REVIEW

# Plant-Derived Extracellular Vesicles in Dermatology: A Review of Emerging Therapeutic Applications

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**OBJECTIVE:** This article aims to evaluate and discuss the therapeutic potential of plant-derived extracellular vesicles (PEVs) in clinical and aesthetic dermatology by examining their mechanisms, clinical application, efficacy, and safety profiles. **METHODS:** A comprehensive literature search was completed using the keywords "plant-derived exosomes," "dermatology," "skin disorders," "treatment," "inflammatory skin conditions," "cosmetic," "regenerative medicine," "wound healing," and "chemotherapeutic skin-related toxicities." The authors reviewed all studies and included those that addressed PEVs. **RESULTS:** PEVs demonstrate multifaceted therapeutic properties: (1) immunomodulation through suppression of proinflammatory cytokines (interleukin 17, tumor necrosis factor-α), (2) restoration of skin barrier function, (3) promotion of tissue regeneration in wounds and scars, and (4) effective stabilization and delivery of therapeutic cargo (microRNAs, hydrophobic drugs). Clinical case studies, particularly with rose stem cell exosomes, show efficacy in atopic dermatitis, psoriasis, wound healing, and chemotherapy-induced dermatologic toxicities, with rapid symptom relief and structural improvement. **LIMITATIONS:** Current evidence is constrained by predominance of preclinical data focused primarily on mammalian-derived exosomes as well as variability in PEV isolation and characterization methods across studies. Clinical data regarding the use of PEVs remains limited in the literature. **CONCLUSION:** PEVs represent a promising new class of dermatologic therapeutics combining plant-derived biocompatibility with targeted therapeutic effects. Future research should prioritize controlled clinical trials, standardization of production methods, and exploration of engineered PEVs for precision medicine applications in dermatology. **KEYWORDS:** Plant-derived exosomes, extracellular vesicles, inflammatory skin diseases, wound healing, scar revision, chemotherapy-induced skin toxicities, targeted drug delivery

Extracellular vesicles (EVs) are small, lipid-bilayer membrane–enclosed structures that are ubiquitously secreted by living cells and reside in the extracellular space.[1] Depending on the cell type of origin, their structure, function, and cargo can vary significantly. These EVs can function as critical intercellular messengers and regulate many biological processes, carrying molecules such as proteins, oligonucleotides, lipids, and metabolites between cells.[1] Exosomes are a subtype of EVs that are the released cargo (intraluminal vesicles) resulting from membrane fusion of multivesicular bodies, while ectosomes commonly constitute EVs formed from budding of the plasma membrane.[1,2] These nano-biomolecules have promise for use in the clinical setting as diagnostic and prognostic biomarkers as well as enhanced therapeutic alternatives.[2,3]

Due to their distinct composition and cargo, these molecules exhibit properties with substantial therapeutic potential, including regulation of inflammation, immune modulation, tissue regeneration, drug delivery, and targeted therapies.[4-6] Investigations of EVs as therapeutic agents remain in the early stages; however, the acceleration in findings combined with the emergence of clinical trials and case reports signify the substantial potential for future application. The primary model for the majority of EV research has focused on EVs of human cell origin, particularly for mesenchymal and, in dermatologic uses, adipose tissue stem cell EVs.[7-9] Exosomes have been implicated in both the diagnosis and therapy of inflammatory and autoimmune skin conditions such as psoriasis, atopic dermatitis (AD), vitiligo, and cutaneous systemic lupus erythematosus (SLE).[3] Additionally, mesenchymal stem cell (MSC)-derived exosomes exhibit regenerative and antifibrotic properties in wound healing and the prevention of scar formation.[3] However, large-scale production of these EVs presents a challenge due to costs and relatively low yield from in vitro or biological fluid purification procedures.[10] Thus, plant-derived EVs have risen as a natural alternative given their sustainable and plentiful sources.[11]

Plant EVs (PEVs), which include plant-derived exosomes, have been shown to be effective in a number of conditions. Properties such as the ability to cross the blood-brain barrier, high circulation time and bioavailability, and potential for targeted cell uptake make these vesicles prime candidates for use in drug delivery.[1] Like mammalian-derived

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exosomes, plant-derived exosomes carry an abundance of cargo that broadens their functions and therapeutic effects.[1] Proteins often carried by PEVs have been implicated in regulation of the plant stress response, cell wall stability and permeability, cell division, membrane trafficking, and logistics of intra- or extracellular transport.[12] The lipid composition of PEVs also alters their ability to interact with neighboring cells, especially animal cells.[11] PEVs host a large number of microRNAs (miRNAs), the function of which has been postulated to target extracellular microbiota[13] and mediate interkingdom communications.[14] Overall, PEVs function to facilitate plant cell-to-cell and cell-microbe interactions, augment the immune response, and maintain structural stability.[11,12]

The exact mechanism by which PEVs penetrate the epidermis and interact with dermal cells is not completely understood. Interaction with keratinocytes and dermal fibroblasts is likely mediated by ligand receptor–directed clathrin or caveolin-dependent endocytosis and/or micropinocytosis.[1,15] Composition of different membrane lipids, such as phosphatidic acid, is also thought to play a role.[15] Topically, synergistic applications with physical treatment such as microneedling or laser may serve to enhance dermal uptake by bypassing percutaneous absorption, showing efficacy in clinical reports.[16,17] Similarly, mechanisms by which PEVs remain stable in various topical formulations remain under investigation. Clinical use of prototype topical products containing PEVs suggests stability and effective uptake.[17-20] Kim et al[21] tested leaf-derived extracellular vesicles against various preservatives and isolation procedures, finding reliable stability and promising cellular uptake with the preservative 1,3-butylene glycol at storage of 4°C. Further research is necessary to fully elucidate and optimize stability of PEVs in topical formulations.

The evidence for the therapeutic potential of PEVs has been growing, covering a wide array of disorders in preclinical studies. Recent literature suggests PEV efficacy in the treatment of inflammatory and immune dysregulation syndromes; malignancy, liver, cardiac, and gastrointestinal (GI) disorders; and infectious disease.[1] This review aims to summarize the currently available data and demonstrate the use of PEVs in clinical dermatology, specifically related to management of inflammatory skin conditions, cutaneous wound healing and scars, cosmetics and aesthetics, and skin related toxicities due to cancer treatments.

## INFLAMMATORY SKIN CONDITIONS

Immune activation, cytokine signaling, and cellular communication drive protective and pathologic processes.[1] Growing preclinical evidence substantiates PEVs' potent immunomodulatory effects across various inflammatory conditions.[1] PEVs from grape, ginger, broccoli, and gradefruit demonstrated efficacy in colitis murine models, including reduced proinflammatory cytokines (tumor necrosis factor [TNF] α, interleukin [IL] 6, IL-1β), enhanced intestinal epithelial repair, and restored microbiome balance.[22,23] Garlic and *Momordica charantia* PEVs were found to modulate toll-like receptor 4 (TLR4)/myeloid differentiation primary response 88 (MyD88) signaling and oxidative stress,[24] while tomato exosomes prevented dysbiosis by selectively inhibiting pathogenic bacteria and promoting probiotic growth.[25] There is also evidence that PEVs can control immune cell activity in vitro: lemon-derived vesicles inhibited nuclear factor (NF)-κB/extracellular signal-regulated kinase (ERK) signaling in macrophages, celery root EVs suppressed T-cell activation, and *Pueraria lobata* exosomes promoted anti-inflammatory M2 macrophage polarization.[26] Immune-stimulatory effects have also been observed via TNF-α/NF-κB activation, suggesting significance for context-dependent application.[1,27]

The majority of research regarding exosome implications in inflammatory skin conditions involves the use of mammalian-derived EVs and have identified promising anti-inflammatory and immunomodulatory effects.[3,28-30] Data on PEVs also support their anti-inflammatory abilities. Cabbage and red cabbage exosomes stimulate keratinocyte growth while reducing inflammation,[31] while lemon-derived PEVs protect against oxidative stress and accelerate wound healing with limited adverse effects.[32] *Aloe vera* vesicles significantly suppress key inflammatory cytokines (IL-1β, IL-6, TNF-α) in skin cells and improve wound repair by modulating collagen activity.[33] In models of AD and psoriasis, grapefruit EVs combined with stem cells had targeted anti-inflammatory effects, highlighting PEVs' potential as multitarget therapies for inflammatory skin conditions.[34] However, the evidence for PEVs is less abundant and, until recently, lacked clinical investigations supporting their effectiveness.

**Atopic dermatitis.** AD affects 15% to 20% of children and up to 10% of adults globally.[35,36] Disease severity correlates with distinct cytokine profiles and biomarkers unique to the disease process. IL-4 and IL-13 are particularly upregulated in AD, which results in disrupted epidermal integrity and amplification of Janus kinase (JAK)/signal transducer and activation of transcription (STAT)–mediated inflammation. IL-31, IL-33, and leukotrienes directly induce pruritus and sustain the itch-scratch cycle.[37,38] Current treatments with the strongest evidence include topical corticosteroids, calcineurin inhibitors, roflumilast, tapinarof, ruxolitinib, and crisaborole to reduce active inflammation and pruritus and sustain remission. However, long-term use of corticosteroids is associated with adverse effects.[39] Systemic treatments for refractory AD primarily involve anti-IL-4/IL-13 biologics dupilumab and tralokinumab and, more recently, lebrikizumab (anti-IL-13); these have been shown to be safe with excellent efficacy.[39] However, these therapies often have barriers to access such as financial cost, availability, and variability in adverse effect profiles.

A growing body of evidence indicates that exosomes, particularly those derived from mammalian cells, exert multifaceted anti-inflammatory and barrier-repair effects in AD models.[3] Subcutaneous or intravenous administration of adipose-derived stem cell (ADSC) exosomes reduced AD inflammatory markers such as serum immunoglobulin E (IgE), immune cell infiltration, and proinflammatory cytokines while restoring stratum corneum hydration and epidermal ceramide production in murine models.[9,28] ADSC exosomes were also found to normalize dysregulated genes involved in barrier function, lipid metabolism, and immune response.[29] Fibroblast-derived exosomes restored critical barrier proteins (filaggrin, loricrin, involucrin) in keratinocytes, facilitating accelerated skin recovery.[40] These findings underscore exosomes' capacity to simultaneously address immune dysregulation and barrier defects, positioning them as compelling candidates for long-term AD therapy.

Further therapeutic effect can be achieved by engineering exosomes to express or carry therapeutic cargo. Engineering of miR-147a-enriched ADSC exosomes was found to suppress angiogenesis via targeting the 3'-UTR of vascular

endothelial growth factor A mRNA while simultaneously inhibiting the myocyte enhancer factor 2A-thymic stromal lymphopoietin axis, resulting in reduced inflammatory responses in AD in vivo and in vitro models. This achieved dual modulation of pathological angiogenesis and inflammatory signaling, supporting the potential and precision of engineered miRNA-based exosome therapy for AD.[30]

Literature on applications of plant-derived exosomes in the treatment of AD is limited. In one study, Huang et al[34] fused grapefruit-derived exosome–like nanovesicles with CCR6-engineered gingival MSC-derived exosomes. The hybrid molecule was subsequently loaded with the hydrophobic immunosuppressant CX5461, providing a stable delivery mechanism.[34] These loaded hybrid vesicles enhanced targeting of CCL20-rich inflammatory lesions, exhibited intrinsic anti-inflammatory and antioxidant effects, and delivered CX5461 to the affected tissues, resulting in cell cycle arrest. In 2,4-dinitrochlorobenzene–induced AD murine models, intravenous administration significantly reduced disease severity scores by Day 21, maintaining low immunogenicity while outperforming standard dexamethasone treatment in the reduction of both clinical symptoms (erythema, scaling) and inflammatory cytokine expression.[34]

Clinical efficacy of exosomes in AD was reported in a recent case series published using rose stem cell exosomes on various dermatologic conditions.[17] In the representative case, a 21-year-old woman with chronic, lichenified hand eczema achieved complete symptomatic pruritus resolution and significant lesion improvement on her left hand after 2 weeks of topical Damask rose stem cell exosome (RSCE) application. Her right hand, which was treated with the previously used emollient control, remained unchanged. Notably, these clinical benefits persisted at the 6-week follow-up, with the patient reporting sustained skin smoothing and hydration, exhibiting both rapid and durable effects. These findings correlate with the anti-inflammatory and barrier-repair mechanisms demonstrated in preclinical models and highlight the clinical safety and efficacy for the potential clinical application of PEVs.

**Psoriasis.** Psoriasis is a chronic inflammatory skin disorder that affects 2% to 4% of the global population, with plaque psoriasis representing about 80% to 90% of cases.[28,39] It is associated with significant morbidity, including psoriatic arthritis, cardiometabolic syndrome, and depression.[39,41] The pathogenesis of psoriasis is broadly related to dysregulated autoimmune reaction in the skin and production of proinflammatory cytokines, such as IL-23/IL-17, resulting in keratinocyte hyperproliferation and sustained inflammation.[28,42] Similar to AD, management of psoriasis relies on continued use of anti-inflammatory topicals such as corticosteroids and calcineurin inhibitors as well as topical vitamin D analogs.[41] Biologics and JAK inhibitors have revolutionized treatment; however, these medications face similar barriers to access, and disease recurrence remains common upon therapy withdrawal, underscoring the need for novel therapeutic strategies.[28,41]

Exosomes have displayed efficacy against the dysregulated immune response in psoriasis in many preclinical models.[43-45] Topical application of epidermal stem cell-derived exosomes reduced aberrant cytokine levels in imiquimod-induced psoriatic mice.[43] When injected subcutaneously, human umbilical cord MSC exosomes were able to further suppress pathogenic cytokines in keratinocytes, inhibit dendritic cell activation, promote polarization of macrophages to their anti-inflammatory M2 form, and suppress T-cell proliferation.[44,45] Both exosomes led to clinically observed improvement in psoriatic lesions in their respective murine models.[43-45]

Exosomes are also capable of maintaining biologic stability of various cargo, including nucleic acids and hydrophobic agents, as well as efficient targeting ability.[46,47] Umbilical cord MSC exosomes were effective in delivery of miRNA oligonucleotides to suppress psoriasis by targeting helper T-cell 17 ($T_H17$) cells and reducing inflammatory cytokines in skin lesions with improved drug stability and delivery efficiency.[48] Similarly, keratinocyte-derived exosomes were loaded with tofacitinib, which exhibited enhanced lowering of TNF-α, IL-23, and IL-6 expression compared to tofacitinib alone.[49]

In a recent clinical trial (n=12), intradermal injection of adipose-derived MSC exosomes at doses of 50 µg, 100 µg, and 200 µg significantly improved psoriatic plaques, primarily with higher doses (100-200 µg) showing the most robust effects. Treatment with these exosomes resulted in clinical reduction in lesion thickness, erythema, and induration, while tissue examination revealed downregulation of psoriatic inflammatory markers and upregulation of anti-inflammatory cytokines FOXP3 and IL-10. Importantly, the treatment was well tolerated, with only mild transient injection-site reactions and no significant adverse reactions, providing supporting evidence for the safety profile of exosomes. However, given the small sample size and lack of long-term follow-up, more robust trials are essential for further characterization of exosomes in the clinical setting.[50]

## WOUND HEALING AND SCARS

PEVs have significant potential in modulating wound repair, scar formation, and scar revision, representing a novel approach to tissue regeneration. Emerging evidence suggests PEVs can accelerate epithelialization, reduce fibrosis, and restore extracellular matrix homeostasis.[51]

**Wound healing.** The normal wound healing process involves four phases: hemostasis, inflammation, fibroproliferation, and remodeling.[52] Dysregulation in any phase, such as excessive inflammation, delayed epithelialization, or aberrant collagen remodeling, can lead to pathological outcomes (ie, hypertrophic scarring, chronic wounds). Given the demonstrated efficacy of exosomes in dysregulated inflammation, PEVs may have a role in the management of wound healing and tissue regeneration.

In experimental models, PEVs displayed suppression of inflammation and necroptosis while enhancing re-epithelialization and hair follicle stem cell activation, resulting in scarless regeneration in murine models.[53] Evidence also suggests they may promote fibroblast proliferation, collagen synthesis, and angiogenesis while inhibiting aberrant myofibroblast differentiation.[54] Additional studies revealed that wheat exosomes promoted skin cell proliferation and migration and collagen I synthesis,[55] beet juice exosomes enhanced collagen production,[56] and aloe EVs prevented wound chronicity by stimulating angiogenesis.[57] These natural anti-inflammatory and wound stabilizing properties combined with the ability to stabilize hydrophobic phytochemicals create potential for PEVs as drug carriers to provide synergistic therapeutic activity in wound healing. This was further reported in citrus exosomes loaded with doxorubicin, providing dual therapeutic effects and accelerated postsurgical wound closure through fibroblast stimulation.[58]

A previously published case series evaluated the clinical efficacy of RSCEs and provided evidence of accelerated wound healing across diverse injury types in the clinical setting.[17] In

burn injuries (beverage-induced and sunburn), topical RSCE application achieved complete epithelialization within 6-7 days, with no residual hyperpigmentation in treated sunburns. In the case of a traumatic wound, a 42-year-old patient with a 2-week-old leg laceration had marked improvement within 4 days of twice-daily RSCE therapy after conventional healing creams had stalled progress. Finally, in the case of healing postlaser resurfacing treatment on the neck of a 37-year-old man, one side was treated with RSCE application while the other was left to heal spontaneously. The RSCE-treated side fully healed by Day 6 of treatment while the other side's healing was prolonged. Additionally, the patient reported improved symptoms to the treated side, highlighting potential applications for PEVs in postcosmetic, ablative healing.[17]

**Keloids, hypertrophic scars, and scar revision.** Mammalian-derived exosomes are associated with significant antiscarring potential through diverse mechanisms. Systemically administered adipose-derived exosomes reduced scar formation in later stages by downregulating collagen expression and promoting remodeling, while human-induced pluripotent stem cell-derived exosomes enhanced re-epithelialization, angiogenesis, and collagen maturity, similar to wound healing mechanisms as described above.[59] ADSC-derived exosomes enriched in antifibrotic cargos in vitro inhibited proliferation, migration, and collagen synthesis and promoted apoptosis of keloid fibroblasts as well as suppressed production of extracellular matrix by these cells, reducing collagen and angiogenesis in keloid tissue explants.[60,61]

In a clinical study on facial acne scarring, ADSC-derived exosomes were applied to atrophic acne scars in combination with fractional carbon dioxide ($CO_2$) laser resulting in accelerated wound healing and reduced postlaser adverse effects.[62] With regards to PEVs, a case series on RCSEs resulted in marked improvement in scar revision, including skin color and texture, when combined with microneedling treatments in the management of a facial scar in a 36-year-old man who had previously been treated with intralesional steroid injections at 6 weeks intervals.[17] These findings, combined with the multitude of preclinical data in favor of exosomal effects in scar management, herald the importance of future investigation in the clinical efficacy of PEVs in wound healing and scar revision.

## COSMETIC

Application of exosomes for anti-aging therapy has been rising, particularly given their demonstrated abilities in modulating cell-cell communication and fibroblast functions. Investigations of mammalian-derived exosomes have indicated potential to increase collagen and elastin synthesis, decrease UV-induced cellular damage, and reverse senescence of aged dermal fibroblasts in various in vitro studies.[59,63-65] Given the established cosmetic and therapeutic potency, *Aloe vera* EVs were studied to further investigate their potential efficacy in vitro.[66] Beyond confirming their dose-dependent antioxidant activity, these EVs exhibited an ability to initiate antioxidant defense mechanisms and stimulate the wound healing process via modulation of messenger RNA (mRNA) expression, highlighting potential mechanisms for their use as a rejuvenation agent.[66] Ginseng EVs have also been shown in vitro to be protective against cell senescence and pigmentation without observed cytotoxicity.[19,67]

Additionally, EVs sourced from a number of medicinal herbs display substantial inhibitory effects on key enzymes involved in melanin synthesis in vitro, potentially being useful for the treatment of hyperpigmentation.[1] These EVs act via decreased gene expression, suppression of melanogenic factors such as oxidative stress, and reduction of melanin content in the epidermis of healthy female volunteers.[67] Patients in a case series using RCSEs experienced marked improvement in facial discoloration and melasma when combined with microneedling treatments as well as skin surface smoothening and improved moisture retention.[17] A number of studies have reported the efficacy of mammalian-derived exosomes in the promotion of follicle development and growth for alopecia areata, and in producing accelerated anagen induction and increased follicle keratinocyte activity in vivo and in vitro studies.[68]

## CHEMOTHERAPEUTIC SKIN-RELATED TOXICITIES

Cutaneous toxicities resulting from systemic cancer therapies represent a frequent and often dose-limiting challenge to adequate treatment, with distinct patterns emerging across various treatment classes.[69] Common toxicities include radiation dermatitis, alopecia, drug-induced maculopapular rash, and kinase inhibitor-associated photosensitivity.[70] These impose burdens on patients, leading to substantial functional and emotional impairments.[71] Epidermal growth factor receptor inhibitors (EGFRi), which are used to treat a variety of malignancies such as metastatic colorectal cancer and breast cancer, have been increasingly used due to their relatively favorable systemic toxicity profile[72]; however, dermatologic-related toxicities are common.[73,74]

Cutaneous adverse effects of EGFRi include acneiform eruptions, xerotic or pruritic rashes, and hyperkeratotic follicular syndromes, frequently leading to treatment discontinuation and, rarely, hospitalization.[75,76] Other cutaneous side effects are alopecia, trichomegaly, and nail disorders.[73] Though these may diminish over the course of treatment, papulopustular rash/folliculitis, hair abnormalities, xerosis, paronychia, and, more rarely, mucositis persisted for many months, highlighting the chronic nature of these toxicities.[74] The mechanism for most reactions stems from the effect of the EGFRi on keratinocyte differentiation and increased inflammation in the skin.[77,78] Currently, management consists of emollients, topical corticosteroids, oral tetracyclines, or systemic glucocorticoids.[79] The efficacy of these treatments is limited and often provides incomplete relief with compounded immunosuppressive risks,[72,79] underscoring the need for novel therapies that can prevent or reverse these pathologies without compromising anticancer efficacy.

Literature related to use of exosomes in the treatment of these cutaneous toxicities is limited. Implications for MSC-derived exosomes for the management of radiation-induced toxicities have been discussed in recent literature, producing protective and regenerative effects in radiation-induced skin, bone, and lung injury.[80] Yang et al[76] further discussed stem cell exosomes as potential treatments for radiation induced skin toxicities, noting their efficacy in murine models to promote wound healing as compared to placebo controls. Fan et al[78] indicated therapeutic efficacy of mesenchymal stem cell-derived exosomes as "decoys" to reduce and reverse doxorubicin-induced heart and liver toxicities in murine models.

PEVs may be a promising therapy for chemotherapy-related cutaneous toxicities due to their capabilities for cell-mediated and cytokine inflammatory regulation, high biocompatibility, and favorable side effect

profile. A recent case study describes the use of RSCE in the treatment of refractory EGFRi-induced acneiform rash and pruritus in a 41-year-old woman with metastatic colorectal cancer.[18] After failing multiple standard therapies including oral antihistamines and topical corticosteroids, topical Damask RSCE was applied to the affected areas on the face on initial presentation and twice a day after. The patient achieved rapid symptom relief, reporting pruritus reduction within 1 hour and complete resolution by Day 3. Clinical evaluation of the affected area revealed significant improvement in cutaneous erythema and acneiform lesions, and the success led to further treatment of hip lesions with RSCE-enriched balm with similar efficacy.[18] The mechanism in which relief was achieved was likely related to RSCE-mediated downregulation of key inflammatory cytokines such as IL-6, IL-1β, and TSLP.[3, 9, 34, 81] These findings highlight PEVs' potential to address both acute inflammatory and chronic barrier-disruptive aspects of EGFRi toxicity through targeted cytokine modulation. Further investigation of PEVs in EGFRi-related dermatologic toxicities is warranted, particularly given their potential to maintain anticancer efficacy while improving treatment tolerability and quality of life.

## CONCLUSION

PEVs have the potential to serve as versatile therapeutics by targeting core pathologic processes in various dermatologic conditions. Their intrinsic anti-inflammatory, proregenerative, and barrier-repair properties enable simultaneous modulation of immune dysregulation, fibroblast activity, and epithelial restoration. Clinical case studies, particularly involving RSCEs, observed rapid symptom relief and structural improvement. PEVs can overcome key limitations of conventional therapies by improving safety profiles and reducing the costs associated with purifying mammalian-derived exosomes. Furthermore, PEVs hold promise for treating chemotherapy-related cutaneous toxicities and as stable, precise drug delivery conduits. Additional clinical data are required to further validate their efficacy and long-term safety. As the field advances, PEVs could redefine dermatologic care and enhance precision in nanotherapeutics.

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