Journal of Drug Delivery Science and Technology 127 (2027) 108910

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Review Article

Natural bioenhancers for dermal delivery: Mechanisms, formulation design and cosmeceutical applications

Emran Habibi [a,*], Leila Panahi [a], Gamal Moustafa Mahmoud Abdelfattah [a], Mohammad Hossein Hosseinzadeh [b], Madiha Kousar [a], Satyajit D. Sarker [a], Lutfun Nahar [a,c,**]

[a] Centre for Natural Products Discovery (CNPD), School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, James Parsons Building, Byrom Street, Liverpool, L3 3AF, United Kingdom
[b] Pharmaceutical Sciences Research Center, Institute of Herbal Medicines and Metabolic Disorders, Mazandaran University of Medical Sciences, Sari, 48157-33971, Iran
[c] Laboratory of Growth Regulators, Palacký University and Institute of Experimental Botany, The Czech Academy of Sciences, Šlechtitelů 27, Olomouc, Czech Republic

ARTICLE INFO

Keywords:
Natural bioenhancers
Skin permeation mechanisms
Formulation strategies
Cosmeceutical applications

ABSTRACT

Natural bioenhancers have emerged as promising strategies for improving dermal and transdermal delivery of cosmetic and therapeutic products. Natural bioenhancers comprise diverse chemical classes, including alkaloids, fatty acids, polyphenols, polysaccharides, saponins, triterpenoids, and others, each contributing distinct structural features that influence interactions with the stratum corneum. These interactions include modulation of lipid packing, increased membrane fluidity, enhanced hydration, keratin-associated effects and changes in the microenvironment at the formulation-skin interface. Advances in molecular and biophysical studies have clarified how polarity, chain length, unsaturation, volatility and stereochemistry shape enhancer performance across hydrophilic and lipophilic actives. Alongside mechanistic insights, contemporary formulation science has adopted natural bioenhancers within nanoemulsions, lipid carriers, ethosomes, nanoemulgels, hydrogels and natural deep eutectic solvent systems. These platforms support improved solubility, stability and controlled release, while enabling targeted delivery to the stratum corneum, viable epidermis or hair follicles. Applications include anti-ageing, skin-brightening, anti-inflammatory and barrier-repairing products, and scalp-delivery formulations, with growing emphasis on biocompatibility and long-term tolerability. This review integrates current evidence on the chemistry, mechanisms and formulation strategies of natural bioenhancers and outlines their expanding role in cosmeceutical innovation.

1. Introduction

The demand for high-efficacy cosmeceutical formulations has continued to rise as consumers increasingly expect visible and measurable improvements in skin condition. The stratum corneum remains the primary barrier to topical delivery and restricts the permeation of most active ingredients [1,2]. Terminally differentiated corneocytes embedded in an ordered intercellular lipid matrix create a structure with low permeability [3]. This organisation limits the movement of hydrophilic and lipophilic molecules into deeper layers and reduces bioavailability at target sites [4]. These challenges continue to impair the performance of modern cosmeceutical formulations despite advances in ingredient design [2].

Passive diffusion across intact skin favours low-molecular-weight compounds with suitable lipophilicity, while hydrophilic and high-molecular-weight molecules encounter substantial resistance [5]. These limitations sustain interest in strategies that improve dermal delivery without compromising barrier integrity [4]. Natural bioenhancers represent one such approach. These compounds modulate stratum-corneum structure in reversible and biocompatible ways [6]. Plant-derived alkaloids, essential oils, fatty acids, terpenes and related compounds interact with lipid domains, increase membrane fluidity and enhance partitioning of co-delivered active principles. Compared with synthetic penetration enhancers, natural bioenhancers often provide

* Corresponding author.
** Corresponding author. Centre for Natural Products Discovery (CNPD), School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, James Parsons Building, Byrom Street, Liverpool, L3 3AF, United Kingdom.
E-mail addresses: E.habibi@ljmu.ac.uk (E. Habibi), profnahar@outlook.com (L. Nahar).

https://doi.org/10.1016/j.jddst.2026.108910
Received 6 May 2026; Received in revised form 2 September 2026; Accepted 3 September 2026
Available online 4 September 2026

favourable tolerability and support routine cosmeceutical use [7].

Natural bioenhancers can be grouped by chemical structure and by their mode of interaction with the skin barrier. Representative classes include lipid-based compounds, terpenoids, essential-oil constituents and other low-molecular-weight phytochemicals with documented permeation-enhancing activity [4,6]. Although their structures differ, many alter intercellular lipid organisation and increase diffusional pathways. Enhancement outcomes depend on molecular size, lipophilicity, concentration and the formulation environment in which each enhancer is incorporated. A clear understanding of these distinctions is necessary for selecting suitable enhancers for targeted cosmeceutical applications.

Formulation design influences enhancer behaviour by determining enhancer availability, localisation and interaction with stratum corneum lipids and active ingredients [2,4]. The performance of natural bioenhancers is inseparable from formulation context, since penetration outcomes depend on how each enhancer is incorporated, stabilised and released within the chosen delivery system [2]. Contemporary platforms such as nanoemulsions, lipid carriers, ethosomes, nanoemulgels and polysaccharide-based matrices have improved stability, controlled release and skin penetration of both enhancers and active ingredients [4]. Their success relies on optimising enhancer-lipid interactions, solubilisation capacity and microenvironmental effects that influence barrier modulation [4,6]. Overall, these considerations highlight the need for an integrated framework linking mechanisms, formulation design and cosmeceutical applications. This review evaluates natural bioenhancers within this unified framework and examines their roles across emerging cosmeceutical categories, including anti-ageing, skin brightening, anti-inflammatory treatment, barrier repair and hair-scalp delivery.

2. Literature search and selection

Relevant literature was identified through searches of PubMed, Scopus and Web of Science. The literature search was conducted up to August 2026 using combinations of the terms “natural bioenhancer”, “natural penetration enhancer”, “skin permeation”, “dermal delivery”, “transdermal delivery”, “cosmeceutical”, “terpenes”, “essential oils”, “fatty acids”, “natural polymers”, and “natural deep eutectic solvents (NADES)". No publication date restriction was applied. Studies published between 2023 and 2026 were specifically examined to capture recent developments in the field, while earlier studies were retained where they provided important mechanistic evidence or foundational findings relevant to specific natural bioenhancers. Experimental, clinical, and review articles relevant to the mechanisms, formulation strategies, skin delivery, and cosmeceutical applications of natural bioenhancers were evaluated.

3. Skin barrier and the rationale for bioenhancers

3.1. Structure-function relationship of the stratum corneum

The stratum corneum (SC) forms the outermost layer of the epidermis and represents the principal barrier to topical delivery. Its barrier function arises from a highly ordered arrangement in which terminally differentiated corneocytes are embedded within a continuous intercellular lipid matrix, commonly described by the brick-and-mortar model [8]. This architecture provides resistance to chemical, physical and microbial challenges and confers the very low permeability characteristic of intact skin [3].

The intercellular lipid matrix consists mainly of ceramides, cholesterol and free fatty acids arranged in lamellar bilayers. Ceramides dominate the lipid fraction and support barrier integrity, cholesterol modulates lipid mobility and free fatty acids contribute to tight lipid packing [3]. This ordered lipid structure restricts passive diffusion of most molecules across intact skin and underlies the low permeability of the stratum corneum [8].

The presence of multilamellar lipid domains creates complex diffusion pathways that markedly reduce trans-stratum corneum flux and often lead to subtherapeutic concentrations at target sites [9]. Passive permeation is generally limited to small molecules with suitable lipophilicity, while hydrophilic and high-molecular-weight compounds encounter substantial resistance [5]. Even lipophilic actives may be trapped within lipid domains rather than reaching viable layers [4]. These intrinsic structural constraints define the central challenge in dermal and transdermal delivery and provide the mechanistic rationale for controlled reversible enhancement strategies.

3.2. Limitations of synthetic penetration enhancers

Synthetic chemical penetration enhancers have been widely investigated as a means of increasing transdermal flux. Common examples include dimethyl sulfoxide, alcohols, surfactants, fatty acid esters and synthetic amides. These materials increase permeability through mechanisms such as lipid disruption, lipid extraction, increased lipid fluidity and, in some cases, keratin denaturation [7]. Such actions can substantially increase the delivery of poorly permeable compounds.

However, these agents present significant safety concerns. Potent enhancers such as dimethyl sulfoxide can produce irritation, erythema and burning at concentrations required for meaningful enhancement. Alcohols and surfactants can extract essential lipids and increase transepidermal water loss, triggering inflammatory responses [7]. Prolonged or repeated exposure may lead to cytotoxicity, skin sensitisation and irreversible impairment of barrier function, which limits suitability for long-term cosmetic use [9]. These limitations have constrained their application in cosmeceutical formulations and highlighted the need for alternative and better-tolerated strategies.

3.3. Rationale for natural bioenhancers in topical delivery

Natural penetration enhancers have gained increasing attention as safer and more biocompatible alternatives to synthetic agents. Most natural bioenhancers originate from plant sources and include various secondary metabolites. Several natural bioenhancers display favourable biocompatibility and can interact with endogenous skin lipid domains owing to their physicochemical properties. These interactions contribute to modulation of stratum corneum barrier properties and support dermal delivery [4].

In contrast to many synthetic agents, natural bioenhancers typically act through reversible interactions with intercellular lipids. These interactions adjust lipid packing and increase membrane fluidity without permanent disruption of barrier integrity [6,7]. Such reversibility is essential for cosmeceutical applications in which repeated use is expected.

Several natural bioenhancers also provide complementary biological effects, including antioxidant, anti-inflammatory and antimicrobial activities, which may benefit skin physiology and formulation stability [4]. Their biodegradability, favourable tolerability and high consumer acceptance further support their growing use in modern cosmeceutical delivery platforms [10]. These characteristics collectively justify the continued investigation and rational incorporation of natural bioenhancers into topical formulations.

4. Classification of natural bioenhancers

Natural bioenhancers comprise a diverse group of compounds capable of increasing dermal and transdermal delivery through reversible interactions with the stratum corneum. They can be broadly categorised into plant-derived and non-plant sources [11,12]. Plant-derived bioenhancers include terpenes and essential oils, fatty acids and plant oils, alkaloids, polysaccharides and mucilage materials, triterpenoids and saponins, and selected polyphenolic compounds [13].

Although chemically distinct, many of these compounds interact with intercellular lipid domains in ways that modulate barrier organisation and support increased diffusional transport [4,14].

Non-plant-derived bioenhancers include materials obtained from microbial and animal sources, such as hyaluronic acid produced through microbial fermentation, chitosan derived from crustacean shells and microbial exopolysaccharides [15–17]. These macromolecules enhance permeation primarily through hydration, bio-adhesion and modulation of the local microenvironment within the stratum corneum. Natural deep eutectic solvents (NADES) also fall within this category and act through solubilisation and mild lipid modulation. Together, these classes represent the major natural strategies for improving dermal delivery.

4.1. Terpenes and essential oils

Terpenes and essential oils are among the most extensively studied natural bioenhancers. Their lipophilicity and volatile nature support partitioning into stratum corneum lipids and enable reversible modulation of barrier structure. Common examples include cineole, eucalyptol, limonene, menthol and terpineol. Essential oils contain complex mixtures of terpenes and other volatile constituents that contribute to both functional performance and sensory attributes [18,19]. Their compatibility with topical formulations and favourable tolerability profiles have established them as practical alternatives to synthetic penetration enhancers [20,21]. Fig. 1 illustrates representative terpene structures, whereas Table 1 summarises key terpenes and essential oils with documented enhancer activity, including their mechanisms, targets and enhancement outcomes.

4.2. Fatty acids and plant oils

Fatty acids and plant oils represent two distinct categories of natural lipid-based bioenhancers. Fatty acids function as individual lipid molecules, whereas plant oils contain complex mixtures composed predominantly of triglycerides together with naturally occurring fatty acids and other minor lipophilic constituents. Oleic and linoleic acids are widely described as effective enhancers, whereas saturated fatty acids show more variable performance. Plant oils such as almond, coconut, olive and soybean oils act through the combined effects of their triglyceride and fatty acid compositions [29,30]. Their roles span solubilisation, barrier modulation and microenvironmental hydration. Table 2 summarises key fatty acids and plant oils with documented enhancer activity.

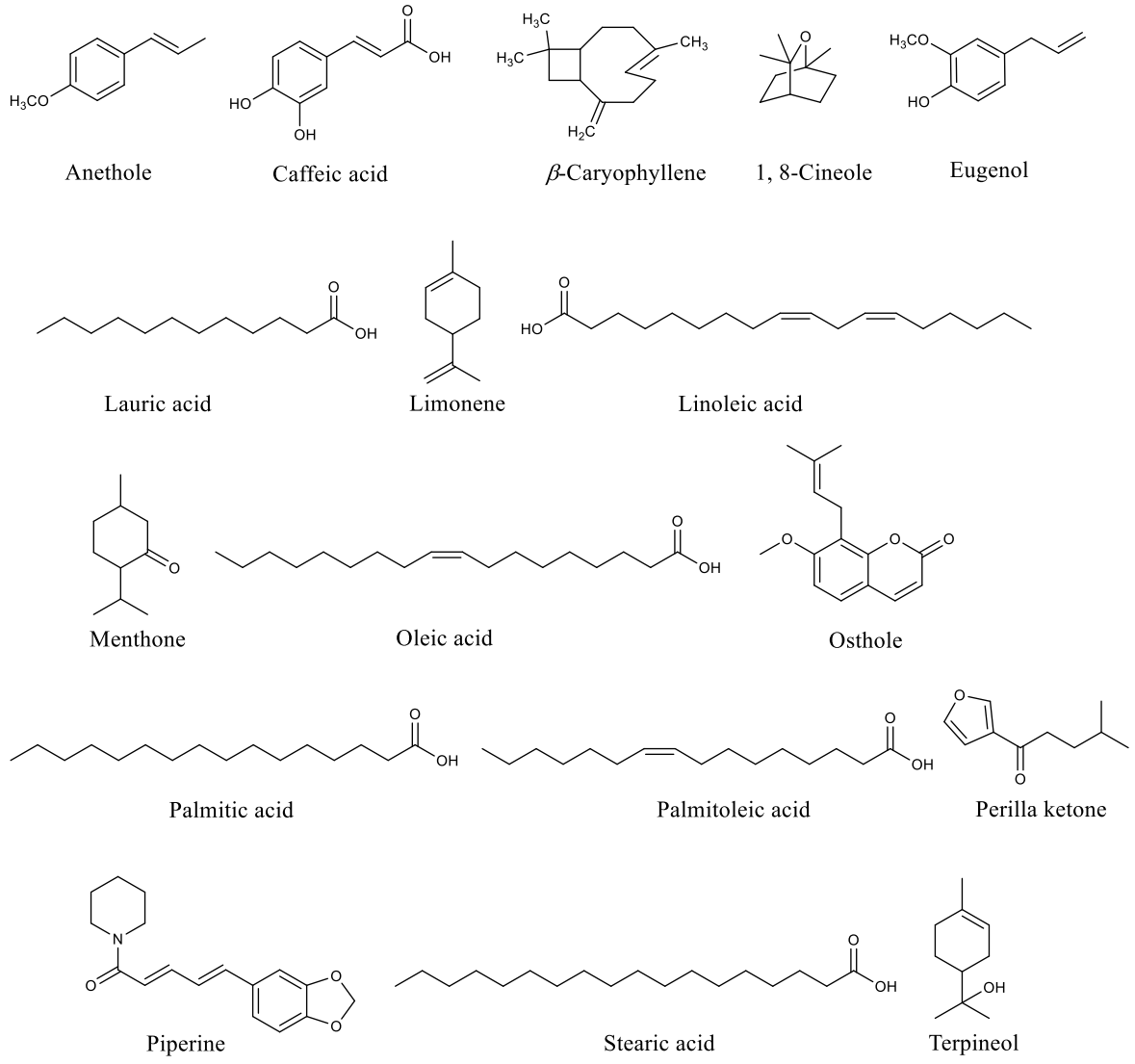

Fig. 1. Chemical structures of selected natural bioenhancers.

Table 1
Selected studies on terpenes and essential oils as natural skin penetration enhancers.

Bioenhancer	Active(s)	Mechanistic insight	Key outcome + Model	Reference
Limonene	Osthole, caffeic acid	Deep penetration into lipid core; disruption of cholesterol-water hydrogen bonding	Strongest lipid disruption; enhanced permeation (Model: MD simulation only)	[21]
Terpineol	Osthole, caffeic acid	Headgroup interaction; increased membrane fluidity	Preferential enhancement of hydrophilic actives (Model: MD simulation only)	[21]
1,8-Cineole	Osthole, caffeic acid	Surface level lipid interaction	Moderate enhancement (Model: MD simulation only)	[21]
D-Limonene	Curcumin	Increased solubility; disruption of stratum corneum lipids	A cumulative absorption of 57% (rat skin)	[22]
Perilla ketone	Puerarin, luteolin, rutin	Polarity-dependent hydrogen bond interactions	Strongest enhancement for puerarin (*in vitro*)	[23]
b-Caryophyllene	FITC, FD-4k	Increased stratum corneum lipid fluidity; enhancer retention	Enhancement ratios 3.4-3.9 (rat skin)	[24]
Anethole	Valsartan	Lipid fluidisation	4.4-fold increase in flux (rat skin)	[25]
Menthone	Valsartan	Disruption of stratum-corneum lipids	4-fold increase in flux (rat skin)	[25]
Eugenol	Valsartan	Phenolic interaction with lipids	3-fold increase in flux (rat skin)	[25]
Menthol	Lornoxicam	Disruption of lipid packing	Highest permeation in ethosomes (rat skin)	[26]
Chuanxiong oil	Ibuprofen	Volatility-dependent lipid modulation	Enhancement ratio 2.6; 88% permeation (rat skin)	[27]
Eucalyptus oil	Curcuminoids	Lipid modulation and increased solubility	3-fold increase in permeation (human skin)	[28]
Clove oil	Nifedipine	Phenolic interaction with lipids	Higher permeation than synthetic enhancer (porcine skin)	[1]

4.3. Alkaloids

Alkaloids are nitrogen-containing secondary metabolites with diverse biological activities. Although less commonly employed as intentional penetration enhancers, selected alkaloids have demonstrated transient barrier-modulating effects under defined conditions. Homoharringtonine (HHT) increased transepidermal water loss for up to 48 h in C57BL/6J mice and enhanced systemic absorption of 4 kDa and 10 kDa dextrans by approximately 15.4-fold and 9.6-fold, respectively. HHT-induced TEWL remained elevated after compound removal. Persistent elevation of TEWL indicates sustained barrier disruption rather than reversible modulation. Quantitative evidence defining barrier recovery was not reported in the original study [37]. Piperine, incorporated into bacterial cellulose membranes, increased curcumin flux across mouse dorsal skin by nearly 1.9-fold, attributed to interactions with stratum corneum lipids and keratin [38]. Overall, alkaloid-mediated enhancement is compound specific and formulation dependent.

4.4. Polysaccharides and mucilage materials

Natural polysaccharides, including cellulose, chitosan, hyaluronic acid, levan, and plant-derived mucilage, function as hydrophilic biopolymers with favourable biocompatibility and hydration-modulating properties.

Their delivery-enhancing effects often arise from increased hydration, enhanced bio-adhesion and subtle interactions with corneocyte or lipid structures [39,40]. Notably, the effect of HA on dermal delivery is highly molecular weight dependent. While high-molecular-weight HA primarily supports hydration and controlled release, selected low-molecular-weight HA fractions (particularly between 5 and 20 kDa) have been reported to act as an active permeation enhancer. HA-based micelles loaded with curcumin significantly increased penetration and deposition in mouse skin through hydration-driven softening of the stratum corneum [41].

Levan increased keratinocyte and fibroblast proliferation by approximately 113-118% and upregulated involucrin, filaggrin and extracellular matrix components, indicating potential utility in dermal delivery and skin-regenerative applications [42]. Bacterial cellulose masks provide prolonged contact and controlled release of cosmetic bioactives, with clinical evaluations confirming good tolerability [43]. Chitosan-based pro-retinal nanoparticles achieved penetration depths of approximately 470 μm in porcine ear skin and increased retinal levels in the stratum corneum 3-fold, with preferential follicular targeting [44].

Plant mucilage systems, including *Aloe vera* and date palm mucilage, have demonstrated improved dermal delivery of lornoxicam and nicotine through hydration and semi-crystalline network effects [45,46]. Poly(γ-glutamic acid)/chitosan nanoparticles improved follicular delivery of a hair-growth herbal extract and induced morphological changes in dermal papilla cells [47].

4.5. Triterpenoids and saponins

Triterpenoids and their glycosidic derivatives, saponins, are amphiphilic plant-derived compounds with inherent surface-active properties. Their dual hydrophobic-hydrophilic nature enables interactions with lipid domains and supports reversible modification of the barrier [48–50]. Oleanolic acid-derived amides enhanced progesterone permeation through synthetic lipophilic membranes by approximately 20-60%, outperforming azone in several cases [51].

Ginsenoside-based nanoparticles markedly enhanced transdermal insulin delivery in Sprague-Dawley rat skin, achieving cumulative permeation of 0.159 mg/cm^2 at 24 h and 0.282 mg/cm^2 at 48 h [52]. Quinoa seed coat extracts rich in triterpenoid saponins increased surface pressure and elasticity of cholesterol-containing lipid monolayers without disrupting the matrix, indicating potential for controlled barrier

Table 2
Studies on fatty acids and plant oils as natural skin penetration enhancers.

Enhancer	Active(s)	Mechanistic insight	Key outcome + Model	Reference
Capric acid (C10)	FD-4	Optimal lipophilicity (logP = 4); lipid fluidisation	Highest enhancement among tested fatty acids (porcine epithelium)	[31]
Coconut oil	Flurbiprofen	Lauric acid-rich lipid modulation	High permeation relative to polyunsaturated oils	[32]
Lauric acid (C12)	FD-4	Strong interaction with stratum corneum lipids	Peak enhancement in skin	[31]
Oleic acid	Meloxicam	Disruption of lipid packing	Highest flux and cumulative permeation	[33]
Oleic acid + Tween 80	5-FU	Combined lipid and surfactant effects	Markedly increased permeation (rat skin)	[34].
Olive oil	Flurbiprofen	High monounsaturated fatty acid content	High permeation (*ex vivo* skin)	[32]
Olive oil	DHQ	Oleic acid-mediated lipid disruption	Significant enhancement (human skin)	[35]
Soybean oil	DHQ	High linoleic acid content	Significant enhancement (human skin)	[35]
Sunflower/Olive/Coconut oils	Collagen	Disruption of lipid cohesion; hydration effects	Moderate enhancement; further increased with zinc oxide nanoparticles	[36]

modulation [53]. Several triterpenoids and saponins are illustrated in Fig. 2.

4.6. Polyphenols

Polyphenols, including flavonoids, phenolic acids and stilbenes, are incorporated into cosmeceutical formulations primarily for antioxidant and anti-inflammatory benefits. Selected flavonoids have demonstrated permeation-enhancing effects. Amentoflavone increased caffeine flux across rat dorsal skin by approximately 2.5-fold, while glabridin and butein produced around 3-fold increases through combined keratin rearrangement and lipid fluidisation [54]. Curcuminoids, a subgroup of polyphenols and the main bioactive constituents of turmeric, including bisdemethoxycurcumin, curcumin and demethoxycurcumin, do not exhibit intrinsic penetration-enhancing properties due to their rigidity, low solubility and limited ability to interact with stratum corneum lipids [55].

4.7. Non-plant bioenhancers

Non-plant-derived bioenhancers include microbial and animal-derived macromolecules and natural deep eutectic solvents (NADES). These systems enhance permeation primarily through hydration, solubilisation and microenvironmental modulation. Microbial hyaluronic acid and chitosan improve hydration, bio-adhesion and controlled release, supporting enhanced delivery of hydrophilic and lipophilic actives [15,16].

NADES, formed from natural metabolites such as sugars, organic acids and amino acids, act through increased solubility and mild lipid modulation [56]. A choline chloride-citric acid NADES hydrogel

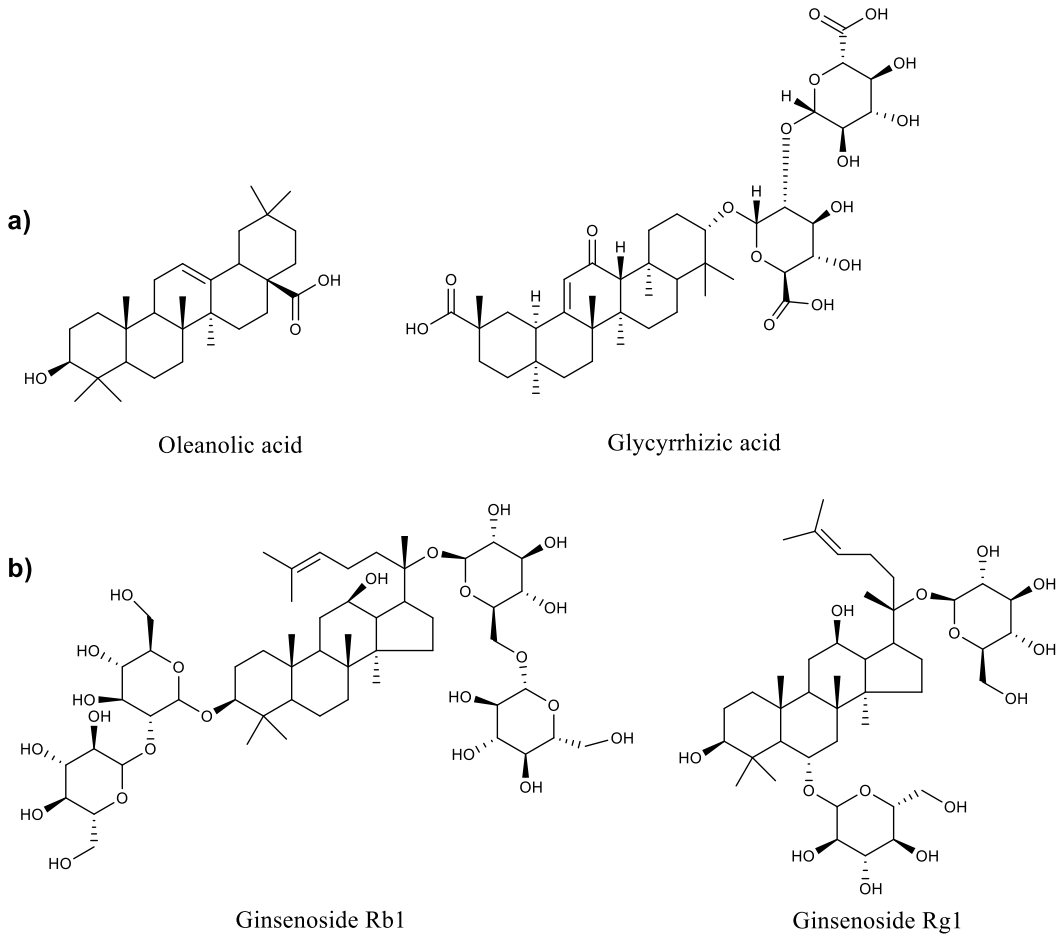

Fig. 2. The structures of a. triterpenoids; b. saponins.

increased lidocaine permeation to 7000 ± 1000 mg/cm^2 after 6 h, compared with 5900 ± 200 mg/cm^2 for a reference hydrogel and 4670 ± 90 mg/cm^2 for a reference ointment, while maintaining barrier integrity and improving hydration [57].

Betaine-citric acid NADES enhanced malvidin permeation in porcine ear skin through solubilisation and lipid modulation [58]. In contrast, chloramphenicol permeation decreased slightly in the presence of NADES due to hydrogen bond interactions with skin proteins [59]. These findings demonstrate the versatility of non-plant-derived bioenhancers in dermal delivery.

5. Mechanistic basis of natural bioenhancers

Natural bioenhancers improve dermal and transdermal delivery through reversible interactions with the stratum corneum (SC). Their effects arise from a limited set of mechanistic pathways that influence lipid organisation, protein structure, hydration state, drug partitioning and paracellular transport, as shown in Fig. 3. These mechanisms often operate simultaneously and are strongly dependent on enhancer chemistry, concentration and formulation context.

5.1. Lipid modulation: fluidisation, disruption and mild extraction

Lipid-directed interactions represent the most widely reported mechanism of natural bioenhancers. Many compounds partition into intercellular lipid domains, where they increase molecular mobility, disturb lamellar packing and expand polar headgroup spacing. These changes reduce barrier density and create transient diffusion pathways [4]. Biophysical studies consistently show CH_2 stretching shifts in FTIR spectra and reduced phase transition temperatures in DSC thermograms, indicating increased lipid disorder [60].

Terpenes such as 1,8-cineole, limonene and menthol disrupt hydrogen bonding within ceramide-rich lamellae and lower lipid transition temperatures, producing strong correlations between lipid disorder and enhancement efficiency [27,61]. Essential oils act similarly, with moderate volatility supporting balanced interaction and efficient permeation enhancement.

Fatty acids also modulate SC lipids due to their structural similarity to endogenous lipids. cis-unsaturated fatty acids such as oleic and linoleic acid induce phase separation and weaken ceramide-rich lamellae, while medium-chain fatty acids increase membrane flexibility and support permeation of lipophilic and antimicrobial compounds [4,62]. Fatty acid esters such as ethyl oleate and glycerol monooleate combine lipid-fluidising and solvating properties with favourable tolerability [63].

Some natural enhancers also induce partial lipid extraction, particularly essential oils, monoterpenes and saponins. These compounds solubilise cholesterol and free fatty acids, increasing SC porosity while maintaining reversibility at formulation-relevant concentrations [4,62]. Biosurfactants and saponins additionally reduce surface tension and promote wetting, complementing their lipid-modulating effects [64].

5.2. Protein interactions and keratin modification

Several natural bioenhancers interact with structural proteins of the SC, particularly keratin. These interactions can weaken corneocyte cohesion and increase diffusional pathways. Hyaluronic acid induces a transition from a-helix to b-sheet conformations in keratin filaments, reducing packing density and softening the corneocyte matrix [40,65,66]. Chitosan enhances permeation through electrostatic interactions with negatively charged SC components, transiently loosening the protein-lipid network [44]. Selected polyphenols and curcuminoids can also influence keratin structure, although their effects are typically secondary to lipid-based mechanisms [67]. Protein-directed pathways are particularly relevant for hydrophilic actives that rely on corneocyte-associated transport.

5.3. Hydration-mediated enhancement and corneocyte softening

Hydration is a central determinant of SC permeability. Increased water content leads to corneocyte swelling, loosening of the corneocyte-lipid interface and reduced diffusional resistance [63]. Hydration-induced expansion disrupts keratin microfibril packing and increases molecular mobility without permanently altering protein structure. Urea disrupts hydrogen bonding networks within corneocytes, increasing plasticity and permeability at appropriate concentrations

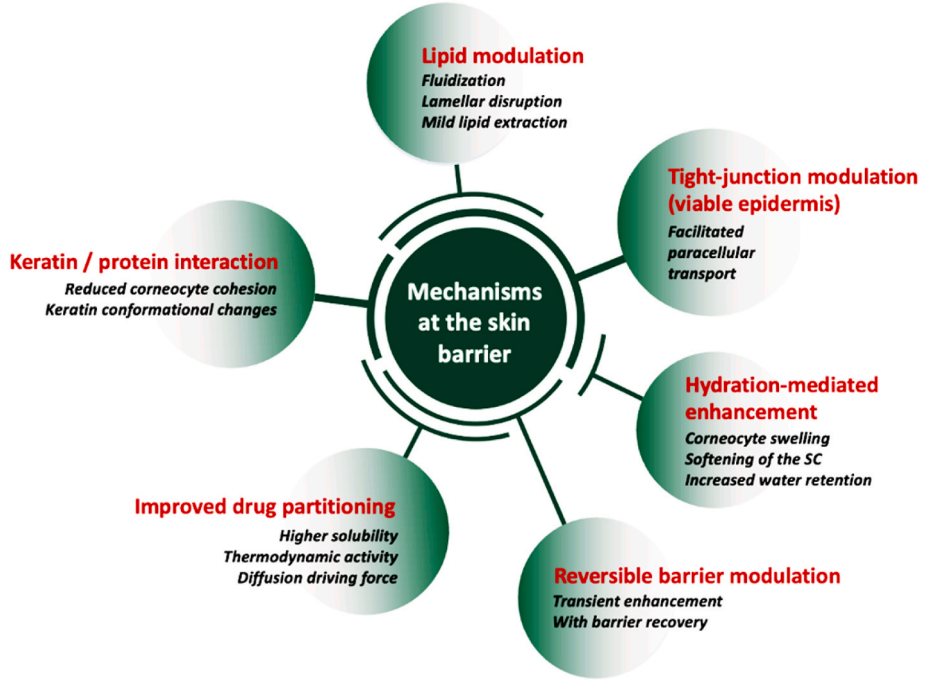

Fig. 3. Key mechanisms of natural bioenhancers at the stratum corneum.

[68]. Glycerol promotes sustained hydration and corneocyte softening, while *Aloe vera* polysaccharides enhance water retention through strong water-binding capacity [61]. Biopolymeric systems such as bacterial cellulose and plant-derived hydrogels maintain a hydrated microenvironment at the skin surface, increasing mobility of hydrophilic and moderately lipophilic compounds and supporting sustained release [43]. Occlusive plant oils such as coconut oil increase hydration and lipid flexibility, while jojoba oil softens the SC through its wax ester composition [69,70]. NADES also contribute to hydration-mediated enhancement through hygroscopicity, corneocyte swelling and widening of intercellular pathways [71].

5.4. Increased drug partitioning and thermodynamic activity

Many natural bioenhancers increase drug solubility and thermodynamic activity within the formulation and SC lipids. By elevating the chemical potential of the active compound, they generate a stronger driving force for diffusion without requiring extensive structural disruption [4,63]. Essential oils, plant oils and fatty acids improve the solubility of lipophilic actives within both the vehicle and SC lipids, enhancing partitioning into the barrier [62]. Fatty acid esters such as ethyl oleate provide a strong solvating capacity with low viscosity [72]. NADES dissolve poorly soluble phytochemicals through extensive hydrogen bonding networks and can simultaneously fluidise SC lipids, support permeation, while stabilising sensitive compounds [71].

5.5. Modulation of tight junctions and intercellular pathways

Although the SC is the primary barrier, tight junctions in the upper viable epidermis regulate paracellular transport. Certain natural compounds transiently influence the expression or arrangement of tight junction proteins such as claudins and occludins, increasing paracellular permeability without permanent disruption [73]. Quercetin derivatives and ginsenosides have been shown to modulate tight junction structure and increase hydrophilic flux through reversible junctional changes [74,75]. Selected fatty acids and plant-derived peptides exhibit similar effects [73].

5.6. Reversible modulation and barrier recovery

Reversibility is essential for safe and repeatable use of natural bioenhancers in cosmeceutical formulations. At formulation-relevant concentrations, natural enhancers typically induce transient changes in lipid organisation, hydration state or corneocyte mechanics, with barrier properties returning toward baseline after removal [76]. Terpenes and fatty acids primarily increase lipid fluidity, whereas polysaccharides and biosurfactants enhance hydration and corneocyte softening. The extent of reversibility depends on enhancer concentration, formulation composition and exposure duration, and should be evaluated alongside irritation and sensitisation data [4,61].

5.7. Interplay of multiple penetration enhancement mechanisms

Natural bioenhancers rarely enhance skin permeation through a single mechanism. Lipid fluidisation, keratin modification, hydration-mediated effects, and increased drug partitioning frequently occur together. Terpenes can increase lipid fluidity while simultaneously enhancing partitioning into stratum corneum lipids and influencing protein organisation [21]. Hydration-mediated corneocyte swelling can further facilitate diffusion by complementing lipid disordering [63]. Relative contributions of individual mechanisms depend on bioenhancer chemistry, permeant characteristics, concentration, and formulation composition. Synergistic interactions between multiple mechanisms can increase permeation efficiency, whereas excessive lipid extraction or unfavourable enhancer-permeant interactions may reduce enhancement outcomes. Permeation-enhancing activity therefore reflects the combined contribution of multiple interacting mechanisms rather than a single dominant pathway [4,63].

6. Formulation strategies

Formulation design plays a central role in determining the performance of natural bioenhancers. Their effects depend not only on intrinsic chemical properties but also on how they are incorporated, stabilised and released within the delivery system. Across conventional and nanotechnology-based platforms, enhancement outcomes reflect the interplay between enhancer structure, vehicle composition, drug solubility and microenvironmental interactions at the skin surface.

6.1. Conventional systems

6.1.1. Solutions

Solution-based vehicles provide a fundamental platform for evaluating natural bioenhancers. Their performance depends on enhancer concentration, solvent polarity, volatility and interactions with stratum corneum lipids. Terpenes such as anethole, eugenol and menthone at 1% enhanced valsartan permeation, with higher concentrations reducing performance due to solubility limitations in ethanol-phosphate buffer systems [25]. Essential oils, including cinnamon, chuanxiong and clove at 3% increased ibuprofen permeation in propylene glycol-isopropyl alcohol vehicles, with moderate volatility supporting optimal lipid interaction [27]. Monoterpenes such as cineole and limonene disrupted long periodicity phase lipids more effectively than sesquiterpenes, consistent with their lower molecular weight and greater diffusivity [77].

Fixed oils rich in unsaturated fatty acids, such as soybean and raspberry seed oil, enhanced dihydroquercetin permeation, whereas saturated oils, such as coconut oil, showed limited activity [35]. Alkaloids and flavonoids also function as high-efficiency enhancers. Perilla ketone at 5% increased the penetration of multiple phytochemicals [23], while amentoflavone enhanced caffeine permeation in both *in vitro* and *in vivo* studies [78]. Homoharringtonine increased macromolecule transport across mouse skin in a concentration-dependent manner [37]. Overall, solution-based systems demonstrate that enhancer structure, volatility and solvent interactions govern permeation outcomes.

6.1.2. Semisolid systems: hydrogels, emulgels and film-forming gels

Semisolid systems provide improved residence time, controlled release and enhanced skin contact compared with simple solutions. Hydrogels incorporating volatile oils such as b-caryophyllene at 5% increased penetration of fluorescein isothiocyanate and dextrans through combined terpene-driven lipid modulation and ethanol-assisted solubilisation [24]. Essential oils at 3% enhanced ibuprofen delivery from Carbopol hydrogels, with formulation performance influenced by oil composition and volatility [79]. Oleanolic acid derivatives at 0.5-1% increased progesterone permeation through structure-dependent interactions with lipid domains [51].

Emulgels combine the solubilisation capacity of emulsions with the structural stability of gels. Oils containing short-chain saturated fatty acids produced higher flurbiprofen flux than oils rich in long-chain fatty acids [32]. Eucalyptus oil at 0.03% enhanced diclofenac permeation in carbopol-based emulgels [80]. *Sapindus mukorossi* extract improved anti-inflammatory performance in aceclofenac emulgels through surfactant-mediated lipid interaction [81]. Film-forming gels (FFGs) create thin, adherent films after application. Chitosan-based FFGs containing oleic acid and Tween 80 enhanced 5-fluorouracil release while maintaining rapid film formation and skin tolerability [34].

6.1.3. Dermal patches

Transdermal patches provide controlled release and sustained enhancer-skin interaction. Matrix-type patches containing nifedipine and clove oil achieved 71.43% release over 16 h, with polymer ratios

influencing mechanical properties and drug diffusion [82]. Oleic acid at 20% increased meloxicam flux in PEG-based solid dispersions [33].

Drug-in-adhesive (DIA) systems incorporating oleic acid improved mirtazapine flux while maintaining adhesive integrity [83]. Cannabinoid patches using Eudragit E100 matrices demonstrated enhancer-dependent differences in flux, with ethoxydiglycol outperforming natural oils [84]. Across conventional systems, enhancer structure, concentration and vehicle composition determine permeation outcomes, with semisolid and patch-based systems offering improved control over release kinetics and skin interaction.

6.2. Nanotechnology-based strategies

6.2.1. Nanoemulsions and nanoemulgels

Nanoemulsions provide high surface area and efficient solubilisation of lipophilic enhancers. D-limonene-based nanoemulsions improved curcumin flux through combined terpene-driven lipid modulation and nanoscale droplet effects [85]. Eucalyptus oil in nanoemulgels enhanced curcuminoid permeation 3-fold, with nanoscale droplets and terpene components acting synergistically [28].

Cineole-containing nanoemulsions increased GABA permeation by 3.37-fold [86]. Glycyrrhizin-based nanoemulgels improved 5-fluorouracil delivery and cytotoxicity through amphiphilic interactions [87]. Hydrophobically modified hyaluronic acid (HA-MA), a chemically modified derivative of the natural polymer hyaluronic acid, provides stabilisation of nanoemulsions and increases the epidermal biodistribution of hydrophobic actives [88].

6.2.2. Other nanocarriers

HA-functionalised liposomes improved methotrexate retention and reduced systemic exposure in psoriasis models [89]. Chitosan nanoparticles enhanced retinal penetration and follicular targeting [44]. PGA/chitosan nanoparticles increased the penetration depth of herbal extracts and supported sustained release [47]. Menthol-containing ethosomes improved lornoxicam permeation and analgesic performance [26].

6.3. Synergistic approaches

6.3.1. Nanocarrier-enhancer synergy

Menthol-containing ethosomal gels increased lornoxicam permeation by 2.42-fold [26]. *Aloe vera*-modified nanocapsule patches increased thymoquinone flux by 42.64% while maintaining sustained release [90].

6.3.2. Dual natural enhancer systems

Aloe vera mucilage combined with lemon oil increased lornoxicam patch permeation to 69.45% over 72 h [45]. Oleic acid and propylene glycol in reservoir patches increased lornoxicam flux and supported near-zero-order release [91]. Nanocarriers improve solubility, stability and skin interaction while enabling synergistic use of natural bioenhancers. Table 3 highlights selected examples of nanotechnology strategies, natural bioenhancers and key outcomes.

6.4. Strategic considerations for the selection of natural bioenhancers in topical formulations

The selection of natural bioenhancers depends on the physicochemical properties of the active ingredient, the structural and molecular characteristics of the bioenhancer, the composition of the formulation vehicle, and the intended site of action within the skin. These factors collectively influence permeation behaviour, residence time, and deposition patterns.

6.4.1. Physicochemical profile of the active permeant and enhancer alignment

The intrinsic physicochemical properties of the active permeant, including lipophilicity [2], polar surface area, hydrogen-bonding capacity [23], and molecular size [37], influence the choice of natural bioenhancer. Lipophilic molecules permeate primarily through intercellular lipid lamellae of the stratum corneum. Bioenhancers that interact with hydrophobic lipid domains and disrupt ceramide hydrogen-bonding networks can increase permeation of lipophilic compounds [25]. Highly lipophilic non-steroidal anti-inflammatory drugs such as ibuprofen and flurbiprofen show improved partitioning and penetration when combined with lipophilic terpenes and fixed plant oils [27,32]. Poorly soluble compounds such as dihydroquercetin demonstrate improved dispersion and epidermal deposition when formulated with lipophilic plant oils [35].

Polar and hydrophilic active ingredients encounter significant resistance within the hydrophobic lipid matrix [94]. Hydration-modifying bioenhancers [54], keratin-modifying agents [54,78], or compounds capable of forming temporary hydrogen-bonded complexes [23] support permeation of these molecules. Highly polar phytochemicals such as puerarin and rutin benefit from bioenhancers with hydrogen-bond acceptor groups, such as perilla ketone, which reduce apparent polarity and improve partitioning into the stratum corneum [23]. Hydrophilic ingredients such as caffeine show increased flux when combined with bioflavonoids including amentoflavone, glabridin, and butein, which bind keratin subunits and induce conformational changes that loosen the protein matrix [54,78]. Small

Table 3
Selected nanotechnology strategies, natural bioenhancers and key outcomes.

Formulation type	Active + Bioenhancer	Key features	Key outcomes	Model (Reference)
Nanoemulsion	Curcumin + D limonene	HLB optimised nanoemulsion, 84 nm	Flux 26.8 mg/cm^2/h; 57% permeation	Rat skin [85]
Nano-emulgel	Curcuminoids + eucalyptus oil	63 nm nanoemulsion incorporated into Carbopol gel	3-fold increase in flux	Human skin [28]
Nanoemulsion	GABA + 1,8 cineole	Soybean oil nanoemulsion, 130 nm	3.37-fold increase in permeation	Porcine skin [86]
Nano-emulgel	5 Fluorouracil + glycyrrhizin	Isopropyl myristate nanoemulsion in gel	IC_{50} reduced to 0.1 mg/mL	Melanoma cells [87]
Nanoemulsion	Hydrophobic actives + hyaluronic acid methacrylate	Hyaluronic acid stabilised nanoemulsion, 282 nm	8-fold increase in epidermal biodistribution	*Ex vivo* skin [88]
HA liposomes	Methotrexate + hyaluronic acid (5 kDa)	CD44-targeted liposomes	2-fold increase in skin retention	Psoriasis models [89]
Novasomes	Rasagiline + eugenol	Multilamellar vesicles	Sustained release and increased therapeutic efficacy	Parkinson's model [92]
Polymeric nanoparticles	Retinal + chitosan	240 nm nanoparticles	3-fold increase in stratum corneum retention	Porcine skin [44]
Hydrogel nanoparticles	4HGF + Poly (g- glutamic acid)/chitosan	382 nm nanoparticles	Penetration depth approximately 2 mm	Hair growth model [47]
Ethosomal gel	Lornoxicam + menthol	349 nm ethosomes	2.42-fold increase in permeation	*In vivo* [26].
Matrix patch	Malvidin + betaine-citric acid NADES	NADES-water matrix	Deposition 431 ng/cm^2	Porcine skin [58]
SLN/NLC	Ibuprofen + bergamot lipids	137-154 nm lipid carriers	3-fold increase in flux	Porcine skin [93]

hydrophilic drugs such as cetirizine respond to cyclic terpenes such as menthol and 1,8-cineole, which disrupt lipid packing, lower phase-transition temperatures, and eliminate diffusion lag time [8]. Large hydrophilic macromolecules such as 4 and 10 kDa dextrans require tissue-level targeting rather than lipid fluidisation. Plant alkaloids such as homoharringtonine transiently modulate tight junction proteins in the stratum granulosum and facilitate paracellular transport [37].

6.4.2. Bioenhancer physicochemical dynamics and structural characteristics

Volatility, molecular conformation, and concentration influence the performance of natural bioenhancers. Highly volatile essential oils and terpenes evaporate rapidly and show limited interaction with stratum corneum lipids. Moderately volatile compounds remain on the skin surface for longer periods and partition more effectively into intercellular lipids [27].

Fatty acid-containing bioenhancers show structure-dependent interactions with the skin barrier. Monounsaturated fatty acids such as oleic acid insert rapidly into lipid bilayers due to their *cis*-conformation, disrupt chain packing, and form fluid microchannels that support high flux and short lag time. Polyunsaturated fatty acids such as linoleic acid experience steric hindrance during initial insertion, which increases lag time, but later induce extensive lipid disruption and support local retention [32,35]. Saturated fatty acids such as lauric acid pack tightly with stratum corneum lipids and increase structural density, which can reduce permeation and promote reservoir formation [32].

Enhancer concentration shows non-linear relationships with flux. Terpene concentrations above optimal thresholds, such as increases from 1% to 3% or 5% in a 40% hydroalcoholic vehicle, reduce permeation owing to solubility limitations and incomplete dissolution of lipophilic enhancers [25].

6.4.3. Structural role and interactions with the vehicle

The relationship between the bioenhancer and the formulation vehicle influences release kinetics and permeation behaviour [27,32]. Natural bioenhancers may function solely as permeation modifiers or may also contribute to formulation structure. Fixed plant oils used as the primary oil phase in emulgels or creams (e.g., 20% w/w) fluidise stratum corneum lipids, reduce transepidermal water loss, and promote hydration and swelling of the stratum corneum [32]. Bioflavonoids such as amentoflavone in semisolid bases act as hydrating and network-stabilising agents while also supporting permeation [54,78].

Vehicle type influences diffusion lag time and release kinetics. Hydrogels with high water activity minimise lag time and support rapid release, whereas hydrophobic and lipidic bases slow release and promote reservoir formation. These vehicle-dependent behaviours influence enhancer selection [27,32].

Mode of application affects enhancer performance. Topical pretreatment with enhancers creates localised liquid pools and weakens lipid bilayers before drug application, supporting high flux and eliminating lag time [94]. Co-formulated systems require balanced solubilisation and thermodynamic partitioning of both enhancer and active ingredient [25,32].

6.4.4. Skin barrier target and biological intent

The intended site of action within the skin influences bioenhancer selection. Penetration depth requirements vary across the stratum corneum, stratum granulosum, viable epidermis, dermis, and systemic circulation. Bioflavonoids can display structure-dependent behaviour. Glabridin has been associated with increased barrier permeability and systemic flux, whereas butein has been associated with greater dermal retention and hydration [78]. Polyunsaturated fatty acids such as linoleic acid extend lag time owing to steric hindrance but later induce lipid disordering that supports epidermal and dermal retention [32,35]. Monounsaturated fatty acids and volatile monoterpenes form fluid microchannels that support deeper penetration and systemic flux [25,32].

7. Applications in cosmeceuticals

Natural bioenhancers are increasingly incorporated into cosmeceutical formulations to improve dermal delivery, stabilise sensitive actives and support targeted biological effects. Their roles span anti-ageing, brightening, moisturising, anti-inflammatory and hair-scalp applications, with benefits arising from enhanced permeation, improved deposition and synergistic interactions with formulation matrices [4,11]. Representative structures of selected cosmeceutical actives are shown in Fig. 4.

7.1. Anti-ageing

Anti-ageing formulations target oxidative stress, collagen degradation, inflammation and impaired epidermal turnover [95]. Natural bioenhancers support these outcomes by improving penetration of antioxidants, retinoids and lipid-soluble actives. Eugenol derivatives enhanced permeation and antioxidant activity in porcine skin, with associated terpenes contributing to deeper delivery and increased radical-scavenging capacity. NADES-based systems improved permeation and intracellular antioxidant activity of grape pomace polyphenols in three-dimensional keratinocyte models, demonstrating their dual role as solubilisers and mild enhancers [58]. Fatty acids such as oleic and linolenic acid increased niacinamide delivery *in vivo,* confirming their utility in human skin [96].

Encapsulation strategies further highlight the value of natural enhancers. Chitosan-gum Arabic Pickering emulsions improved retention and photostability of *trans*-resveratrol [97]. Oleic acid-containing vesicles and nanoemulsions enhanced the delivery of coenzyme Q10 and retinoids, improving collagen density and reducing wrinkle formation in preclinical models [98–100]. Despite these advances, systematic exploration of natural bioenhancers in anti-ageing formulations remains limited, indicating clear opportunities for future development. Fig. 5 illustrates the cosmeceutical applications of natural bioenhancers and their effects.

7.2. Moisturising and barrier repair

Moisturising agents act as humectants, emollients or occlusives, primarily within the stratum corneum [101]. Deep penetration is generally unnecessary, although certain systems benefit from enhanced delivery. Sorbitol-based NADES demonstrated dual functionality as humectants and delivery enhancers, improving hydration, reducing trans-epidermal water loss and showing good tolerability in human volunteers [102].

High-molecular-weight hyaluronic acid exhibits negligible intrinsic permeability and may require specialised carriers for deeper epidermal distribution, whereas low-molecular-weight forms act effectively within superficial layers [103,104]. Barrier-repair agents such as ceramides, niacinamide and peptides primarily act within intercellular lipid pathways. The role of natural enhancers in optimising the delivery of these agents, particularly peptides, remains underexplored [105]. Enhanced dermal permeation is not the desired outcome for all cosmeceutical products. Moisturising and barrier-repair formulations often require retention of active ingredients within the stratum corneum or superficial epidermal layers rather than deep penetration. Excessive permeation may compromise barrier function or reduce intended local effects. Formulation strategies for these applications therefore prioritise superficial retention while preserving skin barrier integrity [101–105].

7.3. Anti-inflammatory

Natural bioenhancers have been widely applied to improve the

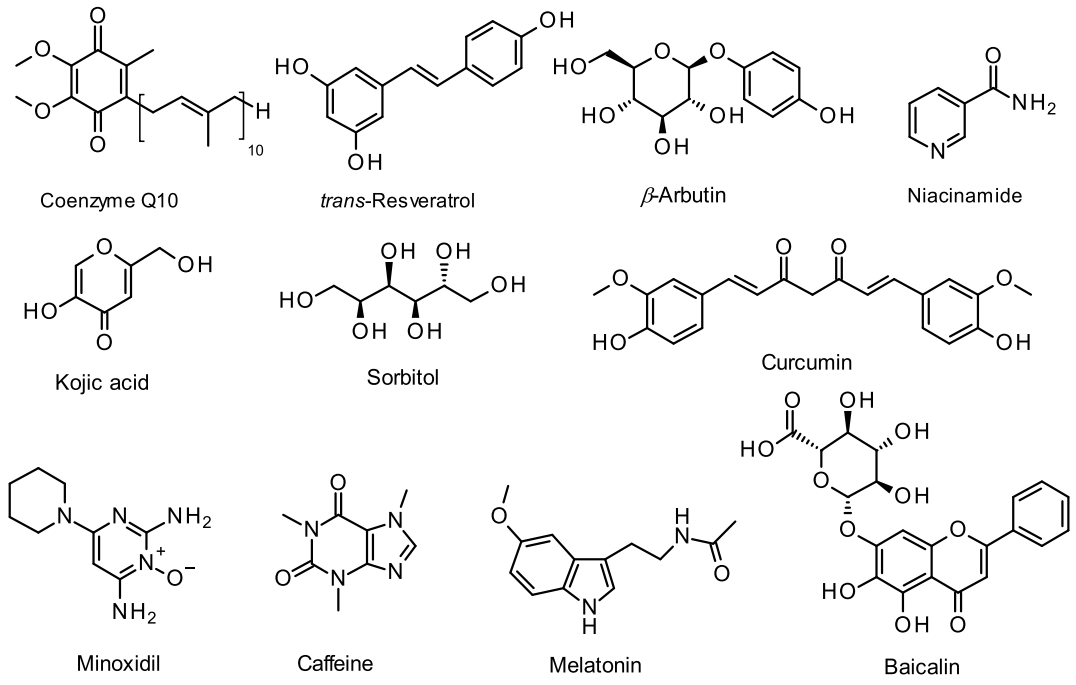

Fig. 4. Chemical structures of selected active compounds from different cosmeceutical functional categories.

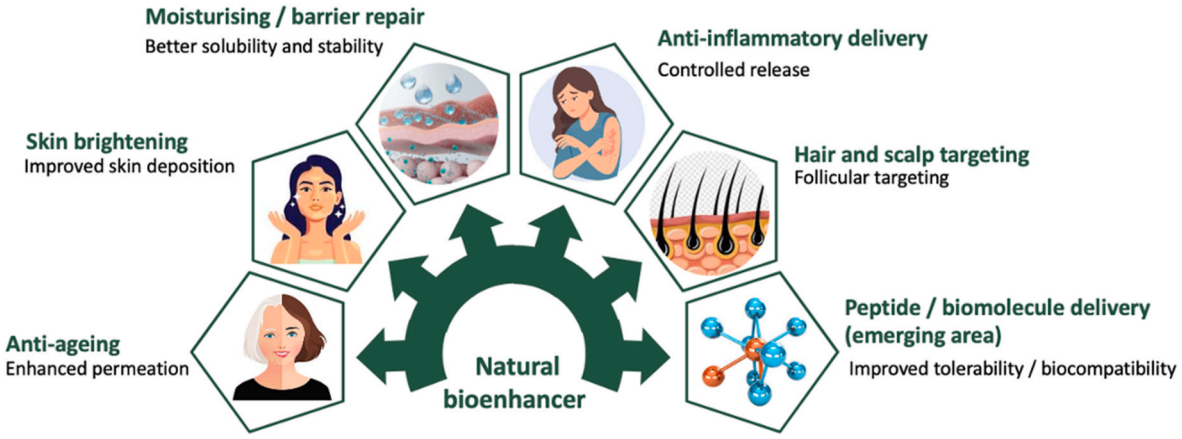

Fig. 5. Cosmeceutical applications of natural bioenhancers and their outcomes.

delivery of anti-inflammatory actives, including curcumin and non-steroidal anti-inflammatory drugs. Curcumin formulated with PVP K25 and myristic acid showed improved solubilisation and penetration [106]. Micelles based on octadecylamine-modified hyaluronic acid increased curcumin deposition and anti-inflammatory activity in *ex vivo* and *in vivo* models [41].

Essential oils such as clove, olive and eucalyptus increased the flux of mefenamic acid, while eucalyptus oil enhanced curcuminoid delivery in nanoemulgels [28,107]. Hybrid systems combining natural polymers and oils improved delivery under compromised skin conditions. Modified Karaya gum-arachis oil gels increased etodolac permeation across thermally injured skin [108].

7.4. Hair and scalp applications

Hair and scalp formulations require targeted delivery to follicles, where natural bioenhancers and biopolymer carriers can improve deposition and retention [109,110]. Chitosan nanoparticles enhanced follicular accumulation of minoxidil and its derivatives, with modified systems providing sustained release and favourable safety [111,112]. Terpene-rich extracts, such as germacrone, increased minoxidil penetration in human skin models [113].

Nanoemulsions containing oleic acid or eucalyptol improved the delivery of hydrophilic actives such as caffeine, with follicles accounting for a significant proportion of total retention [8,114]. Advanced systems such as glycyrrhizin nanomicelles, safflower oil body nanoparticles and chitosan-dextran Pickering emulsions improved follicular delivery of baicalin, hFGF10 and melatonin, respectively [115–117]. Natural materials, such as eucalyptus ash, have also been applied in cosmetic hair treatments, where they modify cuticle and cortex structure and increase anthocyanin dye uptake in *ex vivo* hair models [118].

8. Challenges and future outlook

Natural bioenhancers continue to expand in diversity and functional relevance, yet several scientific, practical and regulatory challenges limit their broader adoption in cosmeceutical formulations. Further progress depends on improved screening, mechanistic clarity,

sustainable sourcing and translational strategies that bridge laboratory findings with real-world performance.

8.1. Emerging natural bioenhancers and screening challenges

Recent studies highlight new botanical and marine-derived enhancers with measurable effects on dermal transport. Perilla ketone increased transdermal flux of multiple model drugs by 2- to 3-fold while showing lower irritation than azone [23]. Essential oil from *Epilobium angustifolium* enhanced ibuprofen and lidocaine permeation by approximately 1.3-fold [114]. Lavender oil improved naproxen absorption and analgesic outcomes *in vivo* [119]. Natural polysaccharides and peptides are also emerging, with bael gum improving mucocutaneous delivery in nanogels and plant-derived skin-penetrating peptides supporting macromolecule uptake [74,120].

Discovery of new enhancers is complicated by botanical variability, batch-to-batch inconsistency and compositional complexity driven by cultivation, climate and extraction conditions [121]. Odour, coloration and molecular size may limit formulation compatibility, while regulatory expectations for irritation, sensitisation and phototoxicity require rigorous testing [122].

Advances in analytical chemistry support systematic screening. Metabolomics-guided profiling enables identification of low-irritation phytochemicals with relevant functional properties [123]. Earlier work demonstrated synergistic enhancement from combinations of small-molecule terpenes, particularly clove- and basil-derived mixtures [124,125]. Screening strategies that integrate chemical profiling, functional evaluation and formulation compatibility are more effective than empirical testing alone.

8.2. Mechanistic insights into skin barrier modulation

Mechanistic understanding remains central for rational deployment of natural bioenhancers. Many plant-derived enhancers modulate stratum corneum lipids by altering lamellar order and increasing acyl chain mobility. Perilla ketone disrupted ordered lipid regions in ATR-FTIR and DSC studies, correlating with increased diffusion [23]. Monoterpenes such as cineole and menthol weakened intercellular hydrogen bonding and induced keratin conformational changes, reducing resistance across intercellular pathways [126].

Enhancer performance depends strongly on the physicochemical properties of both enhancer and permeant. Nonpolar enhancers preferentially increase permeation of lipophilic compounds by fluidising lipid domains, whereas polar enhancers support hydrophilic transport through aqueous pathways [127]. Mechanistic diversity extends beyond terpenes. Polyglyceryl-3 dioleate increased permeation by displacing ceramide-drug interactions, while borneol altered ceramide and fatty acid organisation to support diffusion of larger or less lipophilic molecules [128].

Interpretation remains complicated by the multicomponent nature of essential oils, where synergistic or antagonistic interactions between constituents influence lipid and protein structure [6]. *In vitro* and *ex vivo* models dominate mechanistic research but do not fully capture enzymatic activity, lipid turnover or long-term barrier adaptation in living skin [129]. Multi-scale approaches combining molecular dynamics simulations with high-resolution imaging increasingly support structural mapping of enhancer-lipid interactions and inform formulation design [24,89].

8.3. Sustainable sourcing and supply constraints

Growing demand for natural bioenhancers increases pressure on plant resources and raises sustainability concerns. Many enhancers derive from essential oils, resins or leaves, and unsustainable harvesting threatens biodiversity and ecosystem stability [130]. Ethical sourcing frameworks such as ISSC-MAP and FairWild promote responsible harvesting and support rural communities [131,132].

Valorisation of agricultural by-products provides sustainable alternatives. Pomegranate seed oil enhanced *trans*-resveratrol permeation [133], citrus peel waste supplied D-limonene for nanoemulsion systems [85], and onion peel and olive pruning residues yielded polyphenol-rich extracts with cosmeceutical potential [134].

Availability constraints persist. Medicinal plants show environmental sensitivity that limits large-scale cultivation, with climate, season and geography influencing yield and composition [135]. Green extraction and certified sourcing increase production costs [136]. Biotechnology offers alternatives through fermentation, synthetic biology and plant tissue culture, enabling controlled production of terpenoids and related compounds [137].

8.4. Bridging the translational gap to real-world applications

Laboratory findings often do not translate directly into predictable performance in commercial formulations. Many studies rely on *in vitro* or *ex vivo* diffusion models that use controlled hydration and uniform barrier integrity, conditions that do not reflect real-world variability in human skin [16]. Limited *in vivo* and clinical data further constrain interpretation, and only a small number of natural enhancers have been evaluated in human studies [6].

Regulatory constraints influence translation. Demonstrating enhanced delivery may trigger drug-level regulatory scrutiny, discouraging manufacturers from generating such data [138]. Formulation challenges add complexity. Essential oils may introduce volatility, odour or instability, requiring encapsulation or nanocarrier systems to maintain acceptable sensory and stability profiles [139].

Standardised assessment methods remain limited. Techniques such as tape stripping and confocal imaging provide quantifiable measures but show protocol-dependent variability [140]. Advances in nanocarriers, hybrid delivery systems and minimally invasive enhancement tools continue to support the development of formulations capable of consistent skin penetration when combined with natural enhancers [2,126]. Table 4 summarises selected stability challenges and encapsulation approaches discussed in the literature.

8.5. Future perspectives for skin-brightening applications

Current evidence for natural bioenhancers in skin-brightening formulations remains limited. Brightening agents such as arbutin, kojic acid, and niacinamide are predominantly hydrophilic compounds with restricted permeation across the stratum corneum, which creates persistent delivery challenges [148]. Chitosan-based nanoparticles have improved transdermal delivery of β-arbutin, while formulations containing natural biopolymers and peppermint oil have enhanced diffusion

Table 4
Stability challenges and encapsulation strategies for natural bioactives.

Bioactive	Stability issue	Encapsulation strategy	Reference
Essential oils (e.g., limonene, citrus oils)	Volatility; oxidation during exposure to air, light and heat	Nanoencapsulation	[141, 142]
Hyaluronic acid	Hydrolysis and enzymatic degradation	Nanogels	[65]
Polyphenols (e.g., quercetin, resveratrol)	Oxidation	Liposomes	[143]
Retinol/Retinoids	Degradation by light, heat and oxygen	Microencapsulation	[144]
Vitamin C (L-ascorbic acid)	Oxidation; degradation in aqueous and neutral-alkaline environments	Liposomes	[145, 146]
Vitamin E (tocopherols)	Oxidation and rancidity during storage	Microencapsulation	[147]

of kojic acid [149,150]. Nanocarrier-based systems and formulation technologies account for most reported advances, whereas evidence supporting direct permeation-enhancing effects of natural bioenhancers remains limited [151,152]. Current evidence remains insufficient to define the specific contribution of natural bioenhancers to skin-brightening formulations.

Variability in natural materials, limitations in dermal delivery assessment methods, and limited clinical evidence constrain broader application of natural bioenhancers in cosmeceutical formulations. Computational approaches may support identification of candidate bioenhancers before experimental evaluation. Formulation design should remain aligned with the intended site of action because enhanced skin permeation is not the preferred outcome for all topical applications. Retention within superficial skin layers may provide greater benefit than deeper penetration for selected cosmeceutical indications.

9. Conclusion

This review consolidates current evidence and defines the role of natural bioenhancers within topical delivery systems. Natural bioenhancers represent a diverse class of ingredients used to improve dermal and transdermal delivery in cosmeceutical and topical systems. Findings across solution platforms, semisolid matrices, transdermal patches, hybrid arrangements and nano-enabled carriers show that formulation architecture strongly influences enhancement behaviour. Natural compounds such as alkaloid, fatty acids, flavonoids, polysaccharides, and bioactive terpenes alter stratum corneum properties through effects on lipid packing, fluidity, hydration and intercellular diffusion pathways. Effectiveness depends on alignment between enhancer chemistry, active ingredient characteristics and formulation structure. Anti-ageing systems, barrier-repair preparations, anti-inflammatory formats and scalp or hair applications demonstrate cases where natural enhancers increase penetration efficiency when placed within compatible delivery environments. Analytical, imaging and modelling tools expand mechanistic insight, although uncertainties remain regarding long-term exposure, cumulative effects and *in vivo* relevance. Several constraints influence wider adoption. Variability in natural raw materials, sustainability pressures, formulation instability, limited clinical validation and regulatory ambiguity at the cosmetic-drug boundary remain important considerations. Future progress requires evaluation frameworks supported by reliable sourcing, precise analytical characterisation, targeted formulation design and consistent dermal delivery assessment.

CRediT authorship contribution statement

Emran Habibi: Writing – review & editing, Writing – original draft, Validation, Methodology, Conceptualization. **Leila Panahi:** Writing – original draft, Software. **Gamal Moustafa Mahmoud Abdelfattah:** Writing – original draft. **Mohammad Hossein Hosseinzadeh:** Writing – original draft. **Madiha Kousar:** Writing – original draft. **Satyajit D. Sarker:** Writing – review & editing, Conceptualization. **Lutfun Nahar:** Writing – review & editing, Writing – original draft, Validation, Methodology, Conceptualization.

Funding

No funding was received for this publication.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Authors thank Seyedeh Mahsa Hosseini Nozari for her assistance with all graphical work.

Data availability

No data was used for the research described in the article.

References

[1] S. Das, K. Sen Gupta, A comprehensive review on natural products as chemical penetration enhancer, J. Drug Deliv. Therapeut. 11 (2021) 176–187, https://doi.org/10.22270/jddt.v11i5-S.5077.
[2] Y. Peng, L. Yue, Y. Cong, Enhancing dermal absorption of cosmeceuticals: innovations and techniques for targeted skin delivery, J. Cosmet. Dermatol. 24 (2025) e70514, https://doi.org/10.1111/jocd.70514.
[3] K.R. Feingold, P.M. Elias, Role of lipids in the formation and maintenance of the cutaneous permeability barrier, Biochim. Biophys. Acta Mol. Cell Biol. Lipids 1841 (2014) 280–294, https://doi.org/10.1016/j.bbalip.2013.11.007.
[4] N. Schafer, R. Balwierz, P. Biernat, W. Ochędzan-Siodłak, J. Lipok, Natural ingredients of transdermal drug delivery systems as permeation enhancers of active substances through the stratum corneum, Mol. Pharm. 20 (2023) 3278–3297, https://doi.org/10.1021/acs.molpharmaceut.3c00126.
[5] E. Sparr, S. Björklund, Q.D. Pham, E.H. Mojumdar, B. Stenqvist, M. Gunnarsson, D. Topgaard, The stratum corneum barrier – from molecular scale to macroscopic properties, Curr. Opin. Colloid Interface Sci. 67 (2023) 101725, https://doi.org/10.1016/j.cocis.2023.101725.
[6] B. Alhasso, M.U. Ghori, B.R. Conway, Systematic review on the effectiveness of essential and carrier oils as skin penetration enhancers in pharmaceutical formulations, Sci. Pharm. 90 (2022) 14, https://doi.org/10.3390/scipharm90010014.
[7] V. Sugumar, M. Hayyan, P. Madhavan, W.F. Wong, C.Y. Looi, Current development of chemical penetration enhancers for transdermal insulin delivery, Biomedicines 11 (2023) 664, https://doi.org/10.3390/biomedicines11030664.
[8] E. Abd, Heather A.E. Benson, Michael S. Roberts, Jeffrey E. Grice, Follicular penetration of caffeine from topically applied nanoemulsion formulations containing penetration enhancers: *in vitro* human skin studies, Skin Pharmacol. Physiol. 31 (2018) 252–260, https://doi.org/10.1159/000489857.
[9] Y. Liu, M. Li, D. Xie, G. Chen, N. Zhao, Z. Luo, Research progress of penetration enhancers in transdermal drug delivery systems: multidimensional exploration from mechanisms to clinical application, Int. J. Pharm. X. 10 (2025) 100468, https://doi.org/10.1016/j.ijpx.2025.100468.
[10] M.V. Kodli, P.K. Raikar, P. Kulkarni, U. Kulkarni, K.A. Ahmed, Strategies to enhance the bioavailability of hydrophilic drugs using natural bioenhancers, Biomed. Mater. Devices. 4 (2025) 3067–3088, https://doi.org/10.1007/s44174-025-00442-x.
[11] S.S. Thorat, K.N. Gujar, C.K. Karale, Bioenhancers from mother nature: an overview, Future J. Pharmaceut. Sci. 9 (2023) 20, https://doi.org/10.1186/s43094-023-00470-8.
[12] S. Chettri, C. Sharma, R. Das, P. Roy, An examination of natural bio-enhancers and how they are used in contemporary medicine, Int. J. Pharmacogn Life Sci. 5 (2024).
[13] N. Kumari Radha, S. Prakash, N. Sharma, S. Puri, M. Thakur, J. Singh, M. Kumar, Medicinal and aromatic plants as potential sources of bioactives along with health-promoting activities, Curr. Food Sci. Technol. Rep. 2 (2024) 359–376, https://doi.org/10.1007/s43555-024-00042-8.
[14] A. Abdoh, D. Liu, Y. Mohammed, Enhancement of drug permeation across skin through stratum corneum ablation, RSC Pharmaceutics 1 (2024) 151–160, https://doi.org/10.1039/d4pm00089g.
[15] T.I. Adegbolagun, O.A. Odeniyi, M.A. Odeniyi, Drug delivery applications and future prospects of microbial exopolysaccharides, Polim. Med. 53 (2023) 117–127, https://doi.org/10.17219/pim/176590.
[16] L. Schuh, M. Reginato, I. Florêncio, L. Falcao, L. Boron, E.F. Gris, V. Mello, S. N. Báo, From nature to innovation: the uncharted potential of natural deep eutectic solvents, Molecules 28 (2023) 7653, https://doi.org/10.3390/molecules28227653.
[17] E. Chevé-Kools, Y.H. Choi, C. Roullier, G. Ruprich-Robert, R. Grougnet, F. Chapeland-Leclerc, F. Hollmann, Natural deep eutectic solvents (NaDES): green solvents for pharmaceutical applications and beyond, Green Chem. 27 (2025) 8360–8385, https://doi.org/10.1039/D4GC06386D.
[18] F.D. Mabou, B.N.Y. Yossa, Terpenes: structural classification and biological activities, IOSR J. Pharm. Biol. Sci. 16 (2021) 25–40.
[19] M.E.G. Mosquera, G. Jiménez, V. Tabernero, J. Vinueza-Vaca, C. García-Estrada, K. Kosalková, A. Sola-Landa, B. Monje, C. Acosta, R. Alonso, M.Á. Valera, Terpenes and terpenoids: building blocks to produce biopolymers, Sustain. Chem. 2 (2021) 467–492. https://www.mdpi.com/2673-4079/2/3/26.
[20] J. Mahanty, S.H. Rasheed, S. Kumar, H. Singh, A. Sharma, Potential of essential oils as alternative permeation enhancers for transdermal delivery, World J. Tradit. Chin. Med. 9 (2023) 258–269, https://doi.org/10.4103/2311-8571.351508.

[21] X. Yu, S. Liu, Y. Li, S. Yuan, Molecular insights into the penetration enhancement mechanism of terpenes to skin, J. Phys. Chem. B 128 (2024) 12507–12516, https://doi.org/10.1021/acs.jpcb.4c05910.

[22] J. Yammine, N.-E. Chihib, A. Gharsallaoui, A. Ismail, L. Karam, Advances in essential oils encapsulation: development, characterization and release mechanisms, Polym. Bull. 81 (2024) 3837–3882, https://doi.org/10.1007/s00289-023-04916-0.

[23] N. Zhao, J. Hao, Y. Zhao, B. Zhao, J. Lin, J. Song, M. Wang, Z. Luo, A novel natural penetration enhancer for transdermal drug delivery: *in vitro/in vivo* evaluation and penetration enhancement mechanism, Pharmaceutics 17 (2025) 254, https://doi.org/10.3390/pharmaceutics17020254.

[24] Q. Tang, F. Xu, X. Wei, J. Gu, P. Qiao, X. Zhu, S. Yin, D. Ouyang, J. Dong, J. Yao, Y. Wang, J. Chen, Investigation of β-caryophyllene as terpene penetration enhancer: role of stratum corneum retention, Eur. J. Pharmaceut. Sci. 183 (2023) 106401, https://doi.org/10.1016/j.ejps.2023.106401.

[25] A. Ahad, M. Aqil, A. Ali, The application of anethole, menthone, and eugenol in transdermal penetration of valsartan: enhancement and mechanistic investigation, Pharm. Biol. 54 (2016) 1042–1051, https://doi.org/10.3109/13880209.2015.1100639.

[26] K. Li, S. Gao, B. Tian, Y. Shi, Q. Lv, J. Han, Formulation optimization and *In-vitro* and *In-vivo* evaluation of lornoxicam ethosomal gels with penetration enhancers, Curr. Drug Deliv. 15 (2018) 424–435, https://doi.org/10.2174/1567201815666171207163010.

[27] Q. Jiang, Y. Wu, H. Zhang, P. Liu, J. Yao, P. Yao, J. Chen, J. Duan, Development of essential oils as skin permeation enhancers: penetration enhancement effect and mechanism of action, Pharm. Biol. 55 (2017) 1592–1600, https://doi.org/10.1080/13880209.2017.1312464.

[28] S. Arora, D. Kaushik, M.A. Rahman, R. Dutt, A. Tiwari, S. Garg, R.K. Singla, V. Mittal, Enhanced transdermal delivery of curcuminoids from statistically designed nano-emulgel formulated using eucalyptus oil, Ther. Deliv. 16 (2025) 661–672, https://doi.org/10.1080/20415990.2025.2510888.

[29] A. Kumar, A. Sharma, K.C. Upadhyaya, Vegetable oil: nutritional and industrial perspective, Curr. Genom. 17 (2016) 230–240, https://doi.org/10.2174/1389202917666160202220107.

[30] M.A. Rahim, H. Ayub, A. Sehrish, S. Ambreen, F.A. Khan, N. Itrat, A. Nazir, A. Shoukat, A. Shoukat, A. Ejaz, F. Özogul, E. Bartkiene, J.M. Rocha, Essential components from plant source oils: a review on extraction, detection, identification, and quantification, Molecules 28 (2023) 6881, https://doi.org/10.3390/molecules28196881.

[31] C. Padula, S. Pescina, S. Nicoli, P. Santi, New insights on the mechanism of fatty acids as buccal permeation enhancers, Pharmaceutics 10 (2018) 201. https://www.mdpi.com/1999-4923/10/4/201.

[32] J.M. Viljoen, A. Cowley, J. du Preez, M. Gerber, J. du Plessis, Penetration enhancing effects of selected natural oils utilized in topical dosage forms, Drug Dev. Ind. Pharm. 41 (2015) 2045–2054, https://doi.org/10.3109/03639045.2015.1047847.

[33] N. Nining, A. Amalia, N. Maharani, S.R. Adawiyah, Effect of isopropyl myristate and oleic acid as the penetration enhancer on transdermal patch: characteristics and *in-vitro* diffusion. , Egypt, J. Chem. 66 (2023) 251–259, https://doi.org/10.21608/EJCHEM.2023.180955.7396.

[34] S.N. Hussain Shah, Zulcaif, A. Syed, A. Aslam, N. Zafar, A. Arif, Development of film forming gel for the delivery of 5-flurouracil: *In-vitro/ex-vivo* evaluation, Polym. Bull. 81 (2024) 7121–7137, https://doi.org/10.1007/s00289-023-05004-z.

[35] V. Čižinauskas, N. Elie, A. Brunelle, V. Briedis, Skin penetration enhancement by natural oils for dihydroquercetin delivery, Molecules 22 (2017) 1536, https://doi.org/10.3390/molecules22091536.

[36] N. Shokri, H.A. Javari, Using a synergistic combination of two enhancers for dermal delivery of collagen in pharmaceutical and cosmetic products, J. Pharm. Res. 14 (2015), https://doi.org/10.18579/jpcrkc/2015/14/1/78366.

[37] A. Watari, K. Fujiwara, K. Yagi, K. Tachibana, T. Katsurada, A. Myoui, M. Kondoh, Homoharringtonine is a transdermal granular permeation enhancer, Biochem. Biophys. Res. Commun. 616 (2022) 140–144, https://doi.org/10.1016/j.bbrc.2022.04.067.

[38] C. Jantarat, P. Sirathanarun, S. Boonmee, W. Meechoosin, H. Wangpittaya, Effect of piperine on skin permeation of curcumin from a bacterially derived cellulose-composite double-layer membrane for transdermal curcumin delivery, Sci. Pharm. 86 (2018) 39, https://doi.org/10.3390/scipharm86030039.

[39] I. Benalaya, G. Alves, J. Lopes, L.R. Silva, A review of natural polysaccharides: sources, characteristics, properties, food, and pharmaceutical applications, Int. J. Mol. Sci. 25 (2024) 1322, https://doi.org/10.3390/ijms25021322.

[40] A.M. Juncan, D.G. Moisă, A. Santini, C. Morgovan, L.-L. Rus, A.L. Vonica-Țincu, F. Loghin, Advantages of hyaluronic acid and its combination with other bioactive ingredients in cosmeceuticals, Molecules 26 (2021) 4429, https://doi.org/10.3390/molecules26154429.

[41] J. Niu, M. Yuan, Z. Zhang, L. Wang, Y. Fan, X. Liu, X. Liu, H. Ya, Y. Zhang, Y. Xu, Hyaluronic acid micelles for promoting the skin permeation and deposition of curcumin, Int. J. Nanomed. 17 (2022) 4009–4022, https://doi.org/10.2147/IJN.S372711.

[42] M. Erginer, B. Gökalsin, S. Tornaci, C. Sesal, E. Toksoy Öner, Exploring the potential of *Halomonas levan* and its derivatives as active ingredients in cosmeceutical and skin regenerating formulations, Int. J. Biol. Macromol. 240 (2023) 124418, https://doi.org/10.1016/j.ijbiomac.2023.124418.

[43] P. Perugini, M. Bleve, R. Redondi, F. Cortinovis, A. Colpani, *In vivo* evaluation of the effectiveness of biocellulose facial masks as active delivery systems to skin, J. Cosmet. Dermatol. 19 (2020) 725–735. https://onlinelibrary.wiley.com/doi/abs/10.1111/jocd.13051.

[44] B. Limcharoen, P. Toprangkobsin, W. Banlunara, S. Wanichwecharungruang, H. Richter, J. Lademann, A. Patzelt, Increasing the percutaneous absorption and follicular penetration of retinal by topical application of proretinal nanoparticles, Eur. J. Pharm. Biopharm. 139 (2019) 93–100, https://doi.org/10.1016/j.ejpb.2019.03.014.

[45] G. Subramaniyan, S. Rubina, B.V. Ramana, *Aloe vera* leaf mucilage and lemon oil as potential penetration enhancing agents to increase lornoxicam transdermal administration using nano vesicular gel, Pak. J. Pharm. Sci. 37 (2024).

[46] T. Plyduang, P. Maneewattanapinyo, C. Monton, W. Pichayakorn, K. Panrat, J. Suksaeree, *Phoenix dactylifera* mucilage and polyvinyl alcohol-based plaster gel for nicotine delivery, Adv. Pharmacol. Pharm. Sci. 2025 (2025) 1305224, https://doi.org/10.1155/adpp/1305224.

[47] H.S. Kim, H.-K. Kwon, D.H. Lee, T.N. Le, H.-J. Park, M.I. Kim, Poly(γ-glutamic acid)/chitosan hydrogel nanoparticles for effective preservation and delivery of fermented herbal extract for enlarging hair bulb and enhancing hair growth, Int. J. Nanomed. 14 (2019) 8409–8419, https://doi.org/10.2147/IJN.S227514.

[48] Y.-Q. Yu, X. Yang, X.-F. Wu, Y.-B. Fan, Enhancing permeation of drug molecules across the skin via delivery in nanocarriers: novel strategies for effective transdermal applications, Front. Bioeng. Biotechnol. 9 (2021) 646554, https://doi.org/10.3389/fbioe.2021.646554.

[49] J. Liu, C. Wang, Q. Wang, W. Zhang, Z. Li, S. He, J. Wu, P. Cao, Chapter 27 - triterpenoids and saponins in drug discovery, in: B. Yu, N. Li, C. Fu (Eds.), Privileged Scaffolds in Drug Discovery, Academic Press, 2023, pp. 613–671.

[50] P. Kundu, S.A. Thorat, A. Kiran, K. Goel, G. Zinta, Plant-derived triterpenoid saponins: multifaceted roles and bioengineering prospects, Plant Cell Rep. 44 (2025) 172, https://doi.org/10.1007/s00299-025-03483-0.

[51] B. Bednarczyk-Cwynar, D. Partyka, L. Zaprutko, Simple amides of oleanolic acid as effective penetration enhancers, PLoS One 10 (2015) e0122857, https://doi.org/10.1371/journal.pone.0122857.

[52] J.-J. Zou, J.-Q. Le, B.-C. Zhang, M.-Y. Yang, J.-L. Jiang, J.-F. Lin, P.-Y. Wu, C. Li, L. Chen, J.-W. Shao, Accelerating transdermal delivery of insulin by ginsenoside nanoparticles with unique permeability, Int. J. Pharm. 605 (2021) 120784, https://doi.org/10.1016/j.ijpharm.2021.120784.

[53] I. Jurek, I. Góral, K. Gęsiński, K. Wojciechowski, Effect of saponins from quinoa on a skin-mimetic lipid monolayer containing cholesterol, Steroids 147 (2019) 52–57, https://doi.org/10.1016/j.steroids.2018.11.008.

[54] Y. Ren, F. Song, H. Wang, L. Peng, Amentoflavone: a safe and novel penetration enhancer for transdermal applications, Chin. Herb. Med. 8 (2025) 713–724, https://doi.org/10.1016/j.chmed.2025.10.002.

[55] M. Ahmed Naseem, Z. Hussain, H.E. Thu, S. Khan, M. Sohail, R.M. Sarfraz, A. Mahmood, Nanotechnology-mediated developments for improving physicochemical properties and wound healing efficacy of curcumin: a review, Int. J. Polym. Mater. Polym. Biomater. 74 (2025) 445–464, https://doi.org/10.1080/00914037.2024.2342908.

[56] P. Satija, A. Chambyal, G. Singh, Ritvik, G. Singh, S. Devi, J. Singh, Natural deep eutectic solvents (NADES): Manufacture, characteristics, and their significance as designer solvents, ChemistrySelect 9 (2024) e202401212, https://doi.org/10.1002/slct.202401212.

[57] F. Hasanpour, M. Budai-Szűcs, A. Kovács, R. Ambrus, O. Jójárt-Laczkovich, B. Szalai, B. Pavlić, P. Simon, L. Törteli, S. Berkó, The role of natural deep eutectic solvents in a hydrogel formulation containing lidocaine, Pharmaceutics 17 (2025) 324. https://www.mdpi.com/1999-4923/17/3/324.

[58] A. Punzo, E. Porru, A. Silla, P. Simoni, P. Galletti, A. Roda, E. Tagliavini, C. Samorì, C. Caliceti, Grape pomace for topical application: Green NaDES sustainable extraction, skin permeation studies, antioxidant and anti-inflammatory activities characterization in 3D human keratinocytes, Biomolecules 11 (2021) 1181, https://doi.org/10.3390/biom11081181.

[59] H.L. Nystedt, K.G. Grønlien, H.H. Tønnesen, Interactions of natural deep eutectic solvents (NADES) with artificial and natural membranes, J. Mol. Liq. 328 (2021) 115452, https://doi.org/10.1016/j.molliq.2021.115452.

[60] C. Altunayar-Unsalan, DSC and FTIR study on the interaction between pentacyclic triterpenoid lupeol and DPPC membrane, J. Bioenerg. Biomembr. 56 (2024) 553–561, https://doi.org/10.1007/s10863-024-10030-1.

[61] L. Karami, H.R. Moghimi, A mechanistic study on the fluidization and enhancement effects of cineole toward stratum corneum intercellular lamellar lipids: a Liquid Crystalline Model Approach, Iran. J. Pharm. Res. 78 (2023) 104123.

[62] A. Herman, A.P. Herman, Essential oils and their constituents as skin penetration enhancer for transdermal drug delivery: a review, J. Pharm. Pharmacol. 67 (2015) 473–485, https://doi.org/10.1111/jphp.12334.

[63] A.C. Williams, B.W. Barry, Penetration enhancers, Adv. Drug Deliv. Rev. 64 (2012) 128–137, https://doi.org/10.1016/j.addr.2012.09.032.

[64] D. Kregiel, J. Berlowska, I. Witońska, H. Antolak, C. Proestos, M. Babic, L. Babic, B. Zhang, Saponin-Based, biological-active Surfactants from Plants, InTech, 2017.

[65] W. Feng, J. Ye, S. Li, S. Shao, J. Xiang, Y. Piao, Q. Wei, J. Tang, Z. Zhou, Y. Shen, Non-invasive skin topical delivery of hyaluronan, bioRxiv (2025), 2025.2004.2003.646962, https://www.biorxiv.org/content/biorxiv/early/2025/04/08/2025.04.03.646962.full.pdf.

[66] J. Zhu, X. Tang, Y. Jia, C.-T. Ho, Q. Huang, Applications and delivery mechanisms of hyaluronic acid used for topical/transdermal delivery – a review, Int. J. Pharm. 578 (2020) 119127. https://www.sciencedirect.com/science/article/pii/S0378517320301113.

[67] Z. Mo, J. Yuan, X. Guan, J. Peng, Advancements in dermatological applications of curcumin: clinical efficacy and mechanistic insights in the management of skin

disorders, Clin. Cosmet. Invest. Dermatol. 17 (2024) 1083–1092. https://libkey.io/10.2147/CCID.S467442.
[68] J. Mueller, J.S. Oliveira, R. Barker, M. Trapp, A. Schroeter, G. Brezesinski, R. Neubert, The effect of urea and taurine as hydrophilic penetration enhancers on stratum corneum lipid models, Biochim. Biophys. Acta Biomembr. 1858 (2016) 2006–2018, https://doi.org/10.1016/j.bbamem.2016.05.010.
[69] E. Ranzato, S. Martinotti, B. Burlando, Wound healing properties of jojoba liquid wax: an *in vitro* study, J. Ethnopharmacol. 134 (2011) 443–449, https://doi.org/10.1016/j.jep.2010.12.042.
[70] A. Aziz, M. Sarmidi, R. Aziz, N. Mohamed Noor, The effect of virgin coconut oil loaded solid lipid particles (VCO-SLPS) on skin hydration and skin elasticity, J. Teknol. 62 (2013) 39–43, https://doi.org/10.11113/jt.v62.1248.
[71] A. Paiva, R. Craveiro, I. Aroso, M. Martins, R.L. Reis, A.R.C. Duarte, Natural deep eutectic solvents – solvents for the 21st Century, ACS Sustain. Chem. Eng. 2 (2014) 1063–1071, https://doi.org/10.1021/sc500096j.
[72] M.E. Lane, Skin penetration enhancers, Int. J. Pharm. 447 (2013) 12–21, https://doi.org/10.1016/j.ijpharm.2013.02.040.
[73] J.P. Atkinson, H.I. Maibach, N. Dragicevic, Targets in dermal and transdermal delivery and classification of penetration enhancement methods, in: N. Dragicevic, H.I. Maibach (Eds.), Percutaneous Penetration Enhancers Chemical Methods in Penetration Enhancement: Drug Manipulation Strategies and Vehicle Effects, Springer Berlin Heidelberg, Berlin, Heidelberg, 2015, pp. 93–108.
[74] H. Zhu, M. Liu, Z. Wang, T. Mao, Y. Wu, Z. Wei, X. Li, Y. Lu, Self-assembly of plant-derived bioactive nanostructures in traditional Chinese medicine, iScience 29 (2026) 114667, https://doi.org/10.1016/j.isci.2026.114667.
[75] Q. Wu, N. Cheng, D. Fang, H. Wang, F.-U. Rahman, H. Hao, Y. Zhang, Recent advances on application of polysaccharides in cosmetics, J. Dermatol. Sci. Cosmet. Technol. 1 (2024) 100004, https://doi.org/10.1016/j.jdsct.2024.100004.
[76] L.B. Lopes, M.T. J Garcia, M.V. Lb Bentley, Chemical penetration enhancers, Ther. Deliv. 6 (2015) 1053–1061, https://doi.org/10.4155/tde.15.61.
[77] T. Uchino, I. Hatta, M. Nakajo, Y. Iwano, M. Okada, R. Yumoto, Y. Miyazaki, Y. Kagawa, Evaluation of molecular interaction between intercellular lipid organization in human stratum corneum and terpenes using time-resolved synchrotron X-ray diffraction, Chem. Phys. Lipids 265 (2024) 105435, https://doi.org/10.1016/j.chemphyslip.2024.105435.
[78] Y. Ren, Z. Li, Y. Xu, Y. Ding, Q. Song, Y.-j. Hu, L. Peng, Harnessing flavonoids for transdermal enhancement: sustainable strategies to improve the permeability of hydrophilic drugs through the transformation of keratins and lipids, ACS Sustain. Chem. Eng. 13 (2025) 6433–6450, https://doi.org/10.1021/acssuschemeng.5c02332.
[79] J. Chen, Q.-D. Jiang, Y.-M. Wu, P. Liu, J.-H. Yao, Q. Lu, H. Zhang, J.-A. Duan, Potential of essential oils as penetration enhancers for transdermal administration of ibuprofen to treat dysmenorrhoea, Molecules 20 (2015) 18219–18236, https://doi.org/10.3390/molecules201018219.
[80] D. Chandra Sekhar Naik, M. Shaik Noor, S. Mudigedu, S. Vamsi, P. Hemalatha, Formulation and evaluation of diclofenac emulgel using natural permeation enhancers, J. Appl. Pharm. Res. 13 (2025).
[81] S. Kala, D. Juyal, Investigating the synergistic potential of combination of natural penetration enhancers and a synthetic drug in animal model for improved transdermal delivery, Indian J. Anim. Res. 59 (2025) 252–259.
[82] S. Das, S. Das, S. Bahadur, M. Mukherjee, G. Nandi, S. Manna, Fabrication, evaluation, and enhanced penetration of vinyl and cellulose-engineered transdermal patch of nifedipine using essential oil as penetration enhancer, J. Biomater. Sci. Polym. 35 (2024) 1400–1420, https://doi.org/10.1080/09205063.2024.2330682.
[83] R. Satpute, P.S. Salve, M. Qutub, U.M.H. Hussain, J. Gadge, Enhanced systemic delivery of mirtazapine through transdermal drug-in-adhesive matrix: a sustained-release approach, Next Nanotechnol 8 (2025) 100151, https://doi.org/10.1016/j.nxnano.2025.100151.
[84] E. Wongwad, K. Ingkaninan, N. Waranuch, C. Park, V. Somayaji, N. Na-Ek, R. Löbenberg, Improved transdermal delivery of novel cannabinoid-loaded patches using Eudragit matrix, J. Drug Deliv. Sci. Technol. 96 (2024) 105697, https://doi.org/10.1016/j.jddst.2024.105697.
[85] C.-S. Chiu, P.-H. Huang, Y.-J. Chan, P.-H. Li, W.-C. Lu, d-limonene nanoemulsion as skin permeation enhancer for curcumin prepared by ultrasonic emulsification, J. Agric. Food Res. 15 (2024) 100932, https://doi.org/10.1016/j.jafr.2023.100932.
[86] D. Charnvanich, K. Singpanna, V. Panapisal, Formulation and optimization of nanoemulsions loaded with gamma-aminobutyric acid (GABA) for dermatological application: assessing skin permeation and penetration enhancement, Cosmetics 11 (2024) 19, https://doi.org/10.3390/cosmetics11010019.
[87] N. Gupta, G.D. Gupta, K. Razdan, N.A. Albekairi, A. Alshammari, D. Singh, Development of nanoemulgel of 5-Fluorouracil for skin melanoma using glycyrrhizin as a penetration enhancer, Saudi Pharm. J. 32 (2024) 101999, https://doi.org/10.1016/j.jsps.2024.101999.
[88] P. Zamora, J. Movellan, H.-J. Grande, I. Loinaz, D. Dupin, Hydrophobically-modified hyaluronic acid as stabilizer for oil-in-water emulsions to improve epidermis biodistribution of actives, Int. J. Biol. Macromol. (2025) 148329, https://doi.org/10.1016/j.ijbiomac.2025.148329.
[89] P. Zhang, J. Tang, L. Cheng, Y. Xue, J. Yang, Z. Sun, J. Liu, Hyaluronic acid modified liposomes with enhanced transdermal delivery of methotrexate for psoriasis treatment, Colloids Surf. B Biointerfaces 247 (2025) 114457, https://doi.org/10.1016/j.colsurfb.2024.114457.
[90] E.Z. Dahmash, L.M. Attiany, D. Ali, S.M. Assaf, J. Alkrad, H. Alyami, Development and characterization of transdermal patches using novel thymoquinone-l-arginine-based polyamide nanocapsules for potential use in the management of psoriasis, AAPS PharmSciTech 25 (2024) 69, https://doi.org/10.1208/s12249-024-02781-2.
[91] D. Hashmat, M.H. Shoaib, F.R. Ali, F. Siddiqui, Lornoxicam controlled release transdermal gel patch: design, characterization and optimization using co-solvents as penetration enhancers, PLoS One 15 (2020) e0228908, https://doi.org/10.1371/journal.pone.0228908.
[92] H.N. ElShagea, R.R. Makar, A.H. Salama, N.A. Elkasabgy, A. Salama, E. B. Basalious, Terpene-augmented novasomal gels for the sustainment of rasagiline mesylate delivery; A new approach for treating, J. Drug Deliv. Sci. Technol. 92 (2024) 105369, https://doi.org/10.1016/j.jddst.2024.105369.
[93] P. Volonté, C. Ricci, S. Arnoldi, G. Roda, E. Del Favero, F. Puoci, P. Minghetti, S. Franzè, F. Cilurzo, Bergamot waste derived lipid nanosystems as novel excipients for (trans)dermal drug delivery, J. Drug Deliv. Sci. Technol. 110 (2025) 107085, https://doi.org/10.1016/j.jddst.2025.107085.
[94] S. Mohammad Soleymani, R. Mombeini, A. Salimi, Effect of various herbal and chemical enhancers on skin permeability to cetirizine: a Study of changes in rat skin cells, J. Kerman Univ. Med. Sci. 31 (2024) 126–134, https://doi.org/10.34172/jkmu.2024.21.
[95] O. Crespi, F. Rosset, V. Pala, C. Sarda, M. Accorinti, P. Quaglino, S. Ribero, Cosmeceuticals for anti-aging: mechanisms, clinical evidence, and regulatory insights – A comprehensive review, Cosmetics 12 (2025) 209, https://doi.org/10.3390/cosmetics12050209.
[96] Y. Zhang, C.-P. Kung, F. Iliopoulos, B.C. Sil, J. Hadgraft, M.E. Lane, Dermal delivery of niacinamide – *In vivo* studies, Pharmaceutics 13 (2021) 726, https://doi.org/10.3390/pharmaceutics13050726.
[97] A. Sharkawy, F.M. Casimiro, M.F. Barreiro, A.E. Rodrigues, Enhancing trans-resveratrol topical delivery and photostability through entrapment in chitosan/gum Arabic Pickering emulsions, Int. J.of Biol. Macromol. 147 (2020) 150–159, https://doi.org/10.1016/j.ijbiomac.2020.01.057.
[98] K.A.S. Tou, K. Rehman, W.M.W. Ishak, M.H. Zulfakar, Influence of omega fatty acids on skin permeation of a coenzyme Q10 nanoemulsion cream formulation: characterization, *in silico* and *ex vivo* determination, Drug Dev. Ind. Pharm. 45 (2019) 1451–1458, https://doi.org/10.1080/03639045.2019.1628042.
[99] Q. Ayunin, A. Miatmoko, W. Soeratri, T. Erawati, J. Susanto, D. Legowo, Improving the anti-ageing activity of coenzyme Q10 through protransfersome-loaded emulgel, Sci. Rep. 12 (2022) 906, https://doi.org/10.1038/s41598-021-04708-4.
[100] N. Wongsirojkul, M. Takagi, Y. Wongngam, A. Sattayakhom, I. Prachongsai, W. Chunglok, P. Opaprakasit, D. polpanich, Enhancing transdermal delivery of retinyl acetate via transethosomes with emphasis on the impact of edge activators on penetration, safety, and efficacy, Sci. Rep. 15 (2025) 35172, https://doi.org/10.1038/s41598-025-19050-2.
[101] K. Pradeep, K. Amarjeet, C. Priya, A review article on formulation of moisturizing cream, Int. J. Pharm. Sci. 3 (2025) 666–671, https://doi.org/10.5281/zenodo.15337695.
[102] M. Martinović, I. Nešić, V.M. Tadić, A. Žugić, M. Tasić-Kostov, S. Blagojević, T. Tosti, Skin performance of innovative NaDES-based gels: *in vivo* evaluation of anti-irritation potential and short-term efficacy, Gels 11 (2025) 869, https://doi.org/10.3390/gels11110869.
[103] S. Grégoire, P.D. Man, A. Maudet, M. Le Tertre, N. Hicham, F. Changey, B.-S. Gaëlle, C. Tran, V. Laurence, Hyaluronic acid skin penetration evaluated by tape stripping using ELISA kit assay, J. Pharm. Biomed. Anal. 224 (2023) 115205, https://doi.org/10.1016/j.jpba.2022.115205.
[104] M. Essendoubi, C. Gobinet, R. Reynaud, J.F. Angiboust, M. Manfait, O. Piot, Human skin penetration of hyaluronic acid of different molecular weights as probed by Raman spectroscopy, Skin Res. Technol. 22 (2016) 55–62. https://onlinelibrary.wiley.com/doi/abs/10.1111/srt.12228.
[105] J. Zdrada-Nowak, A. Surgiel-Gemza, M. Szatkowska, Acetyl hexapeptide-8 in cosmeceuticals – A review of skin permeability and efficacy, Int. J. Mol. Sci. 26 (2025) 5722, https://doi.org/10.3390/ijms26125722.
[106] A. Satheesh, S. Paramparambath, E. Kandasamy, S. Selvam, Penetration enhancer accelerated solubilization of curcumin by poly (vinylpyrrolidone), J. Indian Chem. Soc. 96 (2019) 14–18, https://doi.org/10.5281/zenodo.5652587.
[107] A. Salimi, S. Sheykholeslami, The effect of herbal penetration enhancers on the skin permeability of mefenamic acid through rat skin, Turk. J Pharm. Sci. 20 (2023) 108–114, https://doi.org/10.4274/tjps.galenos.2022.60669.
[108] N. Mahdavi, B. Sudhakar, Impact of penetration enhancer and natural oil on transdermal delivery of modified Karaya gum gel, Res. J. Pharm. Technol. 17 (2024) 1685–1691.
[109] M. Hordinsky, A. Andriessen, N. Mesinkovska, H. Woolery-Lloyd, Individual article: insights on the impact of scalp barrier condition on hair health, J. Drugs Dermatol. 24 (2025).
[110] A. Kutaj, T. Savitskaya, Hair and scalp health in modern lifestyle: challenges and natural solutions, Qual. Sport. 45 (2025), https://doi.org/10.12775/QS.2025.45.66557, 66557–66557.
[111] B.N. Matos, T.A. Reis, T. Gratieri, G.M. Gelfuso, Chitosan nanoparticles for targeting and sustaining minoxidil sulphate delivery to hair follicles, Int. J. Biol. Macromol. 75 (2015) 225–229. https://www.sciencedirect.com/science/article/pii/S0141813015000471.
[112] A.H. Naeini, K. Mahdavipour, A. Rastegari, M. Aghsami, H. Montazeri, H. Faghihi, Z. Mohammadi, Chitosan and its amphiphilic derivative nanoparticles loaded with Minoxidil for induction of hair growth: *in vitro* and *in vivo* evaluation, Int. J. Biol. Macromol. 259 (2024) 129122, https://doi.org/10.1016/j.ijbiomac.2023.129122.

[113] J. Srivilai, N. Waranuch, A. Tangsumranjit, N. Khorana, K. Ingkaninan, Germacrone and sesquiterpene-enriched extracts from *Curcuma aeruginosa* Roxb. increase skin penetration of minoxidil, a hair growth promoter, Drug Deliv. Transl. Res. 8 (2018) 140–149, https://doi.org/10.1007/s13346-017-0447-7.
[114] D. Chen, F. Yu, C. Wang, H. Chen, J. Tan, Q. Shi, X. He, X. Liu, F. Wang, H. Zhao, Anti-hair loss effect of a shampoo containing caffeine and adenosine, J. Cosmet. Dermatol. 23 (2024) 2927–2933, https://doi.org/10.1111/jocd.16347.
[115] Q. Zeng, Z. Wang, Z. Zhu, Y. Hu, Y. Wang, Y. Xue, Y. Wu, Y. Guo, P. Liang, H. Chen, Z. Zheng, C. Shen, C. Jiang, H. Zhu, Q. Shen, Y. Yi, H. Li, Z. Yang, L. Liu, Q. Liu, Glycyrrhizin micellar nanocarriers for topical delivery of baicalin to the hair follicles: a targeted approach tailored for alopecia treatment, Int. J. Pharm. 625 (2022) 122109, https://doi.org/10.1016/j.ijpharm.2022.122109.
[116] J. Kong, W. Qiang, J. Jiang, X. Hu, Y. Chen, Y. Guo, H. Liu, S. Sun, H. Gao, Y. Zhang, Y. Gao, X. Liu, X. Liu, H. Li, Safflower oil body nanoparticles deliver hFGF10 to hair follicles and reduce microinflammation to accelerate hair regeneration in androgenetic alopecia, Int. J. Pharm. 616 (2022) 121537, https://doi.org/10.1016/j.ijpharm.2022.121537.
[117] A.A. Elshall, A.M. Ghoneim, N.M. Abd-elmonsif, R. Osman, D.S. Shaker, Boosting hair growth through follicular delivery of Melatonin through lecithin-enhanced Pickering emulsion stabilized by chitosan-dextran nanoparticles in testosterone induced androgenic alopecia rat model, Int. J. Pharm. 639 (2023) 122972, https://doi.org/10.1016/j.ijpharm.2023.122972.
[118] A. Priprem, Y.-C. Lee, W. Limphirat, S. Tiyaworanant, K. Saodaeng, J. Chotitumnavee, N. Kowtragoon, Eucalyptus ash alters secondary protein conformation of human grey hair and facilitates anthocyanin dyeing, PLoS One 13 (2018) e0199696, https://doi.org/10.1371/journal.pone.0199696.
[119] S.S. Rostamkalaei, M. Iman, R. Ataee, Z. Bahari, The effects of *Lavandula angustifolia* essential oil on analgesic effects and percutaneous absorption of naproxen sodium gel; an *in vivo* and *in vitro* study, Clin. Exp. Pharmacol. Physiol. 50 (2023) 298–306, https://doi.org/10.1111/1440-1681.13747.
[120] A. Khanal, S. Dall′ acqua, R. Adhikari, Bael (*Aegle marmelos*), an underutilized fruit with enormous potential to be developed as a functional food product: a review, J. Food Process. Preserv. 2023 (2023) 8863630, https://doi.org/10.1155/2023/8863630.
[121] M. Wang, T. Liu, H. Wang, Z. Wang, J. Zhang, A supramolecular system of bioactive ionic liquid, peony extract, and peptide for enhanced permeability and synergistic skincare benefits, Chem. Eur J. 31 (2025) e202501323, https://doi.org/10.1002/chem.202501323.
[122] P. Sarango-Granda, L.C. Espinoza, N. Díaz-Garrido, H. Alvarado, M.J. Rodríguez-Lagunas, L. Baldomá, A. Calpena, Effect of penetration enhancers and safety on the transdermal delivery of apremilast in skin, Pharmaceutics 14 (2022) 1011, https://doi.org/10.3390/pharmaceutics14051011.
[123] T.J. Ashaolu, Applications of bioactive peptides in cosmeceuticals: a review, J. Zhejiang Univ. - Sci. B. 26 (2025) 527–545, https://doi.org/10.1631/jzus.B2400029.
[124] P. Karande, A. Jain, S. Mitragotri, Discovery of transdermal penetration enhancers by high-throughput screening, Nat. Biotechnol. 22 (2004) 192–197.
[125] R. Parhi, P. Suresh, S. Mondal, P. Mahesh Kumar, Novel penetration enhancers for skin applications: a review, Curr, Drug Deliv. 9 (2012) 219–230.
[126] G. Kaspute, T. Ivaskiene, A. Ramanavicius, S. Ramanavicius, U. Prentice, Terpenes and essential oils in pharmaceutics: applications as therapeutic agents and penetration enhancers with advanced delivery systems for improved stability and bioavailability, Pharmaceutics 17 (2025) 793, https://doi.org/10.3390/pharmaceutics17060793.
[127] W. Xu, C. Liu, Y. Zhang, P. Quan, D. Yang, L. Fang, An investigation on the effect of drug physicochemical properties on the enhancement strength of enhancer: the role of drug-skin-enhancer interactions, Int. J. Pharm. 607 (2021) 120945, https://doi.org/10.1016/j.ijpharm.2021.120945.
[128] W. Yang, X. Chen, Y. Li, S. Guo, Z. Wang, X. Yu, Advances in pharmacological activities of terpenoids, Nat. Prod. Commun. 15 (2020), https://doi.org/10.1177/1934578X20903555.
[129] J.D. Steyn, A. Haasbroek-Pheiffer, W. Pheiffer, M. Weyers, S.E. van Niekerk, J. H. Hamman, D. van Staden, Evaluation of drug permeation enhancement by using *in vitro* and *ex vivo* models, Pharmaceuticals 18 (2025) 195, https://doi.org/10.3390/ph18020195.
[130] Y.D. Wirtu, A review of environmental and health effects of synthetic cosmetics, Front. Environ. Sci. 12 (2024) 1402893, https://doi.org/10.3389/fenvs.2024.1402893.
[131] W. Kathe, D. Harter, U. Schippmann, Sustainability in practice: key aspects, opportunities and challenges in implementing a standard for sustainable use of natural biological resources, Deutschland/Bundesamt für Naturschutz (2018). https://bfn.bsz-bw.de/frontdoor/deliver/index/docId/213/file/Skript_513.pdf.
[132] A.S. van Wyk, G. Prinsloo, Medicinal plant harvesting, sustainability and cultivation in South Africa, Biol. Conserv. 227 (2018) 335–342, https://doi.org/10.1016/j.biocon.2018.09.018.
[133] W. Liu, Q. Zhao, L. Lv, S. Yan, Q. Song, T. Chen, Q. Yao, Pomegranate seed oil enhances the percutaneous absorption of trans-resveratrol, J. Oleo Sci. 67 (2018) 479–487, https://doi.org/10.5650/jos.ess17144.
[134] J. Teichenné, R. Mariné-Casadó, J.M. Alcaide-Hidalgo, J. Tchoumtchoua, K. Leonard, X. Escoté, Photoprotective and anti-inflammatory potential of polyphenol-rich extracts from agricultural by-products of chicory leaves, red onion peel, vineyard pruning, and olive pruning in UV-B-exposed 3D human skin equivalents, J. Agric. Food Res. 23 (2025) 102201, https://doi.org/10.1016/j.jafr.2025.102201.
[135] O. Mykhailenko, B. Jalil, L.J. McGaw, J. Echeverría, M. Takubessi, M. Heinrich, Climate change and the sustainable use of medicinal plants: a call for "new" research strategies, Front. Pharmacol. 15 (2025) 1496792, https://doi.org/10.3389/fphar.2024.1496792.
[136] M. Usman, M. Nakagawa, S. Cheng, Emerging trends in green extraction techniques for bioactive natural products, Processes 11 (2023) 3444, https://doi.org/10.3390/pr11123444.
[137] C. Zhang, K. Hong, Production of terpenoids by synthetic biology approaches, Front. Bioeng. Biotechnol. 8 (2020) 347, https://doi.org/10.3389/fbioe.2020.00347.
[138] M. Sharma, J. Gupta, P. Singh, Preparation and evaluation of *Ficus racemosa* extract transdermal gel for antimicrobial and anti-inflammatory activity, Int. J. Drug Deliv, Tech 14 (2024) 1059–1065.
[139] K. Wadhwa, V. Kadian, V. Puri, B.Y. Bhardwaj, A. Sharma, R. Pahwa, R. Rao, M. Gupta, I. Singh, New insights into quercetin nanoformulations for topical delivery, Phytomed. Plus 2 (2022) 100257, https://doi.org/10.1016/j.phyplu.2022.100257.
[140] L. Wang, Z. Liu, X. Du, M. Song, Z. Liang, X. Gao, G. Lu, W. Chang, G. Zhai, Construction and evaluation of transdermal delivery system of terbinafine-loaded plant exosomes for the treatment of cutaneous fungal infections, Int. J. Drug Deliv. Technol. 102 (2024) 106365, https://doi.org/10.1016/j.jddst.2024.106365.
[141] D. Mori-Mestanza, I. Valqui-Rojas, A.C. Caetano, C. Culqui-Arce, R. Cruz-Lacerna, I.S. Cayo-Colca, E.M. Castro-Alayo, C.R. Balcázar-Zumaeta, Physicochemical properties of nanoencapsulated essential oils: optimizing d-limonene preservation, Polymers 17 (2025) 348, https://doi.org/10.3390/polym17030348.
[142] M.L. Medeleanu, A.C. Fărcaş, C. Coman, L. Leopold, Z. Diaconeasa, S.A. Socaci, Citrus essential oils – based nano-emulsions: functional properties and potential applications, Food Chem. X. 20 (2023) 100960, https://doi.org/10.1016/j.fochx.2023.100960.
[143] C. Caddeo, A. Nacher, A. Vassallo, M.F. Armentano, R. Pons, X. Fernàndez-Busquets, C. Carbone, D. Valenti, A.M. Fadda, M. Manconi, Effect of quercetin and resveratrol co-incorporated in liposomes against inflammatory/oxidative response associated with skin cancer, Int. J. Pharm. 513 (2016) 153–163, https://doi.org/10.1016/j.ijpharm.2016.09.014.
[144] F. Goudon, Y. Clément, L. Ripoll, Controlled release of retinol in cationic co-polymeric nanoparticles for topical application, Cosmetics 7 (2020) 29, https://doi.org/10.3390/cosmetics7020029.
[145] A. Llamedo, P. Rodríguez, C. de Passos, S. Freitas-Rodriguez, A.M. Coto, R. G. Soengas, R. Alonso-Bartolomé, Liposomal formulation of a vitamin C derivative: a promising strategy to increase skin permeability, J. Liposome Res. 35 (2025) 197–205, https://doi.org/10.1080/08982104.2025.2466449.
[146] X. Yin, K. Chen, H. Cheng, X. Chen, S. Feng, Y. Song, L. Liang, Chemical stability of ascorbic acid integrated into commercial products: a review on bioactivity and delivery technology, Antioxidants 11 (2022) 153, https://doi.org/10.3390/antiox11010153.
[147] D. Dias, B.N. Estevinho, Vitamin E microencapsulation via electrohydrodynamic techniques for potential use in skin care and dermatological applications, Molecules 30 (2025) 2306, https://doi.org/10.3390/molecules30112306.
[148] M. Bao, M. Gempeler, R. Campiche, Melanosome transport and processing in skin pigmentation: mechanisms and targets for pigmentation modulation, Int. J. Mol. Sci. 26 (2025) 8630, https://doi.org/10.3390/ijms26178630.
[149] S. Sahudin, N. Sahrum Ayumi, N. Kaharudin, Enhancement of skin permeation and penetration of β-arbutin fabricated in chitosan nanoparticles as the delivery system, Cosmetics 9 (2022) 114, https://doi.org/10.3390/cosmetics9060114.
[150] S. Javaid, T. Rana, M. Zaman, Z. Naeem, A.A. Iqbal, Revolutionizing hyperpigmentation solutions: formulation and characterization of kojic acid gel, Curr. Pharma Res. 2 (2024) 55–88.
[151] Y. Liu, Y. Han, T. Zhu, X. Wu, W. Yu, J. Zhu, Y. Shang, X. Lin, T. Zhao, Targeting delivery and minimizing epidermal diffusion of tranexamic acid by hyaluronic acid-coated liposome nanogels for topical hyperpigmentation treatment, Drug Deliv. 28 (2021) 2100–2107, https://doi.org/10.1080/10717544.2021.1983081.
[152] J.C. Zilles, L.P. Duarte, T.C. Ruaro, A.R. Zimmer, I.C. Kulkamp-Guerreiro, R. V. Contri, Nanoemulsion containing kojic dipalmitate and rosehip oil: a promising formulation to treat melasma, Pharmaceutics 15 (2023) 468, https://doi.org/10.3390/pharmaceutics15020468.