher: *Scientistic Era Private Limited*
Journal Hompage: *https://healthsynapse.org*



Development of a Nanoemulsion-Based Topical Delivery System for Anti-Aging Botanical Actives: A Comprehensive Review

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ARTICLE INFO

KEYWORDS:
Nanoemulsion; skin aging; botanical actives; topical drug delivery; resveratrol; curcumin; oxidative stress; skin permeation; antioxidant activity; nanotechnology

ARTICLE HISTORY
Received Date: 30 September 2026
Revised Date: 15 October 2026
Accepted Date: 30 October 2026
Published Date: 15 November 2026

CITATION
Singh, R. A., Development of a Nanoemulsion-Based Topical Delivery System for Anti-Aging Botanical Actives: A Comprehensive Review, *Journal of Health Synapse (JHS), 1(4), 155-166.* https://doi.org/10.67529/jhs.v1i4.12

A B S T R A C T

Skin aging results from the combined action of intrinsic influences (genetics, hormonal change and chronological age) and extrinsic insults, chiefly ultraviolet (UV) radiation, air pollution, tobacco smoke and lifestyle factors. Together these produce oxidative stress, matrix metalloproteinase (MMP)-driven collagen breakdown and weakened dermal repair, which appear as wrinkles, loss of elasticity, dryness and uneven pigmentation. Botanical polyphenols such as resveratrol, curcumin, quercetin and epigallocatechin gallate (EGCG) show antioxidant, anti-inflammatory and photoprotective activity in experimental systems. Their topical use, however, is restricted by low aqueous solubility, chemical and photochemical instability and poor delivery into the viable skin layers. Oil-in-water nanoemulsions can address several of these limitations by solubilising lipophilic actives, protecting labile molecules and providing a large interfacial area for partitioning into the skin. This review summarises the molecular biology of skin aging, the profiles of key botanical actives, nanoemulsion principles, excipient selection, preparation and optimisation strategies, physicochemical and biological characterisation, stability testing and safety. Preclinical studies, mostly with resveratrol, report enhanced skin deposition and antioxidant protection, but evidence of clinically meaningful wrinkle reduction is still lacking. Nanoemulsions are therefore best regarded as a promising but experimentally unproven platform for botanical anti-aging products.

1. Introduction

The skin is the largest organ of the body. It protects against environmental hazards, limits water loss, helps regulate temperature, contributes to immune surveillance and carries sensory information [1]. These functions depend on coordinated interaction among keratinocytes, dermal fibroblasts, extracellular matrix proteins, barrier lipids and a range of biochemical mediators.

Skin aging is a progressive process with structural, biochemical and functional components. It is conventionally divided into intrinsic aging, which reflects genetic programming, hormonal change and passage of time, and extrinsic aging, which is accelerated by UV radiation, pollution, tobacco exposure and other external factors [2–4]. Visible outcomes include fine lines, wrinkles, dryness, reduced firmness and elasticity, irregular pigmentation and altered texture, and these changes are closely tied to oxidative stress, degradation of collagen and elastin, and impaired cellular repair [5,6].

Reactive oxygen species (ROS) occupy a central place in this process. Excess ROS activate mitogen-activated protein kinase (MAPK) signalling and the transcription factor activator protein-1 (AP-1), which raises expression of matrix metalloproteinases and accelerates breakdown of the dermal matrix [7–9]. This mechanism is summarised in Figure 1.

Plant-derived compounds have attracted dermatological interest because many combine antioxidant and anti-inflammatory activity [10,11], and the use of antioxidant-rich plants is deeply rooted in traditional practice, including in Indian culture [12]. Anti-aging strategies built on such compounds are widely marketed [13]. Yet their delivery through skin is difficult. The stratum corneum restricts the passage of most molecules [14], and although the botanical actives discussed here all have molecular weights below the approximate 500 Da threshold for passive skin penetration [15], their poor aqueous solubility, polarity profile and chemical lability still limit how much active reaches viable epidermis and dermis.

Nanoemulsions have emerged as one formulation approach to some of these limits. They are colloidal dispersions of oil and water stabilised by surfactants, with droplet diameters usually quoted in the range of roughly 20–200 nm, although definitions and reported ranges vary between authors [16–18]. Loading a botanical active into a nanoemulsion may improve its solubilisation, shield it from some degradation pathways and alter its release and skin distribution. A smaller droplet, however, does not by itself guarantee deeper penetration or clinical anti-aging efficacy. This review therefore examines nanoemulsion-based topical delivery of botanical anti-aging actives, covering formulation principles, preparation methods, characterisation, biological evaluation, safety and future prospects.

2. Biology and Mechanisms of Skin Aging

2.1 Intrinsic and extrinsic aging

Intrinsic aging proceeds with advancing age and involves reduced keratinocyte turnover, thinning of the dermis, lower collagen synthesis and diminished repair capacity. Extrinsic aging is driven mainly by environmental exposure, above all solar UV radiation (photoaging), and is increasingly viewed as the cumulative effect of the whole “exposome”, which also includes pollution and smoking [3,4].

The principal changes seen in aged skin are:

1. Reduced collagen synthesis with increased collagen fragmentation;
2. Altered elastin structure and reduced dermal elasticity;
3. Slower epidermal renewal and barrier recovery;
4. Greater oxidative stress and inflammatory signalling;
5. Lower skin hydration and disorganised lipid structure; and
6. Changes in pigmentation and in the composition of the dermal matrix.

2.2 Role of reactive oxygen species

Reactive oxygen species include the superoxide radical, hydrogen peroxide and the hydroxyl radical. At physiological levels they take part in cell signalling, but sustained excess damages proteins, lipids and nucleic acids [5]. UV exposure increases ROS formation in epidermal and dermal cells. This activates MAPK cascades and AP-1, which in turn up-regulate MMP genes and interfere with transforming growth factor-β (TGF-β) signalling, reducing procollagen synthesis [7–9]. Figure 1 shows how these events connect and where botanical antioxidants and a nanoemulsion vehicle are proposed to act.

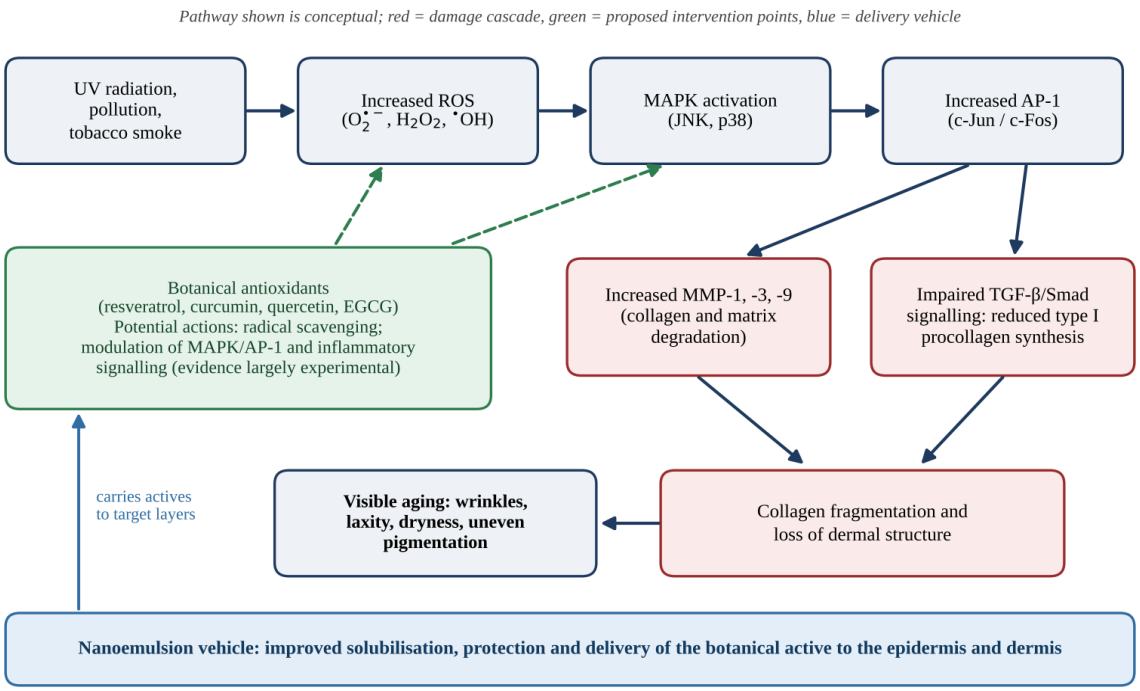


Figure 1. Conceptual pathway of photoaging and proposed points of intervention.

UV radiation and other extrinsic stressors raise ROS, activating MAPK signalling and AP-1. AP-1 increases MMP expression and impairs TGF-β/Smad signalling, leading to collagen fragmentation and visible aging. Botanical antioxidants may act at the ROS and MAPK/AP-1 levels, and a nanoemulsion vehicle is intended to deliver them to the epidermis and dermis. Redrawn from mechanisms described in refs. [7–9].

2.3 Collagen degradation and matrix metalloproteinases

Collagen is the main structural protein responsible for the strength and firmness of skin, with types I and III forming the major part of the dermal extracellular matrix. The matrix metalloproteinases MMP-1 (interstitial collagenase), MMP-3 (stromelysin-1) and MMP-9 (gelatinase B) take part in matrix remodelling, and their raised expression in photoaged skin contributes to collagen fragmentation and loss of structural integrity [2,9]. Botanical antioxidants may modulate some of these pathways, but their effect depends on the concentration reached at the target site, their biological availability and the strength of the supporting experimental evidence.

3. Botanical Actives with Potential Anti-Aging Activity

Medicinal plants contain diverse phytochemicals, including flavonoids, polyphenols, terpenoids, carotenoids and phenolic acids, and several have been studied for antioxidant, anti-inflammatory and skin-protective effects [10,11]. Table 1 compares the actives considered in this review.

3.1 Resveratrol

Resveratrol is a stilbenoid polyphenol found in grapes, berries and some other plants. It has been studied for antioxidant and anti-inflammatory properties and for effects on cellular stress-response pathways [19]. Its low aqueous solubility, extensive metabolism after oral intake and sensitivity to light and other environmental conditions complicate formulation, and the trans isomer, which is regarded as the more active form, can convert to the cis form in solution [20–22]. Because skin metabolism of resveratrol is considerably lower than hepatic metabolism, topical delivery is an attractive route [23].

3.2 Curcumin

Curcumin is a polyphenol obtained from the rhizomes of *Curcuma longa*. Experimental studies show antioxidant and anti-inflammatory activity [24], but low aqueous solubility, chemical instability under some conditions and limited bioavailability restrict its use in conventional formulations [25]. Some medicinal chemists additionally caution that curcumin is chemically reactive and can give misleading results in screening assays, so activity reported for it should be interpreted with care [26].

3.3 Quercetin

Quercetin is a flavonol present in onions, apples, berries and many medicinal plants and has been investigated for antioxidant and anti-inflammatory effects [27]. Its poor aqueous solubility and formulation-dependent stability make it a candidate for lipid-based delivery systems. Related work on phospholipid-based delivery of the flavonoid glycoside rutin illustrates the same rationale [28].

3.4 Epigallocatechin gallate (EGCG)

EGCG is the major catechin of green tea (*Camellia sinensis*). Topical application of green tea polyphenols to human skin reduced markers of UV-induced oxidative stress in one study [29], and natural polyphenols more broadly show photoprotective activity [11]. EGCG is relatively hydrophilic and degrades under certain environmental conditions, so its formulation needs strategies different from those used for lipophilic actives.

3.5 Comparative profile of selected botanical actives

Table 1. Comparative profile of selected botanical actives for topical anti-aging formulations.

Botanical active	Major source	Potential anti-aging relevance	Principal formulation challenge
Resveratrol	Grapes, berries	Antioxidant; anti-inflammatory; stress-response modulation [19]	Low aqueous solubility; photo-isomerisation; instability [20,22]
Curcumin	Turmeric (*C. longa*)	Antioxidant; modulation of inflammatory pathways [24]	Poor solubility; degradation; low bioavailability [25,26]
Quercetin	Onion, apple	Modulation of oxidative stress [27]	Limited aqueous solubility; formulation-dependent stability
EGCG	Green tea	Antioxidant; potential photoprotection [29]	Hydrophilic; oxidative and pH-related instability
Luteolin	Various plants	Anti-inflammatory potential [30]	Limited solubility
Lycopene	Tomato	Antioxidant potential [31]	Highly lipophilic; oxidation-sensitive

For a formulation-oriented research project, resveratrol is a reasonable model botanical active. Its solubility and stability problems provide a clear rationale for nanoemulsion-based delivery, and a substantial body of nanocarrier work already exists for comparison [21,22]. This is a proposed research choice, not a claim that resveratrol is clinically superior to the other compounds in Table 1.

4. Nanoemulsion-Based Drug Delivery Systems

4.1 Definition and basic principles

Nanoemulsions are colloidal dispersions of two immiscible liquids stabilised by surfactants and may be oil-in-water (O/W) or water-in-oil (W/O). Unlike microemulsions, which are thermodynamically stable, nanoemulsions are kinetically stable but thermodynamically unstable systems. Their physical stability therefore depends on droplet size, interfacial properties, viscosity and storage conditions [17,32,33].

4.2 Types of nanoemulsions

Oil-in-water (O/W) nanoemulsions disperse oil droplets in a continuous aqueous phase. They are the usual choice for topical delivery of lipophilic compounds because they give a light, non-greasy product [34].

Water-in-oil (W/O) nanoemulsions disperse aqueous droplets in a continuous oil phase. They may suit some hydrophilic actives and applications that need a more occlusive formulation.

4.3 Skin delivery behaviour and advantages

Actives can cross the stratum corneum mainly through the intercellular lipid pathway, and appendageal routes such as hair follicles may also contribute [14,34]. Figure 2 illustrates the structure of a nanoemulsion droplet and the routes by which a dissolved active may enter the skin. The figure is conceptual: it does not imply that intact droplets routinely cross all skin layers. Delivery of the dissolved active is governed to a large extent by its thermodynamic activity in the vehicle [35], and this was confirmed for resveratrol nanoemulsions, in which skin penetration tracked the thermodynamic activity of the active in each formulation [23]. High solubility in the vehicle is therefore not automatically beneficial, because a more strongly retained active has lower thermodynamic activity.

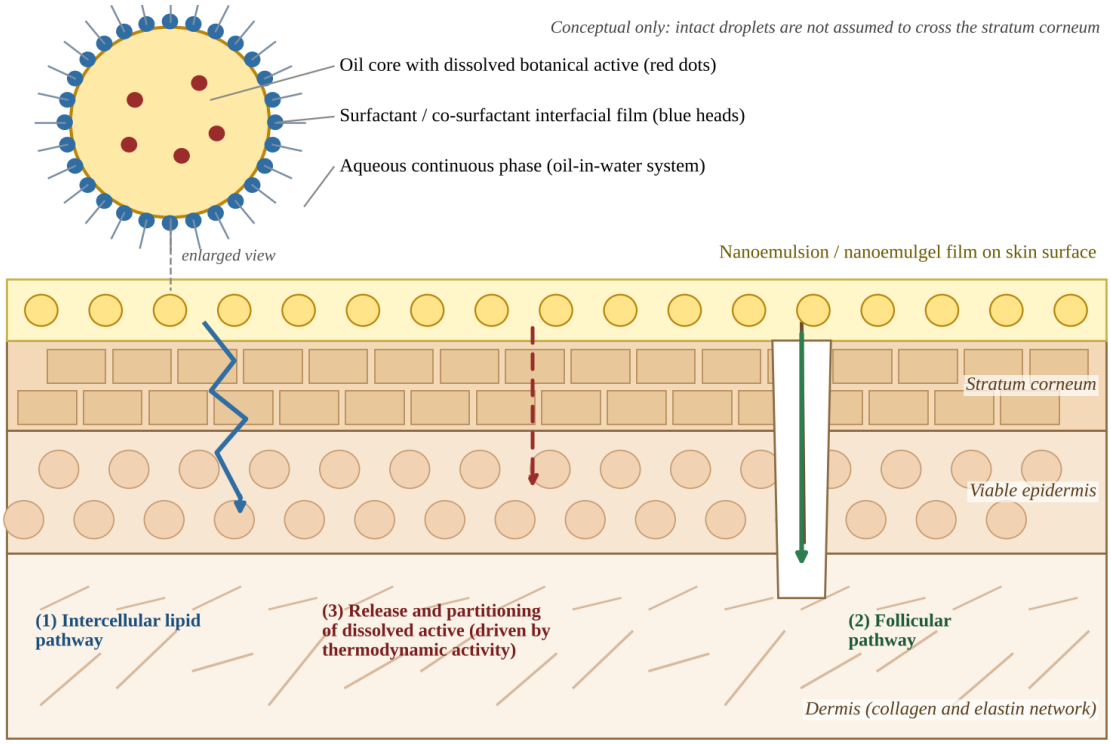


Figure 2. Conceptual structure of an oil-in-water nanoemulsion droplet and possible routes of an incorporated botanical active into the skin: (1) intercellular lipid pathway through the stratum corneum, (2) follicular pathway, and (3) release and partitioning of the dissolved active from the vehicle. Intact droplets are not assumed to cross the stratum corneum.

Nanoemulsions may offer several formulation advantages [34,36]:

1. Improved apparent solubilisation of poorly water-soluble botanical compounds;
2. Greater interfacial area for drug partitioning and release;
3. Possible improvement in skin deposition;
4. Protection of some chemically sensitive actives, depending on composition;
5. Flexible choice of oils, surfactants and co-surfactants; and
6. The option of incorporation into hydrogels to improve viscosity and application properties.

Their limitations include surfactant-related irritation, Ostwald ripening, droplet aggregation, phase separation and difficulty in maintaining long-term chemical stability [33,37].

5. Formulation Components and Their Functions

Excipient choice strongly influences droplet size, stability, skin compatibility and delivery performance (Table 2).

5.1 Selection of the oil phase

The oil phase should solubilise the selected botanical adequately, be compatible with skin and remain stable. For resveratrol, candidates include medium-chain triglycerides, ethyl oleate, isopropyl myristate and selected cosmetic-grade oils such as grape seed oil, which has been used in a resveratrol microemulsion [38]. Terpenes such as eugenol and limonene can act as penetration enhancers and changed both the amount of resveratrol retained in skin and the amount permeating it [23]. The final selection should rest on measured saturation solubility rather than assumption.

5.2 Surfactant and co-surfactant selection

Surfactants lower interfacial tension and enable small droplets to form. Nonionic surfactants are frequently preferred for topical products because suitable members of this class tend to be better tolerated. Co-surfactants alter the flexibility of the interfacial film and influence droplet formation. Total surfactant should be kept as low as stability and performance allow, since high surfactant exposure can compromise skin tolerability [23].

Table 2. Representative components of topical nanoemulsions for botanical actives and their functions.

Component	Representative examples	Function	Key consideration
Oil phase	Medium-chain triglycerides, ethyl oleate, isopropyl	Solubilises the lipophilic active	Measured saturation solubility; oxidative

	myristate, grape seed oil		stability
Surfactant	Nonionic types such as polysorbates and polyoxyl castor-oil derivatives	Lowers interfacial tension; stabilises droplets	Irritation potential; minimum effective level
Co-surfactant / co-solvent	Glycols, short-chain alcohols, diethylene glycol monoethyl ether	Increases film flexibility; aids spontaneous formation	Barrier effects; volatility
Penetration modulator	Terpenes (eugenol, limonene, eucalyptol) [23]	Alters skin permeation	Irritation; sensitisation
Stabiliser	Antioxidants, chelating agents	Limits oxidation of the active	Compatibility and regulatory acceptability
Gelling agent	Carbomer, cellulose derivatives [39,40]	Converts nanoemulsion to nanoemulgel; adjusts viscosity	Effect on release; droplet integrity

6. Methods of Nanoemulsion Preparation

Nanoemulsions can be prepared by high-energy or low-energy emulsification [16,18,36].

6.1 High-energy methods

High-pressure homogenisation subjects a coarse emulsion to intense mechanical forces that reduce droplet size. **Ultrasonication** uses cavitation and shear to disrupt droplets. **Microfluidisation** forces liquid streams at high pressure through interaction chambers to give fine emulsions. Because these methods generate heat and shear, their effect on sensitive botanical actives must be checked.

6.2 Low-energy methods

Spontaneous emulsification produces a nanoemulsion under suitable compositional and mixing conditions through interfacial and diffusion-driven processes, and was used successfully for resveratrol nanoemulsions [23]. The **phase inversion temperature (PIT)** method exploits the change in surfactant affinity with temperature [33], and the **phase inversion composition (PIC)** method relies on controlled changes in composition. Methods that need heating, such as PIT, may be unsuitable for thermolabile botanicals.

7. Optimization of Nanoemulsion Formulations

Optimisation aims at a stable nanoemulsion with acceptable droplet size, drug loading, skin compatibility and release behaviour. Design of experiments (DoE), including factorial, Box–Behnken and central composite designs, allows formulation variables to be studied systematically and fits the quality-by-design framework [41,42]. A formulation-by-design approach has been applied to a carbomer-based resveratrol nanoemulgel [39]. Table 3 lists typical variables.

Table 3. Typical independent and dependent variables in DoE-based nanoemulsion optimisation.

Variable	**Expected influence / role**
Oil concentration (independent)	Drug solubilisation; droplet size
Surfactant concentration (independent)	Interfacial stabilisation; droplet size; irritation
Co-surfactant concentration (independent)	Interfacial properties; phase behaviour
Homogenisation conditions (independent)	Droplet size and distribution
Droplet size, PDI, zeta potential (dependent)	Physical quality and stability
Encapsulation efficiency, drug release, skin deposition (dependent)	Performance and delivery

The optimum should be chosen from a balanced assessment of performance, stability and safety, not from minimum droplet size alone.

8. Physicochemical Characterization of Nanoemulsions

Comprehensive characterisation establishes the quality, stability and performance of the nanoemulsion. The main

techniques are summarised in Table 4.

8.1 Droplet size and polydispersity index

Droplet size and polydispersity index (PDI) are normally measured by dynamic light scattering (DLS). A narrow size distribution aids reproducibility, and a PDI of about 0.3 or below is widely used as a practical screening target for lipid-based nanocarriers, although acceptable values depend on the system and method [43,44].

8.2 Zeta potential

Zeta potential describes the electrokinetic behaviour of the droplets and helps assess electrostatic stabilisation [44]. Nanoemulsions made with nonionic surfactants can remain stable through steric stabilisation even when the absolute zeta potential is low.

8.3 Morphology

Transmission electron microscopy (TEM) or cryogenic electron microscopy may be used to examine droplet shape and size.

8.4 Drug content and encapsulation efficiency

Drug content may be determined with a validated HPLC or suitable spectrophotometric method. Where free and droplet-associated drug can be reliably separated, apparent encapsulation efficiency (EE) can be calculated as:

$$EE\ (\%) = (W_t - W_f) / W_t \times 100 \quad (1)$$

where W_t is the total drug quantity and W_f the measured free drug quantity. The term needs careful interpretation for nanoemulsions, because an active may be distributed between the oil phase, the aqueous phase and the surfactant-rich interface.

8.5 Additional characterisation

Further tests include pH (skin surface pH is on average below 5 [45]), viscosity, refractive index, conductivity, centrifugation stability, thermal stress testing and microscopic examination.

Table 4. Techniques for physicochemical characterisation of botanical nanoemulsions.

Technique	Parameter	Practical consideration
Dynamic light scattering	Droplet size, PDI	PDI ≤ ~0.3 is a common screening target [43]; dilution may alter results
Zeta potential analysis	Surface charge	Less informative for sterically stabilised (nonionic) systems [44]
TEM / cryo-TEM	Morphology	Sample preparation can introduce artefacts
HPLC / UV spectrophotometry	Drug content, EE	Validated, stability-indicating method; separation of free drug
pH, viscosity, conductivity	Skin compatibility; rheology; emulsion type	pH suited to skin [45]
Centrifugation, freeze–thaw, thermal cycling	Physical stability	Early screening of instability

9. In Vitro Drug Release and Ex Vivo Skin Permeation

9.1 In vitro drug release

In vitro release studies assess the rate and extent of release of the active from the nanoemulsion. A suitable diffusion cell or validated release apparatus is used, and the receptor medium must maintain sink conditions and preserve the analytical stability of the botanical. Because resveratrol is light-sensitive, samples should be protected from light. Samples are taken at set intervals and analysed by a validated method.

9.2 Ex vivo skin permeation

Ex vivo permeation is studied in Franz diffusion cells with suitably prepared human or animal skin [46,47]. The steady-state flux (J) and permeability coefficient (K_p) are calculated as:

$$J = (dQ/dt) / A \quad (2)$$

$$K_p = J / C_d \quad (3)$$

where Q is the cumulative amount permeated, t time, A the diffusion area and C_d the drug concentration in the donor. Excised skin lacks metabolism and circulation, and species and site differences affect barrier properties, so results should be interpreted as relative comparisons.

9.3 Skin retention

For an anti-aging product, deposition in relevant skin layers is generally more desirable than extensive systemic permeation. Skin retention studies determine how much active is held in the stratum corneum, viable epidermis and dermis. Published resveratrol nanoemulsion gels showed increased skin deposition and protection against UV-induced oxidative

damage in experimental models [40].

10. Biological Evaluation of Anti-Aging Activity

10.1 Antioxidant activity

Antioxidant potential is commonly examined with the DPPH or ABTS assays [48,49]. These give preliminary information on radical-scavenging capacity but do not establish anti-aging efficacy in human skin. Coloured actives such as curcumin can interfere with absorbance readings, so appropriate blanks are needed.

10.2 Collagenase and elastase inhibition

Collagenase and elastase inhibition assays show whether the actives affect enzymes involved in matrix degradation [50]. Positive controls, concentration–response experiments and interference controls are required.

10.3 Cellular antioxidant activity

Human keratinocytes and dermal fibroblasts can be used to study intracellular oxidative stress, cell viability and selected photoaging markers [51]. Endpoints include ROS production, MMP expression, procollagen synthesis and inflammatory cytokine levels. Nanoparticulate formulations can interfere with some colorimetric viability assays, so assay controls are advisable.

10.4 Skin irritation and compatibility

Irritation assessment is important because surfactants and co-surfactants can alter barrier function. Reconstructed human epidermis models, validated under OECD Test Guideline 439, are preferred over animal testing [52,53], with further justified testing where needed.

11. Stability Studies

Nanoemulsions should be evaluated for physical, chemical and microbiological stability under suitable storage conditions. Key parameters are droplet size, PDI, phase separation, drug content, pH, viscosity, appearance and degradation products. Common physical instability mechanisms are creaming, flocculation, coalescence and Ostwald ripening [33,37]. Because many botanical polyphenols are light-sensitive, photostability testing should follow ICH Q1B [54]. The final protocol should reflect the product classification, packaging and regulatory requirements; ICH Q1A(R2) provides a general framework [55].

12. Evidence from Published Research

Several studies support investigation of nanoemulsion and related nanocarrier systems for topical delivery of botanical compounds (Table 5). Most concern resveratrol, which reflects its use as a model compound. The evidence is preclinical formulation and efficacy-surrogate data, and it is not proof of clinically meaningful wrinkle reduction in humans.

Table 5. Selected preclinical studies of nanocarrier-based topical delivery of resveratrol.

System	Carrier type	Key reported findings	Reference
Nanoemulsion (2% w/w RSV)	Spontaneous-emulsification nanoemulsions with terpenes	Eugenol gave highest penetration into skin layers and limonene highest permeation; enhancement ratios of 9.55 and 12.61 versus saturated solution	[23]
Nanoemulsion gel	O/W nanoemulsion in gel (droplets $_{65\ nm,\ PDI}$ 0.17)	Skin deposition of 62.65% from gel vs 45.65% from nanoemulsion; improved antioxidant enzyme levels and histology in UV-irradiated rats	[40]
Microemulsion	Microemulsion	Up to 60% released within 6 h; protected keratinocytes against oxidative stress	[56]
Solid lipid nanoparticles	SLN	Skin permeation/retention and tyrosinase inhibition; HaCaT cytotoxicity assessed	[57]
Nanoliposomes	Liposomes	Greater penetration and retention; anti-aging and brightening effects in cells, 3D skin and human skin	[58]
Liquid-crystalline system	Lamellar liquid crystal	Reduced UVB-induced inflammation and oxidative stress in mice	[59]

A carbomer-based resveratrol nanoemulgel developed by formulation-by-design [39] and a grape seed oil microemulsion for improved skin delivery [38] further illustrate the breadth of lipid-based approaches. For curcumin and other botanicals the topical literature is smaller. Taken together, these studies show that lipid nanocarriers can raise skin deposition and, in animal models, antioxidant protection, but they rely on surrogate endpoints, differ widely in design

and rarely compare carriers head to head.

13. Safety and Regulatory Considerations

Safety evaluation must cover the active, each excipient and the finished nanoemulsion. Surfactants and co-solvents may irritate or alter barrier function, and some botanicals can sensitise skin or stain it (curcumin is intensely yellow). Testing should follow current guidance for cosmetic ingredients [60-65]. Whether a given nanoemulsion falls under a regulatory definition of nanomaterial, and how it is labelled, depends on the jurisdiction and on whether droplets are insoluble or biopersistent [65-77], so this should be checked early. Claims also matter: statements about structural change in skin may move a product from cosmetic to drug classification, with different evidence requirements.

14. Challenges and Future Perspectives

Despite their promise, nanoemulsions face several challenges: maintaining long-term physical stability, limiting surfactant-related irritation, ensuring reproducible manufacture, preventing degradation of the botanical active and translating laboratory results into clinical outcomes. Future work should emphasise quality-by-design approaches [41,42], advanced human-relevant skin models, standardised botanical extracts, head-to-head comparison of delivery systems and controlled clinical studies. Stronger evidence on safety, batch reproducibility and real-world performance is needed before claims can be made for botanical nanoemulsion products.

15. Conclusion

Nanoemulsion-based topical systems are a promising way to improve the formulation performance of botanical anti-aging compounds. By solubilising poorly water-soluble actives, modifying release and influencing skin deposition, they are attractive for cosmetic and dermatological research.

Resveratrol, curcumin, quercetin and EGCG have biological activities relevant to oxidative stress and inflammation, but their usefulness depends on chemical stability, skin availability, formulation compatibility and demonstrated biological effect. Careful optimisation of the oil phase, surfactant system, droplet size and active loading is essential for a stable, skin-compatible product, and it must be supported by physicochemical characterisation, release and permeation testing, antioxidant assays, irritation studies and stability studies.

Well-designed clinical studies are still required to show whether improved delivery translates into measurable improvement in skin-aging outcomes.

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