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Transdermal delivery of natural products against atopic dermatitis

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[ABSTRACT] Atopic dermatitis (AD) is a chronic inflammatory skin condition. Natural products have gained traction in AD treatment due to their accessibility, low toxicity, and favorable pharmacological properties. However, their application is primarily constrained by poor solubility, instability, and limited permeability. The transdermal drug delivery system (TDDS) offers potential solutions for transdermal delivery, enhanced penetration, improved efficacy, and reduced toxicity of natural drugs, aligning with the requirements of modern AD treatment. This review examines the application of hydrogels, microneedles (MNs), liposomes, nanoemulsions, and other TDDS-carrying natural products in AD treatment, with a primary focus on their effects on penetration and accumulation in the skin. The aim is to provide valuable insights into the treatment of AD and other dermatological conditions.

[KEY WORDS] Transdermal drug delivery system; Natural products; Hydrogels; Microneedles; Atopic dermatitis; Stratum corneum.
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Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin condition that may progress to allergic diseases such as asthma and allergic rhinitis [1, 2]. Global disease studies indicate that AD is among the most burdensome skin disorders, affecting 10% of adults and 15%−20% of children [3]. The primary pathological feature of AD is believed to be an immune response disorder caused by multiple factors, including genetic predisposition, environmental influences, and allergen exposure [4]. Damage to the epidermal barrier facilitates the entry of exogenous allergens into the epidermis, activating the skin's immune system and promoting the production of inflammatory factors such as interleukin-4 (IL-4), IL-5, and IL-13, which ultimately results in the disruption of microbial diversity, reduction of antimicrobial peptide expression, and exacerbation of microbial infection (Fig. 1) [5, 6]. Current topical treatments for AD primarily include corticosteroids, calcineurin inhibitors, phosphodiesterase inhibitors, and Janus kinase inhibitors [7]. Topical corticosteroids remain the first-line treatment, reducing AD recurrence when used intermittently in patients with established disease. Despite the efficacy of these methods, their clinical application is limited by significant side effects, high costs, and variability in individual response [8, 9]. For instance, prolonged use of corticosteroids can damage the skin and impair growth in young children [10], while tacrolimus has been associated with an increased risk of lymphoma [11].

Natural products, considered nature's treasures, serve as significant sources of potential lead drugs. Research has demonstrated the safety and efficacy of natural products in treating AD, including flavonoids, alkaloids, phenols, and terpenoids (Table 1). These natural products primarily alleviate AD progression by combating inflammation through the inhibition of inflammatory cells (neutrophils, monocytes, lymphocytes, Langerhans cells, etc.), cytokines (interleukins, tumor necrosis factor alpha (TNF-α), thymic stromal lymphopoietin (TSLP), immunoglobulin E (IgE), *etc*.), and signaling pathways (Janus kinase/signal transducer and activator of transcription (JAK/STAT), mitogen-activated protein kinase (MAPK), nuclear factor κB (NF-κB), *etc*.). Several natural remedies have shown notable relief of AD symptoms in clinical trials, such as KM110329 (CTR number: NCT01692093) [12], coconut oils (CTR number: NCT04831892) [13], and honey [14], demonstrating significant effects on AD. Com-

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pared with conventional AD drugs, natural products offer significant benefits, including fewer side effects, enhanced safety, and lower costs [15]. However, some natural products exhibit poor stability and water solubility, leading to chal-

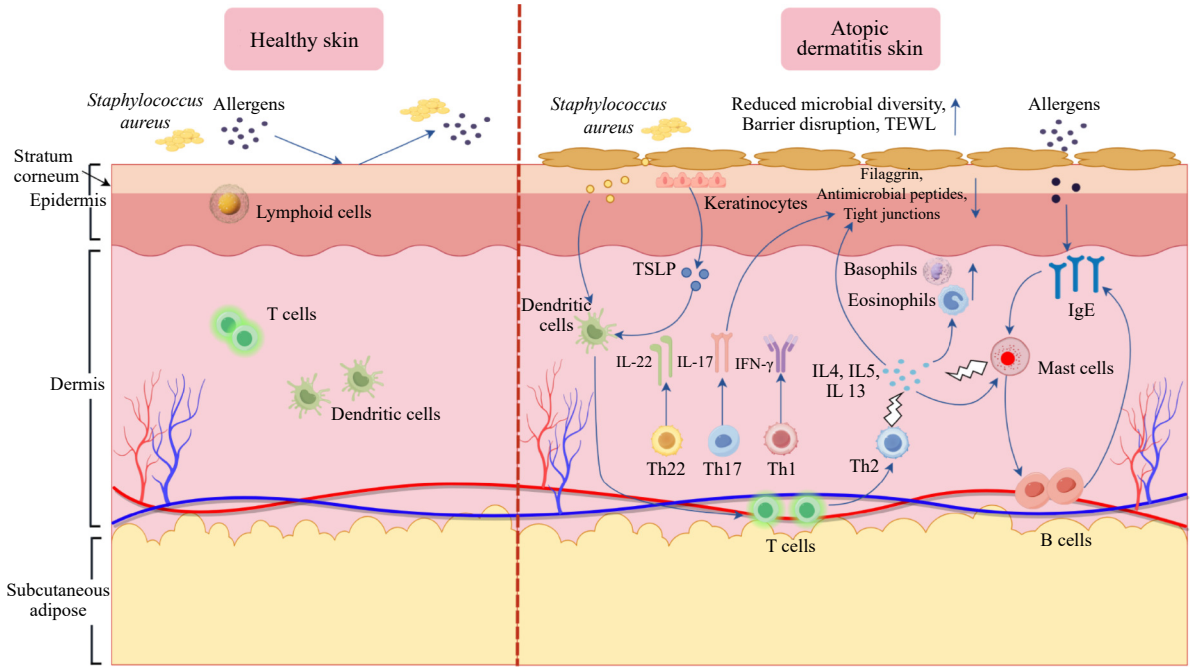

Fig. 1 Mechanisms of AD. In general, thymic stromal lymphopoietin produced by *Staphylococcus aureus* and keratinocytes stimulates T cells to differentiate into Th2 cells *via* dendritic cells following skin barrier disruption. Subsequently, Th2 cells generate cytokines such as IL-4, IL-5, and IL-13, leading to reduced levels of filaggrin, antimicrobial peptides, and tight junctions. This results in compromised skin microbial diversity and exacerbation of infection. TSLP, thymic stromal lymphopoietin. This image was created by Figdraw 2.0.

Table 1 Therapeutic effects of natural products in AD

Species	Natural compounds	Models	Mechanisms and targets	Refs.
Flavonoids	Baicalin	2,4-dinitrochlorobenzene (DNCB) to induce AD-like skin lesions	Inhibiting NF-κB and JAK/STAT signaling pathways	[21]
	Epigallocatechin-3-gallate	Dermatophagoides pteronissinus extract-induced AD-like lesions	Suppressing the expression of MIF and Th1 cytokines	[22]
	Skullcapflavone II	MC903 induced AD-like model	Suppressing IgE and infiltration of immune cells	[23]
	Naringenin	2,4-dinitrofluorobenzene-induced AD-like model, Dermatophagoides farinae-triggered AD in NC/Nga mice	Inhibiting JAK2/STAT3 signaling pathways; Promoting the transformation of the M1 to M2 phenotype and increasing CD36 and IL-10	[24, 25]
	Quercetin	MC903-induced AD-like skin lesions	Reducing TNF-α, histamine, and inhibiting p38/ERK/MAPK signaling pathways	[26]
	Myricetin	MC903-induced AD-like skin lesions	Reducing the expression of TSLP and Th2 cytokines and inhibiting the NF-κB and STAT1 signaling pathways	[27]
	Diosmetin	DNCB-induced AD-like skin lesions	Inhibiting the activation of the JAK/STAT and MAPK pathways, reducing macrophage infiltration and levels of pro-inflammatory cytokines (TNF-α, IL-4, and IL-1β)	[28]
Alkaloids	Piperine	Trimellitic anhydride-induced AD-like mouse model	Inhibiting the STAT6/GATA3/IL-4 signaling pathway	[29]
	Dictamnine	DNFB-triggered AD-like skin lesions	Inhibiting the MrgprA3-TRPA1 pathway; Inhibiting M1 macrophage polarization, up-regulating the expression of LC3, and macrophage autophagy	[30, 31]
	Magnoflorine	DNCB-induced AD-like skin lesions and TNF-α/IFN-γ-stimulated HaCaT	Decreasing CTSBf, Cyte Cg, Bid, and caspase-3/7/8/9 levels	[32]
	Neferine	DNCB-induced AD-like skin lesions and TNF-α/IFN-γ-stimulated HaCaT	Reducing the phosphorylation of MAPK and the NF-κB signaling pathway and inhibiting the expression of cytokines and chemokines	[33]
	Pseudoephedrine	DNCB-induced AD-like skin lesions and TNF-α/IFN-γ-stimulated HaCaT	Suppressing serum TNF-α and IgE levels, inhibiting the activation of MAPKs and NF-κB signaling pathways	[34]

Continued

Species	Natural compounds	Models	Mechanisms and targets	Refs.
Phenols	Paeonol	DNCB-induced AD-like lesions and mast cells	Reducing the expression of TNF-α, histamine, and inhibiting p38/ERK/MAPK signaling pathways	[35]
	Curcumin	Ovalbumin (OVA) induced AD mice	Down-regulating the activation/expression of STAT6 and GATA3 and suppressing the expression of Th2 cytokines	[36]
	Resveratrol	DNCB-induced AD-like lesions; House dust mite extract-induced AD-like lesions	Reducing IL-25, IL-33, TSLP, and caspase-3-positive cells; Inhibiting HMGB1, ERK1/2, NF-κB, IL-1β, IL-4, IFN-γ, and TNF-α levels	[37, 38]
	Tannic acid	House dust mite extract-induced AD-like lesions	Increasing PPARc and inhibiting the expression of HMGB1, RAGE, COX2, and NF-κB signaling pathways	[39]
	Oregonin	Diphenylcyclopropenone induced AD-like skin lesions	Decreasing IgE, eosinophils, and Th2 cytokines	[40]
	Rosmarinic acid	DNCB-induced AD-like lesions	Inducing IgE, IFN-γ, and IL-4 levels	[41]
Terpenoids	Pterostilbene	DNCB-induced AD-like lesions	Reducing IgE, inflammatory cells, and the expression of IL-4, IL-6, TNF-α, and NF-κB	[42]
	Astaxanthin	Phthalic anhydride (PA)-induced AD animal model	Inhibiting the expression of NF-κB subunits and reducing pro-inflammatory cytokines, iNOS, COX2, and IgE levels	[43]
	Glycyrrhizic acid	MC903 induced AD-like model	Suppressing Th1/Th2/Th17-immune responses by inhibiting migration of LCs	[44]
	Oleanolic acid	DNCB-induced AD-like skin lesions and TNF-α/IFN-γ-stimulated HaCaT	Blocking the Akt, NF-κB, and STAT1 signaling pathways	[45]
	Asiatic acid	DNCB-induced AD-like skin lesions and TNF-α/IFN-γ-stimulated HaCaT	Blocking the activity of Th1 and Th2-related cytokines, NF-κB, p-Akt, and suppressing MAPK signaling pathways	[46]
Others	Taxifolin glycoside	Diphenylcyclopropenone-induced AD-like skin lesions	Reducing expressions of IgE, COX2, and iNOS	[47]
	Hirsutenone	House dust mite extract-induced AD-like lesions	Reducing Th2 cytokines (IL-4, IL-5, IL-13), eosinophil, COX2, and iNOS levels	[48]
	Physcion	DNFB-induced AD-like lesional skin	Inhibiting caspase-1/MAPKs/NF-κB signalings and reducing TSLP levels	[49]
	Dihomo-γ-linolenic acid	NC/Tnd mice	Enhancing PGD_1 levels	[50]

lenges in achieving appropriate absorption, distribution, metabolism, and excretion characteristics, resulting in low blood drug concentrations during clinical applications [16]. Additionally, the stratum corneum (SC), formed by keratinocytes and intercellular material resembling "bricks" and "cement", significantly limits the penetration of macromolecular natural products into deeper skin layers, resulting in poor skin permeability and reduced bioavailability [17, 18].

The transdermal drug delivery system (TDDS) offers a promising approach for administering natural drugs, playing a crucial role in enhancing the transdermal efficiency and penetration depth of natural products, thereby amplifying their pharmacological effects. TDDS can be categorized into two types: active enhancement and passive enhancement. The most common passive methods to improve skin permeability involve the use of chemical enhancers [19]. On the other hand, active enhancement methods such as microneedles (MNs) can penetrate the skin through the SC without causing nerve damage, they can create microchannels in the skin and overcome the physical barriers. In fact, TDDS struggles to strike a balance between facilitating transport through the SC and safeguarding deeper tissues from damage. This difficulty arises from the inability to localize their effects to the SC when enhancing permeability, potentially leading to irritation or toxicity to the living cells in the deeper layers of the skin [20]. Therefore, this article reviews the clinical applications and limitations of natural product transdermal preparations, as well as the research progress of hydrogels, MNs, liposomes, nanoemulsions, nanoparticles (NPs), and other novel TDDS to improve the delivery of natural products for the treatment of AD.

Transdermal Preparations of Natural Drugs in Clinical Application

A variety of natural products have demonstrated promising therapeutic effects in the clinical treatment of AD. These natural remedies have been formulated into diverse pharmaceutical dosage forms, including ointments, decoctions, powders, capsules, and granules (Table 2).

A clinical study by Lin *et al*. [51] demonstrated that Lindioil ointment, comprising indigo naturalis powder, reduced the Eczema Area Severity Index (EASI) in AD patients by approximately 49.9%, significantly exceeding the 19.6% observed in the vehicle group. Notably, about 50% of participants receiving Lindioil ointment exhibited an increase in the investigator's global assessment (IGA) and the visual analogue scale (VAS) scores during the 2-week follow-up period post-study. Similarly, Tzu-Yun ointment, prepared with sesame oil, *Angelica sinensis (Oliv.)* Diels, *Lithospermum erythrorhizon*, and yellow wax, also reduced the EASI score in AD patients, demonstrating efficacy comparable to

Table 2 Natural products for the clinical treatment of AD

Dosage forms	Names	Clinical trial numbers	Components	Refs.
Ointments	Lindioil ointment	NCT02669888	*Baphicacanthus cusia*（Nees）Bremek.	[51]
	Tzu-Yun ointment	NA	Sesame oil, *Angelica sinensis*, *Lithospermum erythrorhizon*, and yellow wax	[52]
	Mahonia aquifolium, Viola tricolor and Centella asiatica	NA	*Mahonia aquifolium*, *Viola tricolor* and *Centella asiatica*	[53]
	Olivederma	NA	*Aloe vera, Canarium album*	[54]
	Jaungo	NCT02900131	Lithospermi Radix, Angelica Gigantis Radix and sesame seed oil, beeswax, swine oil	[59]
Decoctions	Hwangryunhaedoktang	ISRCTN26218532	*Scutellaria baicalensis*, *Gardenia jasminoides*, *Coptis chinensis* and *Phellodendron Amurense*	[55]
	Zemaphyte®	NA	*Ledebouriella seseloides*, *Potentilla chinensis*, *Clematis armandii*, *Rehmannia glutinosa*, *Paeonia lactiflora*, *Lophatherum gracile*, *Dictamnus dasycarpus*, *Tribulus terrestris*, *Glycyrrhiza uralensis* and *Schizonepeta tenuifolia*	[56]
	Pei Tu Qing Xin Tang	ChiCTR-TRC-08000156	Pseudostellariae Radix, *Forsythia suspensa*, Ramulus Uncariae cum Uncis, Medulla Junci, Herba Lophatheri, Semen Coicis, Dioscoreae Rhizoma, Ostreae Concha, Glycyrrhizae Radix	[60]
Powders	Xiao-Feng-San	NA	*Saposhnikovia divaricata*, *Schizonepeta tenuifolia*, *Angelica sinensis*, *Rehmannia glutinosa*, *Sophora flavescens*, *Atractylodes lancea*, *Cryptotympana pustulata*, *Linum usitatissimum*, *Anemarrhena asphodeloides*, *Gypsum fibrosum*, *Clematis armandii*, *Glycyrrhiza uralensis* and *Arctium lappa*	[57]
Capsules	PentaHerbs capsule	CUHK_CCT00084	Lonicerae Flos , Menthae Herba , Moutan Cortex, Atractylodis Rhizoma and Phellodendri Cortex	[61]
Granules	*Hochu-ekki-to*	NA	Ginseng Radix, Atractylodis Rhizoma, Astragali Radix, Angelicae Radix, Zizyphi Fructus, Bupleuri Radix and Glycyrrhizae Radix, Zingiberis Rhizoma, Cimicifugae Rhizoma and Aurantii nobilis Pericarpium	[62]

betamethasone [52]. An intriguing study indicated that ointment effects varied with temperature. A one-year clinical study revealed that *Mahonia aquifolium*, *Viola tricolor*, and *Centella asiatica* ointments had no effect on AD skin lesions but improved erythema, edema/papules, oozing/crusting, exfoliation, and lichenification in subjects exposed to temperatures below 10 °C [53]. Further investigations into the specific mechanisms of action of natural products indicated that ointments improved AD by reducing levels of eosinophils, IgE, and interleukin-17 (IL-17) [52, 54]. Topical decoctions [55, 56] and powders [57] are additional formulations of natural products used in treatment, albeit demonstrating efficacy primarily in mild and moderate AD patients.

While traditional formulations of natural products can be efficacious in treating AD, they present certain limitations. Some drugs may be unsuitable for high doses or potentially irritate the skin. Moreover, drug absorption can vary due to individual differences and the specific administration site. Paraffin-based ointments, being greasy and difficult to remove, lack surface evaporation for a cooling effect, potentially exacerbating patient discomfort [58]. Topical decoctions and powders, though used in AD treatment, often result in significant wastage of natural products with low bioavailability. A primary challenge lies in the inability of traditional dosage forms to effectively deliver high molecular weight natural products to the deeper skin layers due to the skin barrier.

TDDS Carrying Natural Product Treatment AD

To address the limitations of conventional dosage forms, researchers employ modern pharmaceutical technology to develop rational drug formulations that enhance transport and absorption, particularly in the TDDS. TDDS utilizes drug-carrier complexes to facilitate the transport of active ingredients through the skin, enabling targeted local delivery or systemic circulation to accumulate at the site of the lesion. These carriers, composed of biocompatible materials, encapsulate active ingredients, thereby overcoming challenges such as low solubility, poor stability, and limited permeability of natural products [63]. In recent years, researchers have developed various TDDS approaches for treating AD, including hydrogels, MNs, liposomes, nanoemulsions, and others (Fig. 2). These delivery systems have been utilized to encapsulate natural products for the treatment of AD (Table 3).

Hydrogels

Hydrogels represent a category of three-dimensional network-structured polymer smart materials characterized by hydrophilic groups. Commonly utilized polymers include alginate, carbomer, chitin/chitosan, polyvinyl alcohol, agarose, hyaluronic acid, and other components [95, 96]. Hydrogels enhance transdermal drug absorption while providing benefits such as uniform spreadability, non-greasy texture, ease of removal, and effective skin hydration. Consequently, they are

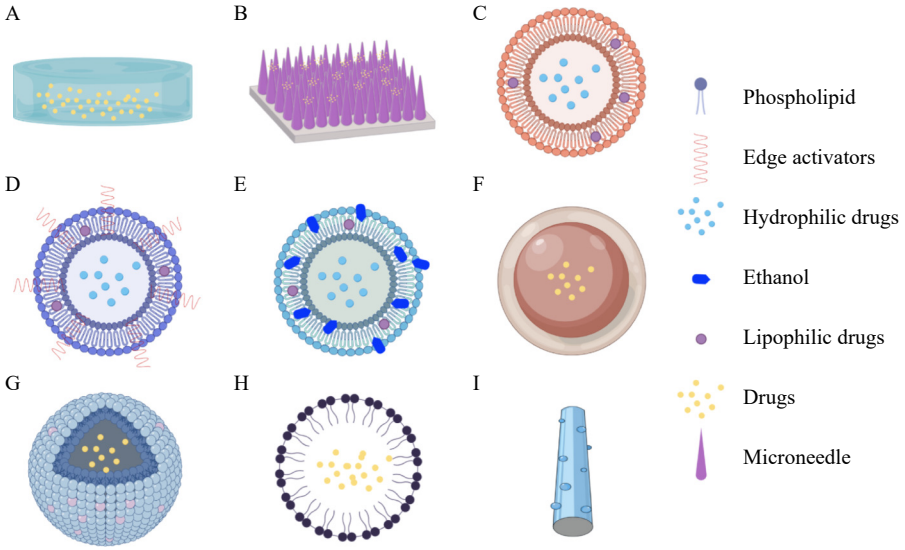

Fig. 2 TDDS for AD. Representative figures of (A) hydrogels; (B) MNs; (C) liposomes; (D) transfersomes; (E) ethosomes; (F) nanoemulsions; (G) NPs; (H) micelles; (I) nanofibers. This image was created by Figdraw 2.0.

Table 3 TDDS-carrying natural products for the treatment of AD

TDDS	Natural products	Composition	Permeability/ Penetrance	Advantages	Refs.
Hydrogels	Salidroside	Quaternized *β*-chitin dextran hydrogel	reached to 95% after 72 h	Moisturizing, transparent, bacteriostatic, and good oxygen permeability	[64]
	Cynaroside	Alginate hydrogel	1351.09 μg·cm^{-2} (4 h)		[65]
	Centella asiatica extract	Hyaluronic acid-dextran hybrid hydrogel	NA		[66]
	Baicalein	Carbopol hydrogel	NA		[67]
	Natural herbal extracts	Polyvinyl alcohol/ propylene glycol hydrogel	NA		[68]
	Resveratrol	Hyaluronic acid hydrogels-containing resveratrol-loaded chitosan NPs	reached 80%(5 d)		[69]
	Tannic acid	Chitosan hydrogel-loaded with hollow manganese dioxide NPs	NA		[70]
	Pomegranate seeds oil	Pullulan films nanocapsules,	NA		[71]
MNs	Epigallocatechin gallate	Poly-*γ* -glutamate (*γ*-PGA)-based MN	63% ± 5% (3 m)	Takes effect quickly and easily in the dermis	[72]
	Jawoongo	NA	NA		[73]
	Curcumin and gallic acid	Double-layered poly(lactic-co-glycolic acid) / sodium hyaluronate MN	26.0% ± 5.5%, (24 h, gallic acid) 96%, (63 d, curcumin)		[74]
Liposomes	Houttuynia cordata water-solubleextract	Egg phosphatidylcholine liposomal	8.49 μg·cm^{-2} (24 h)	Increased drug solubility and easy access to the SC	[75]
	Astaxanthin	Phosphatidylcholine liposomal	NA		[76]
	Paeonol	Phospholipid and cholesterol liposomal	59.94% ± 4.88% (12 h)		[77]
	Tetramethylpyrazine	Lecithin liposomes in sodium alginate chitosan hydrogel	61.07% ± 4.73% (24 h)		[78]
Derivatives of Liposomes	Oregonin	Tat peptide-admixed elastic liposomes	10.19% ± 0.56% (24 h)	Deformable, carrying large amounts of drug into the dermis	[79]
	Hirsutenone	Tat peptide-admixed elastic liposomes	15.48% ± 1.31% (24 h)		[80]
	Taxifolin glycoside	Pep-1 peptide-conjugated elastic liposomes	12.9% ± 1.49% (24 h)		[81]
	Piperine	Phospahtidylcholine ethosomes	33.27% ± 2.84% (7 h)		[82]
	Tea tree oil	Phospahtidylcholineethosomes	33.29% ± 2.74% (7 h)		[83]

Continued

TDDS		Natural products	Composition	Permeability/ Penetrance	Advantages	Refs.
Nanoemulsions		Polyphenol mixture	Diethylene glycol monoethyl ether and caprylocaproyl polyoxyl-8 glycerides nanoemulsions	NA	Low cost, easy to prepare, reduced drug irritation and side effects	[84]
		Chamomile oil	Gelucire 44/14 nanoemulsions	NA		[85]
NPs	Rigid NPs	Dictamnine	PLGA NPs	NA	Small size, easy to penetrate, prevent drug degradation	[86]
		Silibinin	Gellan gum/pullulan bilayer film NPs	7.14% ± 1.34% (24 h)		[87]
		Hederagenin	Maghemite(γ-Fe_2O_3) NPs	NA		[88]
	Soft NPs	Curcumin	Zein NPs	42. 4% ± 8.5% (24 h)		[89]
		Epigallocatechin gallate	Self-assembling gelatin NPs	NA		[90]
Others		Paeonol	Hyaluronic acid cyclodextrin polymeric micelles	14.65% ± 0.96% $\mu g \cdot cm^{-2}$ (12 h)	Small size, stable structure, solubilization	[91]
		Glycyrrhizic acid	Pluronic F127/D-a-tocopheryl polyethylene glycol 1000 succinate mixed micelles-based hydrogel	156.94% ± 20.38% $\mu g \cdot cm^{-2}$ (24 h)		[92]
		Clove oil	Polyethylene glycol Pluronic F127 nanomicelles	148.68 $\mu g \cdot cm^{-2}$ (2 h, epidermis) 127.3 $\mu g \cdot cm^{-2}$ (2 h, dermis)		[93]
		Rose grass oil	Polyvinyl alcohol nanofiber	NA		[94]

progressively evolving into a novel form of TDDS [97].

The pH value of certain natural products differs significantly from that of human skin, potentially causing irritation during prolonged transdermal administration. Hydrogels offer a promising solution for pH regulation and serve as effective carriers for transdermal delivery of natural compounds. He *et al*. [64] incorporated salidroside into a hydrogel composed of quaternary ammonium chitin and oxydextran (QCOD@Sal). Their findings demonstrated that QCOD@Sal exhibited reduced water loss rates and enhanced anti-inflammatory properties, with decreased levels of IL-6 and TNF-α, compared with dexamethasone cream. In a separate study, Yun *et al.* developed a baicalin-loaded carbomer hydrogel, which modulated the infiltration levels of immune cells ($CD3^+$/$CD69^+$, $CCR3^+$, $CD11b^+$/$Gr\text{-}1^+$, $B220^+$/IgE^+) and cytokines (TNF-α and IL-6) in the skin. Additionally, it mitigated AD-induced skin severity scores, suggesting that baicalin can regulate molecular mediators and immune cells associated with AD, potentially alleviating AD symptoms [67].

Hydrogels are primarily suitable for loading compounds with molecular weights below 500 daltons and water-soluble substances [98]. However, their weak tensile strength may result in premature drug release before reaching the target site. To address these limitations, the combination of hydrogels and NPs has emerged as a promising approach. This integration improves drug loading, enhances sustained release control, and increases preparation stability, becoming a research focus in recent years. For example, resveratrol-loaded chitosan NPs (Res-NPs) incorporated into a hyaluronic acid hydrogel (Res@gel) achieved sustained drug release [69]. The study demonstrated that resveratrol (Res-NPs) released 45% and 80% of resveratrol within 1 h and 2 days, respectively, while Res-NPs incorporated into a hyaluronic acid hydrogel (Res@gel) released only 15% of resveratrol within 1 h and maintained stable release for up to 1 week. In another study, Ferrari *et al.* developed pullulan films containing pomegranate seed oil-based nanocapsules (PSONCF) to evaluate their efficacy in AD treatment [71]. The findings indicated that PSONCF exhibited no irritant potential, modulated inflammatory and oxidative stress parameters, and attenuated skin injury and mechanical hypernociceptive behavior in AD-model mice.

MNs

MNs are microstructures fabricated using microelectromechanical systems technology. These devices are characterized by their sharpness and robustness, typically comprising a drug storage cavity and minute protrusions that facilitate transdermal penetration [99]. MNs offer several advantages, including rapid onset of action, reduced pain, and efficient penetration of the SC [100, 101]. Dissolving MNs, in particular, are extensively utilized for the treatment of dermatological conditions, as they do not leave sharp residue and require no further manipulation post-insertion [102].

Despite advancements, challenges persist in delivering large molecular natural products. MNs, a physical enhancement delivery system, have emerged as a promising option for facilitating deep skin penetration of large molecules. Chiu *et al*. [72] developed dissolved MNs composed of polyglutamate and L-ascorbic acid to encapsulate epigallocatechin gallate (EGCG), preventing its rapid degradation. These MNs

achieved an average skin insertion depth of 486 ± 24 μm, with drug release sustained drug release for up to 6 days. This approach enables deep, long-term drug delivery, potentially reducing administration frequency and enhancing patient convenience. Jang *et al.* [73] investigated Jawoongo-loaded MN patches in AD mice, demonstrating direct SC penetration into the epidermis. This method significantly improved skin damage compared to Jawoongo alone and effectively restored the skin barrier in mice. Notably, combining MNs with NPs has shown promise in enhancing sustained drug release and stability. Chen *et al.* developed bilayer-structured MN patches incorporating curcumin-loaded lactic-glycolic acid copolymer (PLGA) and gallic acid-loaded sodium hyaluronate. These MNs penetrated the skin to a depth of 559 ± 48 μm, enabling simultaneous release of curcumin and gallic acid. This combination exerted synergistic antioxidant and anti-inflammatory effects, rapidly reducing AD mice dermatitis scores. The MNs sustained curcumin release for up to 56 days, achieving long-term effective treatment of AD [74].

However, MNs present a notable drawback as they create micron-sized perforations in the patient's skin during treatment, potentially increasing the risk of infection. Furthermore, the application of MNs may induce mild to moderate skin irritation or allergic reactions, manifesting as redness, pain, swelling, and itching [103, 104]. Consequently, addressing these issues is crucial to facilitate the clinical implementation of MNs for AD treatment.

Liposomes

Liposomes are spherical structures composed of lipid bilayers, featuring both hydrophilic and hydrophobic regions, which enhance drug solubility [63, 105]. The primary constituents of the liposomal lipid bilayer are phospholipids and cholesterol, structurally similar to the SC of the skin. Upon application to the skin, liposomes adhere to the SC lipids. This adsorption of liposomal vesicles facilitates their integration into the SC, thereby promoting localized drug effects [106].

The limited solubility of natural products has presented challenges in their application for AD treatment. Liposomes, as vesicles containing both hydrophilic and hydrophobic regions, have emerged as an effective solution to enhance the dissolution of these products. Kwon *et al.* [68] demonstrated this by preparing liposomes coated with lecithin containing a water extract of *Houttuyniae cordata*, which effectively increased skin permeability from 6.85 μg·cm^{-2} to 8.49 μg·cm^{-2}. Another study revealed that astaxanthin liposomes outperformed free astaxanthin in reducing AD symptoms and clinical scores while exhibiting significant advantages in inhibiting signal transducer and activator of transcription 3 (STAT3) and nuclear factor kappa B (NF-*κ*B) [76]. Liposomes have shown particular promise when combined with hydrogels, especially for achieving sustained release and enhancing efficacy. Wang *et al*. [77] reported that the cumulative release rate of paeonol liposomes (PAE-L) reached 72.32% ± 1.68% within 24 h, while the maximum cumulative release rate of PAE-L hydrogel was only 43.47% ± 0.68%. However, the PAE-L hydrogel demonstrated continuous drug release over two days. Xia *et al*. [78] encapsulated tetramethylpyrazine (TMP) into liposomes and incorporated them into a sodium alginate chitosan hydrogel (T-Lip-AC hydrogel). This formulation created a moist healing environment, improved skin permeability, and achieved sustained drug release. Moreover, the hydrogel enhanced the antibacterial, anti-inflammatory, and antioxidant effects of TMP, positioning it as a potentially effective, safe, and novel treatment approach for AD. In conclusion, liposomes show significant potential in facilitating the delivery of water-insoluble drugs and enhancing skin penetration, making them a promising avenue for future AD drug delivery systems.

Derivatives of Liposomes

Transfersomes are nanoscale vesicles composed of phospholipids and edge activators that can traversing the SC through deformation, facilitating deeper drug delivery and enhanced skin permeability [107]. They also improve transepidermal water loss by navigating through the microlamellar spaces between keratinocytes (1/10 of the vesicle diameter), thereby increasing skin moisture [108]. This property positions transfersomes as a potential alternative for drug delivery. Kang *et al*. [79] demonstrated that oregonin-loaded transferosomes exhibited a deformation index four times higher than conventional liposomes. The deformation index correlates directly with the ability to penetrate the skin barrier. Their study revealed that the 24-hour skin steady-state flux and permeability of oregonin in transferosomes were 11.71 ± 0.93 and 8.60 ± 0.22, respectively, surpassing those observed with liposomes (9.92 ± 0.97 and 6.58 ± 0.57, respectively). Additionally, Kang *et al.* developed hirsutenone transferosomes and taxifolin glycoside transferosomes, which demonstrated enhanced skin permeation and significant improvements in both skin severity scores and immune-related responses in AD mice [80, 81].

Ethosomes are single- or multi-layered lipid bilayer vesicles containing a high concentration of ethanol [109]. This ethanol interacts with the hydrophilic groups of the cuticle lipid bilayer, reducing the transition temperature and multilayer density of lipids while improving lipid fluidity [110, 111]. Ethosomes have demonstrated effectiveness in delivering natural products to the epidermis and dermis, albeit with a slower release rate compared to traditional creams. Kumar *et al.* [82] conducted a study where piperine was delivered using ethosomes, resulting in significantly higher accumulation in the epidermis/dermis compared to conventional cream. This enhanced accumulation can be attributed to the sustained release of piperine from the apoplast. Similarly, an ethosomal formulation containing tea tree oil was developed for use in creams [83]. This formulation exhibited a slower release effect, higher deposition in the epidermis and dermis, and significantly reduced inflammatory response compared to conventional cream in AD treatment.

The development of liposomal derivatives has addressed the challenges of liposome fragility and limited SC penetration. These derivatives achieve enhanced skin permeability and penetration depth through improved deformation and lipid flow. However, the inclusion of edge activators and ethanol significantly restricts their clinical application [112, 113]. These components can potentially dissolve and fluidize skin lipids, causing damage to the skin, mucosa, and skin microcirculation surfaces. Furthermore, long-term application may pose carcinogenic risks to mucosal tissues [114-116]. In addition, compared with liposomes, liposomal derivatives also have the disadvantages of complex preparation and high cost.

Nanoemulsions

Nanoemulsions are heterogeneous dispersion systems composed of two or more immiscible liquids, typically stabilized through the use of appropriate surfactants and cosurfactants [117]. These systems are classified into four categories: oil-in-water (O/W), water-in-oil (W/O), water-in-oil-in-water (W/O/W), and oil-in-water-in-oil (O/W/O) [118]. The smaller volume of nanoemulsions provides a larger specific surface area, leading to improved absorption and optical transparency [119]. Additionally, emulsion-based formulations are cost-effective and easily prepared. However, nanoemulsions are thermodynamically unstable systems prone to disintegration due to various chemical or physical processes, which should be considered during their preparation [120, 121].

Nanoemulsions, as multi-phase systems, address challenges associated with volatile and oxidized natural products in AD treatment, serving as effective vehicles for the transdermal delivery of natural remedies. Choi *et al*. [84] demonstrated that a polyphenol mixture water-in-oil-in-water emulsion (PM_W/O/W) applied to AD mice significantly reduced dermatitis scores and serum IgE levels compared to the free polyphenol mixture. The *in vivo* release profile revealed a burst release of PM_W/O within 48 h, while PM_W/O/W exhibited sustained release over 144 h, with a 65% decrease in release after 24 h compared to 1 h. The enhanced therapeutic effect of PM_W/O/W over free PM may be attributed to its prolonged action through continuous drug release. El-Salamouni *et al*. [85] developed a nanoemulsion gel loaded with chamomile oil (CM-EMs) using Tween-80, polyethylene glycolide laurate, and hydroxypropyl methyl cellulose to address these issues. Their study on AD rats revealed that CM-EMs exhibited comparable skin repair effects and reduction of inflammatory factors, with efficacy ranking as CM-EMs-G_1 > CM-EMs-X_1 > CM.

NPs

NPs, defined as particles with a size of 100 nm or less, have gained widespread application in diverse fields, including cosmetics, clinical diagnostics, and therapeutics [122]. Their diminutive size enables NPs, even when encapsulating drug molecules, to penetrate the cuticle barrier imperceptibly, evade immune system clearance, and extend circulation time [123]. In response to challenges associated with easy degradation, which impedes preservation and long-term drug delivery, NPs have emerged as ideal candidate carriers for transdermal delivery of natural products. These small particles offer sustainability and protection against drug degradation.

Rigid NPs

Rigid NPs, including PLGA-nanocarriers and iron oxide NPs, offer significant potential for payload protection and targeted drug delivery. Their ability to modulate drug activity and control release has become a crucial strategy for regulating drug penetration into the skin. Lin *et al*. [86] demonstrated that PLGA-nanocarrier-encapsulated formulations exhibited enhanced drug loading, improving the efficacy of dictamnine through sustained release and increased skin penetration. Gehrcke *et al*. [87] developed a pullulan/gellan gum bilayer film with silibinin-loaded nanocapsules (BFNCSB) for AD treatment, observing that BFNCSB facilitated gradual silibinin release, with accumulation in the injured dermis significantly higher than in normal skin. A notable study revealed that iron oxide NPs containing hederagenin could ameliorate dermatophagoides farinae extract and DNCB-induced skin barrier dysfunction through immunomodulatory and anti-inflammatory effects [88].

Soft NPs

Soft NPs, such as those derived from proteins, gelatin, and self-assembled drug structures, have demonstrated the potential to enhance local drug distribution and overall safety, potentially leading to improved therapeutic outcomes. This effectiveness is attributed to their ability to penetrate the skin intact and avoid phagocytosis by macrophages [124, 125]. Zein, a naturally occurring biodegradable macromolecular material with a highly hydrophobic structure, facilitates transdermal drug delivery through the SC [126]. Zhu *et al*. [89] developed curcumin-loaded NPs using sericin and zein as carriers, demonstrating that these NPs could deliver curcumin subcutaneously, resulting in a potent anti-inflammatory effect. Drew *et al*. [90] fabricated gelatin NPs loaded with EGCG *via* a self-assembly mechanism at room temperature. Both *in vitro* and *in vivo* studies indicated that these NPs enhanced EGCG absorption, significantly improving its bioavailability. *In vitro* findings revealed that EGCG gelatin NPs also exhibited a significantly stronger inhibitory effect on inflammatory factors IL-6 and IL-8 compared to an equivalent concentration of free EGCG.

Upon entering the human body, NPs are deposited in multiple organs, primarily through the generation of reactive oxygen species (ROS), which subsequently affect various cellular pathways [127]. Research indicates that NPs smaller than 10 nm may traverse the blood-brain barrier and accumulate in the brain, potentially inducing neurotoxicity [128, 129]. Consequently, rigorous monitoring of potential adverse effects is essential when utilizing small NPs.

Others

Micelles are two-phase structures comprising a hydro-

phobic core and a hydrophilic shell [118]. These structures significantly enhance the solubility of hydrophobic drugs and evade recognition and early clearance by the reticuloendothelial system, thereby enabling prolonged drug delivery [130-132]. Research has shown that drug-loaded micelles demonstrate enhanced efficacy in treating AD compared to free drugs [133]. Wang *et al*. [91] developed PAE-loaded micelles formed by hyaluronic acid and cyclodextrin (HACD-PAE), which proved more effective than free PAE, HA-PAE, and CD-PAE in reducing ear-back skin thickness and promoting hair growth. Shen *et al*. [92] observed that mixed micelle gels loaded with glycyrrhizic acid (GL-MMs-gel) exhibited sustained release properties and increased GL deposition. Mustafa *et al*. [93] reported that clove oil nanocolloid micelles displayed slow release and enhanced accumulation of clove oil in the epidermis and dermis compared to conventional formulations, indicating the potential of micelles as effective drug carriers for AD treatment.

Nanofibers, characterized by their nanoscale diameters and lengths extending to a few micrometers, have emerged as a crucial component in pharmaceutical materials due to their robust mechanical properties. Azuma *et al*. [134] conducted a study involving the topical application of chitin nanofibers to mice with AD, demonstrating an anti-inflammatory effect that decelerated the progression of experimental AD by inhibiting NF-κB, cyclooxygenase-2 (COX2), and inducible nitric oxide synthase (iNOS). Notably, a rose grass oil/polyvinyl alcohol nanofiber membrane applied to skin lesions of AD patients effectively mitigated pruritus symptoms and lowered the AD score index. Furthermore, the fibrous membrane exhibited significant antibacterial activity without toxicity [94].

Summary and Outlook

In recent years, emerging technologies such as hydrogels, MNs, liposomes, nanoemulsions, and other TDDS have demonstrated significant potential for enhancing the transdermal absorption and penetration depth of natural products, addressing the limitations of these compounds in the treatment of AD. These technologies can facilitate sustained drug release, extend the duration of drug action, and reduce the frequency of drug administration for patients. However, they still possess certain limitations, such as the inability of liposomes to traverse the SC and the potential toxic side effects of liposome derivatives and NPs. MNs are an exception, not only overcoming the limitations of other TDDS, such as insufficient administration depth and high toxicity but also enabling the delivery of macromolecules and vaccines. They are considered a promising approach for the future treatment of AD through transdermal drug delivery. Nevertheless, MNs carry the risk of infection. Furthermore, combining two or more TDDS can potentially mitigate the shortcomings of individual systems, leading to enhanced efficacy and improved treatment outcomes. The ongoing development of TDDS offers a promising outlook for the future treatment of AD and other skin diseases.

Despite the promising potential of TDDS in the clinical treatment of AD, several key challenges remain to be addressed. Primarily, as TDDS directly interfaces with the skin, the active pharmaceutical ingredients, formulation components, and delivery devices may potentially cause skin irritation. Research has demonstrated that enhancing the skin's protective barrier through emollient use can mitigate or prevent these cutaneous side effects [135-137]. Additionally, the industrial production of TDDS necessitates stringent manufacturing conditions and complex quality control processes, requiring substantial time and financial investment. The path to TDDS industrialization remains extensive. However, the establishment of regulatory control strategies throughout the formulation development process and guidance from relevant authorities on appropriate manufacturing conditions may facilitate large-scale TDDS production [138]. Furthermore, while numerous animal studies have shown significant efficacy of drug-loaded TDDS in AD models, these models cannot fully replicate human skin conditions, necessitating clinical studies. Lastly, the unique delivery methods and diverse targets of TDDS create uncertainty in bioequivalence detection methods, impeding development. While clinical endpoint and pharmacodynamic studies are commonly used to evaluate TDDS generic bioequivalence, they are time-consuming, costly, and unable to assess drug effectiveness in the dermis or subcutaneous tissue [139]. Consequently, more sophisticated experimental methods are required to support TDDS bioequivalence detection. Continued pre-clinical and clinical research on TDDS is essential, particularly in natural drug loading. Such advancements could potentially transform AD clinical treatment, offering significant benefits to patients.

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