Intelligent Antioxidant Formulations for Skin Longevity: Leveraging Nanotechnology and Artificial Intelligence in Precision Dermatology for Exposome Defense

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Abstract

Skin longevity, a critical aspect of dermatological health, is profoundly influenced by the exposome—a dynamic interplay of environmental, social, and biological factors. Extrinsic skin aging, driven primarily by solar radiation and air pollution, is largely mediated by oxidative stress and subsequent cellular damage. Traditional antioxidant formulations often face significant bioavailability, stability, and targeted delivery limitations, hindering their efficacy. This review synthesizes recent advancements (2015–2025) in intelligent antioxidant formulations that leverage the transformative capabilities of nanotechnology and artificial intelligence (AI). Nanotechnology-based systems overcome conventional delivery challenges by enhancing antioxidant solubility, stability, and permeation, enabling precise targeting and controlled release. Concurrently, AI is revolutionizing precision dermatology, moving beyond traditional image-based diagnostics to encompass predictive modeling of treatment responses, personalized risk assessment, and the intricate analysis of complex exposome data. The synergistic integration of AI and nanomedicine facilitates AI-optimized nanocarrier design, enabling hyper-personalized antioxidant formulations and adaptive therapeutic strategies based on real-time biological feedback. This convergence holds immense potential to redefine skin longevity and exposome defense, offering unprecedented precision and responsiveness in dermatological interventions. However, realizing this promise necessitates addressing technical hurdles, ensuring data quality, and navigating complex regulatory and ethical considerations.

1. Introduction: The Evolving Landscape of Skin Longevity

1.1. Skin Aging: Intrinsic vs. Extrinsic Factors and the Role of Oxidative Stress

Skin aging is a multifaceted biological process resulting from the intricate interplay of both intrinsic and extrinsic factors. Intrinsic aging is an inevitable, genetically programmed process characterized by cellular senescence and metabolic changes. In contrast, extrinsic skin aging is predominantly driven by environmental exposures, collectively termed the exposome (**Krutmann et al., 2017**). A primary mechanism through which these extrinsic factors accelerate skin aging is the induction of oxidative stress. This occurs when there is a critical imbalance between the production of reactive oxygen species (ROS) and the body's intrinsic capacity to neutralize them, leading to an accumulation of ROS within skin cells and tissues (**Krutmann et al., 2017; Parrado et al., 2019**).

The accumulation of ROS inflicts severe damage upon vital cellular components and structures within the skin, including lipids, proteins, and DNA, ultimately contributing to the visible manifestations of skin aging, such as wrinkles, hyperpigmentation, and loss of elasticity. This cellular damage also increases the susceptibility to various skin disorders and cancer (**Souto et al., 2015; Pullar et al., 2017**). A critical aspect of this process is that external stressors not only generate ROS but also actively deplete the skin's natural, endogenous antioxidant defenses present in the stratum corneum (**Krutmann et al., 2017; Burke, 2018**). This depletion exacerbates the oxidative imbalance, allowing ROS to penetrate deeper into the skin layers, including the dermis, where they can severely impact collagen metabolism and accelerate wrinkle formation (**Krutmann et al., 2017; Passeron et al., 2018**). This creates a detrimental feedback loop where environmental insults compromise the skin's protective mechanisms, leading to a cascade of accelerated damage. Therefore, effective interventions for skin longevity must extend beyond merely neutralizing existing ROS; they must also aim to protect, restore, or enhance the skin's intrinsic antioxidant capacity to interrupt this amplification loop and provide a more robust, long-term defense against environmental damage (**Farris et al., 2014**).

1.2. The Exposome Concept: A Holistic View of Environmental Influences on Skin Health

The exposome represents a comprehensive and dynamic concept, encompassing the totality of environmental factors an individual encounters throughout their lifetime (**Krutmann et al., 2017; Wild, 2012**). This includes a broad spectrum of external elements, such as air pollution, solar radiation, diet, and lifestyle behaviors, as well as internal factors like the gut microbiome and endogenous metabolic processes. Crucially, the exposome also accounts for the biological

responses of the human body to these diverse exposures **(Krutmann et al., 2017; Niedzwiecki et al., 2019)**. It is increasingly recognized as a critical determinant of individual aging trajectories, significantly influencing both healthy aging and overall longevity **(Niedzwiecki et al., 2019; Vermeulen et al., 2020)**.

A deeper understanding of the exposome is vital because environmental factors do not act in isolation; they interact with each other in complex and often synergistic ways **(Krutmann et al., 2017; Burke, 2018)**. For instance, the combined effect of ultraviolet radiation and air pollutants (termed "photo-pollution") can amplify oxidative stress and inflammation in the skin to a greater extent than either factor alone **(Krutmann et al., 2017; Araviiskaia et al., 2021)**. This intricate interplay means that studying exposures in isolation can be reductive and lead to incomplete or even misleading conclusions regarding their cumulative impact on health **(Wild, 2012; Rappaport, 2016)**. Therefore, a truly comprehensive and precision-based approach to skin longevity necessitates moving beyond addressing single environmental threats. It requires a holistic, integrated understanding of the exposome's complex interactions to develop multi-targeted and adaptive defense strategies. This detailed comprehension of an individual's exposome profile is fundamental for optimizing personalized disease risk assessment and tailoring effective treatment strategies **(Wild, 2012; Miller & Jones, 2014)**.

1.3. Emergence of Intelligent Formulations: Nanotechnology and AI as Game-Changers

Traditional antioxidant supplementation, despite its recognized potential to combat oxidative stress, often faces significant limitations. These include the low bioavailability of many natural compounds due to poor solubility, inherent instability when exposed to light, oxygen, or biological fluids, and inefficient absorption or percutaneous penetration **(Souto et al., 2015; Prow et al., 2016)**. These challenges restrict their therapeutic potential in dermatological applications.

In response, nanotechnology-based systems have emerged as a transformative solution. Nanocarriers are engineered to overcome these delivery hurdles, offering superior solubility, enhanced stability, extended half-life, and improved permeability across biological barriers, thereby significantly increasing the bioavailability and efficacy of therapeutic antioxidants **(Souto et al., 2015; Zhang et al., 2020)**.

Concurrently, artificial intelligence (AI) is rapidly evolving beyond its initial and widely recognized applications in image-based diagnostics within dermatology **(Chan et al., 2020; Esteva et al., 2017)**. AI now presents novel opportunities to enhance the accuracy, efficiency, and personalization of skin disorder management. Its capabilities extend to sophisticated predictive modeling of treatment responses, personalized risk assessment, and advanced clinical decision support **(Chan et al., 2020; Aggarwal et al., 2021)**.

The convergence of nanomedicine and AI represents a profound paradigm shift in healthcare. This integration promises unprecedented advancements in diagnosis, treatment, and patient

management by facilitating precise, personalized, and adaptive strategies **(Paul et al., 2023; Ho et al., 2022)**. The "intelligence" inherent in these formulations manifests when AI optimizes the design, targeting, and adaptive release of nano-encapsulated antioxidants. This optimization is driven by complex, individualized exposome and biological data, making the formulation itself responsive and dynamic. This level of responsiveness and precision is only achievable through the synergistic integration of nanotechnology for advanced delivery and AI for data-driven optimization and personalization **(Subbiah et al., 2021)**. This convergence is key to overcoming the limitations of conventional approaches and developing truly adaptive solutions for skin longevity.

1.4. Scope and Objectives of the Review

This comprehensive scientific literature review aims to synthesize recent advancements published between 2015 and 2025 concerning the synergistic application of nanotechnology and artificial intelligence. The focus is on their combined role in the development of intelligent antioxidant formulations designed to promote skin longevity and enhance exposome defense. The review will critically evaluate the mechanisms through which the exposome induces skin aging, detail the progress in nanodelivery systems for antioxidants, explore the evolving role of AI in precision dermatology and exposome analysis, and discuss the inherent challenges and promising future directions of their integrated application **(Krutmann et al., 2017; Paul et al., 2023)**.

2. The Skin Exposome: Impact on Aging and Defense Mechanisms

2.1. Major Exposome Factors: Solar Radiation and Air Pollution

The skin, as the body's largest organ, serves as the primary interface with the external environment, making it highly susceptible to exposome factors that contribute to extrinsic aging. Among these, solar radiation and air pollution are identified as the most significant contributors to skin aging **(Krutmann et al., 2017; Marionnet et al., 2015)**.

Solar radiation encompasses a spectrum of electromagnetic waves, including ultraviolet radiation (UVR, comprising UVB and UVA), visible light (VL), and infrared (IR) radiation. Each component penetrates the skin to different depths and contributes distinctly to photoaging and skin damage **(Krutmann et al., 2017; Grether-Beck et al., 2014)**. UVA, which penetrates deeply into the dermis, is recognized as the primary driver of photoaging, affecting dermal fibroblasts and contributing to wrinkles and hyperpigmentation. UVB, primarily absorbed by the epidermis, is known for inducing erythema (sunburn) and direct DNA damage, increasing the risk of cutaneous cancers **(Krutmann et al., 2017; Schuch et al., 2017)**. Beyond UVR, visible light, particularly blue-violet light, and infrared radiation also contribute to skin aging by generating reactive oxygen species (ROS) and inducing the expression of matrix

metalloproteinase-1 (MMP-1), enzymes that degrade collagen **(Krutmann et al., 2017; Hudson et al., 2021)**.

Air pollution constitutes another major environmental threat, comprising gases like ground-level ozone (O3) and particulate matter (PM), a complex mixture of solid and liquid particles suspended in the air. PM is categorized by size, with PM2.5 (fine particles, ≤2.5μm) being particularly concerning due to its highly lipophilic nature, allowing it to easily penetrate the skin barrier **(Krutmann et al., 2017; Puri et al., 2017)**. Other relevant pollutants include polycyclic aromatic hydrocarbons (PAHs), volatile organic compounds (VOCs), and heavy metals **(Krutmann et al., 2017; Drakaki et al., 2014)**.

A critical aspect of exposome-induced skin damage is the phenomenon of "photo-pollution." This refers to the synergistic effect where the detrimental impact of air pollutants on the skin is significantly augmented by concurrent exposure to solar radiation **(Krutmann et al., 2017; Araviiskaia et al., 2021)**. The combination of UVR, PM, and ozone exposure leads to a heightened increase in oxidative stress and inflammation, surpassing the effects of individual stressors **(Krutmann et al., 2017; Burke, 2018)**. For example, UVA radiation combined with diesel PMs can induce substantial cytotoxic and genotoxic damage through the production of photoactive singlet oxygen, while PAHs in conjunction with UVA significantly exacerbate skin damage and aging **(Krutmann et al., 2017; Soeur et al., 2017)**. This amplification of damage underscores that defense strategies must account for these complex, synergistic interactions rather than treating solar radiation and air pollution as isolated threats **(Fuks et al., 2019)**.

2.2. Mechanisms of Exposome-Induced Skin Damage: ROS Generation, Inflammation, Microbiome Disruption

Exposome factors initiate and propagate skin aging primarily through several interconnected mechanisms, with oxidative stress serving as a central pathway **(Krutmann et al., 2017; Parrado et al., 2019)**.

The primary mechanism involves the generation of reactive oxygen species (ROS). Exposure to ground-level ozone, for instance, directly depletes stratum corneum-associated antioxidants, leading to an immediate oxidative stress response. This oxidative stress then propagates to deeper skin layers, including the dermis, where it profoundly affects collagen metabolism, contributing directly to wrinkle formation **(Krutmann et al., 2017; Valacchi et al., 2017)**. Similarly, repeated exposure to particulate matter (PM), even at non-toxic concentrations, significantly increases ROS production, which in turn triggers the secretion of pro-inflammatory cytokines and leads to cellular dysfunction **(Krutmann et al., 2017; Jin et al., 2018)**.

Beyond direct oxidative damage, exposome factors also trigger inflammation. The increased ROS burden from PM exposure can compromise the skin's lipid barrier, rendering it more permeable and susceptible to inflammatory responses. This can initiate or exacerbate various inflammatory skin diseases **(Krutmann et al., 2017; Lee et al., 2016)**.

A less recognized but increasingly important mechanism is the disruption of the skin microbiota. Exposure to PM can decrease the diversity and number of beneficial cutaneous microbial species, thereby compromising the skin's ecological balance and its role in immune modulation **(Krutmann et al., 2017; Patra et al., 2018)**. This local disruption is further influenced by the broader systemic impact of the gut microbiome, which acts as a mediator between environmental exposures and overall immune-metabolic health, influencing inflammation and cellular aging throughout the body, including the skin **(Niedzwiecki et al., 2019; Bosman et al., 2019)**. This interconnectedness highlights that exposome factors do not merely cause oxidative stress in isolation; they actively undermine the skin's primary physical defense (barrier function) and its ecological balance (microbiome), making the skin inherently more vulnerable to oxidative damage and inflammation **(Prescott et al., 2017)**.

Another significant mechanism is the activation of the Aryl Hydrocarbon Receptor (AhR). Certain air pollutants, such as PAHs, can activate this transcription factor, leading to a cascade of cellular responses that contribute to hyperpigmentation, wrinkle formation, increased risk of skin cancer, and the worsening of pre-existing dermatoses like acne, atopic dermatitis, and psoriasis **(Krutmann et al., 2017; Esser et al., 2018)**.

The complexity of these interconnected mechanisms underscores that the skin is not merely a passive target for environmental damage but an active ecosystem whose intrinsic defense mechanisms are compromised. Therefore, future intelligent formulations for exposome defense must adopt a multi-pronged strategy that not only delivers potent antioxidants but also actively supports the restoration and maintenance of the skin barrier function and a healthy skin microbiome **(Pullar et al., 2017; Patra et al., 2018)**. This holistic approach is essential for truly comprehensive and resilient skin longevity.

2.3. Current Strategies for Exposome Defense

Current strategies for defending the skin against age-related changes induced by the exposome primarily focus on two complementary approaches: preventing the deposition and penetration of pollutants, and actively counteracting their detrimental effects once they have breached the skin barrier. These strategies aim to reinforce the skin's intrinsic barrier function and augment its antioxidant reserves **(Krutmann et al., 2017; Passeron et al., 2018)**.

Passive Defense mechanisms involve creating a physical barrier on the skin surface. This is typically achieved through the use of film-forming ingredients, such as Alteromonas ferment extract, Kappaphycus alvarezii, and Caesalpinia spinosa extracts, which reduce direct contact between the skin and air pollutants **(Krutmann et al., 2017; Fernández et al., 2016)**.

Active Defense strategies, on the other hand, involve the application of bioactive compounds to neutralize or mitigate the effects of exposome factors. These include:

- **Topical Antioxidants:** A wide array of topical antioxidants are employed, including vitamins like Vitamin C (which boosts collagen synthesis, reduces MMPs, and inhibits

tyrosinase), Vitamin E (which decreases MMP-1 and reinforces the skin barrier), and Niacinamide (Vitamin B3) (which improves aging skin appearance, reduces hyperpigmentation, and enhances barrier function) **(Krutmann et al., 2017; Bissett et al., 2016)**. Plant-derived compounds such as ginger oil, *Zingiber montanum*, and *Polypodium leucotomos* offer antioxidant and anti-inflammatory properties **(Krutmann et al., 2017; Parrado et al., 2019)**. Microorganism-derived compounds like Ectoine and *Porphyridium cruentum* also contribute by reinforcing the skin barrier, suppressing inflammation, and activating antioxidant pathways **(Krutmann et al., 2017; Grether-Beck et al., 2016)**. Other anti-pollution ingredients, such as Melatonin and Coenzyme Q10, directly scavenge ROS and reduce pollution-induced inflammation **(Krutmann et al., 2017; Knott et al., 2015)**.

- **Aryl-receptor inhibitors:** These compounds specifically block the activation of the AhR, thereby counteracting pollution-induced hyperpigmentation and other dermatoses **(Krutmann et al., 2017; Esser et al., 2018)**.
- **Sun filters:** Essential for active defense against solar radiation, these ingredients absorb, reflect, or scatter UVR, visible light, and infrared radiation, preventing their harmful effects on the skin **(Krutmann et al., 2017; Schalka et al., 2014)**.

Oral Supplements also play a role in mitigating the systemic and cutaneous effects of the exposome. Carotenoids, ferulic acid, green tea (rich in polyphenols), Polypodium leucotomos, and various vitamins can provide internal antioxidant support and enhance the skin's resilience against environmental stressors **(Krutmann et al., 2017; Parrado et al., 2019)**.

The development of Multi-benefit Photoprotection Formulations represents a growing trend. These formulations, available as both topical sunscreens enriched with anti-pollution actives and oral supplements, are designed to effectively counter both solar and pollution damage. Studies indicate their efficacy in reducing brown spots, increasing skin firmness, and preventing barrier damage, lipid peroxidation, and inflammation **(Krutmann et al., 2017; Narda et al., 2018)**.

Despite these advancements, a significant "precision gap" exists in current exposome defense strategies. While current approaches offer a range of protective and corrective measures, they often lack the ability to precisely identify an individual's specific exposome profile, predict their unique biological response, and then deliver the exact antioxidant or combination of antioxidants at the optimal concentration to the precise cellular target at the most effective time **(Wild, 2012; Vermeulen et al., 2020)**. This level of personalized, adaptive intervention is beyond the capabilities of conventional formulations. This precision gap fundamentally underscores the need for "intelligent" formulations, which require advanced delivery mechanisms (nanotechnology) combined with data-driven decision-making (AI) to move from generalized protection to highly individualized and responsive exposome defense strategies for true skin longevity **(Paul et al., 2023)**.

Table 1: Key Exposome Factors and Their Mechanisms of Skin Aging

Exposome Factor Category	Specific Components/Examples	Primary Mechanisms of Damage	Resulting Skin Effects	Synergistic Interactions
Solar Radiation	UVA, UVB, Visible Light (VL), Infrared (IR)	ROS Generation, DNA Damage (direct/indirect), MMP-1 Induction, Melanogenesis, Inflammation	Wrinkles, Lentigines, Hyperpigmentation, Reduced Elasticity, Sunburn, Skin Cancer Risk	Photo-pollution (UVR + PM/Ozone) (**Krutmann et al., 2017**)
Air Pollution	PM2.5, PM10, Ozone, PAHs, VOCs, Heavy Metals	ROS Generation, Inflammation, Skin Barrier Impairment, AhR Activation, Microbiome Disruption, Collagen Degradation	Wrinkles, Lentigines, Hyperpigmentation, Inflammatory Dermatoses (Acne, AD, Psoriasis), Skin Cancer Risk	Photo-pollution (UVR + PM/Ozone) (**Araviiskaia et al., 2021**)
Lifestyle/Diet	Tobacco Smoke, Unhealthy Nutrition (e.g., Western Diet)	Oxidative Stress, Inflammation, Impaired Cellular Repair	Premature Aging, Dull Complexion, Worsened Dermatoses	Diet affects gut microbiome, influencing systemic inflammation and cellular aging (**Niedzwiecki et al., 2019**)

3. Nanotechnology in Advanced Antioxidant Delivery for Skin

3.1. Overcoming Bioavailability and Stability Challenges with Nanocarriers

Natural antioxidants, despite their potent biological activities, frequently encounter significant limitations that impede their therapeutic efficacy. These include inherently low bioavailability, often stemming from poor solubility in aqueous or lipid environments, susceptibility to rapid

degradation by light, oxygen, or enzymatic activity, and inefficient absorption or penetration across biological barriers **(Souto et al., 2015; Prow et al., 2016)**. For topical dermatological applications, a particularly critical challenge is the inefficient percutaneous penetration of many active compounds, which limits their ability to reach the viable epidermis and dermis—the primary sites where antioxidant action is most needed to combat aging and exposome damage **(Souto et al., 2015; Cevc & Vierl, 2010)**.

Nanotechnology-based systems, specifically designed as nanocarriers, have emerged as a revolutionary approach to circumvent these formidable limitations. These advanced systems are engineered to encapsulate sensitive bioactive substances, thereby offering superior solubility and stability by protecting them from degradation in various biological environments and during cellular metabolism **(Souto et al., 2015; Zhang et al., 2020)**. This protective capability transforms inherently unstable antioxidants into viable and effective therapeutic agents **(Ganesan & Choi, 2016)**.

Furthermore, nanocarriers are adept at significantly enhancing the permeability of active compounds across formidable biological barriers, such as the skin's stratum corneum **(Souto et al., 2015; Palmer & DeLouise, 2016)**. This allows for more effective and deeper delivery of antioxidants to target cells and tissues within the skin. For example, Solid Lipid Nanoparticles (SLNs) can form an occlusive layer on the skin surface, which reduces transepidermal water loss and, crucially, can widen the inter-corneocyte gaps, thereby promoting deeper drug penetration into the skin layers **(Garcês et al., 2023; Müller et al., 2016)**. This multi-functional capability of nanocarriers, acting as both protective envelopes and permeation enhancers, transforms the application of antioxidants from a passive topical treatment to a sophisticated, engineered intervention **(Noh et al., 2017)**. This engineering prowess is a foundational element for developing "intelligent" formulations, as it provides the necessary control over the active ingredient's journey and fate within the skin, ensuring that previously ineffective compounds can now exert their full therapeutic potential for skin longevity **(Escobar-Chávez et al., 2012)**.

3.2. Diverse Nanocarrier Systems: Solid Lipid Nanoparticles, Nanoemulsions, Liposomes, Polymeric Nanoparticles, and Others

The field of nanodermatology has witnessed the development and application of a wide array of nanocarrier systems, each possessing distinct physicochemical properties and offering unique advantages tailored for specific antioxidant delivery challenges **(Souto et al., 2015; Ganesan & Choi, 2016)**. The strategic selection of a nanocarrier is crucial, as there is no universal solution; the choice depends on the specific antioxidant's properties (e.g., hydrophilic or hydrophobic, stability profile), the desired release kinetics, and the target skin layer or cell type **(Palmer & DeLouise, 2016)**.

Among the most prominent systems are:

- **Solid Lipid Nanoparticles (SLNs):** Introduced in 1991, SLNs are composed of lipids that remain solid at both room and body temperatures. They offer high drug loading capacity, enable controlled and sustained release of encapsulated compounds, and provide excellent stability. SLNs are widely applied in anti-aging skincare, sunscreens, and for enhancing skin moisture **(Souto et al., 2015; Garcês et al., 2023)**. Examples of encapsulated antioxidants include N-acetyl-d-glucosamine, Epigallocatechin Gallate (EGCG), Vitamin E, Resveratrol, Caffeine, Sesamol, Umbelliferone, Vitamin A, and phenolic/flavonoid extracts from *Prunus persica* **(Garcês et al., 2023; Wissing & Müller, 2014)**.
- **Nanostructured Lipid Carriers (NLCs):** Representing a second generation of lipid nanoparticles, NLCs are formed from a mixture of solid and liquid lipids. This hybrid composition provides improved stability against drug leakage and often results in higher drug loading capacity compared to SLNs **(Souto et al., 2015; Beloqui et al., 2016)**. NLCs have shown particular promise for the dermal delivery of highly lipophilic antioxidants such as Coenzyme Q10 and tocopherol **(Souto et al., 2015; Teeranachaideekul et al., 2017)**.
- **Nanoemulsions (NEs):** These are thermodynamically stable, isotropic mixtures of oil, water, and surfactant, characterized by very small droplet sizes (typically 20 to 200 nm). They offer increased surface area for absorption, good stability, reduced skin irritation, and protection against degradation of active ingredients **(Souto et al., 2015; Nastiti et al., 2017)**.
- **Polymeric Nanoparticles:** These are solid colloidal nanoparticles (ranging from 10 to 1000 nm) fabricated from synthetic or natural polymers. They are valued for their water solubility, small size, storage stability, biodegradability, and their ability to protect encapsulated compounds from environmental degradation, including photodegradation **(Souto et al., 2015; Kumari et al., 2016)**.
- **Liposomes:** These are spherical, self-closed vesicles composed of phospholipid bilayers surrounding an aqueous interior. Liposomes can increase the residence time of drugs in the stratum corneum and epidermis, making them suitable for delivering antioxidants like Coenzyme Q10 to deeper skin layers **(Souto et al., 2015; Manca et al., 2016)**.
- **Nanocapsules:** These are vesicular systems characterized by a polymeric membrane that encapsulates an inner liquid core at the nanoscale level. They have demonstrated efficacy in increasing the delivery of antioxidants such as resveratrol and curcumin into deeper skin layers **(Souto et al., 2015; Friedrich et al., 2015)**.
- **Niosomes:** Formed from nonionic surfactants, niosomes offer high entrapment efficiency, improved chemical stability, and enhanced penetration. They are often considered less toxic and less expensive alternatives to liposomes **(Souto et al., 2015; Yeo et al., 2018)**.
- **Cubosomes:** These are discrete, submicron, nanostructured particles featuring a bicontinuous cubic liquid crystalline phase. Their unique structure allows them to incorporate large amounts of active compounds, making them suitable for formulations like alpha lipoic acid **(Souto et al., 2015; Esposito et al., 2017)**.

- **Metallic Nanoparticles:** With diameters typically ranging from 1 to 100 nm, these include nanoparticles of silver, gold, titanium, and zinc. Some metallic nanoparticles exhibit intrinsic antioxidant properties themselves, earning them the designation "nano-antioxidants," and can be synthesized for targeted delivery **(Souto et al., 2015; Sánchez-López et al., 2020)**.
- **Microsponge Delivery Systems (MDS):** These are porous, non-collapsible polymeric structures, typically 5–300 μm in diameter, designed for sustained and controlled release of topical agents. MDS can improve patient compliance, enhance safety, extend product stability, and reduce side effects in dermatological applications **(Kaushik et al., 2016; Junqueira et al., 2016)**.
- **Smart Polymers:** Also known as stimuli-responsive materials, these polymers can change their shape, strength, or pore size in response to small external stimuli such as temperature, pH, or UV irradiation **(Kaushik et al., 2016; Cabane et al., 2016)**. This responsiveness makes them highly promising for developing controlled and intelligent drug delivery systems that can adapt to changing physiological conditions within the skin **(Cabane et al., 2016)**.

The significant diversity of these nanocarrier systems underscores that achieving true precision in antioxidant delivery requires a sophisticated understanding of the intricate interplay between the active compound, the specific characteristics of the chosen nanocarrier, and the biological target within the skin **(Palmer & DeLouise, 2016)**. This complex decision-making process is a prime area where artificial intelligence can provide invaluable optimization and predictive capabilities, moving beyond empirical trial-and-error to design highly effective and tailored formulations **(Paul et al., 2023)**.

3.3. Advantages of Nanodelivery: Enhanced Permeation, Targeted Release, Reduced Side Effects

Nanotechnology-based systems offer a multitude of significant benefits over conventional preparations of natural antioxidants, fundamentally enhancing their therapeutic potential and transforming dermatological treatment paradigms **(Souto et al., 2015; Ganesan & Choi, 2016)**. These advantages are crucial for developing intelligent formulations capable of effective exposome defense.

Key benefits include:

- **Superior Solubility and Stability:** Nanocarriers effectively encapsulate sensitive bioactive substances, shielding them from various degradation pathways, such as photodegradation (e.g., for resveratrol) or chemical instability (e.g., for Vitamin A) **(Souto et al., 2015; Manca et al., 2016)**. This protection significantly improves their solubility in biological fluids and maintains their stability, leading to enhanced shelf-life and sustained efficacy **(Souto et al., 2015; Zhang et al., 2020)**.
- **Extended Half-Life and Circulation Time:** By protecting the active compounds from rapid metabolism or clearance, nanocarriers can prolong the therapeutic agent's

presence and activity within the target tissues, ensuring a more sustained effect **(Souto et al., 2015; Beloqui et al., 2016)**.

- **Improved Epithelium Permeability:** Nanoparticles are engineered to effectively overcome the skin's formidable physical and chemical barriers, particularly the stratum corneum **(Souto et al., 2015; Palmer & DeLouise, 2016)**. This enhanced permeability facilitates deeper penetration of active compounds into viable skin layers, ensuring that antioxidants reach their intended sites of action within the epidermis and dermis, where oxidative damage from the exposome is most pronounced **(Cevc & Vierl, 2010)**.
- **Enhanced Tissue Targeting:** Nanomaterials can be designed with specific surface chemistry or stimuli-responsive components, such as smart polymers, that enable controlled and localized release of therapeutic agents at targeted tissues or specific body sites **(Souto et al., 2015; Cabane et al., 2016)**. This precision ensures that the antioxidant is delivered where it is most needed, maximizing its efficacy against localized damage from exposome factors **(Noh et al., 2017)**.
- **Minimized Side Effects:** By enabling targeted delivery and controlled release, nanodelivery systems can significantly reduce the overall dosage required for therapeutic effect and minimize systemic absorption and potential adverse effects **(Souto et al., 2015; Escobar-Chávez et al., 2012)**. This improves the safety profile of antioxidant treatments, making them more suitable for long-term use in skin longevity strategies **(Friedrich et al., 2015)**.

This array of advantages signifies a fundamental shift from passive application to active, strategic therapeutic intervention. The capabilities of "enhanced tissue targeting," "controlled release," and "improved epithelium permeability" imply that the nanocarrier actively directs and manages the antioxidant's journey and release within the skin **(Ganesan & Choi, 2016)**. This transforms antioxidant application from a broad-spectrum topical treatment to a sophisticated, engineered, and strategic therapeutic intervention, maximizing efficacy while minimizing waste and side effects **(Palmer & DeLouise, 2016)**. This evolution towards strategic delivery provides the essential technological foundation for "intelligent" antioxidant formulations, enabling the precise control necessary for AI to optimize delivery based on individualized patient and exposome data **(Paul et al., 2023)**.

3.4. Limitations and Safety Considerations of Nanomaterials

Despite the significant promise and numerous advantages offered by nanodelivery systems, their widespread clinical adoption and integration into intelligent antioxidant formulations face several important challenges and safety considerations **(Souto et al., 2015; Nel et al., 2015)**. Addressing these limitations is crucial for responsible innovation and successful translation.

A primary concern revolves around the potential toxicity of the nanomaterials themselves. While the encapsulated active compounds may be well-studied, the nanocarriers, due to their unique size, surface area, and reactivity, require comprehensive toxicological examination, especially concerning long-term or repeated use **(Souto et al., 2015; Oberdörster et al., 2015)**. The toxicology of nanocomposites can differ significantly from that of their bulk materials or

the loaded bioactive substances, necessitating rigorous and specialized safety assessments (**Nel et al., 2015**).

Another critical challenge lies in optimizing drug release profiles. The design of nanocarriers must carefully balance the release kinetics of the encapsulated antioxidant. A rapid, uncontrolled "burst" drug release can lead to cellular toxicity, systemic side effects, or a rapid depletion of the therapeutic agent. Conversely, an excessively slow release might result in insufficient therapeutic efficacy, failing to deliver the required dose to the target site (**Souto et al., 2015; Müller et al., 2016**). Achieving the ideal controlled and sustained release profile, tailored to the specific antioxidant and dermatological need, remains an active area of research (**Beloqui et al., 2016**).

Furthermore, key unanswered questions persist regarding the bioaccumulation and metabolism of nanomaterials within the human body. It is essential to determine whether applied nanomaterials accumulate in tissues over time, convert into potentially dangerous metabolites, or can be completely degraded and safely excreted after delivery (**Souto et al., 2015; Oberdörster et al., 2015**). Understanding the long-term fate of these materials is paramount for patient safety (**Nel et al., 2015**).

Finally, there are growing environmental impact concerns regarding the potential hazard posed by excreted nanomaterials accumulating in living environments. As these technologies become more widespread, their ecological footprint must be thoroughly evaluated and mitigated (**Souto et al., 2015; Fadeel et al., 2018**).

These considerations highlight a critical tension: the very properties that make nanomaterials so effective (e.g., small size, high surface area, ability to penetrate barriers) also introduce novel safety concerns that are not yet fully understood (**Nel et al., 2015**). This indicates that the scientific community must navigate a delicate balance between pushing innovative boundaries and ensuring the long-term safety and environmental responsibility of these emerging technologies. Therefore, rigorous, standardized toxicological testing, comprehensive long-term safety studies, and the development of clear regulatory frameworks are paramount for the responsible development and widespread clinical translation of nanodelivery systems in dermatology (**Fadeel et al., 2018**). This also suggests a crucial role for AI in predicting and mitigating potential risks during the early design and development phases of nanocarriers (**Paul et al., 2023**).

Table 2: Overview of Nanocarrier Systems for Dermal Antioxidant Delivery

Nanocarrier Type	Composition/Structure	Key Advantages for Dermal Delivery	Specific Antioxidants/Applications Mentioned	Limitations/Considerations
Solid Lipid Nanoparti	Solid lipids (e.g., triglycerides,	High drug loading,	Resveratrol, Vitamin E,	Potential burst release, limited drug

cles (SLNs)	fatty acids) with surfactant coating	controlled/sustained release, enhanced stability, non-toxic, good skin hydration	Vitamin A, Caffeine, Sesamol, Umbelliferone, N-acetyl-d-glucosamine, Prunus persica extract; Anti-aging, Sunscreen, Skin moisture (**Garcês et al., 2023**)	loading for hydrophilic compounds, polymorphic transitions (**Müller et al., 2016**)
Nanostructured Lipid Carriers (NLCs)	Mixture of solid and liquid lipids with surfactant coating	Improved stability, higher drug loading than SLNs, reduced leakage, controlled release	Coenzyme Q10, Tocopherol (**Souto et al., 2015**)	Complex formulation, potential for drug leakage with high liquid lipid content (**Beloqui et al., 2016**)
Nanoemulsions (NEs)	Oil-in-water dispersions (20–200 nm) stabilized by surfactants	Increased surface area, good stability, reduced skin irritation, anti-degradation properties, enhanced intracellular delivery	Quercetin (via microemulsion) (**Nastiti et al., 2017**)	Lower drug loading capacity compared to lipid nanoparticles, potential for creaming/flocculation
Polymeric Nanoparticles	Solid colloidal nanoparticles (10–1000 nm) from synthetic/natural polymers	Water solubility, storage stability, biodegradability, protection from photodegradation, enhanced permeation	Curcumin, Ascorbyl palmitate (**Kumari et al., 2016**)	Potential for toxicity depending on polymer, complex synthesis, scalability

Liposomes	Spherical phospholipid bilayers surrounding aqueous interior	Increased residence time in stratum corneum/epidermis, biocompatible, biodegradable, low toxicity	Coenzyme Q10 **(Manca et al., 2016)**	Low stability, leakage of encapsulated drugs, high production cost
Nanocapsules	Polymeric membrane encapsulating inner liquid core	Enhanced delivery into deeper skin layers, protection of core material	Resveratrol, Curcumin **(Friedrich et al., 2015)**	Potential for polymer toxicity, complex synthesis, limited drug loading for some compounds
Niosomes	Nonionic surfactant vesicles	High entrapment efficiency, improved chemical stability, enhanced penetration, less toxic/expensive than liposomes	Resveratrol, Curcumin **(Yeo et al., 2018)**	Potential for aggregation, lower stability than solid lipid systems
Cubosomes	Discrete, submicron, bicontinuous cubic liquid crystalline phase	Able to incorporate large amounts of drugs/actives, sustained release	Alpha Lipoic Acid **(Esposito et al., 2017)**	Complex preparation, limited stability, high viscosity
Metallic Nanoparticles	Metal particles (1–100 nm) e.g., Ag, Au, Ti, Zn	Intrinsic antioxidant properties (nano-antioxidants), simple synthesis, tunable	(General antioxidant activity) **(Sánchez-López et al., 2020)**	Potential toxicity, bioaccumulation, environmental impact, long-term safety data needed **(Nel et al., 2015)**

		biophysical properties, targeted delivery		
Microsponge Delivery Systems (MDS)	Porous, non-collapsible polymeric structures (5–300 µm)	Sustained/controlled release, enhanced safety, extended stability, reduced side effects, improved patient compliance	(General topical agents) **(Kaushik et al., 2016)**	Larger size than nanoparticles, potential for limited deep penetration **(Junqueira et al., 2016)**
Smart Polymers	Stimuli-responsive materials (e.g., temperature, pH, UV-responsive)	Controlled drug release based on external stimuli, adaptive delivery	(General drug delivery) **(Cabane et al., 2016)**	Complex synthesis, biocompatibility challenges, regulatory hurdles for stimuli-responsive systems

4. Artificial Intelligence in Precision Dermatology and Exposome Analysis

4.1. AI Beyond Image Diagnostics: Predictive Modeling and Personalized Risk Assessment

While artificial intelligence (AI) has garnered significant attention and demonstrated remarkable success in image-based diagnostics for various skin conditions, including the early detection of skin cancer **(Chan et al., 2020; Esteva et al., 2017)**, its applications in dermatology are rapidly expanding into more sophisticated and transformative areas. This evolution represents a fundamental shift from merely reactive diagnosis to a proactive, predictive, and preventative approach to skin health **(Aggarwal et al., 2021)**.

AI offers novel opportunities for AI-enabled predictive modeling of treatment responses. This capability allows clinicians to forecast with increasing accuracy how a patient's specific skin disorder will respond to different therapeutic interventions **(Chan et al., 2020; Du-Harpur et al., 2020)**. By analyzing vast datasets of patient characteristics, disease profiles, and treatment outcomes, AI algorithms can identify subtle patterns and correlations that are beyond human

cognitive capabilities, thereby guiding the selection of the most effective personalized treatment pathways **(Hogarty et al., 2020)**.

Furthermore, AI significantly facilitates personalized risk assessment and stratification. Leveraging extensive patient data, including electronic medical records and genetic information, AI can assess an individual's unique risk of developing certain skin disorders or predict the potential severity and progression of their condition **(Chan et al., 2020; Shrivastava et al., 2019)**. This enables the categorization of patients into distinct risk groups, allowing for tailored management strategies and proactive early detection efforts **(Chan et al., 2020)**. For instance, AI can analyze a patient's historical medical journey, including primary care and emergency room visits, to identify early clues that might have been overlooked, thereby expediting diagnosis and intervention **(Wild, 2012; Carter et al., 2020)**. This capability empowers dermatologists to intervene earlier and more effectively, optimizing long-term skin health outcomes by identifying individuals at higher risk before disease manifestation or significant progression **(Du-Harpur et al., 2020)**.

4.2. AI for Clinical Decision Support and Digital Health Assistants

AI systems are increasingly being developed to serve as powerful clinical decision support tools, designed to assist dermatologists in making more informed, efficient, and accurate decisions regarding diagnosis, treatment selection, and overall management of complex skin conditions **(Chan et al., 2020; Freeman et al., 2021)**. This role of AI is often termed "augmented intelligence," emphasizing that AI is not intended to replace human clinicians but rather to enhance and expand their capabilities **(Esteva et al., 2017; Topol, 2019)**.

In this context, AI guides expert dermatologists in expediting complex data analysis, processing information at speeds and scales far beyond human cognitive abilities **(Esteva et al., 2017; Carter et al., 2020)**. This augmentation ultimately serves to educate clinicians, provide deeper insights into patient data, and facilitate earlier, more precise interventions **(Esteva et al., 2017)**. AI can rapidly analyze vast amounts of patient data, identifying subtle patterns and correlations that might lead to earlier diagnoses and more effective treatment plans **(Hogarty et al., 2020)**.

Beyond direct decision support, AI also contributes significantly to the development of digital assistants and copilots for clinicians. These AI-powered tools can streamline various aspects of dermatological practice, assisting with tasks such as rapid information retrieval from vast medical literature databases, optimizing patient interaction processes, or automating administrative duties **(Chan et al., 2020; Shrivastava et al., 2019)**. By offloading these data-intensive and routine tasks, AI can significantly reduce clinician workload, allowing dermatologists to focus more on complex cases, patient-centered care, and empathetic interactions **(Topol, 2019)**.

Moreover, AI-powered consultation applications and websites are emerging, capable of performing initial patient consultations, answering common patient questions, and providing

real-time medical suggestions and guidance **(Hogarty et al., 2020; Freeman et al., 2021)**. This is particularly beneficial for individuals in remote areas or those with limited access to specialized healthcare, effectively scaling access to high-quality dermatological expertise **(Hogarty et al., 2020)**. This demonstrates AI's critical role in making precision dermatology more widely available and improving patient outcomes by augmenting, rather than replacing, human clinicians **(Carter et al., 2020)**.

4.3. Leveraging AI to Disentangle the Complex Exposome

The human exposome represents an immense and intricate collection of environmental variables, unique to each individual, that interact with genetic predispositions to shape health and disease trajectories **(Wild, 2012; Rappaport, 2016)**. Understanding how these external influences intersect with our genes is crucial for deciphering the etiology of complex diseases and for optimizing truly personalized treatments **(Wild, 2012; Vermeulen et al., 2020)**. However, the sheer scope of environmental exposures and the intricate nature of their interactions make comprehensive exposome analysis a daunting task for traditional analytical methods **(Niedzwiecki et al., 2019)**.

Given this immense complexity, scientists are increasingly turning to artificial intelligence to help disentangle the human exposome **(Wild, 2012; Carter et al., 2020)**. AI is uniquely equipped to analyze a lifetime of environmental exposures, identify subtle patterns within vast datasets, and decode the complex interplay between genes and environment. This capability allows AI to forecast long-term disease risks with greater accuracy, moving beyond simplistic correlations to reveal deeper causal relationships **(Wild, 2012; Miller & Jones, 2014)**.

A particularly valuable application of AI in exposome analysis is its ability to extract patient exposure clues that are already "lurking in existing data" but are often overlooked due to their volume and heterogeneity **(Wild, 2012; Rappaport, 2016)**. This includes analyzing diverse data sources such as electronic medical records, primary care notes, and emergency room visits to construct a more comprehensive picture of a patient's environmental history and health journey before a specific diagnosis **(Wild, 2012; Carter et al., 2020)**. AI's unparalleled capacity to process "big data" and identify multi-dimensional patterns within an individual's lifetime exposure profile is beyond human cognitive capacity. This makes AI an indispensable tool for translating the theoretical understanding of the exposome into actionable, personalized skin health strategies **(Vermeulen et al., 2020)**. By decoding an individual's unique exposome signature, AI can guide the development and application of highly tailored antioxidant formulations and defense mechanisms, moving towards truly individualized skin longevity **(Niedzwiecki et al., 2019)**. Without AI, the exposome would largely remain an intractable "big data" problem, limiting the realization of precision dermatology for exposome defense **(Rappaport, 2016)**.

Table 3: Non-Image-Based AI Applications in Precision Dermatology

Application Area	Description of AI's Role	Specific Benefits/Outcomes	Relevant References
Predictive Modeling of Treatment Responses	Forecasting how a patient's skin disorder will respond to various treatments based on clinical and biological data.	Enables tailored management, optimizes therapeutic efficacy, reduces trial-and-error.	**Chan et al., 2020; Du-Harpur et al., 2020**
Personalized Risk Assessment & Stratification	Analyzing extensive patient data (e.g., genetic, clinical history) to assess individual risk of developing specific skin conditions or their severity.	Facilitates proactive intervention, categorizes patients for tailored preventative strategies, enables early detection.	**Chan et al., 2020; Shrivastava et al., 2019**
Early Detection (Non-Image Focused)	Identifying subtle patterns in diverse data points (e.g., patient records, lab results, lifestyle data) that precede overt disease manifestation.	Expedites diagnosis, allows for earlier interventions, improves long-term patient outcomes.	**Wild, 2012; Carter et al., 2020**
Clinical Decision Support	Assisting clinicians in making informed decisions regarding diagnosis, treatment selection, and patient management.	Augments human expertise, expedites data analysis, provides evidence-based recommendations, reduces cognitive load.	**Chan et al., 2020; Topol, 2019**
Digital Health Assistants/Copilots	Automating tasks like information retrieval, patient interaction, and administrative duties for dermatologists.	Reduces clinician workload, improves efficiency, frees up time for complex patient care.	**Hogarty et al., 2020; Shrivastava et al., 2019**
Exposome Analysis	Disentangling complex environmental and lifestyle exposures, identifying their interactions with genetics, and forecasting long-term health risks.	Enables comprehensive risk assessment, uncovers hidden exposure clues, guides personalized defense strategies.	**Wild, 2012; Vermeulen et al., 2020**

Drug Discovery & Optimization	Accelerating the identification of promising compounds and optimizing nanocarrier design for targeted delivery and efficacy.	Streamlines R&D, identifies optimal drug-nanocarrier combinations, reduces development time and cost.	Paul et al., 2023; Ho et al., 2022

5. Synergistic Convergence: Nanotechnology and AI for Intelligent Skin Longevity

The true transformative potential for skin longevity and exposome defense lies in the synergistic convergence of nanotechnology and artificial intelligence. This integration moves beyond the individual strengths of each field, creating a powerful interface that enables unprecedented levels of precision, personalization, and adaptability in dermatological interventions (**Paul et al., 2023; Subbiah et al., 2021**).

5.1. AI-Optimized Nanocarrier Design and Drug Delivery

The integration of AI with nanomedicine is fundamentally reshaping the approach to drug delivery, moving combinatorial nanotherapy closer to widespread clinical application (**Paul et al., 2023; Ho et al., 2022**). AI plays a pivotal role as a "smart architect" and "predictive engineer" in the rational selection and design of nanoparticles. Machine learning algorithms are crucial for optimizing critical parameters such as nanoparticle size, shape, surface charge, and functionalization, all of which directly influence therapeutic efficacy and safety (**Paul et al., 2023; Subbiah et al., 2021**). These algorithms can predict how nanoparticles will interact within complex biological systems, thereby enhancing their targeting capabilities to specific skin layers or cells affected by exposome damage, and simultaneously minimizing potential off-target effects (**Paul et al., 2023; Wang et al., 2022**).

Beyond initial design, AI significantly optimizes drug-loading capacities and release kinetics. This allows nanocarriers to be precisely tailored for specific biological microenvironments, such as inflamed skin or areas experiencing particular exposome-induced oxidative stress (**Paul et al., 2023; Tao et al., 2020**). AI-driven models can explore a vast design space for nanoparticles (considering materials, surface chemistry, drug loading, and release profiles) far more efficiently than traditional empirical methods. This capability enables the creation of truly "intelligent" delivery systems that are precisely tailored to specific therapeutic needs and biological contexts (**Ho et al., 2022**). Furthermore, AI-driven models accelerate the entire development process of new nanomedicines by efficiently identifying promising compounds and formulations, streamlining research efforts and reducing the time and cost associated with bringing new therapies to market (**Paul et al., 2023; Subbiah et al., 2021**). This precision engineering capability is fundamental for developing highly effective, safe, and truly intelligent

antioxidant formulations that can respond to complex exposome challenges and promote skin longevity **(Wang et al., 2022)**.

5.2. Personalized Antioxidant Formulations Guided by AI and Nanomedicine

The AI-nanomedicine interface is instrumental in achieving unprecedented levels of personalization in dermatological care. This integration allows for a deep understanding of the dynamic patient response to different treatments, providing enhanced accountability for treatment modulation and enabling truly individualized therapeutic strategies **(Paul et al., 2023; Ho et al., 2022)**.

AI algorithms are capable of analyzing vast and diverse datasets, including electronic medical records, genetic profiling, and broader multi-omics data (e.g., proteomics, metabolomics) **(Paul et al., 2023; Vermeulen et al., 2020)**. This comprehensive data analysis informs the selection of optimal drugs and facilitates the creation of highly personalized treatment plans. By accurately predicting individual patient responses to nanomedicine-based therapies, AI guides the selection of the most suitable nanoparticle formulations and drug combinations for a given individual **(Paul et al., 2023; Tao et al., 2020)**. This personalized approach is particularly beneficial for managing complex and heterogeneous dermatological conditions, where a one-size-fits-all approach is often ineffective **(Subbiah et al., 2021)**.

The convergence of AI's ability to analyze an individual's unique exposome profile **(Wild, 2012; Vermeulen et al., 2020)** and multi-omics data **(Paul et al., 2023)** with nanomedicine's capacity for highly targeted and controlled delivery **(Souto et al., 2015; Zhang et al., 2020)** suggests the potential for creating a "digital twin" of a patient's skin and overall biological system. This digital twin, powered by AI, could simulate the patient's unique biological response to various nano-encapsulated antioxidant formulations, predicting efficacy, potential side effects, and optimal dosing strategies before actual application **(Ho et al., 2022)**. This concept is implied by the emphasis on "predicting individual patient responses" and understanding "dynamic patient response" **(Paul et al., 2023)**. This integration moves beyond general recommendations to hyper-personalized, adaptive skin longevity strategies, where formulations are not static but are dynamically selected and potentially adjusted based on an individual's real-time exposome, genetic predispositions, and biological feedback **(Tao et al., 2020)**.

5.3. Real-time Monitoring and Adaptive Therapies for Exposome Defense

The synergistic convergence of nanotechnology and AI also paves the way for dynamic, closed-loop therapeutic systems in dermatology, moving beyond static treatment regimens to adaptive interventions **(Paul et al., 2023; Wang et al., 2022)**. AI-enhanced imaging techniques, when combined with nanoparticle contrast agents, can provide real-time insights into disease progression and treatment response within the skin **(Paul et al., 2023; Subbiah et al., 2021)**. This allows for continuous, non-invasive assessment of the skin's condition and its response to therapeutic agents **(Tao et al., 2020)**.

AI algorithms are capable of analyzing this real-time imaging data to dynamically adapt treatment strategies. This capability ensures timely interventions and maximizes therapeutic efficacy by adjusting the dosage, formulation, or release profile of the intelligent antioxidant formulation as needed **(Paul et al., 2023; Ho et al., 2022)**. For instance, if real-time monitoring indicates an increase in oxidative stress due to acute exposome exposure, the AI could trigger a controlled release of additional antioxidants from smart nanocarriers **(Wang et al., 2022)**.

Furthermore, the integration of wearable biosensors and nanodevices with AI offers the potential for continuous patient monitoring **(Paul et al., 2023; Yetisen et al., 2018)**. These devices can track various skin health parameters, such as oxidative stress markers, inflammation levels, or even specific exposome exposure indicators. This continuous feedback loop enables the early detection of complications, allows for proactive adjustments to treatment, and provides a comprehensive, ongoing assessment of the skin's response to environmental challenges **(Yetisen et al., 2018)**. This dynamic, feedback-driven approach offers unprecedented control and responsiveness in combating exposome-induced skin damage **(Tao et al., 2020)**. It paves the way for truly "intelligent" and potentially self-regulating dermatological interventions, where the treatment adapts to the changing demands of the skin and its environment, thereby optimizing long-term skin longevity **(Wang et al., 2022)**.

Table 4: Synergistic Applications of Nanotechnology and AI for Skin Longevity and Exposome Defense

Synergistic Application Area	Role of Nanotechnology	Role of Artificial Intelligence	Combined Benefit/Outcome	Relevant References
AI-Optimized Nanocarrier Design	Enables precise encapsulation, enhances bioavailability/stability, provides controlled release capabilities.	Rationalizes selection and design parameters, predicts nanoparticle interactions, optimizes drug loading and release kinetics, accelerates R&D.	Development of highly efficient, safe, and custom-designed nanocarriers for specific antioxidants and skin targets.	**Paul et al., 2023; Ho et al., 2022**
Personalized Formulation Selection	Provides diverse range of delivery systems (SLNs, NLCs, etc.) for tailored active compound delivery.	Analyzes multi-omics and exposome data, predicts individual	Hyper-personalized antioxidant formulations precisely matched	**Wild, 2012; Vermeulen et al., 2020**

		patient responses, guides selection of optimal nanocarrier-antioxidant combinations.	to an individual's unique biological and environmental profile.	
Real-time Monitoring & Adaptive Release	Facilitates targeted delivery of contrast agents, enables smart/stimuli-responsive release mechanisms.	Analyzes real-time imaging and biosensor data, dynamically adapts treatment strategies, triggers controlled release from nanocarriers.	Dynamic, closed-loop therapeutic systems that respond to changing skin conditions and exposome exposure, optimizing efficacy.	**Paul et al., 2023; Wang et al., 2022**
Exposome-Guided Targeted Delivery	Delivers antioxidants to specific skin layers/cells affected by identified exposome stressors.	Decodes complex exposome signatures, forecasts long-term risks, identifies specific exposure-induced damage patterns.	Precise delivery of antioxidants to areas and pathways most impacted by an individual's unique exposome.	**Wild, 2012; Subbiah et al., 2021**
Predictive Skin Health Management	Provides advanced delivery platforms for preventative and corrective agents.	Forecasts disease risk, identifies at-risk individuals, informs proactive interventions before significant	Proactive, preventative, and highly individualized strategies for maintaining skin health and promoting longevity.	**Wild, 2012; Tao et al., 2020**

		damage occurs.		

6. Challenges, Ethical Considerations, and Future Directions

The synergistic convergence of nanotechnology and artificial intelligence holds immense promise for revolutionizing skin longevity and exposome defense. However, the successful translation and widespread adoption of intelligent antioxidant formulations necessitate a comprehensive understanding and proactive mitigation of significant technical, regulatory, and ethical challenges (**Freeman et al., 2021; Nel et al., 2015**).

6.1. Technical Hurdles and Data Quality in AI and Nanomedicine

Significant technical hurdles persist in both the AI and nanomedicine domains, and their integration introduces additional complexities (**Freeman et al., 2021; Oberdörster et al., 2015**).

AI-Specific Challenges: A primary concern for AI in dermatology is the quality, quantity, and diversity of the data used to develop and test AI technologies (**Freeman et al., 2021; Carter et al., 2020**). Biases within training datasets can lead to skewed diagnostic accuracy, particularly impacting generalizability across diverse patient demographics and potentially resulting in missed diagnoses for rare skin conditions or subtle changes (**Freeman et al., 2021; Shrivastava et al., 2019**). Furthermore, the rapid evolution of AI technology has outpaced the establishment of standardized, universally accepted methods for rigorously evaluating and regulating AI algorithms in a clinical context, creating uncertainty for developers and clinicians alike (**Freeman et al., 2021; Topol, 2019**).

Nanomedicine-Specific Challenges: Despite advancements, optimizing the physicochemical properties of nanocarriers for ideal drug release profiles remains an essential research challenge. Achieving a controlled and sustained release, avoiding a rapid "burst" that could lead to cellular toxicity or insufficient therapeutic efficacy from overly slow release, is critical (**Souto et al., 2015; Müller et al., 2016**). Moreover, fundamental questions persist regarding the long-term fate of nanomaterials within the human body. Comprehensive studies are needed to determine if applied nanomaterials bioaccumulate in tissues, convert into potentially dangerous metabolites, or can be completely degraded and safely excreted after delivery (**Souto et al., 2015; Nel et al., 2015**).

Integration Challenges: The successful integration of AI and nanomedicine for intelligent formulations requires the ability to process and synthesize vast, heterogeneous datasets. This includes genomic, proteomic, exposome, clinical, and imaging data, transforming them into actionable insights for nanocarrier design and personalized treatment (**Paul et al., 2023; Vermeulen et al., 2020**). Ensuring interoperability and seamless data flow between disparate

systems and platforms presents a significant technical hurdle that requires robust computational infrastructure and standardized data formats **(Carter et al., 2020)**. The effectiveness and safety of AI-optimized nanomedicine are directly contingent upon the integrity and representativeness of the data feeding the AI, as well as the inherent safety profile of the nanocarriers themselves **(Fadeel et al., 2018)**. Flaws in either domain can undermine the entire translational effort. Therefore, future research must prioritize the generation of high-quality, diverse, and ethically sourced datasets for AI training, alongside comprehensive, long-term safety, biocompatibility, and environmental impact studies for nanomaterials, to ensure successful translation to clinical practice **(Oberdörster et al., 2015)**.

6.2. Regulatory and Ethical Implications of Advanced Technologies in Dermatology

The rapid advancements in both AI and nanomedicine in healthcare necessitate the urgent development of robust ethical guidelines and clear regulatory frameworks to ensure patient safety, foster public trust, and enable responsible innovation **(Chan et al., 2020; Fadeel et al., 2018)**.

Key ethical considerations include:

- **Data Privacy and Security:** The integration of diverse and sensitive patient data (e.g., genetic, exposome, clinical records) for personalized AI analysis raises paramount concerns regarding data privacy and cybersecurity **(Chan et al., 2020; Carter et al., 2020)**. Robust safeguards are essential to prevent unauthorized access, misuse, or breaches of highly personal health information **(Topol, 2019)**.
- **Algorithmic Bias and Fairness:** AI algorithms, if trained on biased or unrepresentative datasets, can perpetuate or even amplify existing health disparities, leading to inaccurate diagnoses or suboptimal treatment recommendations for certain patient populations **(Freeman et al., 2021; Shrivastava et al., 2019)**. Ensuring algorithmic fairness and generalizability across diverse demographics is a critical ethical imperative **(Carter et al., 2020)**.
- **Accountability and Liability:** As AI systems become more autonomous in decision-making (e.g., optimizing nanocarrier design or adaptive release), defining accountability and liability when AI-driven decisions or nanocarrier-related issues lead to adverse patient outcomes becomes complex **(Chan et al., 2020; Topol, 2019)**. Clear legal and ethical frameworks are needed to address these questions **(Fadeel et al., 2018)**.
- **Informed Consent:** The complexity of AI-driven and nanotech-based interventions necessitates clear and comprehensive informed consent processes, ensuring that patients fully understand the nature, benefits, risks, and limitations of these advanced technologies **(Chan et al., 2020; Carter et al., 2020)**.

Regulatory Challenges: The lack of clear consensus on AI's precise role and position within clinical workflows, particularly in diagnostic pathways, presents significant regulatory hurdles

(**Freeman et al., 2021; Topol, 2019**). Standardized evaluation methods and certification processes for AI in medicine are still evolving. For nanomedicine, the unique physicochemical properties of nanomaterials often fall outside existing regulatory categories for traditional pharmaceuticals or medical devices, requiring specialized and adaptive regulatory scrutiny (**Souto et al., 2015; Fadeel et al., 2018**). Public acceptance is also a crucial factor, as overcoming barriers related to trust, usability, and acceptability among healthcare professionals and the general public is essential for the successful implementation and widespread adoption of intelligent antioxidant formulations (**Freeman et al., 2021**). Without robust ethical frameworks, clear regulatory pathways, and proactive engagement with stakeholders, the societal acceptance and widespread adoption of intelligent antioxidant formulations will be significantly hampered, regardless of their scientific merit (**Carter et al., 2020**). The future success of intelligent antioxidant formulations hinges on a commitment to "responsible innovation," requiring a multi-stakeholder approach involving researchers, policymakers, industry, and patient advocacy groups to collaboratively develop and implement ethical guidelines, regulatory standards, and public education initiatives that foster trust and ensure equitable access and safe deployment (**Fadeel et al., 2018**).

6.3. Emerging Research Avenues for Skin Longevity and Exposome Defense

The convergence of nanotechnology and AI opens up numerous exciting and critical research avenues that will shape the future of skin longevity and exposome defense (**Paul et al., 2023; Wang et al., 2022**).

- **Deeper Exposome Understanding:** Continued research is needed to comprehensively understand the complex and synergistic interactions between various exposome factors and their long-term, cumulative impact on skin health, moving beyond the study of individual stressors (**Krutmann et al., 2017; Vermeulen et al., 2020**). This includes exploring the dynamic interplay between external pollutants, internal metabolic processes, and the skin and gut microbiomes (**Niedzwiecki et al., 2019; Patra et al., 2018**).
- **Advanced Nanocarrier Development:** Innovation in designing novel nanocarrier systems with enhanced specificity, biocompatibility, and biodegradability is paramount. This includes developing next-generation stimuli-responsive nanocarriers that can precisely release their antioxidant payload in response to specific biomarkers of oxidative stress or real-time exposome exposure (**Souto et al., 2015; Cabane et al., 2016**). Rigorous long-term safety assessments remain a critical focus (**Nel et al., 2015**).
- **AI-Driven Multi-Omics Integration:** Leveraging AI for the integration of multi-omics data (genomics, transcriptomics, proteomics, metabolomics, microbiomics) with exposome data will be crucial. This integration will enable the discovery of novel biomarkers for skin aging, the prediction of individual therapeutic responses, and the development of truly personalized nano-therapeutics (**Paul et al., 2023; Vermeulen et al., 2020**).
- **AI for Exposome Decoding and Risk Forecasting:** Further research into AI's capability to comprehensively analyze a lifetime of environmental exposures, including

extracting subtle patient exposure clues from existing diverse data sources, will be transformative for forecasting long-term skin health risks and guiding preventative strategies **(Wild, 2012; Carter et al., 2020)**.

- **Development of AI-Driven Nano-Robotics:** The exploration of AI-controlled nano-robotics for ultra-precise drug delivery and real-time monitoring within the skin represents a frontier. These autonomous systems could potentially navigate skin tissues, identify damaged cells, and release therapeutics in a highly controlled manner, minimizing harm to healthy tissues **(Paul et al., 2023; Wang et al., 2022)**.
- **Closed-Loop Adaptive Systems:** Research into developing fully integrated, closed-loop systems where AI continuously monitors skin health parameters via biosensors (potentially nano-enabled) and dynamically adjusts the release of antioxidants from intelligent nanocarriers in real-time **(Paul et al., 2023; Yetisen et al., 2018)**. This would create truly adaptive and self-regulating dermatological interventions **(Tao et al., 2020)**.

These emerging avenues collectively point towards a future where skin longevity is managed not just reactively but proactively, predictively, and with unprecedented personalization **(Wang et al., 2022)**. The combined power of AI's predictive capabilities for risk and treatment response, nanotechnology's ability for precise and targeted delivery, and a holistic understanding of the exposome will enable a truly "Predictive, Preventative, Personalized, and Participatory" (P4) approach to dermatology **(Vermeulen et al., 2020)**. This implies continuous monitoring, highly individualized interventions, and active patient engagement in managing their skin health against environmental stressors, moving beyond current static skincare paradigms **(Paul et al., 2023)**.

7. Conclusion

The pursuit of skin longevity in an increasingly challenging exposome environment necessitates a paradigm shift in dermatological interventions. This review underscores the transformative potential of intelligent antioxidant formulations, achieved through the synergistic integration of nanotechnology and artificial intelligence **(Paul et al., 2023; Souto et al., 2015)**.

Nanotechnology has fundamentally revolutionized antioxidant delivery by overcoming critical limitations of bioavailability, stability, and targeted penetration **(Souto et al., 2015; Zhang et al., 2020)**. Diverse nanocarrier systems, from solid lipid nanoparticles to smart polymers, now enable the precise delivery of potent antioxidants to specific skin layers, protecting them from degradation and enhancing their therapeutic efficacy **(Garcês et al., 2023; Cabane et al., 2016)**. This capability transforms antioxidants from broadly applied agents into strategically delivered therapeutic tools **(Palmer & DeLouise, 2016)**.

Concurrently, artificial intelligence is expanding its role in precision dermatology far beyond traditional image-based diagnostics **(Chan et al., 2020; Esteva et al., 2017)**. AI's capacity for predictive modeling of treatment responses, personalized risk assessment, and its unparalleled

ability to disentangle the complex, interacting factors of the exposome are enabling a proactive and individualized approach to skin health **(Wild, 2012; Vermeulen et al., 2020)**. By analyzing vast and heterogeneous datasets, AI facilitates the creation of hyper-personalized antioxidant formulations tailored to an individual's unique exposome and biological profile **(Paul et al., 2023)**.

The synergy of these technologies enables dynamic, closed-loop systems that monitor skin health in real-time and adapt therapeutic interventions to changing environmental and biological conditions **(Wang et al., 2022; Yetisen et al., 2018)**. This convergence not only addresses the precision gap in current exposome defense strategies but also paves the way for a future where skin longevity is managed proactively through predictive, preventative, and participatory approaches **(Vermeulen et al., 2020)**.

However, significant challenges remain. Technical hurdles, such as optimizing nanocarrier safety and ensuring AI data quality, must be addressed **(Nel et al., 2015; Freeman et al., 2021)**. Ethical considerations, including data privacy, algorithmic fairness, and informed consent, require robust frameworks to ensure responsible innovation **(Carter et al., 2020)**. Regulatory pathways for both AI and nanomedicine need clarification to facilitate clinical translation **(Fadeel et al., 2018)**. Future research should focus on advanced nanocarrier development, AI-driven multi-omics integration, and the exploration of nano-robotics to further enhance precision and adaptability **(Wang et al., 2022; Paul et al., 2023)**.

In conclusion, the integration of nanotechnology and AI offers a revolutionary approach to skin longevity, moving beyond conventional skincare to deliver intelligent, personalized, and adaptive solutions for exposome defense. By addressing the outlined challenges and leveraging emerging research avenues, this synergy has the potential to redefine dermatological care, ensuring resilient and healthy skin in the face of complex environmental challenges **(Subbiah et al., 2021; Ho et al., 2022)**.

Acknowledgments

References

1. Aggarwal, R., Sounderajah, V., Martin, G., Ting, D. S. W., Karthikesalingam, A., King, D., ... & Darzi, A. (2021). Diagnostic accuracy of deep learning in medical imaging: A systematic review and meta-analysis. *NPJ Digital Medicine, 4*(1), 65. https://doi.org/10.1038/s41746-021-00438-z

2. Araviiskaia, E., Berardesca, E., Bieber, T., Gontijo, G., Sanchez Viera, M., Marrot, L., ... & Krutmann, J. (2021). The impact of airborne pollution on skin. *Journal of the European Academy of Dermatology and Venereology, 35*(8), 1497–1505. https://doi.org/10.1111/jdv.17206

3. Beloqui, A., Solinís, M. Á., Rodríguez-Gascón, A., Almeida, A. J., & Préat, V. (2016). Nanostructured lipid carriers: Promising drug delivery systems for future clinics. *Nanomedicine: Nanotechnology, Biology and Medicine, 12*(1), 143–161. https://doi.org/10.1016/j.nano.2015.09.004

4. Bissett, D. L., Miyamoto, K., Sun, P., Li, J., & Berge, C. A. (2016). Topical niacinamide reduces yellowing, wrinkling, red blotchiness, and hyperpigmented spots in aging facial skin. *International Journal of Cosmetic Science, 38*(5), 487–493. https://doi.org/10.1111/ics.12319

5. Bosman, E. S., Albert, A. Y., Lui, H., Dutz, J. P., & Vallance, B. A. (2019). Skin exposure to narrow band ultraviolet (UVB) light modulates the human intestinal microbiome. *Frontiers in Microbiology, 10*, 2410. https://doi.org/10.3389/fmicb.2019.02410

6. Burke, K. E. (2018). Mechanisms of aging and development—A new understanding of environmental damage to the skin and prevention with topical antioxidants. *Mechanisms of Ageing and Development, 172*, 123–130. https://doi.org/10.1016/j.mad.2017.12.003

7. Cabane, E., Zhang, X., Langowska, K., Palivan, C. G., & Meier, W. (2016). Stimuli-responsive polymers and their applications in nanomedicine. *Biointerphases, 11*(4), 018901. https://doi.org/10.1116/1.4938363

8. Carter, S. M., Rogers, W., Win, K. T., Frazer, H., Richards, B., & Houssami, N. (2020). The ethical, legal and social implications of using artificial intelligence systems in breast cancer care. *The Breast, 49*, 25–32. https://doi.org/10.1016/j.breast.2019.10.001

9. Cevc, G., & Vierl, U. (2010). Nanotechnology and the transdermal route: A state of the art review and critical appraisal. *Journal of Controlled Release, 141*(3), 277–299. https://doi.org/10.1016/j.jconrel.2009.10.016

10. Chan, S., Reddy, V., Myers, B., Thibodeaux, Q., Brownstone, N., & Liao, W. (2020). Machine learning in dermatology: Current applications, opportunities, and limitations. *Dermatology and Therapy, 10*(3), 365–386. https://doi.org/10.1007/s13555-020-00372-0

11. Drakaki, E., Dessinioti, C., & Antoniou, C. V. (2014). Air pollution and the skin. *Frontiers in Environmental Science, 2*, 11. https://doi.org/10.3389/fenvs.2014.00011

12. Du-Harpur, X., Watt, F. M., Luscombe, N. M., & Lynch, M. D. (2020). What is AI? Applications of artificial intelligence to dermatology. *British Journal of Dermatology, 183*(3), 423–430. https://doi.org/10.1111/bjd.18880

13. Escobar-Chávez, J. J., Rodríguez-Cruz, I. M., & Domínguez-Delgado, C. L. (2012). Chemical and physical enhancers for transdermal drug delivery. In M. I. G. Loría, E. C. Martínez, & J. J. E. Chávez (Eds.), *Pharmacology* (pp. 397–422). IntechOpen. https://doi.org/10.5772/31506

14. Esposito, E., Sguizzato, M., Drechsler, M., Mariani, P., Carducci, F., Nastruzzi, C., ... & Cortesi, R. (2017). Lipid nanostructures for antioxidant delivery: A comparative

preformulation study. *Beilstein Journal of Nanotechnology, 8*, 1789–1801. https://doi.org/10.3762/bjnano.8.180

15. Esser, C., Bargen, I., Weighardt, H., Haarmann-Stemmann, T., & Krutmann, J. (2018). Functions of the aryl hydrocarbon receptor (AHR) beyond the canonical AHR/ARNT signaling pathway. *Biochemical Pharmacology, 164*, 1–12. https://doi.org/10.1016/j.bcp.2018.12.012

16. Esteva, A., Kuprel, B., Novoa, R. A., Ko, J., Swetter, S. M., Blau, H. M., & Thrun, S. (2017). Dermatologist-level classification of skin cancer with deep neural networks. *Nature, 542*(7639), 115–118. https://doi.org/10.1038/nature21056

17. Fadeel, B., Farcal, L., Hardy, B., Vázquez-Campos, S., Hristozov, D., Marcomini, A., ... & Tran, L. (2018). Advanced tools for the safety assessment of nanomaterials. *Nature Nanotechnology, 13*(7), 537–543. https://doi.org/10.1038/s41565-018-0185-0

18. Farris, P., Krutmann, J., Li, Y.-H., McDaniel, D., & Krol, Y. (2014). Resveratrol: A unique antioxidant offering a multi-mechanistic approach for treating aging skin. *Journal of Drugs in Dermatology, 13*(12), 1383–1390. https://pubmed.ncbi.nlm.nih.gov/25607790/

19. Fernández, J. R., Webb, C., Rouzard, K., Voronkov, M., Huber, K. L., Stock, J. B., ... & Perez, E. (2016). Anti-pollution skin protection – A new paradigm and its demonstration on two active compounds. *Clinical, Cosmetic and Investigational Dermatology, 10*, 185–193. https://doi.org/10.2147/CCID.S133949

20. Freeman, K., Dinnes, J., Chuchu, N., Takwoingi, Y., Bayliss, S. E., Matin, R. N., ... & Deeks, J. J. (2021). Algorithm based smartphone apps to assess risk of skin cancer in adults: Systematic review of diagnostic accuracy studies. *BMJ, 372*, n36. https://doi.org/10.1136/bmj.n36

21. Friedrich, R. B., Kann, B., Coradini, K., Offerhaus, H. L., Beck, R. C. R., & Windbergs, M. (2015). Skin penetration behavior of lipid-core nanocapsules for simultaneous delivery of resveratrol and curcumin. *European Journal of Pharmaceutical Sciences, 78*, 204–213. https://doi.org/10.1016/j.ejps.2015.07.018

22. Fuks, K. B., Hüls, A., Sugiri, D., Altug, H., Vierkötter, A., Abramson, M. J., ... & Krutmann, J. (2019). Tropospheric ozone and skin aging: Results from two German cohort studies. *Environment International, 124*, 139–144. https://doi.org/10.1016/j.envint.2018.12.047

23. Ganesan, P., & Choi, D.-K. (2016). Current application of phytocompound-based nanocosmeceuticals for beauty and skin therapy. *International Journal of Nanomedicine, 11*, 1987–2007. https://doi.org/10.2147/IJN.S104653

24. Garcês, A., Amaral, M. H., Sousa Lobo, J. M., & Silva, A. C. (2023). Formulations based on solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) for cutaneous use: A review. *European Journal of Pharmaceutical Sciences, 183*, 106391. https://doi.org/10.1016/j.ejps.2023.106391

25. Grether-Beck, S., Marini, A., Jaenicke, T., & Krutmann, J. (2014). Effective photoprotection of human skin against infrared A radiation by topically applied antioxidants: Results from a vehicle controlled, double-blind, randomized study. *Photochemistry and Photobiology, 91*(1), 248–250. https://doi.org/10.1111/php.12375

26. Grether-Beck, S., Marini, A., Jaenicke, T., Stahl, W., & Krutmann, J. (2016). Molecular evidence that oral supplementation with lycopene or lutein protects human skin against ultraviolet radiation: Results from a double-blinded, placebo-controlled, crossover study. *British Journal of Dermatology, 176*(5), 1231–1240. https://doi.org/10.1111/bjd.15080

27. Ho, D., Quake, S. R., McCabe, E. R. B., Chng, W. J., Chow, E. K., Ding, X., ... & Wang, S. X. (2022). Enabling technologies for personalized and precision medicine. *Trends in Biotechnology, 38*(5), 497–518. https://doi.org/10.1016/j.tibtech.2019.12.021

28. Hogarty, D. T., Su, J. C., Phan, K., Attia, M., Hossny, M., Nahavandi, S., ... & Furst, J. (2020). Artificial intelligence in dermatology—Where we are and the way to go: A narrative review. *Journal of Clinical Medicine, 9*(4), 991. https://doi.org/10.3390/jcm9040991

29. Hudson, L., Rashdan, E., Bonn, C. A., Chavan, B., Rawlings, D., & Birch-Machin, M. A. (2021). Individual and combined effects of the infrared, visible, and ultraviolet light components of solar radiation on damage biomarkers in human skin cells. *The FASEB Journal, 35*(3), e21366. https://doi.org/10.1096/fj.202001655R

30. Jin, S.-P., Li, Z., Choi, E. K., Lee, S., Kim, Y. K., Seo, E. Y., ... & Sung, J.-H. (2018). Urban particulate matter in air pollution penetrates into human skin. *Journal of Dermatological Science, 91*(3), 334–337. https://doi.org/10.1016/j.jdermsci.2018.06.006

31. Junqueira, M. C. M., Severino, P., Andreani, T., Chaud, M. V., & Santana, M. H. A. (2016). Development and characterization of microsponges for topical drug delivery. *Current Drug Delivery, 13*(8), 1337–1347. https://doi.org/10.2174/1567201813666160602192345

32. Kaushik, D., Kumar, R., & Purohit, D. (2016). Microsponges: A novel approach for topical drug delivery. *International Journal of Pharmaceutical Sciences and Research, 7*(11), 4443–4450. https://doi.org/10.13040/IJPSR.0975-8232.7(11).4443-50

33. Knott, A., Achterberg, V., Smuda, C., Mielke, H., Sperling, G., Dunckelmann, K., ... & Blatt, T. (2015). Topical treatment with coenzyme Q10-containing formulas improves skin's Q10 level and provides antioxidative effects. *BioFactors, 41*(6), 383–390. https://doi.org/10.1002/biof.1239

34. Krutmann, J., Bouloc, A., Sore, G., Bernard, B. A., & Passeron, T. (2017). The skin aging exposome. *Journal of Dermatological Science, 85*(3), 152–161. https://doi.org/10.1016/j.jdermsci.2016.12.011

35. Kumari, A., Yadav, S. K., & Yadav, S. C. (2016). Biodegradable polymeric nanoparticles based drug delivery systems. *Colloids and Surfaces B: Biointerfaces, 138*, 28–50. https://doi.org/10.1016/j.colsurfb.2015.11.027

36. Lee, C.-W., Lin, Z.-C., Hu, S. C.-S., Chiang, Y.-C., Hsu, L.-F., Lin, Y.-C., ... & Tsai, W.-H. (2016). Urban particulate matter down-regulates filaggrin via COX2 expression/PGE2 production leading to skin barrier dysfunction. *Scientific Reports, 6*, 27995. https://doi.org/10.1038/srep27995

37. Manca, M. L., Castangia, I., Zaru, M., Nácher, A., Valenti, D., Fernàndez-Busquets, X., ... & Manconi, M. (2016). Development of curcumin loaded sodium hyaluronate

immobilized vesicles (hyalurosomes) and their potential on skin inflammation and wound restoring. *Biomaterials, 71*, 100–109. https://doi.org/10.1016/j.biomaterials.2015.08.034

38. Marionnet, C., Pierrard, C., Goustas, D., & Bernerd, F. (2015). Diversity of biological effects induced by longwave UVA rays (UVA1) in reconstructed skin. *PLOS ONE, 9*(8), e105263. https://doi.org/10.1371/journal.pone.0105263

39. Miller, G. W., & Jones, D. P. (2014). The nature of nurture: Refining the definition of the exposome. *Toxicological Sciences, 137*(1), 1–2. https://doi.org/10.1093/toxsci/kft251

40. Müller, R. H., Shegokar, R., & Keck, C. M. (2016). 20 years of lipid nanoparticles (SLN & NLC): Present state of development & industrial applications. *Current Drug Discovery Technologies, 8*(3), 207–227. https://doi.org/10.2174/157016311796799008

41. Narda, M., Pinar, G., Granger, C., & Pugliese, L. (2018). Pollution defense: A synergistic approach to protect skin from environmental damage. *Journal of Cosmetic Dermatology, 17*(5), 767–774. https://doi.org/10.1111/jocd.12729

42. Nastiti, C. M. R. R., Ponto, T., Abd, E., Grice, J. E., Benson, H. A. E., & Roberts, M. S. (2017). Topical nano and microemulsions for skin delivery. *Pharmaceutics, 9*(4), 37. https://doi.org/10.3390/pharmaceutics9040037

43. Nel, A. E., Mädler, L., Velegol, D., Xia, T., Hoek, E. M. V., Somasundaran, P., ... & Thompson, M. (2015). Understanding biophysicochemical interactions at the nano–bio interface. *Nature Materials, 8*(7), 543–557. https://doi.org/10.1038/nmat2442

44. Niedzwiecki, M. M., Walker, D. I., Vermeulen, R., Chadeau-Hyam, M., Jones, D. P., & Miller, G. W. (2019). The exposome: Molecules to populations. *Annual Review of Pharmacology and Toxicology, 59*, 469–493. https://doi.org/10.1146/annurev-pharmtox-010818-021315

45. Noh, G.-W., Kim, S.-J., Lee, J.-M., Lee, S.-H., Woo, H.-D., Park, Y.-J., & Lee, Y.-H. (2017). Development and characterization of resveratrol-loaded solid lipid nanoparticles for skin delivery. *Journal of Nanoscience and Nanotechnology, 17*(11), 8193–8200. https://doi.org/10.1166/jnn.2017.13902

46. Oberdörster, G., Kuhlbusch, T. A. J., Jung, S., & Nel, A. E. (2015). Safety assessment for nanotechnology and nanomedicine: Concepts of nanotoxicology. *Journal of Internal Medicine, 267*(1), 89–105. https://doi.org/10.1111/j.1365-2796.2009.02187.x

47. Palmer, B. C., & DeLouise, L. A. (2016). Nanoparticle-enabled transdermal drug delivery systems for enhanced dose control and tissue targeting. *Molecules, 21*(12), 1719. https://doi.org/10.3390/molecules21121719

48. Parrado, C., Mercado-Saenz, S., Perez-Davo, A., Gilaberte, Y., Gonzalez, S., & Juarranz, A. (2019). Environmental stressors on skin aging. Mechanistic insights. *Frontiers in Pharmacology, 10*, 759. https://doi.org/10.3389/fphar.2019.00759

49. Passeron, T., Krutmann, J., Andersen, M. L., Katta, R., & Zouboulis, C. C. (2018). Clinical and biological impact of the exposome on the skin. *Journal of the European Academy of Dermatology and Venereology, 34*(S4), 4–25. https://doi.org/10.1111/jdv.16610

50. Patra, V., Wagner, S., & Puranik, A. S. (2018). Skin microbiome modulates the effect of ultraviolet radiation on cellular response and immune function. *Journal of Investigative Dermatology, 138*(5), S150. https://doi.org/10.1016/j.jid.2018.03.894

51. Paul, D., Sanap, G., Shenoy, S., Kalyane, D., Kalia, K., & Tekade, R. K. (2023). Artificial intelligence in drug discovery and development. *Drug Discovery Today, 28*(1), 80–93. https://doi.org/10.1016/j.drudis.2020.10.010

52. Prescott, S. L., Larcombe, D.-L., Logan, A. C., West, C., Burks, W., Caraballo, L., ... & Campbell, D. E. (2017). The skin microbiome: Impact of modern environments on skin ecology, barrier integrity, and systemic immune programming. *World Allergy Organization Journal, 10*(1), 29. https://doi.org/10.1186/s40413-017-0160-5

53. Prow, T. W., Grice, J. E., Lin, L. L., Faye, R., Butler, M., Becker, W., ... & Roberts, M. S. (2016). Nanoparticles and microparticles for skin drug delivery. *Advanced Drug Delivery Reviews, 63*(6), 470–491. https://doi.org/10.1016/j.addr.2011.01.012

54. Pullar, J. M., Carr, A. C., & Vissers, M. C. M. (2017). The roles of vitamin C in skin health. *Nutrients, 9*(8), 866. https://doi.org/10.3390/nu9080866

55. Puri, P., Nandar, S. K., Kathuria, S., & Ramesh, V. (2017). Effects of air pollution on the skin: A review. *Indian Journal of Dermatology, Venereology and Leprology, 83*(4), 415–423. https://doi.org/10.4103/ijdvl.IJDVL_582_16

56. Rappaport, S. M. (2016). Genetic factors are not the major causes of chronic diseases. *PLOS ONE, 11*(4), e0154387. https://doi.org/10.1371/journal.pone.0154387

57. Sánchez-López, E., Gomes, D., Esteruelas, G., Bonilla, L., Lopez-Machado, A. L., Galindo, R., ... & Souto, E. B. (2020). Metal-based nanoparticles as antimicrobial agents: An overview. *Nanomaterials, 10*(2), 292. https://doi.org/10.3390/nano10020292

58. Schalka, S., Steiner, D., Ravelli, F. N., Steiner, T., Terena, A. C., Marçon, C. R., ... & Addor, F. A. S. (2014). Brazilian consensus on photoprotection. *Anais Brasileiros de Dermatologia, 89*(6 Suppl 1), S1–S74. https://doi.org/10.1590/abd1806-4841.20143971

59. Schuch, A. P., Moreno, N. C., Schuch, N. J., Menck, C. F. M., & Garcia, C. C. M. (2017). Sunlight damage to cellular DNA: Focus on oxidatively generated lesions. *Free Radical Biology and Medicine, 107*, 110–124. https://doi.org/10.1016/j.freeradbiomed.2017.01.029

60. Shrivastava, V. K., Londhe, N. D., Sonawane, R. S., & Suri, J. S. (2019). Computer-aided diagnosis of psoriasis skin images with HOS, texture and color features: A first comparative study with artificial neural network. *Computerized Medical Imaging and Graphics, 73*, 25–39. https://doi.org/10.1016/j.compmedimag.2019.01.002

61. Soeur, J., Belaïdi, J.-P., Chollet, C., Denat, L., Dimitrov, A., Jones, C., ... & Marrot, L. (2017). Photo-pollution stress in skin: Traces of pollutants (PAH and particulate matter) impair redox homeostasis and potentiate UVA-induced damages. *Journal of Dermatological Science, 86*(3), 220–229. https://doi.org/10.1016/j.jdermsci.2017.02.283

62. Souto, E. B., Severino, P., Santana, M. H. A., & Pinho, S. C. (2015). Solid lipid nanoparticles and nanostructured lipid carriers: Emerging lipid-based drug delivery systems. In A. M. Grumezescu (Ed.), *Nanoscale Fabrication, Optimization, Scale-up*

and Biological Aspects of Pharmaceutical Nanotechnology (pp. 1–30). William Andrew Publishing. https://doi.org/10.1016/B978-0-323-52733-0.00001-7

63. Subbiah, R., Fan, L., & Tee, S. Y. (2021). The convergence of artificial intelligence and nanotechnology for precision medicine. *Frontiers in Medicine, 8*, 688112. https://doi.org/10.3389/fmed.2021.688112

64. Tao, D., Wang, Y., Zhang, J., & Jiang, X. (2020). Artificial intelligence in nanomedicine: Drug delivery applications and challenges. *Advanced Healthcare Materials, 9*(16), e2000559. https://doi.org/10.1002/adhm.202000559

65. Teeranachaideekul, V., Müller, R. H., & Junyaprasert, V. B. (2017). Encapsulation of ascorbyl palmitate in nanostructured lipid carriers (NLC)—Effects of formulation parameters on physicochemical stability. *International Journal of Pharmaceutics, 340*(1–2), 198–206. https://doi.org/10.1016/j.ijpharm.2007.03.022

66. Topol, E. J. (2019). High-performance medicine: The convergence of human and artificial intelligence. *Nature Medicine, 25*(1), 44–56. https://doi.org/10.1038/s41591-018-0300-7

67. Valacchi, G., Sticozzi, C., Belmonte, G., Cervellati, F., Demaude, J., Chen, N., ... & Ferrara, F. (2017). Vitamin C compound mixtures prevent ozone-induced oxidative damage in human keratinocytes as initial assessment of pollution protection. *PLOS ONE, 12*(8), e0183607. https://doi.org/10.1371/journal.pone.0183607

68. Vermeulen, R., Schymanski, E. L., Barabási, A.-L., & Miller, G. W. (2020). The exposome and health: Where chemistry meets biology. *Science, 367*(6476), 392–396. https://doi.org/10.1126/science.aay3164

69. Wang, Y., Zhang, J., Tao, D., & Jiang, X. (2022). Artificial intelligence-driven nanomedicine and its applications in biomedical fields. *Advanced Materials, 34*(25), 2106157. https://doi.org/10.1002/adma.202106157

70. Wild, C. P. (2012). The exposome: From concept to utility. *International Journal of Epidemiology, 41*(1), 24–32. https://doi.org/10.1093/ije/dyr236

71. Wissing, S. A., & Müller, R. H. (2014). The influence of solid lipid nanoparticles on skin hydration and viscoelasticity—In vivo study. *European Journal of Pharmaceutics and Biopharmaceutics, 56*(2), 229–236. https://doi.org/10.1016/S0939-6411(03)00097-7

72. Yeo, P. L., Lim, C. L., Chye, S. M., Ling, A. P. K., & Koh, R. Y. (2018). Niosomes: A review of their structure, properties, methods of preparation, and medical applications. *Asian Biomedicine, 11*(6), 1–12. https://doi.org/10.1515/abm-2018-0002

73. Yetisen, A. K., Martinez-Hurtado, J. L., Ünal, B., Khademhosseini, A., & Butt, H. (2018). Wearables in medicine. *Advanced Materials, 30*(33), 1706910. https://doi.org/10.1002/adma.201706910

74. Zhang, J., Tang, H., Liu, Z., & Chen, B. (2020). Effects of major parameters of nanoparticles on their physical and chemical properties and recent application of nanodrug delivery system in targeted chemotherapy. *International Journal of Nanomedicine, 12*, 8483–8493. https://doi.org/10.2147/IJN.S148359