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# Synergistic convergence of selenium and nanotechnology in dermatological therapeutics: Mechanistic insights and clinical prospects

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ABSTRACT

As an essential micronutrient, selenium (Se) plays crucial roles in maintaining cutaneous homeostasis through multifaceted mechanisms including redox regulation, immunomodulation, and anti-tumorigenic activity. While epidemiological and preclinical studies substantiate the therapeutic promise of Se in managing dermatological pathologies such as psoriasis, atopic dermatitis, and cutaneous malignancies, conventional Se formulations face translational challenges due to suboptimal bioavailability and dose-limiting hepatotoxicity. Recent advancements in nanobiotechnology have catalyzed the emergence of Se nanoparticles (SeNPs) as next-generation therapeutic platforms. These engineered nanostructures exhibit superior pharmacokinetic profiles characterized by enhanced epithelial permeability, stimuli-responsive drug release kinetics, and targeted biodistribution. This comprehensive review systematically examines: (1) pathophysiological barriers in dermatologic therapy; (2) Se-mediated molecular circuitry; (3) nano-enabled theranostic breakthroughs; (4) preclinical validation of SeNPs-based combinatorial regimens. By critically evaluating structure-activity relationships of various nanoformulations, we delineate a translational roadmap bridging nanomaterial design principles with clinical needs in precision dermatology. This synthesis aims to accelerate the clinical deployment of Se nanotechnology while addressing key regulatory and manufacturing challenges.

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## 1. Introduction

Selenium (Se) is a fundamental micronutrient in humans, with its key biological roles predominantly governed by selenoproteins [1,2]. On a molecular scale, Se is selectively integrated into the catalytic domains of selenoproteins *via* selenocysteine (Sec).This incorporation process involves dynamic reprogramming of the UGA codon and relies on the synergistic action of selenocysteine insertion sequences (SECIS) and specific transfer RNAs [3]. To date, 25 human selenoproteins have been identified that are instrumental in regulating redox homeostasis, immune responses, and epigenetic modifications. These proteins provide a molecular foundation for understanding Se's multifaceted effects in disease prevention and treatment [3,4]. As research increasingly highlights Se's critical role in numerous biological processes within the human body, it has emerged as a promising adjunctive treatment option across diverse medical fields.

Skin diseases represent a major burden on global health. Epidemiological findings reveal that roughly 30 % of the worldwide population suffers from chronic skin conditions, with accompanying disability and psychological stress significantly compromising patients' quality of life [5]. Current clinical treatment modalities primarily consist of topical medications, systemic immune modulation, and physical therapies. However, the long-term use of these treatments often leads to various adverse reactions. For instance, prolonged application of glucocorticoids may result in skin atrophy and thinning. Biological agents can induce immune drift and drug resistance. Additionally, extended use of ultraviolet B (UVB) therapy may exacerbate photoaging or even elevate cancer risk [6,7]. The restricted effectiveness of existing treatments presents a considerable dilemma. Meanwhile, the complex structural features of the skin barrier, including the integrity of the stratum corneum and the homeostasis of the microbiome, continually con-

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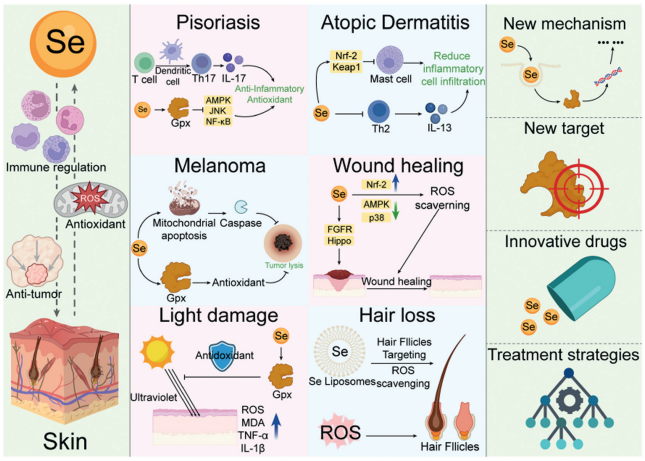



**Fig. 1.** Biological functions of Se and their mechanisms in skin diseases.

strain the efficiency of transdermal drug delivery and the efficacy of local treatments. These therapeutic bottlenecks have spurred the exploration of novel treatment strategies. Se, an essential trace element with multiple biological activities, has shown considerable potential in the treatment of skin diseases [8]. However, the clinical application of traditional Se preparations in dermatology has been limited due to low bioavailability and dose-dependent toxicity [9,10].

Over the last few years, progress in nanotechnology has opened novel pathways for harnessing Se in managing skin diseases. Leveraging their adjustable particle dimensions, large surface area, and prolonged-release properties, Se nanoparticles (SeNPs) can traverse the stratum corneum and accurately target inflamed or neoplastic microenvironments [11]. In addition, nanoemulgels and stimulus-responsive nanoplatforms further improve the transdermal efficiency and lesion targeting of SeNPs [12–14]. These advances show that Se nanodrugs have unique advantages in optimizing the balance between efficacy and risk, breaking through the limitations of the skin barrier, and providing a new paradigm for breaking through the bottleneck of skin disease treatment (Fig. 1).

## 2. Biological functions of Se and its mechanism of action in skin diseases

### 2.1. Antioxidant effects and skin protection

Se is a pivotal element in the skin's antioxidant defense network [4,15,16]. It can integrate into glutathione peroxidase 4 (GPx4) and thioredoxin reductase (TrxR) catalytic sites, neutralizing reactive oxygen species (ROS) and halting lipid peroxidation. Additionally, by activating the nuclear factor erythroid 2-related factor 2 (Nrf2)/Kelch-like ECH-associated protein 1 (KEAP1) signaling axis, Se promotes antioxidant selenoprotein expression at both the transcriptional and translational stages, thereby establishing a two-tier defense mechanism [17].

### 2.2. Immune regulation and inflammation inhibition

Se occupies a pivotal position in modulating immune responses and curbing inflammation. By modulating T-cell expansion and specialization, Se helps uphold immune homeostasis [4]. This immunomodulatory effect helps to alleviate the excessive inflammatory response of the skin and alleviate skin disorders caused by oxidative stress.

### 2.3. Promote skin repair and regeneration

A key regulatory function of Se is the regeneration and regeneration of skin tissue. Se deficiency can affect the integrity of the skin barrier because it is an essential trace element for the physiological function of keratinocytes [15]. During the wound-healing process, Se accelerates recovery by promoting angiogenesis and collagen production [15,16].

### 2.4. Inhibition of tumor progression

Se restrains tumor cell propagation and spread through multiple mechanisms. By activating the p53 tumor suppressor and modulating B-cell lymphoma 2 (Bcl-2) family proteins, Se induces aberrant apoptosis and suppresses cell proliferation. It also inhibits DNA methyltransferases (DNMTs) to mediate epigenetic control, reversing excessive methylation that silences oncogenes like cellular myelocytomatosis oncogene (c-Myc). Through downregulating vascular endothelial growth factor A (VEGF-A) and hypoxia-inducible factor 1-alpha (HIF-1$\alpha$), Se inhibits angiogenesis in cutaneous squamous cell carcinoma (CSCC) [18].

## 3. Breakthroughs in nanotechnology in the diagnosis and treatment of Se

Recent breakthroughs in nanotechnology have ushered in transformative advancements in the field of medicine. Compared with conventional Se compounds, SeNPs offer the following key benefits:

### 3.1. Improved bioavailability, safety and drug delivery

SeNPs exhibit higher bioavailability than inorganic Se and organic Se. With nanoscale dimensions (often $<$100 nm), SeNPs are readily internalized by cells and can traverse biological interfaces like the blood-brain barrier. Their large surface-to-volume ratio notably boosts solubility and biodistribution, thereby amplifying therapeutic effectiveness [19,20]. Exhibiting markedly reduced toxicity compared with typical organic Se compounds (*e.g.*, SeMet and Se-MetSeCys), SeNPs still delivered comparable enhancements in selenoenzyme function and tissue Se levels. The median lethal dose ($LD_{50}$) of SeNPs was measured at 113 mg/kg, substantially exceeding that of SeMet (28 mg/kg) and Se-MetSeCys (19 mg/kg) in mice, underscoring the toxicity-reducing advantages of SeNPs [9,11,20].

SeNPs function as promising carriers in precision medicine. By conjugating folic acid, they selectively bind receptors abundantly expressed by tumor cells (Figs. 2A and B) [19,21]. Additionally, keeping SeNP diameters between 10 nm and 100 nm extends their blood circulation and exploits the enhanced permeability and retention (EPR) effect in solid tumors for passive targeting [19,22].

### 3.2. To achieve the integration of diagnosis and treatment

SeNPs have unique advantages in the combination of diagnosis and treatment. Combining SeNPs with gadolium ($Gd^{3+}$) or quantum dots to construct Se@Gd or Se@QDs complexes can achieve enhanced magnetic resonance (MRI) contrast and fluorescence tracing at the tumor site [21,23]. Gold-Se core-shell nanoplatforms (Au@SeNPs) provoke localized anticancer immune responses with robust tumor-suppressing effects under tumor-associated antigens and effectively reprogram tumor-associated macrophages (TAMs) from the protumor M2 type to the tumoricidal M1 state, thereby promoting system-wide clearance *via* distant phagocytosis (Figs. 2C and D) [24]. Liu *et al.* showed that SeNPs, when tailored with

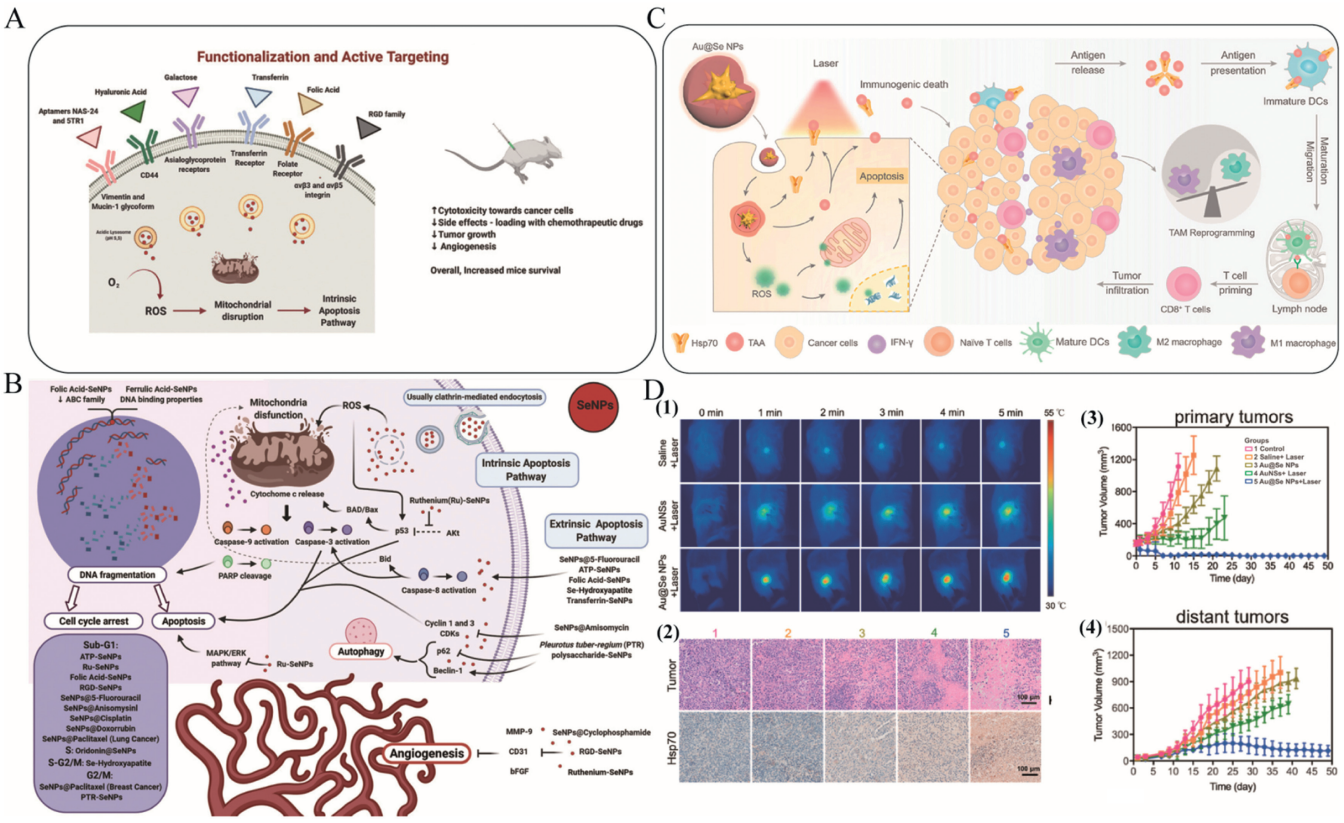



**Fig. 2.** Breakthroughs in theranostic applications of SeNPs. (A) Key compounds and their cognate receptors for SeNPs functionalization. (B) Antitumor mechanisms of SeNPs vary depending on surface modification/functionalization strategies and drug-loading properties. Reproduced with permission [19]. Copyright 2021, Wiley-VCH. (C) Nanotherapeutic Au@SeNPs for photothermal-based immunotherapy: Modulating immunosuppressive tumor conditions and activating systemic anticancer responses. (D) Thermal imaging of the Au@Se NPs + PTT group indicated a pronounced rise in tumor temperature (1). Histopathological examination revealed extensive tumor cell apoptosis with prominent Hsp70 expression (2), alongside significant suppression of both the primary (3) and distant tumor growth (4). Reproduced with permission [24]. Copyright 2020, Elsevier Ltd.

specific components, can act as diagnostic platforms across multiple imaging methods, encompassing fluorescence (FRI), MRI, computed tomography (CT), and photoacoustic imaging (PAI). For instance, molybdenum diselenide-polyethylene glycol ($MoSe_2$-PEG), constructed with transition metal dichalcogenide (TMDC) architecture, offers heightened relaxivity and functions as a $T_1$-weighted MRI contrast medium for *in vivo* tumor detection [23].

## 4. Application of Se and nanomedicine in the diagnosis and treatment of various skin diseases

### *4.1. Application of Se in the treatment of psoriasis*

Psoriasis is a chronic immune-driven dermatological condition which typically appears as erythematous plaques with silver-white scaling [25]. In psoriatic lesions, keratinocytes proliferate at an accelerated rate. Both proinflammatory cytokines such as interleukin-17 (IL-17) and oxidative stress are the major component in psoriasis pathogenesis. Psoriasis management typically involves topical agents (such as corticosteroids, vitamin $D_3$ derivatives, and cyclosporine) as well as systemic treatments (for instance, methotrexate or adalimumab). Although these treatments are effective, long-term use is often accompanied by adverse reactions. Se shows a great talent to the treatment psoriasis.

Clinical trials indicate that Se combined with vitamin E and coenzyme Q10 substantially lowers oxidative stress markers (malondialdehyde (MDA) reduced by 34.7 %) and improves psoriasis area and severity index (PASI) scores in psoriasis patients [26]. By generating ROS, these nanoparticles encouraged keratinocyte apoptosis and curbed lesion expansion. The immunomodulatory actions of SeNPs are also crucial. Nazıroğlu *et al.* observed that Se reduces tumor necrosis factor-alpha (TNF-$\alpha$) and alleviates inflammation by limiting UVB-induced proinflammatory cytokine release in human keratinocytes [27]. Moreover, SeNPs modulated key pathways such as mitogen-activated protein kinases (MAPKs), signal transducer and activator of transcription 3 (STAT3), glycogen synthase kinase 3 beta (GSK-3$\beta$), protein kinase B (Akt), lowered proliferation markers (proliferating cell nuclear antigen (PNCA), Ki67, cyclin D1) in keratinocytes, and reduced IL-1$\beta$ and IL-17A, thus mitigating cutaneous inflammation and hyperplasia in psoriatic mice (Fig. S1 in Supporting information) [28]. Multiple studies have demonstrated that nanoparticles possess heightened bioavailability and stability, enabling efficient transdermal drug transport while minimizing systemic toxicity [29,30–32]. Nanoparticle-facilitated delivery of methotrexate or steroids enhances cutaneous permeability while reducing systemic exposure [31]. Gangadevi *et al.* showed that applying SeNPs topically in the imiquimod (IMQ) model led to improved penetration into deeper skin layers, aided by their small size and high surface area. Owing to their robust encapsulation and controlled release capabilities, nanoparticles provide sustained release of active agents in psoriasis therapy, thereby improving therapeutic efficacy and delaying drug resistance [33].

### *4.2. Application of Se in the treatment of atopic dermatitis*

Atopic dermatitis (AD), a chronic inflammatory skin condition, presents as xerosis, erythema, pruritus, and recurrent rash. Its pathophysiology is centered on a dominant Th2-type immune

response, propelled by cytokines including IL-4, IL-13, and IL-5. These mediators not only intensify inflammation but also disrupt the skin barrier, thereby amplifying allergic reactions and inflammation. The treatment of AD mainly relies on topical agents (such as steroids and calcineurin inhibitors) and systemic immunosuppressants. However, long-term use of these drugs often causes several adverse reactions, such as skin atrophy and emergence of drug resistance [6,34–37].

Multiple investigations indicate that insufficient Se can aggravate AD symptoms, whereas Se supplementation helps modulate the Th2 immune pathway, adjust cytokines such as IL-4 and IL-13, curtail inflammation [38,39]. Voss *et al*. combined a water-soluble Se formulation (SeTal) with gelatin–alginate (Gel–Alg) membranes to serve as localized therapeutic carriers, and their interactions with hydrocortisone (HC) or vitamin C were comprehensively evaluated. Findings revealed that these composite membranes substantially lowered both myeloperoxidase (MPO) activity and nitric oxide metabolites (NOx) in the ear and dorsal skin of AD mice model, signifying notable anti-inflammatory and antioxidant effects (Figs. S2A and B in Supporting information) [40]. Xie *et al*. determined that anti-allergic SeNPs (LET-SeNPs) demonstrated strong therapeutic outcomes for allergic dermatitis in the nonhuman primate model of allergic dermatitis. It can effectively trigger the Nrf2-Keap1 pathway while inhibiting ROS-driven cyclooxygenase-2 (COX-2) and mitogen-activated protein kinases (MAPK) pathway, thereby modulating selenoproteins and boosting their antioxidant expression at both mRNA and protein levels and suppressing mast cell activation and reducing histamine, $\beta$-hexosamine, and inflammatory mediators, produces potent anti-allergy benefits (Figs. S2C and D in Supporting information) [17]. Meanwhile, nanoparticles can precisely target AD lesions, minimize adverse effects and enhance localized treatment efficacy. For instance, nano-micelles, liposomes, and solid lipid nanoparticles (SLNs) can increase skin permeability for agents such as steroids and calcineurin inhibitors, thereby improving therapeutic results [6,37,41,42].

### 4.3. Application of Se in melanoma therapy

Melanoma, regarded as one of the most lethal skin malignancies, once metastasis develops, survival rates drop sharply [43,44]. The etiology of melanoma is intricate, shaped by multiple factors that principally involve UV-induced DNA damage, oxidative stress, and genetic predisposition. At present, the treatment methods for melanoma emerge in an endless manner. Beyond standard surgery, radiotherapy, and chemotherapy, more advanced treatments, such as targeted therapy, immunotherapy, and chimeric antigen receptor T-cell (CAR-T) therapy, have also yielded promising results. However, the issue of drug resistance to single-agent regimens in melanoma has become progressively more apparent. Therefore, exploring new combined treatment strategies to reduce the drug resistance rate and adverse reactions has become the general trend of melanoma treatment in the future [43–45].

Liu *et al*. reported that Se triggers apoptosis in melanoma cells by modulating endogenous oxidative stress signaling [46]. Liu *et al*. conjugated SeNPs with the 5-fluorouracil (5-FU), demonstrating that 5-FU-functionalized SeNPs (5FU-SeNPs) boost 5-FU uptake, drive apoptosis in A375 melanoma cells, and activate mitochondrial cell death through ROS generation. This synergistic therapy not only strengthened the anticancer effect but also minimized systemic toxicity by elevating local drug concentrations [47]. In a related analysis, Badea *et al*. reviewed diverse nanoparticle systems (including liposomes, polymeric particles, and dendrimers) for melanoma therapy and reported that nanomaterials can counteract drug resistance while enhancing treatment outcomes by increasing intratumoral drug concentration, promoting intracellular uptake, and reducing drug efflux [48–52]. Gong *et al*. developed a platinum with selene-based nanoenzyme PS@CS, and Mohammadi *et al*. used Se-polyvinyl alcohol-curcumin (Se-PEG-Cur) nanoparticles to generate ROS through photothermal and ultrasonic effects to further enhance the anti-tumor effect (Figs. S3A and B in Supporting information). Through this dual-mode treatment, it can simultaneously exert anti-tumor, anti-bacterial and promote wound healing of postoperative infection [53,54]. Using a double-emulsion procedure, Yang *et al.* formulated NMDS-IR780 nanoparticles as an ultrasound contrast agent. These nanoparticles displayed favorable size distribution, stability, and biocompatibility, enabling them to target cutaneous melanoma cells effectively. In both *in vitro* and *in vivo* assessments, they facilitated dual-mode imaging and photothermal therapy, suggesting a novel route for the precise diagnosis and treatment of malignant melanoma (Figs. S3C and D in Supporting information) [55].

### 4.4. Application of Se in wound healing

Wound healing is a complex, intricately regulated process that engages the skin, blood vessels, immune defenses, and extracellular matrix [56,57]. The process of wound healing often affected by multiple factors such as oxidative stress, inflammation, and cell regeneration. Several researches found that the concentration of Se at the edge of the wound was significantly increased, which promoted the immune defense and early healing process of the wound by regulating antioxidant enzymes and cell migration [58,59]. Cimmino *et al*. found that selenosaccharide combined with salicylic acid compounds had anti-inflammatory and anti-oxidative effects in human keratinocytes hair through nuclear factor kappa-light-chain-enhancer of activated B Cells (NF-$\kappa$B) and p38 MAPK signaling pathways, thereby promoting wound healing [60]. Zheng *et al.* developed a carboxymethyl chitosan (CMCS)/polyvinylpyrrolidone (PVP)/$MoSe_2$/platelet-rich plasma (PRP) hydrogel by integrating molybdenum selenide ($MoSe_2$) with PRP. They observed that $MoSe_2$ nanozymes effectively remove free radicals at the wound site and bolster antioxidant defenses, while PRP releases growth factors that foster angiogenesis (Figs. S4A and B in supporting information) [61].

Also, nanotechnology has shown great potential in wound repair. Yang *et al.* developed hydrogen selenide (H2Se)-based nanotherapeutics capable of releasing bio-heterojunctions (bio-HJs) upon near-infrared (NIR, 808 nm) laser irradiation and revealed that bio-HJs synergistically enhanced selenoprotein biosynthesis pathways, upregulating GPx1 expression, thereby effectively inhibiting senescent cell accumulation [62]. Akhiani *et al.* applied Se nanoparticle oxide (NSeO) in a rat flap model and found that NSeO improved flap survival through antioxidant effects [63]. Cao *et al.* revealed that Nano-Se notably improved fin regeneration and accelerated wound repair in diabetic skin in zebrafish caudal fin and diabetic mouse models [64]. Subsequently, they created Nano-S@bFGF by integrating sulfur Se nanocomposites with basic fibroblast growth factor (bFGF). RNA-seq analysis demonstrated that Nano-S@bFGF promoted wound closure by co-activating FGFR and Hippo pathways leading to considerable enhancement in zebrafish tail fin regrowth and diabetic mouse skin healing, underscoring its potential in regenerative medicine (Figs. S4C and D in Supporting information) [65].

### 4.5. Application of Se in infectious diseases

Infectious skin diseases include a variety of skin conditions caused by bacteria, fungi and viruses. Skin infections are commonly encountered and include bacterial, fungal, and viral types [66,67].

Bacteria infiltrate the skin primarily by compromising the barrier, which facilitates local infections. Pathogens such as *Staphylococcus aureus* (*S. aureus*) and *Staphylococcus epidermidis* (*S. epidermidis*) can form biofilms on the skin surface, a phenomenon that shields them from antibiotics and contributes to chronic infections [66]. Han *et al.* demonstrated that SeNPs exhibit strong antibacterial activity against pathogens including methicillin-sensitive *S. aureus* (MSSA) and methicillin-resistant *Staphylococcus aureus* (MRSA). These nanoparticles disrupt bacterial cell membranes, leading to the leakage of intracellular contents and subsequent cell death. When combined with linezolid, SeNPs exert a synergistic effect that effectively curtails the growth of drug-resistant strains [68].

Fungi commonly colonize moist skin regions, such as armpits and groin, where they form biofilms that enhance both drug resistance and pathogenicity [66]. De Siqueira *et al*. demonstrated that the organic Se compound $(MeOPhSe)_2$ significantly inhibited the growth of *Candida krusei*, prolonged its lag phase, suppressed biofilm formation, and reduced adhesion to cervical epithelial cells. These effects were attributed to enhanced production of superoxide radicals [69,70]. Further research indicates that SeNPs not only exert direct antifungal effects but also improve Se bioavailability by enhancing solubility and potentiating drug efficacy. For instance, when SeNPs were combined with nystatin to form SeNP@PVP_Nystatin nanocomposites, reverse transcription-polymerase chain reaction (RT-PCR) analysis revealed significant inhibition of *C. albicans* biofilm formation and morphological transitions through downregulation of key genes in the Rat sarcoma (RAS)/cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) pathway, such as Als3, Hwp1, and Efg1 [71]. Huang *et al*. developed antimicrobial peptide-functionalized SeNPs ($\varepsilon$-PL-SeNPs) *via* $\varepsilon$-poly-L-lysine coating. These nanoparticles displayed broad-spectrum antibacterial activity with a lower tendency for resistance development and exhibited potent antifungal effects against *C. albicans* (Fig. S5 in supporting information) [72].

Viruses evade immune detection by entering a latent state within host cells, reactivating later to cause new infections [73]. Lavaee *et al*. demonstrated that Se enhances immune defense by promoting GPx activity and facilitating free radical removal, thereby mitigating viral infection [74]. Another study indicated that dietary antioxidants, including Se, zinc, and vitamins A and C, offer protection against high-risk HPV (hrHPV) infection [75]. Moreover, nanotechnology has been employed to improve acyclovir's transdermal delivery, with an optimized nanoemulsion showing a 535.2 % increase in bioavailability [76].

### 4.6. Application of Se in alopecia

Alopecia, a common clinical dermatological condition, includes androgenetic alopecia (AGA), telogen effluvium (TE), alopecia areata (AA) and so on. Oxidative stress, a common pathogenic mechanism among these conditions, damages cellular metabolism and disrupts the normal hair follicle cycle through excessive ROS, leading to hair follicular dysfunction and accelerating hair loss [77,78]. Current clinical treatments for hair loss predominantly involve topical formulations such as minoxidil and oral medications like finasteride. However, long-term use of these treatments may induce side effects such as skin irritation and allergic reactions [79].

Se plays the importance role of hair follicle development and immune regulation. Hosomi *et al*. demonstrated that Se facilitates normal hair growth by modulating oxidative stress through its role as a cofactor for antioxidant enzymes such as GPx [80], and mice lacking GPx4 exhibited abnormal hair formation, epidermal hyperplasia, and inflammatory cell infiltration [81]. Additionally, Thompson *et al*. found that Se may help alleviate alopecia areata by modulating the immune response, notably by affecting Th1 cell proliferation [82]. Advances in nanotechnology have introduced promising drug delivery systems for alopecia treatment. Pereira *et al*. showed that various lipid-based nanoparticles, including SLNs, nanostructured lipid carriers (NLCs), liposomes, and acetozolids, possess excellent hair follicle targeting capabilities, effectively delivering drugs like minoxidil and finasteride with reduced systemic side effects [83,84]. Thepphankulngarm *et al*. developed a nanoparticles delivery system and demonstrated that this formulation effectively promoted hair follicle growth, and enhanced both biocompatibility and targeted drug delivery by using porcine skin models and human hair follicle dermal papilla cells (HFDPCs) [85].

### 4.7. Current nanotechnology strategies in vitiligo management

Vitiligo is a common acquired pigmentary disorder marked by non-scaly white patches on the skin, typically resulting from localized or systemic immune dysregulation that leads to the targeted destruction of melanocytes [86]. Although its precise etiology remains unclear, vitiligo is believed to arise from a complex interplay of immune responses, genetic susceptibility, environmental triggers, and oxidative stress [86–88].Conventional treatments for vitiligo, such as topical corticosteroids, phototherapy, and immunosuppressive agents, are often limited by adverse reactions and the potential for drug resistance during long-term use [86,87].

Although studies on serum Se levels in vitiligo patients have produced conflicting findings, the biological importance of Se in this context remains evident. As a key component of GPx, Se reduces oxidative stress by scavenging hydrogen peroxide, which is typically elevated in vitiligo [87,89]. Furthermore, Se deficiency may disrupt the Th1/Th2 immune balance and promote the secretion of pro-inflammatory cytokines (*e.g.*, chemokine (C-X-C motif) ligand (CXCL) 9 and CXCL10), a scenario that aligns with increased serum IL-15 levels in active vitiligo cases [87,90]. Meanwhile, nanotechnology takes the advantages of drugs delivery. It can penetrate the skin barrier with high efficiency and act directly on the targeted areas, reducing systemic toxic side effects. The recent study by Sahu *et al*. has highlighted nanotech-based drug delivery systems, including liposomes, polymer nanoparticles, hydrogels, microneedles, and transdermal patches, which enhance skin permeability and bioavailability *via* controlled release, significantly improving therapeutic efficacy and patient outcomes [91].

### 4.8. The therapeutic potential of Se in other skin diseases

Selenium is closely associated with the onset and progression of diverse dermatological conditions. For instance, Zujko-Kowalska et al. linked an antioxidant-rich diet containing selenium to a significant improvement in quality of life among rosacea patients. Individuals with a high antioxidant diet quality index (DAQI) experienced marked relief of skin symptoms alongside conventional cosmetic treatments [92]. In a murine seborrheic dermatitis model, this nanocomposite exhibited robust antifungal activity and effectively reduced inflammatory markers, without causing significant skin irritation in dermal toxicity tests [93]. In another investigation, Socha *et al*. quantified serum Se levels using atomic absorption spectroscopy in 101 relapsing-remitting multiple sclerosis (MS) patients and 63 healthy controls, while also assessing GPx activity and total antioxidant status (TAS) with commercial assay kits. In addition, Se and SeNPs also hold great potential in the treatment of various skin conditions such as acne, melasma, and photoaging [94].

To sum up, SeNPs has shown universal applicability in the intervention of many common skin diseases by virtue of its unique multi-effect regulatory functions such as antioxidant, immunomodulatory and pro-repair. SeNPs can effectively alleviate the inflam-

matory cascade, inhibit pathogen proliferation, promote barrier reconstruction, and overcome the limitations of traditional therapies such as low bioavailability, drug resistance and systemic toxicity [95,96]. In short, SeNPs is expected to become a new direction for multi-target treatment of skin diseases.

## 5. Conclusions and prospects

This review systematically investigates the biological effects of Se compounds and their nanostructures in skin disease interventions, with a particular focus on three core mechanisms: antioxidant protection, immune homeostasis regulation, and skin barrier restoration, while highlighting its substantial potential for diverse dermatological applications, thereby providing a robust scientific basis for the development of innovative treatment strategies. Future research should further explore Se–nanotechnology synergistic systems to facilitate the translation of basic research into clinically valuable precision therapies.

### *5.1. In-depth mechanism analysis and target innovation*

The wide heterogeneity of skin diseases means that the mechanisms underlying Se's therapeutic effects remain incompletely understood. Current studies primarily focus on classical pathways such as Nrf2/GPx4 and Janus kinase (JAK)-STAT, leaving the diverse modes of action for different Se compounds (including SeNPs and organic Se forms) in disease-specific microenvironments largely unexplored. Future research should address these gaps to provide a robust theoretical basis for the precise clinical application of Se. Furthermore, advanced multi-omics approaches, such as single-cell sequencing and spatial transcriptomics, could be helpful for uncovering new regulatory targets.

### *5.2. Rational design of intelligent delivery system*

Based on molecular targets identified through studies of disease microenvironments and Se's mechanisms, there is a clear need to develop an "environmental response-active targeting" dual-modality Se delivery system. Moreover, strategies that integrate exosome-based delivery or metal–organic frameworks (MOFs) can overcome the limitations posed by the skin barrier and achieve spatiotemporal controlled release of Se. In the future, Se composites conjugated with photosensitizer can be designed to release active Se components by NIR light, and simultaneously activate photodynamic/photothermal synergistic effects. These designs all reflect the advantages of SeNPs in precision treatment.

### *5.3. Systematic construction of clinical translation system*

The clinical conversion of SeNPs is subject to a strict regulatory scientific framework. At present, Food and Drug Administration (FDA), European Medicines Agency (EMA) and National Medical Products Administration (NMPA) have initially established characterization standards (such as particle size distribution, surface charge, and encapsulation rate) for nanomaterials. However, the regulation of skin local delivery systems still needs to be further refined.

Although SeNPs have demonstrated promising therapeutic effects in laboratory studies, their long-term safety, toxicity profiles, and *in vivo* metabolic behavior in clinical applications remain inadequately validated. Se's biological activity is dose-dependent, and both insufficient and excessive intake can compromise efficacy—chronic overconsumption may even lead to adverse effects such as liver toxicity. Future research should focus on investigating the *in vivo* kinetics of SeNPs, their interactions with skin cells, and comprehensive toxicological evaluations to ensure clinical safety and effectiveness. To facilitate the clinical translation of Se-based therapies, it is essential to establish a comprehensive validation framework that integrates mechanistic research, technological innovation, and clinical trials. Prior to launching clinical trials, the use of skin organoid models combined with AI-driven simulation techniques is recommended to accurately predict transdermal drug characteristics and dose–toxicity thresholds. Additionally, systematic monitoring of liver and kidney function indicators is required to evaluate the safety of Se formulations, and standardized quantitative measures for assessing lesion improvement should be established. Current research should further elucidate the synergistic mechanisms between Se and other agents, such as biologics and immunosuppressants, while also developing personalized treatment protocols based on genetic polymorphisms related to Se metabolism.

In summary, with ongoing advancements in Se nanotechnology, future research should prioritize: (1) target identification: elucidating Se's therapeutic mechanisms in skin pathologies; (2) delivery strategy: engineering precision systems based on Se metabolism; (3) holistic evaluation: a 3D framework for safety, efficacy, and personalized therapy. In particular, exploring the drug-loading adaptability of SeNPs is imperative to achieve enhanced therapeutic efficacy with reduced toxicity through combination treatment strategies. This systematic research approach will propel the translation of Se and its nanoformulations from experimental studies to routine clinical applications in skin disease management.

## Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT for language polishing. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the 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.

## CRediT authorship contribution statement

**Yangxia Chen:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Wei Liu:** Writing – original draft, Methodology, Data curation. **Yinghui Liu:** Supervision, Methodology, Data curation. **Sirui Li:** Methodology. **Hongfang Liu:** Validation, Data curation. **Shuoshan Li:** Visualization, Software. **Luo Ying:** Data curation. **Rongyi Chen:** Writing – review & editing, Funding acquisition, Data curation. **Tianfeng Chen:** Writing – review & editing, Supervision, Conceptualization.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2025.111298.

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